National Institute for Health and Care Excellence

Draft for consultation

Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults

[C] Evidence review: Safe withdrawal

NICE guideline <TBC>

Evidence reviews underpinning recommendations 1.5.1, 1.5.2 , 1.5.3 , 1.5.4, 1.5.5, 1.5.6, 1.5.7, 1.5.8 , 1.5.10, 1.5.11, 1.5.12, 1.5.15, 1.5.16, 1.5.17, 1.5.18, 1.5.19, 1.5.20, 1.5.21 and the research recommendations in the NICE guideline.

October 2021

Draft for Consultation

These evidence reviews were developed by the National Guideline Centre]

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1 Safe Withdrawal

1.1 Review question:

What are the most clinically and cost-effective pharmacological and non-pharmacological strategies, for example, tapered withdrawal or education and support, for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids and antidepressants)?

1.1.1 Introduction

When dependence-forming medicines are discontinued, people taking them may experience a range of very unpleasant and sometimes dangerous withdrawal effects. The withdrawal process varies between individuals: it may be prolonged and can have a significant impact on quality of life. Some withdrawal symptoms may persist for many months or longer. It is important that both the patient and the prescriber have a good understanding of what to expect when medicines are withdrawn. Coming off medicines is challenging, and this difficulty needs to be acknowledged.

This review explores the evidence to support prescribers and people coming off medicines to do so safely and with the least burdensome experience in relation to withdrawal symptoms.

Every clinical situation is unique to the prescriber and the patient and decisions about withdrawal need to be collaborative and aligned to the individual's preferences and sufficient time needs to be given for people to discuss the information they have. The review questions should identify strategies for withdrawal from each medicine class studied and give prescribers and people taking medicines, the best advice regarding timing and rate of withdrawal, use of appropriate medicine formulations, mitigation of withdrawal effects, and support for withdrawal.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (≥18 years) taking prescribed medicines that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants). Prescription medicines which can also be bought over the counter (e.g., codeine, co-codamol) also included. **Stratification** <u>Drug class</u> • Opioids • Benzodiazepines, • Z-drugs • Gabapentinoids • Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others)

Interventions	• Approaches to treatment of dependence, discontinuation/withdrawal including:
	  ○ Dose reduction
	  ○ Tapered withdrawal strategies (e.g., versus rapid or abrupt withdrawal)
	  ○ Managed withdrawal (e.g., the Ashton manual)
	• Pharmacological interventions
	• Non-pharmacological interventions

	See the full protocol Appendix A for examples. Any withdrawal intervention will be included and the protocol lists examples only.
Comparisons	Compared to each other or usual care for withdrawal

Outcomes	• Validated Health related Quality of life, including:
	  ○ Physical health
	  ○ Psychological health
	  ○ Social functioning
	• Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)
	• Reduction/cessation of prescribed drug use
	• Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome
	• Relapse into medication use
	• Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs
	• Non-fatal overdose
	• Reduced tolerance
	• Patient Satisfaction
	• Self-harm or harm to others
	• Increase in symptoms for which the medication was originally prescribed
	• Improvements in adverse effects commonly associated with long-term prescribed substance use such as cognitive deficits or constipation associated with opioids
	• Distress (e.g., CORE10).

Study design	Randomised controlled trials Systematic review of randomised controlled trials. Published network meta-analyses (NMAs) and individual patient data (IPD) meta-analyses will be considered for inclusion. Non-randomised comparative studies will only be considered for any drug class stratifications for which no RCT evidence is identified (non-randomised studies (NRSs) accounting for confounding using multivariate analysis will be given preference).

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

As specified in the protocol for this review question, any approach to the withdrawal of medicines (such as a taper schedule) or any withdrawal intervention was included. For an intervention to be considered a withdrawal intervention, it needed to incorporate an aim to reduce or withdraw medicines. The committee was aware of various studies reporting interventions used to treat an underlying condition (for example, CBT for insomnia), which may subsequently result in a reduction in the medicine dose, due to efficacy of the intervention. However, treatment of the underlying condition was outside the scope of this guideline. Therefore, such studies were excluded. For a study to be included, the intervention needed to be alongside a reduction or withdrawal schedule, in order to be considered an intervention used to aid withdrawal. An exception to this was for studies reporting a comparison group of 'usual care'. If it was clear from the study that there was not an attempt to withdraw medicines in the comparison arm, for example, if a study stated that people were continued on their medication, then the study was excluded. However, if a study only stated 'usual care' without any description of what the usual care entailed, this was included but

downgraded for indirectness, as per the protocol. This was because, for medicines where long-term use is not advised it was considered plausible that usual care could include an element of deprescribing. However, just because people are on medicines for which long-term use is not advised, this does not always mean people will be discontinued from the medicines, if left to usual care. Therefore, usual care could encompass anything from 'little or no intervention for support of withdrawal' to 'a comprehensive support for withdrawing from the prescribed medicine'.

As specified in the protocol, studies were only included if at least 80% of the population were on medicines listed on the guideline medicine list (see Appendix K), which details those medicines available to be prescribed within the NHS. Some studies were excluded from this review as they were in a population with the majority of people not on one of these medicines. This was particularly the case for benzodiazepines, where studies reported populations on older benzodiazepines that are no longer licensed or those used in other countries. If a study had no breakdown of the number of people on specific medicines, but some people were on medicines not listed on the guideline medicine list, the study was included but the population was downgraded for indirectness.

Zaleplon is a Z-drug that was originally included within the guideline medicine list. Subsequent to the start of the development of the guideline, it was discovered that zaleplon no longer had a UK marketing authorisation. It was therefore excluded from the medicines to be considered in the guideline. However, a small number of studies included within this review were kept within the evidence. These studies were in populations on a range of Z-drugs, for which some may have been on zaleplon. The committee deemed that these studies were still relevant to the review, as it is likely that only a small proportion of the included population were on zaleplon, and therefore the studies would still be relevant to the intended population. Additionally, the committee agreed that Z-drugs could be pooled as a class, as the considerations are likely to be the same, and therefore inclusion of some people taking zaleplon would not be expected to influence the effectiveness of withdrawal interventions.

The protocol for this review specified the withdrawal symptoms and symptoms for which the medicine was originally prescribed as distinct outcomes (in order to identify re-emergence of symptoms). In some cases, the included studies reported whether a particular symptom was a withdrawal symptom, or whether it was a symptom for which the medicine was originally prescribed (for example, a relapse of major depression). However, in other studies, individual symptoms were reported separately, such as anxiety, without a definition of whether this was a withdrawal symptom or not. In these cases, if the reported symptom was the same as what the population had been prescribed the medicine for (for example, insomnia reported in a study population of people taking benzodiazepines for insomnia) then this study outcome was classified by the reviewer as a protocol outcome of 'symptoms for which the medicine was originally prescribed'. However, if the reported symptom was different from what the population had been prescribed the medicine for, or if the population was mixed (for example, insomnia reported in a study population of people taking benzodiazepines for a mixture of reasons) then this study outcome was classified by the reviewer as a protocol outcome of 'withdrawal symptoms.'

1.2 Opioids

1.2.1 Effectiveness evidence

1.2.1.1 Included studies

Five RCTs relevant to opioid withdrawal were included in the review;[114, 118, 253, 297, 298] these are summarised in **Table 2** below. Evidence from these studies is summarised in the clinical evidence summaries below (**Table 3** to **Table 8**).

One study compared varenicline plus an interdisciplinary treatment program (ITP) based on a cognitive behavioural model and including medically directed opioid taper to placebo plus ITP. One study compared acupuncture plus standard medication management and opioid weaning to standard medication management and opioid weaning. One study compared multicomponent psychological opioid taper support (including motivational interviewing and CBT) together with a taper program to usual prescribing. Although the usual prescribing group did not receive a taper program, both arms had been shown a video with people who had successfully tapered off opioids concerning what they had gained from this. Two studies compared real electroacupuncture with sham electroacupuncture. One of these had a concurrent medication reduction schedule in both arms, the other had concurrent pain medication management (including a taper schedule) in both arms. This latter study was a 3-arm trial and also compared both arms to pain medication management (including a taper schedule) alone.

See also the study selection flow chart in Appendix C. Other relevant Appendices include study evidence tables in E.1, forest plots in F.1 and GRADE tables in G.1.

1.2.1.2 Excluded studies

See the excluded studies list in Appendix I.

One Cochrane review[64] was identified in the search as potentially relevant to the opioid stratum of this review. However, this Cochrane review protocol differed to this review question and protocol, as it included some studies with a comparison group that was maintained on opioids. Therefore, this Cochrane review could not be included in this review in its entirety, but all included studies were cross-checked for inclusion in this review as relevant. The Cochrane review did not use GRADE to assess the quality of evidence, and therefore the relevant studies included within it were assessed fully within the guideline review, rather than reusing any analysis undertaken within the Cochrane review.

Four studies initially considered for inclusion for the opioid stratum[58, 85, 86, 106] of this review were subsequently noted not to have interventions that matched the review protocol and were therefore excluded. These studies assessed interventions that aimed to treat dependence or aberrant drug-related behaviours, but without the specific aim to withdraw opioids.

A number of Cochrane reviews are available in the literature assessing the effectiveness of interventions for the withdrawal of illicit opioids or looking at substitution therapy for people who were dependent on illicit opioids. These Cochrane reviews did not match the guideline review population of prescribed medicines and were not considered for inclusion in this review.

1.2.2 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review (Opioids)

Study	Intervention and comparison	Population	Outcomes	Comments
Hooten 2015[114]	Varenicline plus Interdisciplinary Treatment Program (ITP) based on a cognitive behavioural model and including medically directed opioid taper. Vs Placebo plus ITP based on a cognitive behavioural model and including medically directed opioid taper Duration: 15 days	Adults with chronic pain undergoing medically directed opioid detoxification as part of an interdisciplinary treatment program N=21 Median age (IQR): Varenicline: 49 (36-60) years Placebo 46 (29-53) years USA	Number of people who discontinued Decrease in severity of withdrawal symptoms (Clinical Opiate Withdrawal scale - COWS) At dismissal (inferred to be 3 weeks i.e., the duration of the detoxification program)	ITP is of 3-week duration and a cognitive behavioural model served as the basis for treatment. The primary goal of treatment was functional restoration The study also reported the outcomes of time to completion of tapering, and pain severity, however these outcomes were not reported in a format which could be analysed, or quality assessed.
Jackson 2021[118]	Acupuncture + standard outpatient medication management with opioid weaning (as below) Vs Standard outpatient medication management with opioid weaning (monthly visits with gradual reductions, 10-20%, in combination with adjuvant nonopioid medications and therapies) Duration: until opioid weaning complete.	Chronic pain; referred to the pain management clinic for opioid weaning and/or discontinuation N=16 Mean age (SD): 56.5 (17.3) years. USA	Morphine equivalent dose (MED; protocol outcome: reduction in prescribed medication use) Subjective withdrawal symptoms (clinical institute narcotic assessment CINA) Pain (numerical rating scale NRS; protocol outcome: symptoms for which the medication was originally prescribed)	Completion of the opioid weaning regimen was determined by overall MED (<90 MED) and individual patient functionality as determined by the treating provider. Further reductions in MED were encouraged but often not attainable. Not all people had full withdrawal of opioids (unclear how many). As part of standard medication management both groups could have adjuvant nonopioid medications and therapies.

Study	Intervention and comparison	Population	Outcomes	Comments
			All at post-intervention	
Sullivan 2017[253]	Multicomponent psychological opioid taper support (including motivational interviewing and CBT) + taper vs Usual care (usual prescribing) 22 weeks Both groups were first shown a video of people who had successfully tapered off opioids concerning what they had gained from this.	Chronic non-cancer pain patients with a daily morphine equivalent dose (MED) >50 mg, willing to taper their opioid use by at least 50% (or to 120 mg MED, whichever was less). N=35 Mean age (SD): 54.4 (10.1) years. 67% of participants in the taper support group attended all self-management training sessions, 17% attended 10-17 sessions, 11% 1-5 sessions and 6 % no sessions. USA	QoL: Patient Global Impression Change (PGIC) Opioid discontinuation Opioid dose (mean daily MED in the past week, obtained via self-reports or electronic medical records if self-report data unavailable) Opioid dose reduction by 50% or more Pain severity (BPI) (protocol outcome: increase in symptoms for which the medication was originally prescribed) Insomnia severity (ISI) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use) At 22 weeks (completion of the taper support intervention) and at 34 weeks.	There was no specific aim to taper in the usual care group, but willingness to taper was part of the inclusion criteria and all participants were shown the same video on tapering at the start. After enrolment began, the requirement for a 50% (or 120 mg) taper goal, were removed and the required opioid dose at study entry was lowered to >25 mg MED in order to increase enrolment.

Study	Intervention and comparison	Population	Outcomes	Comments
Zheng 2008[298]	Real electroacupuncture (with concurrent opioid-like medication (OLM*) reduction schedule) Vs Sham electroacupuncture (with concurrent OLM reduction schedule) 6 weeks In addition, a researcher phoned each participant to inform them of the OLM reduction schedule developed by the pain physician (based on their weekly consumption) and encouraged them to reduce OLM consumption. In total 3 telephone calls were made to each participant during the 20 weeks of the study.	Chronic non-cancer pain opioid-like medication (OLM*) users N=35 Mean age (SD): 49.71 (11.86) years The majority had pain in the musculoskeletal system and took codeine, morphine, oxycodone and/or tramadol. Mean (SD) baseline OLM (morphine equivalent consumption) Electroacupuncture vs Sham (mg/week): 461.6 (462.6) vs 295.5 (288) mg/day Australia	OLM (morphine equivalent) consumption (mg/week) Average pain: Pain intensity (Visual Analogue Scale) (protocol outcome: increase in symptoms for which the medication was originally prescribed) Pain duration (hr/day; protocol outcome: increase in symptoms for which the medication was originally prescribed) Post-intervention (study week 8) and at follow-up (study week 20) for OLM consumption. All outcome measures were self-reported in a diary or questionnaire form.	20-week pilot randomised study (2-week baseline assessment, 6-week intervention, 12-week follow-up) *Types of OLM were: Codeine, methadone, oxycodone, morphine, tramadol Paper also reports: The types of OLM related side-effects experienced by more than half of the participants in each group; these were fatigue, drowsiness, lethargy and constipation in the REA group, and nausea, dizziness, fatigue, drowsiness, blurred vision, sedation, lethargy and anxiety in the sham electroacupuncture group
Zheng 2019[297]	All participants received pain medication management (PMM which was provided by pain specialists in the fifth week assisted by a standard manual and were randomised to: Electroacupuncture + PMM (taper schedule)	Chronic non-cancer musculoskeletal pain opioid medication (OM) users N=108 Mean age (SD): 56.32 (12.49))	QoL (SF-36 total, Mental health, Physical health) Opioid dosage (OM dosage) 50 % OM reduction Weekly consumption of non-OMs for pain	Study also reports results at three months after treatment (for electroacupuncture vs sham); at 3-month follow up PMM participants had received 10 weeks of electroacupuncture, as they were offered the intervention at the end of the PMM period.

Study	Intervention and comparison	Population	Outcomes	Comments
	vs Sham electroacupuncture + PMM (taper schedule) Vs Education alone: PMM (taper schedule); 10 weeks Following the 10-week period PMM participants were given the opportunity to have electroacupuncture treatment.	Type of OM morphine equivalent dose for the majority in each group was 'low (<560 mg/wk.)' Mean (SD) baseline morphine equivalent OM dose (mg/week) was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group and 871.4 (1,772.3) in the PMM group Australia	(Medication quantification scale, version III) (protocol outcome: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs) Intensity of the highest pain (VAS; protocol outcome: increase in symptoms for which the medication was originally prescribed) Intensity of the average pain (VAS; protocol outcome: increase in symptoms for which the medication was originally prescribed) Weekly opioid-related adverse events (average number of OM-related AEs per person) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use) Severity of opioid-related AEs (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	

Study	Intervention and comparison	Population	Outcomes	Comments
			Post treatment (average of weeks 11-14) & at end of three-month follow-up (study week 26) for OM dosage	

See section E.1 in the Appendices for full evidence tables.

1.2.3 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Varenicline + ITP (which included taper) vs Placebo + ITP (which included taper) for opioid withdrawal

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + taper program	Risk difference with Varenicline + taper program
Number of people who discontinued assessed at dismissal (3 weeks)	18 (1 RCT)	⨁⨁◯◯ LOW [a]	RR 1.00 (0.81 to 1.24)	1,000 per 1,000	0 fewer per 1,000 (190 fewer to 240 more)
Decrease in severity of withdrawal symptoms assessed with: COWS at dismissal-3 weeks	18 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.96 (0.79 to 4.89)	364 per 1,000	349 more per 1,000 (76 fewer to 1,415 more)

a. Downgraded by 2 increments as the evidence was at very high risk of bias
b. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8 and 1.25)

Table 4: Clinical evidence summary: Acupuncture + standard medication management with opioid weaning vs standard outpatient medication management with opioid weaning

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with Acupuncture + taper
Morphine equivalent dose (MED; protocol outcome: reduction in prescribed medication use) at post-intervention	15 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean MED at post-intervention was 125	MD 47 lower (150.3 lower to 56.3 higher)
Subjective withdrawal symptoms (clinical institute narcotic assessment; CINA; range of values unclear) at post-intervention	15 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean CINA at post-intervention was 7.1	MD 0.7 lower (4.54 lower to 3.14 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with Acupuncture + taper
Pain (numerical rating scale; NRS; range of values unclear; protocol outcome: symptoms for which the medication was originally prescribed) at post-intervention	15 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean pain NRS at post-intervention was 6.9	MD 1.7 lower (3.34 lower to 0.06 lower)
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias. b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of intervention and control groups for continuous outcomes). Calculated MIDs for continuous outcomes were as follows: MED: 48; CINA: 2.9; NRS: 2.83					

Table 5: Clinical evidence summary: Multicomponent taper support + taper for opioid withdrawal vs usual prescribing

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual prescribing	Risk difference with Multicomponent taper support + taper
QoL-Patient global impression of change (22 weeks)	29 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 2.44 (0.83 to 7.20)	231 per 1,000	332 more per 1,000 (39 fewer to 1,431 more)
QoL-Patient global impression of change (34 weeks)	31 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.78 (0.86 to 3.68)	375 per 1,000	293 more per 1,000 (53 fewer to 1,005 more)
Discontinuation (at 22 weeks)	31 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.94 (0.06 to 13.68)	67 per 1,000	4 fewer per 1,000 (63 fewer to 845 more)
Discontinuation (at 34 weeks)	32 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.00 (0.16 to 6.25)	125 per 1,000	0 fewer per 1,000 (105 fewer to 656 more)
Mean daily dose in the past week (mg; at 22 weeks)	35 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median mean daily dose in the past week	MD 42.9 lower (92.42 lower to 6.62 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual prescribing	Risk difference with Multicomponent taper support + taper
				(mg; at 22 weeks) was 169.85	
Mean daily dose in the past week (mg; at 34 weeks)	35 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median mean daily dose in the past week (mg; at 34 weeks) was 138.24	MD 26.71 lower (83.04 lower to 29.62 higher)
Opioid dose reduction by 50% or more (at 22 weeks)	34 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 3.11 (0.75 to 12.87)	125 per 1,000	264 more per 1,000 (31 fewer to 1,484 more)
Opioid dose reduction by 50% or more (at 34 weeks)	32 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.80 (0.77 to 4.19)	313 per 1,000	250 more per 1,000 (72 fewer to 997 more)
Pain severity (at 22 weeks; BPI); protocol outcome: increase in symptoms for which the medication was originally prescribed	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The median pain severity (at 22 weeks; BPI) was 5.77	MD 0.68 lower (2.01 lower to 0.65 higher)
Pain severity (at 34 weeks; BPI) protocol outcome: increase in symptoms for which the medication was originally prescribed	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The median pain severity (at 34 weeks; BPI) was 6.16	MD 0.91 lower (2.3 lower to 0.48 higher)
Insomnia severity (at 22 weeks; ISI): Protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The median insomnia severity (at 22 weeks; ISI) was 16.80	MD 3.13 lower (7.22 lower to 0.96 higher)
Insomnia severity (at 34 weeks; ISI): Protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The median insomnia severity (at 34 weeks; ISI) was 15.50	MD 1.19 lower (5.49 lower to 3.11 higher)
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments as the evidence was at very high risk of bias					

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual prescribing	Risk difference with Multicomponent taper support + taper
b. Downgraded by 1 increment as the control group stayed on medication ('usual prescribing')					
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes;0.5 * median of baseline SD of the intervention and control group)					
MIDs for continuous outcomes were as follows. Mean daily dose in the past week 154.18, Pain severity 0.71, Insomnia severity 3.54					

Table 6: Electroacupuncture + taper (taper schedule alone or taper as part of pain medication management (PMM)) vs sham electroacupuncture + taper (taper schedule alone or taper as part of PMM) for opioid withdrawal

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham electroacupuncture + taper (PMM)	Risk difference with Electroacupuncture + taper (PMM)
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)	77 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14) was 39.3	MD 2.3 higher (5.48 lower to 10.08 higher)
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)	77 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14) was 34.3	MD 0.7 higher (6.53 lower to 7.93 higher)
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)	77 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14) was 44.9	MD 3.6 higher (5.14 lower to 12.34 higher)
Opioid consumption (mg/week; post-intervention: week 8/average of weeks 11-14))	112 (2 RCTs)	⨁⨁⨁◯ MODERATE [a c]	-	The median opioid consumption (mg/week; post-	MD 3.77 lower (76.38 lower to 68.84 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham electroacupuncture + taper (PMM)	Risk difference with Electroacupuncture + taper (PMM)
				intervention: week 8/average of weeks 11-14)) was 378.25	
Opioid consumption (mg/week; at 12-week follow-up)	80 (2 RCTs)	⊕⊕◯◯ LOW [a c]	-	The median opioid consumption (mg/week; at 12-week to 3-month follow-up) was 357.25	MD 48.99 lower (120.47 lower to 22.47 higher)
50% OM reduction (at end of treatment: average of weeks 11-14)	77 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.68 (0.30 to 1.56)	276 per 1,000	88 fewer per 1,000 (193 fewer to 154 more)
Non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14) protocol outcome: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs	77 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The median non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14) was 9.3	MD 0.3 higher (2.91 lower to 3.51 higher)
Intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	77 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The median intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14) was 5.9	MD 0.1 higher (0.88 lower to 1.08 higher)
Average pain (VAS; 0-10; post-intervention: week 8/average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	112 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	-	The median average pain (VAS; 0-10; post-intervention: week 8/average of weeks 11-14) was 5.1	MD 0.61 lower (1.46 lower to 0.25 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sham electroacupuncture + taper (PMM)	Risk difference with Electroacupuncture + taper (PMM)
Duration of pain (hr/day; post-intervention) protocol outcome: increase in symptoms for which the medication was originally prescribed	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The median duration of pain (hr/day; post-intervention) was 14.6	MD 1.8 higher (1.65 lower to 5.25 higher)
Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	77 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median OM-related adverse events per person (at end of treatment: average of weeks 11-14) was 3.2	MD 1.8 lower (3.44 lower to 0.16 lower)
Severity of OM-related adverse events (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	77 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median severity of OM-related adverse events (at end of treatment: average of weeks 11-14) was 12.9	MD 7.3 lower (15.18 lower to 0.58 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments as the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes unless published measure-specific MIDs are available e.g., for the SF-36. Where baseline SDs were not reported, 0.5 * median of final value SD of the intervention and control group was used (intensity of the highest pain).

c. Difference in baseline opioid dose potentially problematic; electroacupuncture vs sham Zheng 2008: 461.6 (462.6) vs 295.5 (288) mg/day, Zheng 2019 463.3 (438.6) vs 620.8 (792.5)

MIDs for continuous outcomes were as follows: QoL: SF-36 2, SF-36-Physical health 2, SF-36-Mental health 3; Opioid consumption 225.3; non-OM dosage 5.55; average pain (VAS) 0.93; intensity of the highest pain (VAS) 1.06; duration of pain 2.48; OM-related adverse events per person 1.9; Severity of OM-related adverse events 9.98.

Table 7: Electroacupuncture + PMM vs PMM alone for opioid withdrawal

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Electroacupuncture + PMM
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)	79 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14) was 35.8	MD 5.8 higher (2.9 lower to 14.5 higher)
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)	79 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14) was 30.6	MD 4.4 higher (3.28 lower to 12.08 higher)
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)	79 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The median QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14) was 41.1	MD 7.4 higher (2.71 lower to 17.51 higher)
Opioid dosage (mg; end of treatment: average of weeks 11-14)	79 (1 RCT)	⊕⊕⊕◯ MODERATE [a c]	-	The median opioid dosage (mg; end of treatment: average of weeks 11-14) was 585.2	MD 58.6 lower (133.75 lower to 16.55 higher)
50% OM reduction (at end of treatment: average of weeks 11-14)	79 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.45 (0.49 to 4.31)	129 per 1,000	58 more per 1,000 (66 fewer to 427 more)
Non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14) protocol outcome: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs	79 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The median non-OM dosage (Medication quantification scale III; at end of	MD 0.5 lower (3.56 lower to 2.56 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Electroacupuncture + PMM
				treatment: average of weeks 11-14) was 10.1	
Intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	79 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14) was 6.6	MD 0.6 lower (1.58 lower to 0.38 higher)
Intensity of the average pain (VAS; 0-10; end of treatment: average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	79 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median intensity of the average pain (VAS; 0-10; end of treatment: average of weeks 11-14) was 5.8	MD 0.7 lower (1.68 lower to 0.28 higher)
Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	79 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median OM-related adverse events per person (at end of treatment: average of weeks 11-14) was 2.5	MD 1.1 lower (2.49 lower to 0.29 higher)
Severity of OM-related adverse events (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	79 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median severity of OM-related adverse events (at end of treatment: average of weeks 11-14) was 11.4	MD 5.8 lower (13.07 lower to 1.47 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Electroacupuncture + PMM
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes unless published measure-specific MIDs are available e.g., for the SF-36). Where baseline SDs were not reported, 0.5 * median of final value SD of the intervention and control group was used (intensity of the highest pain). c. Mean (SD) baseline morphine equivalent OM dose (mg/week) in the electroacupuncture vs PMM group was 463.3 (438.6) vs 871.4 (1,772.3) in the PMM group MIDs for continuous outcomes were as follows: QoL: SF-36 2, SF-36-Physical health 2, SF-36-Mental health 3; Opioid dosage 662.38, non-OM dosage 4.9; average pain (VAS) 0.9; intensity of the highest pain (VAS) 1.08; Weekly OM-related adverse events per person 1.9; Severity of OM-related adverse events 7.75.					

Table 8: Sham electroacupuncture + PMM vs PMM alone for opioid withdrawal

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Sham electroacupuncture + PMM
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)	60 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14) was 35.8	MD 3.5 higher (5.68 lower to 12.68 higher)
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)	60 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14) was 30.6	MD 3.7 higher (4.49 lower to 11.89 higher)
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)	60 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The median QoL (SF-36-Mental health; 0-100; at	MD 3.8 higher (6.67 lower to 14.27 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Sham electroacupuncture + PMM
				end of treatment: average of weeks 11-14) was 41.1	
Opioid dosage (mg; at end of treatment; average of weeks 11-14)	60 (1 RCT)	⊕⊕⊕◯ MODERATE [a c]	-	The median opioid dosage (mg; at end of treatment; average of weeks 11-14) was 585.2	MD 47.8 lower (131.79 lower to 36.19 higher)
50 % OM reduction (at end of treatment: average of weeks 11-14)	60 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 2.14 (0.72 to 6.35)	129 per 1,000	147 more per 1,000 (36 fewer to 690 more)
Non-OM dosage (Medication quantification scale III; at end of treatment (average of weeks 11-14) protocol outcome: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs	60 (1 RCT)	⊕⊕◯◯ LOW [a]	-	The median non-OM dosage (Medication quantification scale III; at end of treatment (average of weeks 11-14) was 10.1	MD 0.8 lower (4.27 lower to 2.67 higher)
Intensity of the highest pain (VAS; 0-10; at end of treatment: average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	60 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The median intensity of the highest pain (VAS; 0-10; at end of treatment: average of weeks 11-14) was 6.6	MD 0.7 lower (1.81 lower to 0.41 higher)
Intensity of the average pain (VAS; 0-10; at end of treatment: average of weeks 11-14) protocol outcome: increase in symptoms for which the medication was originally prescribed	60 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The median intensity of the average pain (VAS; 0-10; at	MD 0.4 lower (1.65 lower to 0.85 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PMM alone	Risk difference with Sham electroacupuncture + PMM
				end of treatment: average of weeks 11-14) was 5.8	
Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	60 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The median OM-related adverse events per person (at end of treatment: average of weeks 11-14) was 2.5	MD 0.7 higher (1.16 lower to 2.56 higher)
Severity of OM-related adverse events (at end of treatment: average of weeks 11-14) (protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use)	60 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The median severity of OM-related adverse events (at end of treatment: average of weeks 11-14) was 11.4	MD 1.5 higher (8.39 lower to 11.39 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes unless published measure-specific MIDs are available e.g., for the SF-36). Where baseline SDs were not reported, 0.5 * median of final value SD of the intervention and control group was used (intensity of the highest pain).

c. Mean (SD) baseline morphine equivalent OM dose (mg/week) in Sham electroacupuncture vs PMM group was 620.8 (792.5) vs 871.4 (1,772.3)

MIDs for continuous outcomes were as follows: QoL: SF-36 2, SF-36-Physical health 2, SF-36-Mental health 3; Opioid dosage 641.2, non-OM dosage 3.75; average pain (VAS) 1.03; intensity of the highest pain (VAS) 1.10; Weekly OM-related adverse events per person 1.85; Severity of OM-related adverse events 7.93

See Appendix G section G.1 for full GRADE tables

1.2.4 Economic evidence

1.2.4.1 Included studies

No health economic studies comparing withdrawal strategies for opioids were included.

1.2.4.2 Excluded studies

No relevant health economic studies on opioids were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.2.5 Summary of included economic evidence

No health economic studies comparing withdrawal strategies for opioids were included

1.2.5.1 Cost Analysis

A cost analysis was conducted to assess the cost of strategies to discontinue medication opioids included in the clinical review.

Multicomponent psychological opioid taper support

The cost of the multicomponent psychological opioid taper support described by Sullivan[253] was evaluated. The intervention consists in a visit with the principal investigator who is a psychiatrist, one motivational interviewing-based session and 17 weekly 30-minute sessions with a physician assistant, and 3 booster phone-calls (See **Table 9**). It was assumed that both the visit with the principal investigator and the motivational interviewing-based session with the physician's assistant lasted for 1 hour whereas the phone calls lasted for an average of 30 minutes. The main NHS resource use involved in these interventions is staff time and this was costed using a standard national source.[51]

Table 9: intervention components

Psychological therapy	Group Size	Frequency	Duration	Number of clinical staff required
Visit with principal investigator	1	1 session	1 hour	1 consultant psychiatrist
Interviewing-based session	1	1 session	1 hour	1 band 4 physician assistant
Weekly session	1	17 sessions	30 minutes	1 band 4 physician assistant
Booster phone call	1	3 calls	30 minutes	1 band 4 physician assistant

In addition to that, the physician assistant was supervised throughout the trial by the principal investigator and two clinical psychologists. The supervision consisted of one initial training session conducted by the two clinical psychologists, regular individual sessions with the clinical psychologists, and weekly group supervision with the psychologists and the principal investigator (see **Table 10** for more details). It was assumed that the duration of each supervision component was 1 hour and that both the regular and individual sessions occurred on a weekly basis, for 17 weeks.

Table 10: supervision components

Psychological therapy	Frequency	Duration	Number of clinical staff required
Training session	1 session	1 hour	1 band 4 physician assistant and 2 band 7 clinical psychologists
Regular individual sessions	17 sessions	1 hour	1 band 4 physician assistant and 1 band 7 clinical psychologist
Group weekly sessions	17 sessions	1 hour	1 band 4 physician assistant, 2 band 7 clinical psychologists and 1 consultant psychiatrist

The cost per hour including qualification cost of each healthcare professional was recovered using PSSRU database[52] and it is presented in **Table 11**

Table 11: UK costs of healthcare professionals involved

Staff member	Band	Cost per hour of patient contact
Physician Assistant	4	£33
Clinical Psychologist	7	£60
Consultant Psychiatrist		£146

Source[s]: PSSRU (2020) including qualification costs

Table 12 reports the cost of the intervention calculated using the methodology described above.

Table 12: cost per patient of multicomponent psychological opioid taper support

Psychological Therapy	Therapy	Supervision	Total
Multicomponent psychological opioid taper support	£509	£379	£888

1.2.6 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.2.7 Evidence statements

1.2.7.1 Economic

- No relevant economic evaluations were identified.

1.3 Benzodiazepines

1.3.1 Effectiveness evidence

1.3.1.1 Included studies

Twenty seven papers reporting twenty four RCTs were included in the review;[6, 10, 17, 35, 39, 40, 48, 67, 93, 111, 137, 170-172, 176, 180, 194, 201-203, 225, 235, 256, 261, 266, 270, 271] these are summarised in **Table 13** below.

The following comparisons were identified in the evidence for benzodiazepines:

- Cognitive behavioural therapy (CBT) plus a tapered withdrawal compared to CBT plus an abrupt withdrawal.
- CBT plus a taper compared to taper alone.
- Group CBT plus a taper compared to group work plus a taper.
- CBT plus a taper compared to usual care.
- Taper alone compared to usual care.
- Lorazepam substitution plus a taper compared to diazepam substitution plus a taper.
- Buspirone substitution plus a taper compared to imipramine substitution plus a taper.
- Buspirone substitution plus a taper compared to placebo substitution plus a taper.
- Imipramine substitution plus a taper compared to placebo substitution plus a taper.
- Melatonin substitution plus a taper compared to placebo substitution plus a taper.
- Dothiepin substitution plus a taper compared to placebo substitution plus a taper.
- Valproate substitution plus a taper compared to taper alone.
- Propranolol substitution plus an abrupt withdrawal compared to a tapered withdrawal.
- Patient advice and biofeedback guided information plus a taper compared to patient advice plus a taper.
- Psychological intervention, education and training plus a taper compared to psychological intervention, education and advice plus a taper.
- Patient advice, education and support plus a tapered withdrawal compared to patient advice, education and support plus an abrupt withdrawal.
- Patient advice and information compared to patient advice.
- Patient advice and information compared to usual care.
- Brief advice, education and support compared to usual care.
- Brief advice, education and support (multiple letters) compared to brief advice, education and support (single letter).
- Brief advice, education and support (multiple letters) compared to brief advice, education and support (GP letter).
- Brief advice, education and support (single letter) compared to brief advice, education and support (GP letter).

Evidence from these studies is summarised in the clinical evidence summaries below (**Table 14** to **Table 35**).

See also the study selection flow chart in Appendix C. Other relevant Appendices include study evidence tables in section E.2, forest plots in section F.2 and GRADE tables in section G.2.

1.3.1.2 Excluded studies

See the excluded studies list in Appendix I.

One Cochrane systematic review[9] was identified in the search as potentially relevant to the benzodiazepine stratum of this review. However, the Cochrane review protocol differed to this review protocol, as the population was users of any benzodiazepine (not limited to benzodiazepines prescribed on the NHS), and a large number of the studies included within the Cochrane review had over 20% of the population receiving benzodiazepines not listed on the guideline medicine list. The committee agreed that this was not applicable to the UK context and findings could not be generalised. There were also studies included in the Cochrane review in which it was unclear whether the populations were on prescribed benzodiazepines, and the primary studies suggested the populations were using both illicit and prescribed benzodiazepines. The guideline review is specific to withdrawal from prescribed medicines only, and therefore studies of withdrawal from illicit benzodiazepine use are not relevant to the current review protocol. Additionally, the guideline review also excluded pharmacological withdrawal interventions which are not licenced within the UK, and therefore cannot be recommended for use within the NHS. These were not excluded from the Cochrane review which included some studies investigating the use of pharmacological interventions which are not licenced in the UK. Taking all of these factors into account, the Cochrane review was consequently not included within the guideline, but the inclusion list was checked for any relevant studies.

1.3.2 Summary of studies included in the effectiveness evidence

Table 13: Summary of studies included in the evidence review (Benzodiazepines)

Study	Intervention and comparison	Population	Outcomes	Comments
Ashton 1990[6]	**Buspirone substitution + tapered withdrawal.** Diazepam treatment was administered in four-week treatment blocks. From the first week all patients were maintained on their usual dose. At the start of the third four-week block, diazepam was slowly withdrawn reducing the concentration of the syrup by 25% each week until it was zero. For the fourth four-week block all patients continued on a placebo syrup. At the start of the fifth four-week cycle all patients syrup administration was stopped. At the start of the second four-week block, patients were given buspirone (5mg t.d.s.). At the start of the fifth four-week block, buspirone was replaced with placebo tablets. **Placebo substitution + tapered withdrawal.** Diazepam treatment was administered in four-week treatment blocks. From the first week all patients were maintained on their usual dose. At the start of the third four-week block, diazepam was slowly withdrawn reducing the concentration of the syrup by 25% each week until it was zero. For the fourth four-week block all patients	Aged ≥18 years, had been on continuous benzodiazepine therapy for ≥6 months, wished to withdraw from benzodiazepine therapy, were not taking psychotropic medication nor abusing alcohol or drugs, and free from any psychiatric or physical disease. N=23 Mean age (SD): 41.8 years (10.6) UK	Cessation of benzodiazepine at 12 months Withdrawal symptoms at 16 weeks Anxiety (protocol outcome: withdrawal symptoms) at 16 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
	continued on a placebo syrup. At the start of the fifth four-week cycle all patients syrup administration was stopped. At the start of the second four-week block patients received additional placebo tablets until the end of the fifth four-week block. 20 weeks			
Baillargeon 2003[10]	**CBT + tapered withdrawal.** Cognitive-behavioural treatment involved behavioural, cognitive and educational components. Gradual tapering began concurrently with the initiation of CBT. The proposed schedule was a 25%reduction of dosage at 1- or 2-week intervals. **Tapered withdrawal alone.** Gradual tapering was supervised by a physician who met with each participant weekly over an 8-week period. The proposed schedule was a 25%reduction of dosage at 1- or 2-week intervals. 8 weeks	Patients aged 50 years or older; daily benzodiazepine use at bedtime for the past 3 months or more; and diagnosis of chronic insomnia, defined as insomnia for a period of 6 months or more in accordance with the American Sleep Disorders Association. Inability to refrain from taking sleeping pills at night because of fear of a bad night's sleep or sleep efficiency of less than 80% over a 2-week period. Participants also had to be experiencing impaired daytime functioning, irritability or mood disturbances. N= 65 Mean age (SD): 67.4 years (6.8) Canada	Cessation of benzodiazepine at post-intervention and 12 months Reduction of benzodiazepine • Daily dose at post-intervention • >50% reduction at post-intervention and 12 months	Other outcomes reported: Dose of benzodiazepine (means reported with no SD so unable to report)
Bashir 1994[17]	**Brief advice education and support.** Patients received minimal intervention, consisting of general	Chronic users of benzodiazepine who had been on benzodiazepines	Reduction of benzodiazepine use	No detail provided on the composition of 'usual care'. Participants recruited with the

Study	Intervention and comparison	Population	Outcomes	Comments
	practitioner advice on coming off benzodiazepines plus a self-help booklet which patients took away to read. **Usual care.** Patients received no study intervention (detail not provided).	for at least a year and who took tablets at least three times weekly. N=107 Mean age (range): 62 years (32-86) UK	Reduction in psychiatric morbidity (protocol outcome: symptoms for which the medication was originally prescribed) Withdrawal symptoms All reported at 6 months	intention of addressing long-term benzodiazepine use. Other outcomes reported: Withdrawal symptoms (reported as median no. of symptoms – unable to analyse)
Busto 1986[35]	**CBT + tapered withdrawal.** Participants switched to receive equivalent dose of diazepam. At the first therapy session goals were set for dose reduction of 1 to 5 mg per week of the study drug. The goal was to reduce the dose to zero within five to six weeks. All patients also received weekly CBT sessions. **CBT + abrupt withdrawal.** Participants switched to receive equivalent dose of placebo. At the first therapy session goals were set for dose reduction of 1 to 5 mg per week of the placebo. The goal was to reduce the dose to zero within five to six weeks. All patients also received weekly CBT sessions. 8 weeks	People aged 18 to 69 years with daily use of benzodiazepine for at least three months, with cumulative benzodiazepine exposure above 2700 mg of diazepam or equivalent, and problems attributed to the use of benzodiazepine or inability to stop taking the drug because of subsequent symptoms. N=40 Mean age (SD): 41 years (11.9) Canada	Withdrawal symptoms • no. of symptoms at 8 weeks • severity of symptoms at 8 weeks	Other outcomes reported: Relapse (median time to supplementation – unable to analyse) Withdrawal symptoms outcome reported at 8 weeks. At this timepoint, it had been 8 weeks since the last dose of benzodiazepine for the abrupt withdrawal group and only a couple of weeks since the last dose of benzodiazepine for the tapered withdrawal group
Cantopher 1990[39]	**Propranolol substitution + abrupt withdrawal.** Diazepam was replaced with placebo. Propranolol	Patients aged 18-70 years who had been taking benzodiazepine for at least 6 months for anxiety, and	Cessation of benzodiazepine	

Study	Intervention and comparison	Population	Outcomes	Comments
	(40 mg t.d.s) supplemented abrupt withdrawal. Propranolol was stopped at week 10 and placebo stopped at week 12. **Tapered withdrawal alone.** Diazepam + propranolol placebo. Diazepam placebo was added in a stepwise manner from week 0 to week 10. Diazepam stopped at week 10 and placebo stopped at week 12. 12 weeks	were receiving at least 15 mg diazepam daily or equivalent. N=31 Mean age (SD): 45.9 years (13.2) UK	Withdrawal symptoms All reported at 6 months	
Cappell 1987[40]	**Advice education and support + abrupt withdrawal.** Behavioural intervention + Benzodiazepine placebo. At baseline, diazepam was switched with a placebo drug. Patients received behavioural treatment sessions. Sessions provided information on symptoms of withdrawal and set goals to reduce dose of the study drug. Up to 8 sessions were offered. **Advice education and support + tapered withdrawal**. Patients received behavioural treatment sessions. Sessions provided information on symptoms of withdrawal and set goals to reduce dose of the study drug. Up to 8 sessions were offered. At the conclusion of each weekly treatment, daily and weekly goals	Chronic users of benzodiazepines, being a daily user for at least 3 months, and a cumulative benzodiazepine exposure higher than 2700mg diazepam or equivalent, and an inability to discontinue because of symptoms resulting from abstinence. N=40 Mean age (range): 41 years (20-59) Canada	Relapse (unauthorised benzodiazepine use) at 8 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
	for diazepam use were agreed, targeting a gradual dose reduction. 8 weeks			
Cormack 1994[48]	**Advice education and support.** Patients received a letter from their general practitioner asking them to try to reduce or stop their benzodiazepine medication and advising that this should be done gradually, followed at monthly intervals by four information sheets giving advice about reducing medication, including practical suggestions for coping without drugs. **Brief intervention and advice.** Patients received a letter from their general practitioner asking them to try to reduce or stop their benzodiazepine medication and advising that this should be done gradually. **Usual care.** Control group received no information or advice 5 months	Long-term regular users of benzodiazepines. N=209 Mean age (range): 69 years (34-102) UK	Cessation of benzodiazepine Reduction of benzodiazepine All reported at 6 months	Indirect comparison: Study included control group who received usual care. Unclear if there was any intention to withdraw from benzodiazepine in this group.
Elliott 2005[67]	**Psychological intervention, education and training + tapered withdrawal.** Patients received fortnightly psychological intervention and an information booklet covering: a) information and	Illicit drug users undergoing mandatory reduction in prescribed diazepam. N=53	Reduction of benzodiazepine (daily dose) Relapse from taper Illicit use of benzodiazepine	

Study	Intervention and comparison	Population	Outcomes	Comments
	education about effects of withdrawal, anxiety, and sleep patterns; b) visualising withdrawal symptoms; c) breathing, muscle relaxation exercises, and imagery to address anxiety; d) sleep planning and good sleeping habits. After six visits, participants were given further skills training to practice and develop the basic techniques to aid withdrawal, anxiety, and sleep problems. All participants were placed on a diazepam reduction plan, with monthly prescription reduction set at 10%. **Psychological intervention, education and advice + tapered withdrawal.** Received fortnightly psychological intervention and an information booklet covering a) information and education about effects of withdrawal, anxiety, and sleep patterns; b) visualising withdrawal symptoms; c) breathing, muscle relaxation exercises, and imagery to address anxiety; d) sleep planning and good sleeping habits. After six fortnightly visits, participants were given verbal advice only on request and referred back to information booklet. These visits continued for six months. All participants were placed on a diazepam reduction plan, with	Mean age (SD): 30.6 years (6.5) UK	Anxiety (withdrawal symptom) Depression (withdrawal symptom) All reported at 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	monthly prescription reduction set at 10%. 6 months			
Gnjidic 2019[93]	**Brief intervention and advice.** Patient-empowerment booklet. Information in the booklet aimed to cause cognitive dissonance with effects associated with benzodiazepine use. It also used successful cessation examples and a tapering protocol as a guide to help stop use of benzodiazepine. Participants were asked to read the booklet and discuss any concerns about their benzodiazepine medications with their doctor or pharmacist following hospital discharge. **Usual care.** Patients in the control group received usual care (no more information)	Patients over 65 years of age and admitted to cardiology, renal, endocrine, general medicine, rheumatology or surgical orthopaedic wards were screened. Patients who were prescribed one or more benzodiazepines on the inpatient medication chart were invited into the study. N=42 Median age (IQR): 71.5 years (69-80.3) Australia	Cessation of benzodiazepine at 1 month	Indirect comparison: Study included control group who received usual care. Unclear if there was any intention to withdraw from benzodiazepine in this group.
Heather 2004[111]	**Advice, education and support.** GPs provided information about benzodiazepines, benefits to reduce medication and a timetable that could be used to plan withdrawal. Copies of a self-help booklet were given to patients during the consultation, along with a leaflet about sleeping problems. **Brief intervention and advice**.	Long-term benzodiazepine users were defined in our study as patients of any age or gender who had taken benzodiazepines continuously for at least six months (i.e., had received at least one prescription for benzodiazepines every two months during the previous six). N=284	Quality of life Cessation of benzodiazepine Reduction of benzodiazepine All reported at 6 months	Indirect comparison: Study included control group who received usual care. Unclear if there was any intention to withdraw from benzodiazepine in this group. Other outcomes reported: Quality of life (SF-36) – narratively reported no significant differences between study groups in changes on

Study	Intervention and comparison	Population	Outcomes	Comments
	Patients received a letter from their general practitioner asking them to try to reduce or stop their benzodiazepine medication and advising that this should be done gradually. **Usual care.** Patients in the control group received usual care (no more information)	Mean age (SD): 69.2 years (11.5) UK		any of the nine SF-36 sub-scores – unable to analyse.
Lader 1987[137]	**Buspirone substitution + withdrawal.** Maintained on benzodiazepine for the first 2 weeks. Then, withdrawn stepwise over 4 weeks: during the first of these 2 weeks, buspirone was substituted for the benzodiazepine in an initial dosage of 5 mg (one capsule) twice daily, followed by 10 mg (two capsules) twice daily during the second phase when the patient had stopped benzodiazepine medication. **Placebo substitution + withdrawal**. Both groups were maintained on their pre withdrawal benzodiazepine medication and dosage for the first 2 weeks (1 and 2). Then, they were withdrawn stepwise from these medications over 4 weeks: during the first of these 2 weeks (3 and 4), placebo was substituted for the benzodiazepine in an initial dosage of 5 mg (one capsule) twice daily,	Outpatients on long-term (> 6 months) therapeutic dose benzodiazepine medication for anxiety, deemed not to require any further benzodiazepine medication. N=24 Mean age 39.1 years UK	Successful completion of withdrawal at post-intervention	Participants were free from symptoms of the anxiety which had originally led to the prescription of benzodiazepines, but problems on attempting to lower the dosage of their medication had been encountered previously; thus, they had been regarded as physically dependent.

Study	Intervention and comparison	Population	Outcomes	Comments
	followed by 10 mg (two capsules) twice daily during the second phase when the patient had stopped benzodiazepine medication. 10 weeks			
Morin 2004[170]/ Morin 2005[171]	**CBT + Tapered withdrawal.** Patients received both the tapering program and CBT. Patients attended 10 weekly therapy sessions. Treatment consisted of an intervention involving behavioural, cognitive, and educational components that targeted different facets of insomnia. Taper as in comparison group. **Tapered withdrawal.** Subjects met weekly with a physician for 10 brief consultation sessions. The content of those sessions focused on reviewing a taper schedule, documenting changes in insomnia symptoms, and monitoring withdrawal effects. Patients were provided with a step-by-step withdrawal plan, with the goal of eliminating benzodiazepine use by the 8th week of treatment. 10 weeks	Patients who were chronic users of benzodiazepines for insomnia who wished to discontinue. N=76 Mean age (SD): 62.5 years (6.3) Canada	Cessation of benzodiazepine at post-intervention and 12 months Reduction of benzodiazepine at post-intervention and 12 months Relapse into benzodiazepine use at 24 months Insomnia (increase in symptoms for which the medication was originally prescribed) at post-intervention and 12 months	Study also included a third arm which was CBT for insomnia without the taper. This comparison was not included in the review as per the review protocol, as there was no aim to withdrawal in this arm. The study states that patients who received CBT alone were 'not expected to change their medication use and were not provided guidance about reducing their medication intake'. Other outcomes reported: Withdrawal symptoms – narratively reported no significant difference in withdrawal symptom score at follow-up for any groups or between groups – unable to analyse
Morton 1995[172]	**Buspirone + taper.** 2 weeks on current benzodiazepine dose, followed by buspirone in flexible	Outpatients who previously had increases in symptoms when attempting to discontinue	Cessation of benzodiazepine at 16 weeks	Mixed population: majority diazepam with 3 on lorazepam at baseline

Study	Intervention and comparison	Population	Outcomes	Comments
	dosage according to clinical need (minimum 15mg/day in divided doses). After 4 weeks stabilisation, benzodiazepine was tapered with reduction to 0 in 6 weeks. At week 16 buspirone was halved and then stopped 2 weeks later. **Placebo + taper.** 2 weeks on current benzodiazepine dose, followed by placebo in flexible dosage according to clinical need (minimum 15mg/day in divided doses). After 4 weeks stabilisation, benzodiazepine was tapered with reduction to 0 in 6 weeks. At week 16 placebo was halved and then stopped 2 weeks later. 20 weeks	benzodiazepines who were taking a mean dose of <30mg diazepam or equivalent daily for a > 6 months. N=24 Age: mean 46 years UK	Adverse events: insomnia, giddiness, GI symptoms, headache (reported in study as adverse events, reviewer hypothesised these to fall under the protocol outcome: withdrawal symptoms) at 20 weeks	Other outcomes: HAM-D, Benzodiazepine Withdrawal Scale, Mood rating scale could not be reported as no figures given.
Murphy 1991[176]	**Lorazepam + taper.** Patients were provided with lorazepam tablets in roughly equivalent dosage to their original benzodiazepine. The change was made to the appropriate number of tablets, each containing 1mg of lorazepam. Each patient remained on this dosage until the end of the fourth week, after which the dosage was reduced in 25% aliquots at 2-week intervals until complete withdrawal by the end of the tenth week.	Psychiatric outpatients who had taken benzodiazepines regularly at a mean dose of 2-16mg for ≥6 months and had putative dependence N=45 Age (mean): 49.6 years (diazepam group), 42.1 years (lorazepam group)	Mortality (suicide) Study completers (protocol outcome: cessation of prescribed drug use) All reported at 14 weeks	Includes study arm on bromazepam (not included as not a benzodiazepine on the guideline medicine list) 25 patients were on diazepam and 19 on lorazepam at baseline- may have been randomised to their current drug. Other outcomes: Withdrawal symptoms (BWSQ)-graph data only

Study	Intervention and comparison	Population	Outcomes	Comments
	Diazepam + taper. Patients were provided with diazepam tablets in roughly equivalent dosage to their original benzodiazepine. The change was made to the appropriate number of tablets, each containing 5mg of diazepam. Each patient remained on this dosage until the end of the fourth week, after which the dosage was reduced in 25% aliquots at 2-week intervals until complete withdrawal by the end of the tenth week. If patients were unable to reduce their drugs at the appropriate time they were regarded as dropouts for the purpose of this study. 20 weeks	UK		Total psychopathology (CPRS)- graph data only
Nathan 1986[180]	**Biofeedback assisted stress management + taper.** Individual sessions which included taped relaxation training twice daily at home, EMG and skin temperature biofeedback and limited, supportive stress management counselling. A small galvanic skin response and temperature unit, the GSR-II was given to patients for home practice. **Brief withdrawal counselling +taper.** Individual sessions to simulate counselling and encouragement of traditional medical care. Brief but intensive, individual psychoanalytic	Females with Generalised anxiety disorder (GAD) using benzodiazepines daily for > 6 months N= 7 Age: inclusion criteria 25-50 years USA	Cessation of benzodiazepine at 10 weeks	Indirect population- only drugs in intervention group reported (unclear if all were on benzodiazepines on the guideline medicine list). Extra outcomes: Benzodiazepine use at 1 year (for one group only)

Study	Intervention and comparison	Population	Outcomes	Comments
	psychotherapy was also offered to decrease further attrition. All patients were advised to decrease benzodiazepine use by 20% of their original dose every 2 weeks. 10 weeks			
O'Connor 2008[194]	**CBT + tapered withdrawal.** The programme was divided into three sections covering (a) preparation; (b) severance; (c) maintaining abstinence. The PASS programme began with a 4-week period of preparation which preceded the tapered withdrawal schedule. The preparation period involved psychoeducation and cognitive restructuring through providing information on withdrawal and addressing beliefs about cessation. Discontinuation began at the fifth week, and passed through four stages, each of 4 weeks duration: getting started; keeping going; nearly there; staying there. As well as the weekly group meetings, participants also attended at three weekly intervals for a consultation with a treating physician who controlled the taper regime. In order to help coping with getting started, the participants had recourse to 10 resource documents which could be discussed in the PASS group	Patients taking benzodiazepine for at least 2 years; having a diagnosis of benzodiazepine dependence for at least 2 months; and presenting an anxiety problem and/ or insomnia for at least 3 months. N=48 Mean age: 47.8 years Canada	Quality of life at 3 months follow-up Cessation of benzodiazepine at post-intervention (20 weeks) Relapse into medication use at 11 months Withdrawal symptoms at post-intervention (20 weeks) and 3 months follow-up Anxiety (increase in symptom for which benzodiazepine prescribed) at post-intervention (20 weeks) and 3 months follow-up Psychological distress at post-intervention (20 weeks) and 3 months follow-up	Indirect population: Did not state names of benzodiazepine patients were using - may include those not in review protocol

Study	Intervention and comparison	Population	Outcomes	Comments
	under the direction of the facilitators. **Group work + tapered withdrawal.** The Group Support (GS) Programme participants met at the same regularity as the PASS group and followed identical taper regimes. The principal difference was in the lack of any specific directions for changing thoughts and behaviours. In this GS condition, no CBT strategies were presented, and exchanges took the form of open-ended discussion on themes. No direct action or strategy to deal with any problems was suggested. Any requests for specific help were deflected back to the group. Following open discussion, participants noted the key points of discussion and also continued to reflect on the themes throughout the following week. Each week a different theme was discussed and any personal request for a strategy was referred for group discussion. 20 weeks			
Oude Voshaar 2003[202]/ 2006[203]/2006[201]	**CBT+ tapered withdrawal.** Attended group CBT in addition to the dose reduction visits to their general practitioner. The aim of the group therapy was to support the participants during the tapering-off	Patients with long-term use of benzodiazepine who were unable to quit their usage benzodiazepines by themselves after receiving a discontinuation letter from their GP.	Quality of life at 18 months Cessation of benzodiazepine at 15 months	Indirect comparison: unclear if usual care group intended to reduce their benzodiazepine use.

Study	Intervention and comparison	Population	Outcomes	Comments
	process and to prevent relapse thereafter. The therapy programme included psychoeducation, teaching and practising relaxation exercises, and cognitive restructuring of the interpretation of withdrawal symptoms. The daily dose of diazepam was reduced by 25% a week during four weekly visits. **Tapered withdrawal.** The daily dose of diazepam was reduced by 25% a week during four weekly visits. Participants had the opportunity to divide the last step into two steps of 12.5%for 4 days **Usual care.** Participants in the usual care control group were informed about the randomisation by letter. They did not receive any help with benzodiazepine reduction. 4 weeks	Mean age (SD): 63 years (12) N=180 Netherlands	Withdrawal symptoms at 3 months Patients using alcohol (Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs) at 3 months	Indirect population - Breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list Oude Voshaar 2003[203] an economic evaluation of trial Other outcomes reported: reduction of benzodiazepine use (reported as median % reduction of those who failed to successfully discontinue – unable to analyse)
Rickels 2000[225]	**Buspirone substitution + tapered withdrawal. P**atients were kept on a stable dose of their benzodiazepine for 2–4 weeks. They were then assigned to treatment with buspirone, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of	To be enrolled in the program, patients were required to have a diagnosis of generalized anxiety disorder and to have been taking diazepam, lorazepam, or alprazolam in therapeutic doses continuously for the past 12 months. Age - Mean (SD): 48 (14).	Cessation of benzodiazepine at 3 months	Indirect population - Breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	approximately 25% per week. The taper phase was followed by a 5-week benzodiazepine-free phase. **Imipramine substitution + tapered withdrawal. P**atients were kept on a stable dose of their benzodiazepine for 2–4 weeks. They were then assigned to treatment with imipramine, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of approximately 25% per week. The taper phase was followed by a 5-week benzodiazepine-free phase. **Placebo substitution + tapered withdrawal. P**atients were kept on a stable dose of their benzodiazepine for 2–4 weeks. They were then assigned to treatment with placebo, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of approximately 25% per week. The taper phase was followed by a 5-week benzodiazepine-free phase.	N=107 USA		

Study	Intervention and comparison	Population	Outcomes	Comments
	15-19 weeks			
Sanchez-Craig 1987[235]	**CBT + tapered withdrawal.** CBT included: Identification of functions served by benzodiazepines, goal setting and feedback, coping with expected withdrawal symptoms, coping with negative emotions and inability to sleep. In most instances the weekly goal was a reduction not great than 5mg of diazepam or its placebo equivalent per day. Vs **CBT + abrupt withdrawal of benzodiazepine.** Received same CBT intervention as tapered group. Subjects received inert tablets and were monitored weekly as per the gradual withdrawal group. Duration: 5 therapy sessions	Adults using benzodiazepines (daily dose range 5-45mg) for at least 3 months seeking treatment N=42 Age - Mean (range): CBT+ tapering: 40.1 (20-59) CBT+placebo: 41.8 (21-57). Canada	Cessation of benzodiazepine Reduction in benzodiazepine use Use of rescue drug	Indirect population - Breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list
Ten Wolde 2008[256]	**Advice, education and support (single letter).** Each letter was based on an individual assessment. The information was designed to 1) increase the perceptions of the positive outcome expectations of discontinuing benzodiazepine use 2) lower the perceptions of the positive outcome expectations of the use of benzodiazepine and 3)	GP outpatients Mean duration of benzodiazepine use 8.1 years weekly dose diazepam equivalent 49.3mg N=861 Age (mean) 62.3 years The Netherlands	Cessation of benzodiazepine at 12 months	15.8% taking >1 type of benzodiazepine Indirect population – Full breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	increase self-efficacy expectations with regard to discontinuing usage. The intervention consisted of one letter of 5-6 pages of information (approx. 1200 words). Vs **Advice, education and support (multiple letters).** Multiple tailored letter As per single tailored letter, plus an additional two subsequent letters based on a separate individual assessment. It consisted of three letters of about three pages each (approx. 400 words) sent at intervals of 1 month. **Advice, education and support (GP letter).** Standard letter used to inform patients about benzodiazepine s. Pinpointed disadvantages of benzodiazepine use and contained brief advice on discontinuation. Letter was approx. 200 words.			
Tyrer 1996[261]	**Dothiepin substitution + tapered withdrawal.** Weeks 1-4: Dothiepin tablets in flexible increasing dosage, up to 150mg/day. Weeks 5-12: taper involving a reduction of the initial benzodiazepine dosage by 20% every 2 weeks	People with benzodiazepine dependence who had tried unsuccessfully to reduce or stop medication because of apparent withdrawal symptoms. N= 87	Cessation of benzodiazepine Patient satisfaction All reported at 14 weeks	Indirect population - Breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo substitution + tapered withdrawal. Weeks 1-4: Placebo tablets in flexible increasing dosage. Weeks 5-12: taper involving a reduction of the initial benzodiazepine dosage by 20% every 2 weeks 14 weeks	Age: NR UK		Dothiepin/dosulepin is no longer routinely prescribed and is available under prescription by a specialist only. Other outcomes: Benzodiazepine dosage (medians only reported, unable to analyse) Withdrawal symptoms (graph only) Withdrawal symptoms (BWSQ)- no SDs provided Anxiety - no SDs provided Depression – no SDs provided Global outcome (composite outcome of withdrawal symptoms, success in withdrawing from benzodiazepine and satisfaction with treatment): not included in this review as weighting given to each component unclear, and two components already available as individual outcomes).
Vicens 2006[266]	**Advice education and support.** Included: what benzodiazepine s are and what they are used for, treatment of symptoms vs treatment of their cause, untoward effects of benzodiazepine s, problems of long-term use and information on how to withdraw	Long-term benzodiazepine users N= 139 Age: average 59 (11.4) years 82% female	Cessation of benzodiazepine Reduction of benzodiazepine All reported at 12 months	Extra outcomes: Abstinence symptoms (insomnia, anxiety and irritability) in standardised advice group only.

Study	Intervention and comparison	Population	Outcomes	Comments
	benzodiazepine s through a stepwise reduction in dose. Follow-up consultations involved stressing the issues discussed on the first visit, evaluating possible abstinence or withdrawal symptoms and positive reinforcement of achievements. Taper: gradual reduction of benzodiazepine dose, with control visits every 15 days. The dose was reduced between 10 and 25% of the initial dose fortnightly. **Usual care.** Routine clinical practice, managed according to usual practice and informed of the convenience of reducing the use of benzodiazepines. 12 months	Spain		
Vissers 2007[270]	**Melatonin substitution + tapered withdrawal.** Participant benzodiazepine was converted to an equivalent dose of diazepam and stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose. 5 mg melatonin was added which had to be taken 4 h before patients went to bed. After stopping diazepam, the use of melatonin was continued for six more weeks.	Adult patients who used benzodiazepine as a sleeping medication for more than three months (defined as long-term use) with a minimum use of three days per week. N=38 Age: <50 years: 6; 50-59 years: 6; 60-69 years: 13; 70-79 years: 11; >80 years: 2 Netherlands	Cessation of benzodiazepine at post-intervention and 1 year	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo substitution + tapered withdrawal. Participant benzodiazepine was converted to an equivalent dose of diazepam and stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose. 5 mg placebo was added which had to be taken 4 h before patients went to bed. After stopping diazepam, the use of placebo was continued for six more weeks. 18 weeks			
Vorma 2011[271]	**Valproate substitution + tapered withdrawal.** Valproate 20mg/kg per day for 2 weeks with a reduction during the 3rd week. Gradual tapering- after the initial benzodiazepine dose, dosages were reduced by 10mg daily until 40mg per day was reached, after which reductions were 5mg daily. Vs **Tapered withdrawal alone**. Gradual benzodiazepine tapering, where subjects reported dosage was converted into an equivalent dose of diazepam, with a maximum of 80 mg per day. After the initial dose, dosages were reduced by 10mg daily until 40mg per day was	Adults with opioid dependence and benzodiazepine dependence who were admitted for inpatient induction of opioid maintenance treatment Median diazepam dose in valproate group was 60mg/day; 30mg/day in placebo group. N=30 Age - Mean (SD): Valproate: 32 (6.7), taper alone 32 (5.3). Finland	Withdrawal symptoms (CIWA-B) at days 15-20 Use of illicit drugs during 3-week intervention period	Population were dependent on opioids and continued to take these during the study. Indirect population - Breakdown of people on each study drug not provided. Unclear in >80% were on a benzodiazepine on the guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	reached, after which reductions were 5 mg daily. 3 weeks			

See section E.2 for full evidence tables.

1.3.3 Summary of the effectiveness evidence

Table 14: Clinical evidence summary: CBT + tapered withdrawal vs CBT + abrupt withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT + abrupt withdrawal	Risk difference with CBT + tapered withdrawal
Cessation of benzodiazepine follow up: post-intervention	42 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.68 (0.36 to 1.28)	579 per 1,000	185 fewer per 1,000 (371 fewer to 162 more)
Cessation of benzodiazepine follow up: 12 months	42 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.52 (0.20 to 1.32)	421 per 1,000	202 fewer per 1,000 (337 fewer to 135 more)
Reduced benzodiazepine use assessed with 50% reduction in benzodiazepine plasma level follow up: post-intervention	42 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.83 (0.19 to 3.63)	158 per 1,000	27 fewer per 1,000 (128 fewer to 415 more)
Reduced benzodiazepine use assessed with 50% reduction in benzodiazepine plasma level follow up: 12 months	42 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 3.30 (0.40 to 27.13)	53 per 1,000	121 more per 1,000 (32 fewer to 1,375 more)
Withdrawal symptoms assessed with mean per patient follow up: post-intervention	40 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	-	The mean withdrawal symptoms score was 9.7	MD 6.2 lower (8.99 lower to 3.41 lower)
Withdrawal symptom severity score Scale from: 0 to 10 follow up: post-intervention	40 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	-	The mean withdrawal symptom severity score was 8.5	MD 4.8 lower (6.6 lower to 3 lower)
Relapse assessed with additional use of own benzodiazepine supply follow up: post-intervention	42 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.12 (0.02 to 0.88)	368 per 1,000	324 fewer per 1,000 (361 fewer to 44 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. The majority of the evidence had an indirect population. For Sanchez-craig 1987, 4/9 dose equivalences reported in study are for drugs not in protocol.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT + abrupt withdrawal	Risk difference with CBT + tapered withdrawal
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: withdrawal symptoms - 2.1, withdrawal severity - 1.45.					

Table 15: Clinical evidence summary: CBT + tapered withdrawal vs tapered withdrawal only for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal only	Risk difference with CBT + tapered withdrawal
Quality of life - Physical function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Physical function was 65	MD 3 higher (6.42 lower to 12.42 higher)
Quality of life - Social function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Social function was 64	MD 4 higher (4.72 lower to 12.72 higher)
Quality of life - Role limitation (physical) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Role limitation (physical) was 54	MD 3 higher (12.59 lower to 18.59 higher)
Quality of life - Role limitation (emotional) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Role limitation (emotional) was 76	MD 9 lower (23.5 lower to 5.5 higher)
Quality of life - Mental health assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Mental health was 76	MD 5 lower (15.87 lower to 5.87 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal only	Risk difference with CBT + tapered withdrawal
Quality of life - Vitality assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Vitality was 61	MD 2 higher (5.25 lower to 9.25 higher)
Quality of life - Pain assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - Pain was 61	MD 6 higher (3.6 lower to 15.6 higher)
Quality of life - General health assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean quality of life - General health was 57	MD 5 higher (2.07 lower to 12.07 higher)
Cessation of benzodiazepine follow up: post-intervention	115 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	RR 1.89 (1.36 to 2.64)	426 per 1,000	379 more per 1,000 (153 more to 699 more)
Cessation of benzodiazepine follow up: 3 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.94 (0.70 to 1.26)	617 per 1,000	37 fewer per 1,000 (185 fewer to 160 more)
Cessation of benzodiazepine follow up: range 12 months to 15 months	242 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	RR 1.30 (0.68 to 2.47)	381 per 1,000	114 more per 1,000 (122 fewer to 561 more)
Reduction of benzodiazepine assessed with weekly benzodiazepine use - diazepam eqv (mg) follow up: post-intervention	52 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	-	The mean reduction of benzodiazepine was 11.4 mg	MD 10.1 mg lower (28.21 lower to 8.01 higher)
Reduction of benzodiazepine assessed with weekly benzodiazepine use - diazepam eqv (mg) follow up: 12 months	52 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	-	The mean reduction of benzodiazepine was 13.28 mg	MD 8.85 mg lower (27.86 lower to 10.16 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal only	Risk difference with CBT + tapered withdrawal
Reduction of benzodiazepine assessed with: >50% dose reduction follow up: post-intervention	63 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.41 (1.09 to 1.81)	690 per 1,000	283 more per 1,000 (62 more to 559 more)
Reduction of benzodiazepine assessed with: >50% dose reduction) follow up: 12 months	61 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.57 (1.06 to 2.32)	517 per 1,000	295 more per 1,000 (31 more to 683 more)
Relapse into drug use follow up: 24 months	34 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	RR 1.09 (0.39 to 2.99)	308 per 1,000	28 more per 1,000 (188 fewer to 612 more)
Withdrawal symptoms assessed with: BWSQ Scale from: 0 to 40 follow up: 3 months	146 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The mean withdrawal symptoms score was 6.2	MD 0.6 higher (1.72 lower to 2.92 higher)
Increase in symptoms for which the medication was originally prescribed assessed with: Insomnia severity index Scale from: 0 to 28 follow up: post intervention	52 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	-	The mean withdrawal symptoms score - insomnia was 12.72	MD 1.54 lower (4.56 lower to 1.48 higher)
Increase in symptoms for which the medication was originally prescribed assessed with: Insomnia severity index Scale from: 0 to 28 follow up: 12 months	52 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	-	The mean withdrawal symptoms score - insomnia was 9.97	MD 1.09 higher (2.09 lower to 4.27 higher)
Patients using alcohol follow up: 3 months	146 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.95 (0.71 to 1.61)	575 per 1,000	29 fewer per 1,000 (169 fewer to 155 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. The majority of the evidence had an indirect population. For Oude Voshaar 2003, Oude Voshaar 2006 & Baillargeon 2003, the specific benzodiazepine used by patients was not reported.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal only	Risk difference with CBT + tapered withdrawal
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.33, insomnia severity: 2.68, reduction of benzodiazepine 27.69mg.					
d. Heterogeneity, I^2=50%, unexplained by subgroup analysis (unable to perform subgroup analysis insufficient reporting detail of benzodiazepine half-life)					

Table 16: Clinical evidence summary: CBT + tapered withdrawal vs Group work + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Group work + tapered withdrawal	Risk difference with CBT + tapered withdrawal
Quality of life assessed with: systemic QoL inventory follow up: 3 months	21 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The mean quality of life was 8.35	MD 0.05 higher (1.15 lower to 1.25 higher)
Cessation of benzodiazepine follow up: post-intervention	45 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.30 (0.78 to 2.18)	500 per 1,000	150 more per 1,000 (110 fewer to 590 more)
Withdrawal symptoms assessed with: BWSQ Scale from: 0 to 40 follow up: post-intervention	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean withdrawal symptoms score was 8.64	MD 1.07 lower (4.38 lower to 2.24 higher)
Withdrawal symptoms assessed with: BWSQ Scale from: 0 to 40 follow up: 3 months	21 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean withdrawal symptoms score was 7.22	MD 0.45 higher (3.25 lower to 4.15 higher)
Relapse into drug use follow up: 11 months	20 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.00 (0.07 to 13.87)	100 per 1,000	0 fewer per 1,000 (93 fewer to 1,287 more)
Increase in symptoms - Anxiety assessed with: Spielberger state Scale from: 0 to 80 follow up: post-intervention	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean anxiety was 43.18	MD 0.11 higher (8.28 lower to 8.5 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Group work + tapered withdrawal	Risk difference with CBT + tapered withdrawal
Increase in symptoms - Anxiety assessed with: Spielberger state Scale from: 0 to 80 follow up: 3 months	21 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean anxiety was 41.9	MD 6.57 lower (14.99 lower to 1.85 higher)
Increase in symptoms - Anxiety assessed with: Spielberger trait Scale from: 0 to 80 follow up: post-intervention	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean anxiety was 45.4	MD 3.33 lower (11.42 lower to 4.76 higher)
Increase in symptoms - Anxiety assessed with: Spielberger trait Scale from: 0 to 80 follow up: 3 months	21 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean anxiety was 42.56	MD 3.56 lower (11.75 lower to 4.63 higher)
Distress assessed with: Psychological Distress Inventory Scale from: 0 to 100 follow up: post-intervention	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean distress was 49.5	MD 3.07 lower (5.07 lower to 11.21 higher)
Distress assessed with: Psychological Distress Inventory Scale from: 0 to 100 follow up: 3 months	21 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean distress was 54.4	MD 9.96 lower (20.85 lower to 0.93 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. O'Connor 2008, the specific benzodiazepine used by patients was not reported.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: systemic QoL inventory 1.8, BWSQ: 3.09, anxiety - state: 5.5; anxiety - trait: 5.26; distress: 7.91.

Table 17: Clinical evidence summary: CBT + tapered withdrawal vs Usual care for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with CBT + tapered withdrawal
Quality of life - Physical function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Physical function was 72	MD 4 lower (16.03 lower to 8.03 higher)
Quality of life - Social function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Social function was 69	MD 1 lower (10.24 lower to 8.24 higher)
Quality of life - Role limitation (physical) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Role limitation (physical) was 76	MD 19 lower (36.88 lower to 1.12 lower)
Quality of life - Role limitation (emotional) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Role limitation (emotional) was 70	MD 14 lower (29.35 lower to 1.35 higher)
Quality of life - Mental health assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Mental health was 81	MD 10 lower (21.97 lower to 1.97 higher)
Quality of life - Vitality assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	84 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Vitality was 63	MD 0 (10.56 lower to 10.56 higher)
Quality of life - Pain assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	82 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Pain was 66	MD 2 lower (12.78 lower to 8.78 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with CBT + tapered withdrawal
Quality of life - General health assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	117 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - General health was 55	MD 7 higher (0.44 lower to 14.44 higher)
Cessation of benzodiazepine follow up: 3 months	91 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,d]	RR 3.94 (1.70 to 9.11)	147 per 1,000	432 more per 1,000 (103 more to 1,193 more)
Cessation of benzodiazepine follow up: 15 months	101 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	RR 1.94 (0.80 to 4.71)	152 per 1,000	142 more per 1,000 (30 fewer to 562 more)
Withdrawal symptoms assessed with: BWSQ Scale from: 0 to 40 follow up: 3 months	107 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean withdrawal symptoms score was 5.8	MD 1 higher (2 lower to 4 higher)
Patients using alcohol follow up: 3 months	107 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	RR 1.04 (0.71 to 1.51)	529 per 1,000	21 more per 1,000 (154 fewer to 270 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Oude Voshaar 2003 & Oude Voshaar 2006, the specific benzodiazepine used by patients was not reported.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.13.

d. The majority of the evidence had an indirect comparison. For Oude Voshaar 2003 & Oude Voshaar 2006, the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 18: Clinical evidence summary: Tapered withdrawal vs Usual care for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Tapered withdrawal
Quality of life - Physical function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Physical function was 72	MD 7 lower (19 lower to 5 higher)
Quality of life - Social function assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Social function was 69	MD 5 lower (14.87 lower to 4.87 higher)
Quality of life - Role limitation (physical) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Role limitation (physical) was 76	MD 22 lower (41 lower to 3 lower)
Quality of life - Role limitation (emotional) assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Role limitation (emotional) was 81	MD 5 lower (19.94 lower to 9.94 higher)
Quality of life - Mental health assessed with: SF36 Scale from: 0 to 100 follow up: 18	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Mental health was 81	MD 5 lower (19.94 lower to 9.94 higher)
Quality of life - Vitality assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Vitality was 63	MD 2 lower (12.54 lower to 8.54 higher)
Quality of life - Pain assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	83 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - Pain was 69	MD 8 lower (18.91 lower to 2.91 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Tapered withdrawal
Quality of life - General health assessed with: SF36 Scale from: 0 to 100 follow up: 18 months	118 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean quality of life - General health was 55	MD 2 higher (5.59 lower to 9.59 higher)
Cessation of benzodiazepine follow up: 3 months	94 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,d]	RR 4.19 (1.82 to 9.65)	147 per 1,000	469 more per 1,000 (121 more to 1,272 more)
Cessation of benzodiazepine follow up: 15 months	102 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	RR 2.39 (1.01 to 5.68)	152 per 1,000	211 more per 1,000 (2 more to 709 more)
Withdrawal symptoms score assessed with: BWSQ Scale from: 0 to 40 follow up: 3 months	107 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	The mean withdrawal symptoms score was 5.8	MD 0.4 higher (2.51 lower to 3.31 higher)
Patients using alcohol follow up: 3 months	107 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	RR 1.09 (0.75 to 1.58)	529 per 1,000	48 more per 1,000 (132 fewer to 307 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Oude Voshaar 2003 & Oude Voshaar 2006, the specific benzodiazepine used by patients was not reported.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.25.

d. The majority of the evidence had an indirect comparison. For Oude Voshaar 2003 & Oude Voshaar 2006, the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 19: Clinical evidence summary: Lorazepam substitution + tapered withdrawal vs Diazepam substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam substitution + tapered withdrawal	Risk difference with Lorazepam substitution + tapered withdrawal
Mortality - suicide follow up: 14 weeks	45 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 7.07 (0.14 to 356.89)	0 per 1,000	40 more per 1,000 (70 fewer to 160 more) [c]
Cessation of benzodiazepine follow up: 14 weeks	45 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 0.78 (0.50 to 1.21)	727 per 1,000	160 fewer per 1,000 (364 fewer to 153 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

c. Calculated from risk difference due to zero events in control arm.

Table 20: Clinical evidence summary: Buspirone substitution + tapered withdrawal vs Imipramine substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Imipramine substitution + tapered withdrawal	Risk difference with Buspirone substitution + tapered withdrawal
Cessation of benzodiazepine follow up: 3 months	51 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.82 (0.60 to 1.13)	826 per 1,000	149 fewer per 1,000 (330 fewer to 107 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Rickles 2000, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 21: Clinical evidence summary: Buspirone substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo substitution + tapered withdrawal	Risk difference with Buspirone substitution + tapered withdrawal
Cessation of benzodiazepine follow up: post-intervention	48 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.71 (0.29 to 1.69)	522 per 1,000	151 fewer per 1,000 (370 fewer to 360 more)
Cessation of benzodiazepine follow up: 3 months	52 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 1.81 (1.02 to 3.22)	375 per 1,000	304 more per 1,000 (8 more to 833 more)
Cessation of benzodiazepine follow up: 12 months	23 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.60 (0.34 to 1.05)	917 per 1,000	367 fewer per 1,000 (605 fewer to 46 more)
Withdrawal symptoms - anxiety assessed with: Hospital Anxiety and Depression (HADS) anxiety Scale from: 0 to 21 follow up: 16 weeks	12 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean withdrawal symptoms score- anxiety was 11.75	MD 2.75 higher (2.83 lower to 8.33 higher)
Withdrawal symptoms - insomnia follow up: post-intervention	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 3.00 (0.36 to 24.92)	83 per 1,000	167 more per 1,000 (53 fewer to 1,993 more)
Withdrawal symptom score assessed with tool unclear Scale from: 0 to 147 follow up: 16 weeks	15 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean withdrawal symptom score was 26.09	MD 1.34 lower (14.31 lower to 11.63 higher)
Withdrawal symptoms: giddiness follow up: post-intervention	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.75 (0.69 to 4.44)	333 per 1,000	250 more per 1,000 (103 fewer to 1,147 more)
Withdrawal symptoms: GI symptoms follow up: post-intervention	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.00 (0.65 to 6.20)	250 per 1,000	250 more per 1,000 (88 fewer to 1,300 more)
Withdrawal symptoms: headache follow up: post-intervention	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.50 (0.05 to 4.81)	167 per 1,000	83 fewer per 1,000 (158 fewer to 635 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: HADS anxiety 2.51, withdrawal symptoms score 6.92.

Table 22: Clinical evidence summary: Imipramine substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo substitution + tapered withdrawal	Risk difference with Imipramine substitution + tapered withdrawal
Cessation of benzodiazepine follow up: 3 months	47 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 2.20 (1.27 to 3.82)	375 per 1,000	450 more per 1,000 (101 more to 1,057 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Rickels 2000, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

Table 23: Clinical evidence summary: Melatonin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo substitution + tapered withdrawal	Risk difference with Melatonin substitution + tapered withdrawal
Cessation of benzodiazepine follow up: post-intervention	38 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.20 (0.67 to 2.15)	500 per 1,000	100 more per 1,000 (165 fewer to 575 more)
Cessation of benzodiazepine follow up: 12 months	36 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.02 (0.47 to 2.22)	412 per 1,000	8 more per 1,000 (218 fewer to 502 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 24: Clinical evidence summary: Dothiepin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo substitution + tapered withdrawal	Risk difference with Dothiepin substitution + tapered withdrawal
Cessation of benzodiazepine follow up: 14 weeks	77 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.74 (0.40 to 1.36)	415 per 1,000	108 fewer per 1,000 (249 fewer to 149 more)
Patient satisfaction assessed with: Satisfaction analogue scale Scale from: 0 to 100 follow up: 14 weeks	40 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean patient satisfaction was 47.6	MD 22.9 higher (3.19 higher to 42.61 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Tyrer 1996, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: satisfaction 15.63.

Table 25: Clinical evidence summary: Valproate substitution + tapered withdrawal vs Tapered withdrawal alone for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal alone	Risk difference with Valproate substitution + tapered withdrawal
Withdrawal symptoms assessed with: CIWA-B Scale from: 0 to 18 follow up: post-intervention	29 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean withdrawal symptoms score was 6.3	MD 1.1 lower (3.87 lower to 1.67 higher)
Use of illicit drugs follow up: post-intervention	30 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.14 (0.08 to 16.63)	63 per 1,000	9 more per 1,000 (58 fewer to 977 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal alone	Risk difference with Valproate substitution + tapered withdrawal
b. The majority of the evidence had an indirect population. For Vorma 2011, 2 out of the 7 benzodiazepines listed (that people could be on) are not included in guideline medicine list, but no breakdown provided. Unclear if >80% were on relevant study drug. c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: CIWA-B 1.55.					

Table 26: Clinical evidence summary: Propranolol substitution + abrupt withdrawal vs Tapered withdrawal alone for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Tapered withdrawal alone	Risk difference with Propranolol substitution + abrupt withdrawal
Cessation of benzodiazepine follow up: 6 months	31 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 0.39 (0.16 to 0.96)	688 per 1,000	419 fewer per 1,000 (578 fewer to 28 fewer)
Withdrawal symptoms follow up: 6 months	31 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 1.36 (0.95 to 1.94)	688 per 1,000	248 more per 1,000 (34 fewer to 646 more)
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).					

Table 27: Clinical evidence summary: Patient advice & biofeedback guided information + tapered withdrawal vs Patient advice + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Patient advice + tapered withdrawal	Risk difference with Patient advice & biofeedback guided information + tapered withdrawal
Cessation of benzodiazepine follow up: post-intervention	6 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Peto OR 7.39 (0.15 to 372.38)	0 per 1,000	330 more per 1,000 [d] (240 fewer to 910 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Patient advice + tapered withdrawal	Risk difference with Patient advice & biofeedback guided information + tapered withdrawal
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. b. The majority of the evidence had an indirect population. For Nathan 1986, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug. c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes). d. Calculated from risk difference due to zero events in control arm					

Table 28: Clinical evidence summary: Psychological intervention, education and training + tapered withdrawal vs Psychological intervention, education and advice + tapered withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Psychological intervention, education and advice + tapered withdrawal	Risk difference with Psychological intervention, education and training + tapered withdrawal
Reduction of benzodiazepine (mg) follow up: 6 months	53 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean reduction of benzodiazepine (mg) was -12.3 mg	MD 4.4 mg higher (0.01 lower to 8.81 higher)
Relapse assessed with Weeks of taper suspension follow up: 6 months	53 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean relapse was 8.2	MD 2.2 higher (1.01 lower to 5.41 higher)
Relapse assessed with illicit use of benzodiazepine follow up: 6 months	39 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.88 (0.50 to 1.53)	600 per 1,000	72 fewer per 1,000 (300 fewer to 318 more)
Withdrawal symptoms - anxiety assessed with: HADS - anxiety	39 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-	The mean withdrawal symptoms score - anxiety was 1.6	MD 2.4 lower (5.35 lower to 0.55 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Psychological intervention, education and advice + tapered withdrawal	Risk difference with Psychological intervention, education and training + tapered withdrawal
Scale from: 0 to 21 follow up: 6 months					
Withdrawal symptoms -depression assessed with: HADS - depression Scale from: 0 to 21 follow up: 6 months	39 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean withdrawal symptoms score - depression was 2.3	MD 5.1 lower (8.69 lower to 1.51 lower)
Withdrawal symptoms - Sleep quality assessed with: PSQI Scale from: 0 to 21 follow up: 6 months	(1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean withdrawal symptoms score - Sleep quality was 2.3	MD 2.7 lower (5.49 lower to 0.09 higher)

a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of benzodiazepine 5.9, weeks of taper suspension 2.95, HADS anxiety 2, HADS depression 2.8, PSQI 2.1.

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 29: Clinical evidence summary: Patient advice, education & support + gradual withdrawal vs Patient advice, education & support + abrupt withdrawal for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Patient advice, education & support + abrupt withdrawal	Risk difference with Patient advice, education & support + gradual withdrawal
Relapse assessed with: unauthorised use of benzodiazepine follow up: post-intervention	40 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	RR 0.40 (0.21 to 0.75)	842 per 1,000	505 fewer per 1,000 (665 fewer to 211 fewer)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 30: Clinical evidence summary: Patient advice & information vs Patient advice for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Patient advice	Risk difference with Patient advice & information
Cessation of benzodiazepine follow up: 6 months	323 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.74 (0.43 to 1.29)	157 per 1,000	41 fewer per 1,000 (89 fewer to 45 more)
Reduction of benzodiazepine follow up: 6 months	140 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.34 (0.90 to 1.98)	369 per 1,000	126 more per 1,000 (37 fewer to 362 more)
Reduction of benzodiazepine assessed with diazepam eqv (mg) follow up: 6 months	183 (1 RCT)	⨁⨁⨁⨁ HIGH	-	The mean reduction of benzodiazepine was 123.17	MD 2.16 lower (29.44 lower to 25.12 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Cormack 1994, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of benzodiazepine 53.55.

Table 31: Clinical evidence summary: Patient advice & information vs Usual care for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Patient advice & information
Cessation of benzodiazepine follow up: 6 months	328 (2 RCTs)	⨁⨁◯◯ LOW [a,d]	RR 1.86 (0.90 to 3.85)	63 per 1,000	54 more per 1,000 (6 fewer to 180 more)
Cessation of benzodiazepine assessed with: ≤1 use in previous 15 days follow up: 12 months	135 (1 RCT)	⨁⨁◯◯ LOW [b]	RR 4.96 (2.22 to 11.05)	94 per 1,000	371 more per 1,000 (114 more to 942 more)
Reduction of benzodiazepine follow up: 6 months	144 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	RR 3.09 (1.72 to 5.57)	159 per 1,000	333 more per 1,000 (115 more to 729 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Patient advice & information
Reduction of benzodiazepine assessed with diazepam eqv (mg) follow up: 6 months	184 (1 RCT)	⊕⊕⊕◯ MODERATE [d]	-	The mean reduction of benzodiazepine was 126.76	MD 5.75 lower (34.93 lower to 23.43 higher)
Reduction of benzodiazepine assessed with: ≥50% reduction follow up: 12 months	135 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 1.31 (0.66 to 2.61)	172 per 1,000	53 more per 1,000 (58 fewer to 277 more)

a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of benzodiazepine 57.73 mg.

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

c. The majority of the evidence had an indirect population. For Cormack 1994, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

d The majority of the evidence had an indirect comparison. For Cormack 1994 & Heather 2004, the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 32: Clinical evidence summary: Brief advice, education & support vs Usual care for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Brief advice, education & support
Cessation of benzodiazepine follow up: 1 months	22 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.86 (0.43 to 1.73)	636 per 1,000	89 fewer per 1,000 (363 fewer to 465 more)
Cessation of benzodiazepine follow up: 6 months	311 (2 RCTs)	⊕⊕◯◯ LOW [b,c]	RR 2.49 (1.23 to 5.02)	63 per 1,000	94 more per 1,000 (15 more to 254 more)
Reduced benzodiazepine use follow up: 6 months	224 (2 RCTs)	⊕◯◯◯ VERY LOW [a,c]	RR 2.02 (1.30 to 3.13)	195 per 1,000	199 more per 1,000 (58 more to 415 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Usual care	Risk difference with Brief advice, education & support
Reduction of benzodiazepine assessed with diazepam eqv (mg) follow up: 6 months	177 (1 RCT)	⊕⊕⊕◯ MODERATE [c]	-	The mean reduction of benzodiazepine was 126.76 mg	MD 3.59 mg lower (34.61 lower to 27.43 higher)
Increase in symptoms - psychiatric morbidity assessed with increase of ≥2 on GHQ follow up: 6 months	93 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.29 (0.83 to 2.01)	404 per 1,000	117 more per 1,000 (69 fewer to 408 more)
Withdrawal symptom score assessed with scoring tool unclear follow up: 6 months	93 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean withdrawal symptom score was 5.7	MD 1.6 higher (0.86 lower to 4.06 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of benzodiazepine 55.31 mg, withdrawal symptom score 2.58.

c. The majority of the evidence had an indirect comparison. For Bashir 1994, Cormack 1994, Heather 2004, & Gnjidic 2019 the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 33: Clinical evidence summary: Brief advice, education & support (multiple letters) vs Brief advice, education & support (single letter) for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Brief advice, education & support (single letter)	Risk difference with Brief advice, education & support (multiple letters)
Cessation of benzodiazepine follow up: 12 months	349 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 0.96 (0.66 to 1.40)	245 per 1,000	10 fewer per 1,000 (83 fewer to 98 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Brief advice, education & support (single letter)	Risk difference with Brief advice, education & support (multiple letters)
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).					

Table 34: Clinical evidence summary: Brief advice, education & support (multiple letters) vs Brief advice, education & support (GP letter) for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Brief advice, education & support (GP letter)	Risk difference with Brief advice, education & support (multiple letters)
Cessation of benzodiazepine follow up: 12 months	345 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.64 (1.03 to 2.58)	145 per 1,000	93 more per 1,000 (4 more to 229 more)
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.					
b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug.					
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).					

Table 35: Clinical evidence summary: Brief advice, education & support (single letter) vs Brief advice, education & support (GP letter) for benzodiazepines

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Brief advice, education & support (GP letter)	Risk difference with Brief advice, education & support (single letter)
Cessation of benzodiazepine follow up: 12 months	322 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.70 (1.07 to 2.70)	145 per 1,000	101 more per 1,000 (10 more to 246 more)
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.					

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Brief advice, education & support (GP letter)	Risk difference with Brief advice, education & support (single letter)
b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug. c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).					

See full GRADE tables in Appendix G, section G.2.

1.3.4 Economic evidence

1.3.4.1 Included studies

Two health economic studies with relevant comparisons were included in this review.[94, 203] These are summarised in the health economic evidence profile below (Table 36and Table 37 and the health economic evidence tables in Appendix H section H.2.

1.3.4.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[169] These are listed in Appendix D, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix D.

1.3.5 Summary of included economic evidence

Table 36: Health economic evidence profile: Benzodiazepines - discontinuation letter vs consultation vs usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Godfrey 2008[94] (UK)	Directly applicable	Potentially serious limitations[(b)]	• Within-RCT analysis Heather 2004[111] • Population: Long-term benzodiazepine users • Comparators: Benzodiazepine discontinuation letter vs GP medication review vs usual care • Time horizon: 6 months	Discontinuation letter costs £383.23 [(c)] less than usual care Consultation costs £40.10 more than usual care [(c)]	n/a	n/a	No exploration of uncertainty

Abbreviations: QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) The time horizon of 6 months might be too short to capture long-term outcomes. Effectiveness data were collected from a single RCT rather than from a systematic review. No exploration of uncertainty through a sensitivity analysis was attempted. The assumption that there is no difference in health outcomes between the intervention is partially contradicted by the companion study which found an improvement in SF-36 mental score for patients undergoing a reduction of 25% or more of benzodiazepine
(b) 2005 UK pounds

Table 37: Health economic evidence profile: Benzodiazepine tapering off with cognitive behavioural therapy vs tapering off alone vs usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Oude Voshaar 2006 [203] (Netherlands)	Partially applicable [(a)]	Potentially serious limitations[(b)]	Within-RCT analysis Oude Voshaar 2003[202] Population: Long-term benzodiazepine users who had not discontinued 3 months after receiving a letter of	TO+CBT costs £176[(c)] more than usual care per person	TO+CBT gives 14% more benzodiazepine successful	TO+CBT costs £1300 for every extra successful discontinuation compared with usual care	No sensitivity analysis was conducted.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			discontinuation by their GP Comparators: Tapering off with cognitive behavioural therapy vs tapering off vs usual care Time horizon: 18 months	TOA costs £171[(c)] more than TO+CBT per person	discontinuation than UC TOA gives 7% more benzodiazepine successful discontinuation than TO+CBT UC gives 0.03 more HUI-3 score than TOA TOA gives 0.11 more HUI-3 than TO+CBT	TOA costs £2400 for every extra successful discontinuation compared with TO+CBT Cost-utility analysis suggests that UC dominates the other two strategies	

Abbreviations: CBT= cognitive behavioural therapy; QALY= quality-adjusted life years; RCT= randomised controlled trial, TOA= Tapering-off alone; UC= Usual care.

(a) Cost perspective is the Netherlands health service.

(b) The time horizon might be too short. Effectiveness data come from a single RCT rather than systematic review. Baseline characteristics and costs are heavily unbalanced between the comparators. The ICER is hard to interpret as there is no threshold value that can be used as a comparison

(c) 2001 Euro converted to UK pounds.[196]

1.3.6 Economic model

A health economic model was developed to assess whether CBT alongside tapering off is cost effective against tapering off alone and usual care to help people discontinue benzodiazepine medication. The full report and results can be found in the separate economic analysis report.

Population and strategies

The population of the analysis was people continuously taking benzodiazepines and the strategies compared were:

1. Group cognitive behavioural therapy plus tapering off (CBT+TO)
2. Tapering off alone (TOA)
3. Usual care (UC) - no attempt to discontinue the medication.

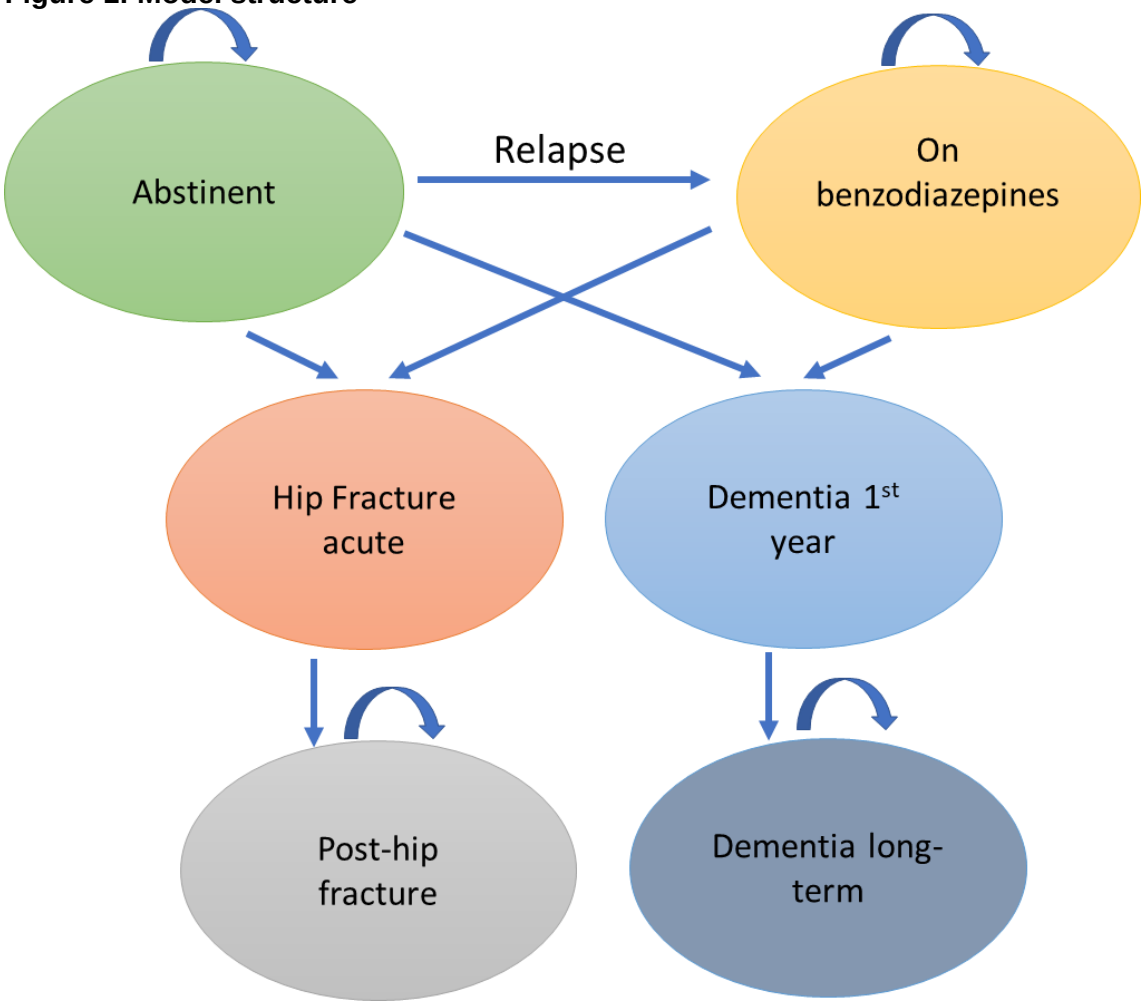
A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects.[181]

Methods and data sources

Model structure

- A Markov model (Figure 1) was developed including the following health states: abstinent, on benzodiazepines, hip fracture, post-hip fracture, dementia 1st year, dementia long-term. Hip fracture and dementia 1st year are tunnel states.
- The Markov model was run for 50 cycles representing 50 years of life.
- In each cycle,
    - Individuals can transition to the dementia or hip fracture states
    - individuals are at risk of a number of short-term adverse events (road traffic accidents and falls) that cause a temporary loss of utility and treatment cost lasting for one cycle only.
- People in the abstinent states have the general population risk of having a short-term or long-term adverse event. People in the benzodiazepine state have a higher risk of experiencing adverse events informed by the available literature.
- Hip fracture and dementia are irreversible states, so the model assumes that a person cannot recover from dementia or hip fracture.
- People transiting to one of the long-term outcomes are assumed to withdraw immediately from the medication.

Figure 1: Model structure



Note: people in each health state also have a state- and age-specific probability of transitioning to the dead health state.

Treatment effect and data sources

- Incidence of adverse events and transition probabilities to dementia and hip fracture were sought from large observational studies, predominantly conducted in the UK.[56, 110, 115, 158]
- The impact of benzodiazepine use on events and transition probabilities was estimated by looking at recent literature reviews.[15, 42, 60, 151, 223]
- Treatment effects on benzodiazepine cessation rates of TOA and CBT+TO were collected from the meta-analysis of three trials conducted for the clinical review (see **Table 15** in section 1.3.3).
- Mortality in the benzodiazepine state was slightly higher than mortality in the abstinent states due to the higher number of road traffic accidents (and suicide in the sensitivity analysis) in people taking benzodiazepine.
- Mortality in dementia and hip fracture state was calculated using the risk ratio and hazard ratio found in the literature.

Costs and utilities

- The resource use associated with the intervention was taken from the trials.[10, 170, 201] (see Table 39).

- The cost of benzodiazepine consumption was calculated using BNF[120] and Prescription Cost Analysis.[184]
- The cost of falls and hip fracture was calculated using two UK cost analyses.[49, 142] Likewise, the cost of dementia was calculated using an English analysis.[289] Finally, the cost of road traffic was estimated using Department of Transport data.[57]
- Utility scores at 1 year were calculated from one of the trials included in the clinical review.[203] Quality of life detriments caused by adverse events or health states were sought from the literature.[44, 104, 140]

Table 38: Base case scenario probabilistic results[a]

	Baillargeon [10]	Morin [170]	Oude Voshaar [201]	Base case scenario (average)
Cognitive behavioural therapy without tapering off				
Group size	6	5	4	5
Number of sessions	9	10	5	8
Duration (hour)	1.5	1.5	2.0	1.7
Cost per hour	£61	£58	£58	£58
CBT cost (per patient)	£131	£174	£145	£150
Tapering off				
Group size	1	1	1	1
Number of visits to GP	8	10	4	7.33
Duration (hour)	0.25	0.25	0.25	0.25
Cost per hour	£153	£153	£153	£153
TO cost (per patient)	£264	£330	£132	£242

Results

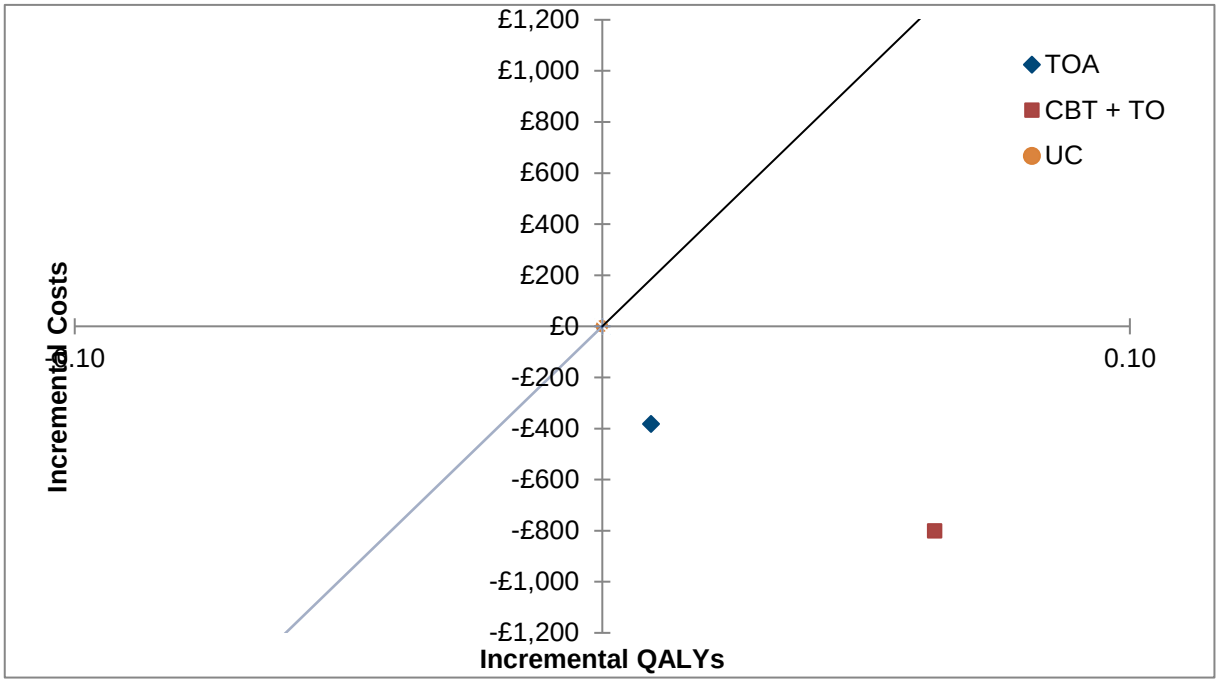
The probabilistic base case results are illustrated in Table 39 and in **Figure 2**.

Table 39: Base case scenario probabilistic results (per patient)

	CBT + TO	TOA	Usual Care
Intervention cost	£438	£281	£0
Benzodiazepine cost	£473	£613	£775
Fall Injuries cost	£8,177	£8,459	£8,781
Hip fractures cost	£1,500	£1,503	£1,505
Road traffic accident cost	£58	£61	£66
Dementia cost	£3,807	£3,955	£4,127
Total cost	£14,453	£14,872	£15,254
QALYs	8.63	8.57	8.57
NMB (20k)[a]	**£158,113**	**£156,620**	**£156,053**
NMB rank	**1**	**2**	**3**

(a) Net monetary benefit at a threshold of £20,000 per QALY gained

Figure 2: Cost effectiveness plane



Both TOA and CBT + TO are less expensive than usual care and are associated with a higher quality of life gain. Therefore, they both dominate usual care. When compared with each other, CBT + TO dominates TOA, making it the first ranked strategy by net monetary benefit. The probabilistic analysis revealed that CBT+TO is cost-effective in 88% of the simulations compared to usual care, and in 68% of the simulations compared to TOA.

Table 40 shows the results of the deterministic scenario analysis.

Table 40: Deterministic results of the scenario analysis

Scenarios	CBT + TO vs TOA INMB[a]	CBT + TO vs UC INMB[a]	TOA vs UC INMB[a]	Ranking
Base case	£1,473	£2,209	£737	1. CBT + TO 2. TOA 3. Usual care
Starting age = 50	£1,236	£1,538	£302	1. CBT + TO 2. TOA 3. Usual care
Starting age = 70	£1,389	£2,075	£686	1. CBT + TO 2. TOA 3. Usual care
Same relapse factor in the second year	£701	£1,179	£479	1. CBT + TO 2. TOA 3. Usual care
5 years relapse duration	£1,047	£698	-£348	1. CBT + TO 2. Usual care 1. TOA
Relapse in UC equal to relapse in TOA	£1,473	£2,597	£1,124	1. CBT + TO 2. TOA 1. Usual care
Savings due to dose reduction included	£1,438	£2,289	£852	1. CBT + TO 2. TOA

Scenarios	CBT + TO vs TOA INMB[a]	CBT + TO vs UC INMB[a]	TOA vs UC INMB[a]	Ranking
				1. Usual care
Age-specific OR for RTA	£1,473	£2,209	£737	2. CBT + TO 3. TOA 1. Usual care
Benzodiazepine increases suicide risk	£1,473	£2,209	£737	2. CBT + TO 3. TOA 1. Usual care
No convergence in utility	£6,059	£730	-£5,329	2. CBT + TO 3. Usual care 1. TOA
Convergence after 5 years	£2,941	£1,739	-£1,203	2. CBT + TO 3. Usual care 1. TOA
Self-reported EQ-5D for dementia	£1,318	£1,852	£534	2. CBT + TO 3. TOA 1. Usual care
Baillargeon intervention cost	£1,493	£2,204	£711	2. CBT + TO 3. TOA 1. Usual care
Morin intervention cost	£1,447	£2,082	£635	2. CBT + TO 3. TOA 2. Usual care
Oude Voshaar intervention cost	£1,478	£2,342	£864	2. CBT + TO 3. TOA 3. Usual care
Police cost included in RTA cost	£1,474	£2,212	£738	4. CBT + TO 5. TOA 6. Usual care

(a) Incremental net monetary benefit calculated using a threshold of £20,000

In each scenario tested, CBT + TO remains the most cost-effective strategy. The ranking changes only in the scenarios where utility differences are assumed to converge later and in the scenario with relapses lasting for five years. In all three scenarios, usual care is cost-effective against TOA although CBT+TO still dominates them both.

1.3.7 Evidence statements

1.3.7.1 Economic

- One cost-comparison analysis found that discontinuation letters cost less than both consultation and usual care for discontinuing benzodiazepines. The analysis was assessed as directly applicable with potentially serious limitations.
- One cost-effectiveness analysis found that
  - tapering off alone cost more but was more effective than CBT + tapering off (ICER: £2,400 per successful discontinuation).
  - tapering off alone cost more but was more effective than usual care (ICER: £1,300 per successful discontinuation).

  The analysis was assessed as partially applicable with potentially serious limitations.

- One original cost-utility analysis found that group CBT + tapering off dominated both tapering off alone and usual care. The analysis was assessed as directly applicable with minor limitations.

1.4 Z-drugs

1.4.1 Effectiveness evidence

1.4.1.1 Included studies

Two papers reporting one RCT were included in the review;[23, 24] these are summarised in **Table 41** below. The studies were conducted in Sweden and compared acupuncture with CBT.

Evidence from these studies is summarised in the clinical evidence summary below (**Table 42**).

See also the study selection flow chart in Appendix C. Other relevant Appendices include study evidence tables in section E.3, forest plots in section F.3 and GRADE tables in section G.3.

1.4.1.2 Excluded studies

See the excluded studies list in Appendix I.

1.4.2 Summary of studies included in the effectiveness evidence

Table 41: Summary of studies included in the evidence review (Z-drug)

Study	Intervention and comparison	Population	Outcomes	Comments
Bergdahl 2016[24]/Bergdahl 2017[23]	**Acupuncture** Auricular acupuncture - twice a week for 4 weeks. During each session, the participants were treated with five acupuncture needles in each of the outer ears for 45 minutes; no needle stimulation was performed. During the treatment the participants sat in chairs and were instructed by the acupuncturist to close their eyes and to focus on keeping their breathing calm and regular. The acupuncturists aimed to have the same attitude and behaviour in order to make the treatment as similar as possible for all participants. When the needles had been inserted the acupuncturist left the room. Participants were instructed to discontinue their hypnotic drug treatment 3-5 days before the intervention. vs **CBT** The CBT-i group received manual-based group treatment, focused on cognitive restructuring, once a	People with insomnia and long-term (>6 months) use of Z-drugs N= 67 Age - Mean (SD): 60.5 (9.4). Sweden	Cessation of Z-drugs at 6 months Insomnia (protocol outcome: symptoms for which the medication was originally prescribed) at post-intervention (4 or 6 weeks) and 6 months Depression (protocol outcome: withdrawal symptoms) at post-intervention (4 or 6 weeks) and 6 months Anxiety (protocol outcome: withdrawal symptoms) at post-intervention (4 or 6 weeks) and 6 months	Taper occurred before intervention

Study	Intervention and comparison	Population	Outcomes	Comments
	week for six weeks. The sessions contained information regarding sleep physiology, different ways of coping with sleeping problems, sleep restriction, maintaining factors, stimulus control, and relaxation techniques. Each session lasted for 90 minutes. Three registered psychologists who all had undergone CBT training and were experienced in giving CBT-i treatment carried out the treatments. All sessions were performed in hospital facilities. Participants were instructed to discontinue their hypnotic drug treatment 3-5 days before the intervention. 6 months			

See section E.3 for full evidence tables.

1.4.3 Summary of the effectiveness evidence

Table 42: Clinical evidence summary: acupuncture vs CBT

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with acupuncture
Cessation of drug Follow-up 4-6 weeks	49 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 0.84 (0.62-1.15)	840 per 1,000	134 fewer per 1,000 (319 fewer to 126 more)
Anxiety post intervention (Protocol outcome: withdrawal symptoms) (HADS anxiety) assessed with: Hospital Anxiety and Depression Scale Scale from: 0 to 21 follow up: 4-6 weeks	50 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean HADS anxiety score in the control group was 5.24	MD 0.22 lower (1.61 lower to 1.17 higher)
Anxiety (Protocol outcome: withdrawal symptoms) (HADS anxiety) assessed with: Hospital Anxiety and Depression Scale Scale from: 0 to 21 follow up: 6 months	45 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean HADS anxiety score in the control group was 5.32	MD 0.25 higher (1.29 lower to 1.79 higher)
Depression (Protocol outcome: withdrawal symptoms) (HADS depression) assessed with: Hospital Anxiety and Depression Scale Scale from: 0 to 21 follow up: 4-6 weeks	50 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean HADS depression score in the control group was 5.29	MD 0.1 higher (1.36 lower to 1.56 higher)
Depression (Protocol outcome: withdrawal symptoms) (HADS depression) assessed with: Hospital Anxiety and Depression Scale Scale from: 0 to 21 follow up: 6 months	45 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean HADS depression score in the control group was 4.78	MD 0.29 higher (0.91 lower to 1.49 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with acupuncture
Insomnia (Protocol outcome: increase in symptoms for which the medication was originally prescribed) (ISI) assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 4-6 weeks	50 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean Insomnia Severity Scale score in the control group was 9.6	MD 6.09 higher (3.32 higher to 8.86 higher)
Insomnia (Protocol outcome: increase in symptoms for which the medication was originally prescribed) (ISI) assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 6 months	45 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean Insomnia Severity Scale score in the control group was 11.66	MD 2.82 higher (0.25 lower to 5.89 higher)

a Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5* median of baseline SDs of intervention and control groups. MIDs were calculated as follows: ISI: 1.83, HADS anxiety 1.42 and HADS depression 1.42

See full GRADE tables in Appendix G, section G.3.

1.4.4 Economic evidence

1.4.4.1 Included studies

No health economic studies on Z-drugs were included.

1.4.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.4.5 Summary of included economic evidence

None.

1.4.6 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.4.7 Evidence statements

1.4.7.1 Economic

- No relevant economic evaluations were identified.

1.5 Antidepressants

1.5.1 Effectiveness evidence

1.5.1.1 Included studies

Ten papers reporting eight randomised-control trials (RCTs) relevant to antidepressant withdrawal were included in the review,[70-72, 80, 124, 177, 192, 240, 244, 258] these are summarised in **Table 43** below. Evidence from these studies is summarised in the clinical evidence summaries below (**Table 44** to **Table 55**).

Evidence was identified for the following population strata, according to the type of antidepressant medication people were taking:

- Tricyclic antidepressants (TCAs): 2 studies[71, 72] compared an intervention of cognitive behavioural therapy (CBT) plus an antidepressant taper to clinical management plus taper. In one of these studies[72], a small number of people who could not tolerate TCAs were switched to SSRIs, however, only 5 people (11%) were switched to SSRIs, therefore the study was included in the TCA stratum.
- Other antidepressants:
  - 1 study[124, 192] in people on desvenlafaxine compared abrupt discontinuation to a 1-week taper.
  - 1 study[80] in people on desvenlafaxine compared abrupt discontinuation to three different taper regimens.
- Mixed antidepressants: all the other studies were in a mixed population across the different types of antidepressants, the following interventions were compared:
  - 1 study[258] compared a longer (14-day) taper to a shorter (3-day) taper.

- 1 study[240] compared group CBT sessions plus a taper to a tapered withdrawal. People in the control arm had individualised sessions with psychiatrists.
- 1 study[244] compared mindfulness-based cognitive therapy plus a taper to a placebo substitution taper,
- 1 study (reported in 2 papers)[70, 177] compared advice given to the GP to discontinue the patient's antidepressants to usual care. As there was no specific aim to withdraw or taper antidepressants in the control group, this study was downgraded for indirectness.

Tint 2008 was downgraded for indirectness, as the study population was people discontinuing an antidepressant in order to switch to another antidepressant, and it was unclear why people were switching to a new antidepressant (i.e., whether it was because it was not having an effect). The outcomes extracted in this review were taken prior to initiation of the new antidepressant, and therefore the study still matched the protocol. However, the downgrade was deemed appropriate as this differed from the other studies, which included people discontinuing their antidepressants due to a successful response or being in remission. Two further studies, Khan 2014 and Gallagher 2012, only stated that people were included if they completed the open-label treatment period (24 weeks for Khan 2014 and at least 5 of the 15-week phase for Gallagher 2012), and it did not specify whether people needed to have shown a successful response. All the other included studies included people discontinuing their antidepressants due to a successful response or being in remission. Gallagher 2012 was the only study in a population not on antidepressants for depression or anxiety. This study was in women with vasomotor symptoms associated with menopause.

In Khan 2014 and Gallagher 2012, the antidepressant used was desvenlafaxine. This is not licenced for use in the UK and was not on the guideline medicine list for included medicines (see Appendix K). However, in the context of withdrawal, it was considered that desvenlafaxine was sufficiently similar to venlafaxine as it is the active metabolite of venlafaxine; and these studies were included in the evidence.

For antidepressants, withdrawal symptoms were often reported on the discontinuation emergent signs and symptoms checklist (DESS). One study[124] reported withdrawal symptoms from the DESS checklist in a number of ways: the total DESS score as a continuous outcome, the number of people with discontinuation syndrome (increase in DESS score of ≥4) as a dichotomous outcome, and a breakdown of the number of people with mild, moderate and severe symptoms for all 43 items on the DESS checklist. It was agreed not to include the 43 individual symptoms from the DESS checklist, as it was deemed to be double-counting, as two other measures from the DESS checklist were already reported for this study. This was not the case for any other studies in the review. This study was also included in the withdrawal symptoms evidence review, where the breakdown of individual symptoms was extracted.

See also the study selection flow chart in Appendix C. Other relevant Appendices include study evidence tables in section E.4, forest plots in section F.4 and GRADE tables in section G.4.

1.5.1.2 Excluded studies

See the excluded studies list in Appendix I

1.5.2 Summary of studies included in the effectiveness evidence

Table 43: Summary of studies included in the evidence review (Antidepressants)

Study	Intervention and comparison	Population	Outcomes	Comments
PANDA trial: Eveleigh 2018[70] (Muskens 2013[177])	Letter to GP: a patient-specific letter was sent to the GP with the recommendation to discontinue. A gradual tapering programme was recommended. The GP invited the patient to discuss the recommendation Vs Usual care: no restrictions on GPs to deliver care or to refer to specialised mental health care, including the continuation or discontinuation of psychotropic drugs. Since baseline psychiatric diagnostics was not disclosed for patients who have given informed consent in a control practice, expected continuation of antidepressant drug treatment in most cases. 12 months follow-up	Long-term users of antidepressants (≥9 months). Excluded people with appropriate use of long-term antidepressants according to the Dutch guidelines for depressive and anxiety disorders (that is, a history of recurrent depression (≥3 episodes) and/or a recurrent psychiatric disorder with at least two relapses after antidepressant discontinuation). Mixed antidepressants: 73% were on SSRIs; 12% on SNRIs; 6% on TCAs; 8% on other non-TCAs N=146 Age - Mean (SD): Intervention: 56 (12.9); control: 56 (14.3). Netherlands	Antidepressant discontinuation Antidepressant restart at 1 year (protocol outcome: relapse into medication use) Relapse: depressive or anxiety disorder during the 1-year follow-up, as assessed by the Composite International Diagnostic Interview (CIDI) (protocol outcome: Increase in symptoms for which the medication was originally prescribed)	Note: population is people without a current indication for antidepressants. Cluster randomised. Downgraded for indirectness as the usual care group had no specific aim to taper or discontinue. Study also reports the proportion of participants who successfully discontinued their long-term antidepressant use after 1 year. Successful discontinuation is defined as no antidepressant use during the preceding 6 months (prior to 1 year follow up) and the absence of a depressive or anxiety disorder during the 1-year follow-up, as assessed by the CID. This outcome was not extracted due to the overlap with the protocol outcomes of total number of people who discontinued and the total number of people who relapsed
Fava 1994[71]	CBT + taper: ten 40-minute sessions once every other week. The psychiatrist used strategies	People with major depressive disorder and successful response to	Discontinuation of antidepressants at 20 weeks	The aim of the study was to explore the feasibility of a psychotherapeutic approach to the residual symptoms of

Study	Intervention and comparison	Population	Outcomes	Comments
	and techniques designed to help depressed patients correct their distorted views and maladaptive beliefs. Whenever appropriate, as in the case of residual symptoms related to anxiety, exposure strategies were planned with the patient. Vs Clinical management + taper: ten 40-minute sessions once every other week. Clinical management consisted of monitoring medication tapering, reviewing the patient's clinical status, and providing the patient with support and advice if necessary. Taper details: antidepressant drug use was tapered at the rate of 25 mg of amitriptyline or its equivalent every other week, and then the drugs were withdrawn completely. 20-week intervention (2-year follow-up)	antidepressant drugs (only the patients in full remission were included in the study). Only included people with residual symptoms after treatment with antidepressants. TCAs stratum: all on TCAs N=49 Age - Mean (SD): CBT + taper: 43.7 (3.2); clinical management + taper: 48.5 (3.3). Italy	Relapse (episode of major depression) at 2 years (protocol outcome: increase in symptoms for which the medication was originally prescribed). Residual symptoms score at 20 weeks (protocol outcome: increase in symptoms for which the medication was originally prescribed).	depression after successful treatment with antidepressant drugs. Therefore, the study excluded people with no residual symptoms after treatment with antidepressants, according to Paykel Clinical Interview for Depression (covering 19 symptom areas) - to evaluate prodromal and residual symptoms.
Fava 1998[72]	CBT + taper: ten 30-minute sessions once every other week. CBT consisted of the following 3 main ingredients: (1) CBT of residual symptoms of major depression, (2) Lifestyle	People with recurrent depression (≥3 episodes of depression) who had been successfully treated with antidepressant drugs (only	Discontinuation of antidepressants at 20 weeks Relapse (episode of major depression) at 2 years	Similar interventions as Fava 1994[71], but different population (recurrent depression). Does not state that people with no residual symptoms were excluded (as

Study	Intervention and comparison	Population	Outcomes	Comments
	modification, (3) Well-being therapy. Vs Clinical management + taper: ten 30-minute sessions once every other week. Clinical management consisted of monitoring medication tapering, reviewing the patient's clinical status, and providing the patient with support and advice if necessary. Taper details: tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week, and then the drugs were withdrawn completely 20-week intervention (2-year follow-up)	the patients in full remission were included in the study). TCAs stratum: 89% on TCAs (if people couldn't tolerate TCAs they were switched to SSRIs – 11% on SSRIs). N=45 Age - Mean (SD): CBT + taper: 45.1 (10.3); Clinical management + taper: 48.7 (12.1). Italy	(protocol outcome: increase in symptoms for which the medication was originally prescribed). Residual symptoms score at 20 weeks (protocol outcome: increase in symptoms for which the medication was originally prescribed).	with Fava 1994), but the aims of the study included the effect of CBT on the residual symptoms after successful treatment with antidepressant drugs.
Gallagher 2012[80]	Desvenlafaxine succinate 50mg/d for 7 days followed by 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) Vs Desvenlafaxine succinate 50 mg/d every other day for 14 days (Desvenlafaxine 50-every other (eo) taper)	Postmenopausal women who experienced ≥ 50 moderate to severe hot flashes per week during each of the 2 weeks immediately preceding randomization. For inclusion in the taper phase: participants who completed the open-label phase or had received at least 5 weeks	Discontinuation Emergent Signs and Symptoms score at 1 week after final taper dose (post-intervention; protocol outcome: withdrawal symptoms) Incidence of 8 individual DESS checklist symptoms (dizziness, headaches, increased dreaming/nightmare,	People were not on antidepressants at baseline, but were entered into a 15-week open label treatment with desvenlafaxine prior to the discontinuation. People who completed the open-label phase or had received at least 5 weeks of open-label treatment at the time of discontinuation were randomly assigned to the taper phase. The study also included a titration phase prior to the treatment phase. People

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs Desvenlafaxine succinate 50 mg/d for 7 days followed by placebo for 7 days (Desvenlafaxine 50-placebo taper) Vs Placebo (abrupt discontinuation)	of open-label treatment at the time of discontinuation N=384 (randomised to taper phase) Mean (SD) age: Desvenlafaxine 50-25 taper: 54.52 (5.01), Desvenlafaxine 50-eo taper: 54.40 (6.37), Desvenlafaxine 50-placebo taper: 53.98 (5.16), placebo (abrupt): 53.48 (5.27) Country not reported	irritability, nausea, sudden worsening of mood, sweating more than usual, Trouble sleeping/ insomnia) at 1 week after final taper dose (post-intervention; protocol outcome: withdrawal symptoms) Patient Satisfaction at week 3 (final timepoint, at least 1 week after last taper dose in all timepoints)	were also randomised to a titration strategy, but there was a re-randomisation for the taper stage, so this was deemed acceptable. Study provided data at timepoints 1, 2 and 3 weeks after the start of taper. Four arm trial with an abrupt discontinuation, a taper with the final dose at the 1-week timepoint and two taper strategies with the final dose at the 2-week timepoint. Therefore, the timepoint extracted for each group was 1 week following the final dose of antidepressant (1 week of drug-free wash-out), as a post-intervention timepoint. The study reported the incidence of 8 individual symptoms from the 43-item DESS checklist. These 8 symptoms appear to have been selected as they are the commonly reported 8 ‘consensus panel symptoms.’ Therefore, the outcome was not downgraded for selective outcome reporting. *Study also reports the incidence of individual symptoms spontaneous adverse events, some of which might be considered withdrawal symptoms. There is overlap between some of the individual symptoms reported as adverse events, and those in the DESS, but not all overlap (some adverse events such as*

Study	Intervention and comparison	Population	Outcomes	Comments
				hypertension not in DESS). The incidence of DESS symptoms were extracted under the protocol outcome of withdrawal symptoms, and not the spontaneous adverse events, as the DESS was assessed in everyone rather than just from spontaneous reports Study also reports the incidence of taper emergent adverse events. However, percentages were provided in the paper and the total number in the analysis was unclear, in order to calculate the dichotomous data.
Khan 2014[124] (Ninan 2015[192])	Abrupt discontinuation: switch straight to placebo for 4 weeks Vs 1 week taper: received 25mg/d desvenlafaxine for 1 week, then placebo for 3 weeks 6 weeks (4-week intervention and 2-week follow-up)	Adult outpatients (≥ 18 years of age) with a primary diagnosis of single or recurrent MDD without psychotic features. Patients were required to have depressive symptoms for ≥ 30 days prior to the screening visit and a 17-item Hamilton Depression Rating Scale total score ≥ 14 at baseline. Entered into 24-week treatment trial. Other antidepressants stratum: all on desvenlafaxine N=288	Deaths Completing the double-blind phase (i.e., antidepressant discontinuation) at 4 weeks Discontinuation Emergent Signs and Symptoms score at 2 weeks (during intervention; protocol outcome: withdrawal symptoms) People with Discontinuation syndrome (increase in DESS score of ≥4 at 2 weeks; during intervention; protocol	People were not on antidepressants at baseline, but were entered into a 24-week open label treatment trial. People who completed this were randomly assigned. DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes. All on desvenlafaxine 3rd arm in study: continuation on antidepressants (excluded from review)

Study	Intervention and comparison	Population	Outcomes	Comments
		Age - Mean (SD): Taper: 47.9 (11.2); abrupt discontinuation (placebo): 47.8 (13.7). USA	outcome: withdrawal symptoms) Taper/posttherapy–emergent adverse events (TPAEs) - defined as any adverse event that started or increased in severity during the double-blind phase at 4 weeks (protocol outcome: withdrawal symptoms) Suicidal ideation reported on the Columbia Suicide Severity Rating Scale (C-SSRS) at 6 weeks (protocol outcome: withdrawal symptoms: reviewer judged as withdrawal symptom) Suicide attempt (intentional drug overdose of a non-study medication) at 6 week (protocol outcome: self-harm or harm to others) Depressive symptoms (Quick Inventory of Depressive Symptomatology Self-Report, QIDS-SR16) at 4 weeks (protocol outcome: increase in symptoms for	Study also reports the breakdown of incidence of mild/moderate/severe for all 43 items on the DESS checklist. These were not reported as it was deemed to be double counting, as two other measures from the DESS checklist were already reported for this study.

Study	Intervention and comparison	Population	Outcomes	Comments
			which the medication was originally prescribed)	
Scholten 2018[240]	CBT discontinuation consisted of 8 group sessions of relapse prevention, targeting vulnerability factors and discontinuation symptoms (states CBT also offered after full discontinuation) Vs Discontinuation without CBT: guided by psychiatrists in individual sessions Taper details: antidepressants were tapered every 2 weeks according to a fixed schedule (depending on the type and dosage of antidepressant), with full discontinuation completed well within 4 months 4 months intervention & discontinuation period, 12 month follow up	People on antidepressants and at least a lifetime but no current anxiety panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and generalized anxiety disorder. Mixed antidepressants (n=69 on SSRIs, n=14 on SNRIs, n=2 on TCAs, n=2 on mirtazapine) N=87 Age CBT: 42.7 (11.9); taper: 40.8 (13.4). Netherlands	Suicide at 16 months Recurrence of the previous anxiety disorder at 16 months (protocol outcome: increase in symptoms for which the medication was originally prescribed)	Inclusion was stopped prematurely for ethical reasons and lack of effect (futility), though assessments of included participants continued until 16 months. Study also reported the following outcomes: re-/occurrence of any anxiety disorder; re-/occurrence of any anxiety disorder or major depressive disorder, these were judged not to match the protocol outcome as well as recurrence of the previous anxiety disorder, and reporting may result in 'double counting'. Percentage of people with complete assessments who discontinued antidepressants reported, but unable to calculate numbers due to uncertainty over the number of people who completed assessments.
Segal 2010[244]	Mindfulness-based cognitive therapy (MBCT) + taper: attended 8 weekly group meetings of 2 hours duration and a retreat day held between sessions 6 and 7. Medication tapered gradually, during a 4-week period, via reduced pill count (no placebo), at the recommended rate for their	Patients diagnosed with major depressive disorder, a score of 16 or higher on the HRSD, 2 or more previous episodes of MDD. People were not on antidepressants at the start of the study, but had at least 8 months treatment during the open-	Relapse (recurrence of major depressive episode) at 18 months (protocol outcome: increase in symptoms for which the medication was originally prescribed)	Note: taper involved substitution with placebo in the control arm, but not in the intervention arm. People were not on antidepressants at the start of the study, but had at least 8 months treatment during the open-label phase prior to randomisation. During the open label

Study	Intervention and comparison	Population	Outcomes	Comments
	specific medication. Once patients in the MCBT group had finished their taper, they no longer took any pills. Vs Placebo substitution taper: medication tapered gradually, during a 4-week period, via placebo substitution at the recommended rate for their specific medication 18-month follow-up	label phase prior to randomisation. For inclusion in the discontinuation phase: patients meeting criteria for treatment response (50% reduction in HRSD score) and clinical remission (HRSD score, <8 for 8 weeks) were treated for 5 additional months to ensure full remission. Mixed antidepressants: all started on SSRIs, but 14 of 84 (17%) required a second treatment step. N=56 (2 relevant treatment arms included in this review) Age - Mean (SD): MBCT: 44.8 (9.4); placebo: 41.9 (11.6). Canada		phase, all patients received 2-step antidepressant pharmacotherapy according to the Texas Medication Algorithm Project guidelines. Step 1: citalopram hydrobromide (or sertraline hydrochloride if that couldn't be tolerated). Patients of failure during this phase of at least 8-week trial were switched to step 2 (either venlafaxine hydrochloride or mirtazapine). Study also had a third arm of the trial (not included in the analysis for this review) - this arm of the trial was continuation on antidepressant treatment.
Tint 2008[258]	Longer taper (14 days), individualised according to antidepressant, dose and tablet formulation Vs Shorter taper (3 days), individualised according to	Clinical diagnosis of major depressive disorder, treated with an SSRI or venlafaxine for ≥6 weeks and in whom the treating clinician wanted to switch antidepressant. Mixed antidepressants: 82% were on SSRIs; 18% on venlafaxine	Discontinuation syndrome (≥3 new symptoms on the DESS checklist) at 5-7 days after drug washout (protocol outcome: withdrawal symptoms)	Population downgraded for indirectness as the included population are discontinuing antidepressants in order to switch to another antidepressant. Study was looking at people discontinuing antidepressants in order to switch to another antidepressant (14 were switched to an

Study	Intervention and comparison	Population	Outcomes	Comments
	antidepressant, dose and tablet formulation 5-7 day follow-up after taper	N=28 Age - Mean (SD): 39 (12). UK		antidepressant in the same class, 14 to a different antidepressant class), all participants then commenced a new antidepressant. They were reassessed after commencing the new antidepressant, but these results are not included in the current review

See section E.4 for full evidence tables.

1.5.3 Summary of the effectiveness evidence

Table 44: Clinical evidence summary: TCAs: CBT + taper vs clinical management + taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clinical management + taper	Risk difference with CBT + taper
Discontinuation of antidepressants assessed with calculated from the information on the number of people in whom discontinuation was not feasible follow up: 20 weeks	88 (2 RCTs)	⨁⨁◯◯ LOW [a]	RR 1.00 (0.88 to 1.14)	909 per 1,000	0 fewer per 1,000 (109 fewer to 127 more)
Relapse (episode of major depression): protocol outcome: increase in symptoms for which the medication was originally prescribed assessed with occurrence of a Research Diagnostic Criteria-defined episode of major depression during	83 (2 RCTs)	⨁⨁◯◯ LOW [a]	RR 0.37 (0.20 to 0.68)	595 per 1,000	375 fewer per 1,000 (476 fewer to 190 fewer)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clinical management + taper	Risk difference with CBT + taper
follow up follow up: 2 years [b]					
Residual symptoms score, protocol outcome: increase in symptoms for which the medication was originally prescribed assessed with: Total score on the modified version of the Paykel Clinical Interview for Depression – range of values not reported, assumed to be 133 (based on 19 symptom areas and a 1–7-point scale) Top=High is poor outcome follow up: 20 weeks [c]	80 (2 RCTs)	⨁◯◯◯ VERY LOW [a,d,e]	-	The median residual symptoms score was 27.18	MD 2.61 lower (3.92 lower to 1.29 lower)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. For Fava 1994 this is including the people who were unable to discontinue during the taper stage, as it specifically states that these people were withdrawn because of relapse during the medication tapering phase. For Fava 1998, this does not include the people who were unable to discontinue during the taper stage, as does not specifically state that these people were unable to discontinue due to taper, and the study excluded these from further analysis.

c. people in the study had residual symptoms after successful treatment with antidepressants (baseline) - this score was assessed again after CBT or CM + taper.

d. Heterogeneity, I2=50%, unexplained by subgroup analysis (unable to perform subgroup analysis due to only 2 studies)

e. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: residual symptoms 1.64)

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Table 45: Clinical evidence summary: Other antidepressants (desvenlafaxine): abrupt discontinuation vs 1 week taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 1 week taper	Risk difference with abrupt discontinuation
Mortality follow up: 6 weeks	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)
Completing the double-blind phase (i.e., antidepressant discontinuation) follow up: 4 weeks	288 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	RR 1.03 (0.96 to 1.10)	907 per 1,000	27 more per 1,000 (36 fewer to 91 more)
Discontinuation Emergent Signs and Symptoms score: protocol outcome withdrawal symptoms assessed with: DESS total score (unclear if there is a range of values, suggests this is the number of DESS) Top=High is poor outcome follow up: 2 weeks [f]	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	-	The mean discontinuation Emergent Signs and Symptoms score: protocol outcome withdrawal symptoms was 4.8	MD 0.5 higher (0.88 lower to 1.88 higher)
Discontinuation syndrome (increase in DESS score of ≥4): protocol outcome withdrawal symptoms follow up: 2 weeks [f]	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	RR 0.98 (0.63 to 1.54)	216 per 1,000	4 fewer per 1,000 (80 fewer to 117 more)
Taper/post-therapy–emergent adverse events (TPAEs): protocol outcome withdrawal symptoms assessed with any adverse event that started or increased in severity during the double-blind phase follow up: 4 weeks	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,c,d]	RR 1.32 (1.02 to 1.72)	388 per 1,000	124 more per 1,000 (8 more to 280 more)
Suicidal ideation, protocol outcome withdrawal symptoms (judged by reviewer) assessed with: C-SSRS follow up: 6 weeks	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	RR 0.95 (0.06 to 15.07)	7 per 1,000	0 fewer per 1,000 (7 fewer to 101 more)
Suicide attempt (intentional drug overdose of a non-study medication): protocol outcome, self-harm or harm to others follow up: 6 weeks	285 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	Peto OR 7.04 (0.14 to 355.37)	0 per 1,000	10 more per 1,000 (10 fewer to 30 more) [g]

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 1 week taper	Risk difference with abrupt discontinuation
Depressive symptoms (QIDS-SR16): protocol outcome increase in symptoms for which the medication was originally prescribed assessed with: Quick Inventory of Depressive Symptomatology Self-Report 0-27 Top=High is poor outcome follow up: 4 weeks [e]	285 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean depressive symptoms (QIDS-SR16): protocol outcome increase in symptoms for which the medication was originally prescribed was 6.2	MD 0.3 higher (0.77 lower to 1.37 higher)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Only one study with zero events in both arms, sample size >70<350

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS score 0.9; QIDS-SR16 2.15

d. Downgraded for outcome indirectness

e. Range of the QIDS-SR16 not reported by the study. Online resources suggest this is a 16 item self-report measure of depression, with a total range of scores from 0-27 (0-5 no depression, 6-10 mild depression, 11-15 moderate depression, 16-20 severe depression, 21-27 very severe depression)

f. DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes.

g. Calculated from risk difference due to zero events in control arm.

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Table 46: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs abrupt (placebo)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50-25
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	-	The mean DESS total score was 7.07	MD 2.96 lower (5.02 lower to 0.9 lower)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.71 (0.45 to 1.13)	418 per 1,000	121 fewer per 1,000 (230 fewer to 54 more)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.68 (0.36 to 1.25)	286 per 1,000	91 fewer per 1,000 (183 fewer to 71 more)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.49 (0.26 to 0.92)	357 per 1,000	182 fewer per 1,000 (264 fewer to 29 fewer)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.60 (0.30 to 1.18)	265 per 1,000	106 fewer per 1,000 (186 fewer to 48 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕⊕◯◯ LOW [b]	RR 0.31 (0.13 to 0.75)	286 per 1,000	197 fewer per 1,000 (249 fewer to 71 fewer)
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper).	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.31 (0.11 to 0.86)	224 per 1,000	155 fewer per 1,000 (200 fewer to 31 fewer)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50-25
Protocol outcome: withdrawal symptoms [a]					
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.74 (0.48 to 1.14)	449 per 1,000	117 fewer per 1,000 (233 fewer to 63 more)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	155 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.60 (0.35 to 1.04)	378 per 1,000	151 fewer per 1,000 (245 fewer to 15 more)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	106 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.98 (0.76 to 1.28)	685 per 1,000	14 fewer per 1,000 (164 fewer to 192 more)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; placebo (abrupt): week 1).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.85

Table 47: Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-every other (eo) taper) vs abrupt (placebo)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50 every other
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	-	The mean DESS total score was 7.07	MD 3.85 lower (5.72 lower to 1.98 lower)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.53 (0.31 to 0.90)	418 per 1,000	197 fewer per 1,000 (289 fewer to 42 fewer)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕⊕◯◯ LOW [b]	RR 0.24 (0.09 to 0.64)	286 per 1,000	217 fewer per 1,000 (260 fewer to 103 fewer)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕⊕◯◯ LOW [b]	RR 0.33 (0.16 to 0.70)	357 per 1,000	239 fewer per 1,000 (300 fewer to 107 fewer)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.70 (0.38 to 1.32)	265 per 1,000	80 fewer per 1,000 (164 fewer to 85 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕⊕◯◯ LOW [b]	RR 0.30 (0.12 to 0.73)	286 per 1,000	200 fewer per 1,000 (251 fewer to 77 fewer)
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.53 (0.24 to 1.16)	224 per 1,000	106 fewer per 1,000 (171 fewer to 36 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50 every other
week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]					
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.79 (0.53 to 1.19)	449 per 1,000	94 fewer per 1,000 (211 fewer to 85 more)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	157 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.54 (0.31 to 0.95)	378 per 1,000	174 fewer per 1,000 (261 fewer to 19 fewer)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	107 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.72 (0.52 to 0.99)	685 per 1,000	192 fewer per 1,000 (329 fewer to 7 fewer)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-eo taper: week 3; placebo (abrupt): week 1).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.48

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Table 48: Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper) vs abrupt (placebo)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50-placebo
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	177 (1 RCT)	⨁⨁◯◯ LOW [b,c]	-	The mean DESS was 7.07	MD 2.61 lower (4.61 lower to 0.61 lower)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁◯◯ LOW [b,c]	RR 0.64 (0.41 to 0.98)	418 per 1,000	151 fewer per 1,000 (247 fewer to 8 fewer)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	RR 0.35 (0.17 to 0.73)	286 per 1,000	186 fewer per 1,000 (237 fewer to 77 fewer)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	RR 0.35 (0.19 to 0.67)	357 per 1,000	232 fewer per 1,000 (289 fewer to 118 fewer)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁◯◯◯ VERY LOW [b,c]	RR 0.86 (0.51 to 1.45)	265 per 1,000	37 fewer per 1,000 (130 fewer to 119 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁◯◯ LOW [b,c]	RR 0.66 (0.38 to 1.15)	286 per 1,000	97 fewer per 1,000 (177 fewer to 43 more)
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1	177 (1 RCT)	⨁◯◯◯ VERY LOW [b,c]	RR 1.01 (0.59 to 1.76)	224 per 1,000	2 more per 1,000 (92 fewer to 171 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with abrupt (placebo)	Risk difference with Desvenlafaxine 50-placebo
week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]					
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁◯◯ LOW [b,c]	RR 0.65 (0.43 to 0.98)	449 per 1,000	157 fewer per 1,000 (256 fewer to 9 fewer)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	177 (1 RCT)	⨁⨁◯◯ LOW [b,c]	RR 0.74 (0.48 to 1.14)	378 per 1,000	98 fewer per 1,000 (196 fewer to 53 more)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	94 (1 RCT)	⨁◯◯◯ VERY LOW [b,c]	RR 1.06 (0.81 to 1.38)	685 per 1,000	41 more per 1,000 (130 fewer to 260 more)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention time point was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-placebo taper: week 2; placebo (abrupt): week 1).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 3.01

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Table 49: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50 every other	Risk difference with Desvenlafaxine 50-25
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	-	The mean DESS was 3.22	MD 0.89 higher (1.05 lower to 2.83 higher)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.35 (0.73 to 2.53)	220 per 1,000	77 more per 1,000 (59 fewer to 337 more)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 2.85 (0.96 to 8.42)	68 per 1,000	125 more per 1,000 (3 fewer to 503 more)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.48 (0.60 to 3.62)	119 per 1,000	57 more per 1,000 (47 fewer to 311 more)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.85 (0.38 to 1.89)	186 per 1,000	28 fewer per 1,000 (116 fewer to 166 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.04 (0.32 to 3.39)	85 per 1,000	3 more per 1,000 (58 fewer to 203 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50 every other	Risk difference with Desvenlafaxine 50-25
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.59 (0.18 to 1.91)	119 per 1,000	49 fewer per 1,000 (97 fewer to 108 more)
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.94 (0.57 to 1.55)	356 per 1,000	21 fewer per 1,000 (153 fewer to 196 more)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms [a]	116 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.12 (0.56 to 2.25)	203 per 1,000	24 more per 1,000 (89 fewer to 254 more)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	105 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.37 (0.98 to 1.91)	491 per 1,000	182 more per 1,000 (10 fewer to 446 more)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the time point 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; Desvenlafaxine 50-eo taper: week 3).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.14

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Table 50: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50-placebo	Risk difference with Desvenlafaxine 50-25
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	136 (1 RCT)	⊕⊕◯◯ LOW [b]	-	The mean DESS was 4.46	MD 0.35 lower (2.41 lower to 1.71 higher)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.12 (0.65 to 1.93)	266 per 1,000	32 more per 1,000 (93 fewer to 247 more)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.91 (0.82 to 4.43)	101 per 1,000	92 more per 1,000 (18 fewer to 347 more)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.39 (0.62 to 3.11)	127 per 1,000	49 more per 1,000 (48 fewer to 267 more)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.69 (0.34 to 1.43)	228 per 1,000	71 fewer per 1,000 (150 fewer to 98 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.46 (0.18 to 1.20)	190 per 1,000	103 fewer per 1,000 (156 fewer to 38 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50-placebo	Risk difference with Desvenlafaxine 50-25
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.31 (0.11 to 0.86)	228 per 1,000	157 fewer per 1,000 (203 fewer to 32 fewer)
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.14 (0.69 to 1.89)	291 per 1,000	41 more per 1,000 (90 fewer to 259 more)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	136 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.82 (0.45 to 1.48)	278 per 1,000	50 fewer per 1,000 (153 fewer to 134 more)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	92 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.93 (0.71 to 1.21)	725 per 1,000	51 fewer per 1,000 (210 fewer to 152 more)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the time point 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; Desvenlafaxine 50-placebo taper: week 2).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.67

Table 51: Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50-placebo	Risk difference with Desvenlafaxine 50 every other
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	-	The mean DESS was 4.46	MD 1.24 lower (3.12 lower to 0.64 higher)
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.83 (0.45 to 1.52)	266 per 1,000	45 fewer per 1,000 (146 fewer to 138 more)
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.67 (0.21 to 2.12)	101 per 1,000	33 fewer per 1,000 (80 fewer to 113 more)
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.94 (0.38 to 2.32)	127 per 1,000	8 fewer per 1,000 (78 fewer to 167 more)
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.82 (0.42 to 1.60)	228 per 1,000	41 fewer per 1,000 (132 fewer to 137 more)
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.45 (0.17 to 1.16)	190 per 1,000	104 fewer per 1,000 (158 fewer to 30 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Desvenlafaxine 50-placebo	Risk difference with Desvenlafaxine 50 every other
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.52 (0.23 to 1.16)	228 per 1,000	109 fewer per 1,000 (175 fewer to 36 more)
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 1.22 (0.75 to 1.99)	291 per 1,000	64 more per 1,000 (73 fewer to 288 more)
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]	138 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.73 (0.39 to 1.35)	278 per 1,000	75 fewer per 1,000 (170 fewer to 97 more)
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)	93 (1 RCT)	⊕◯◯◯ VERY LOW [b,c]	RR 0.68 (0.48 to 0.95)	725 per 1,000	232 fewer per 1,000 (377 fewer to 36 fewer)

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the time point 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-eo taper: week 3; Desvenlafaxine 50-placebo taper: week 2).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.29

Table 52: Clinical evidence summary: Mixed antidepressants: longer (14 day) taper vs shorter (3 day) taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with shorter (3 day) taper	Risk difference with longer (14 day) taper
Discontinuation syndrome (≥3 new symptoms on the DESS checklist) post-taper: protocol outcome withdrawal symptoms follow up: 5-7 days	28 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.99 (0.45 to 2.20)	467 per 1,000	5 fewer per 1,000 (257 fewer to 560 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded for population indirectness: population differs from others included in this review, as the included population are discontinuing antidepressants in order to switch to another antidepressant, not because they no longer require to be on the antidepressant

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).

Table 53: Clinical evidence summary: Mixed antidepressants: CBT + taper vs taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
Suicide follow up: 16 months	87 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 7.94 (0.16 to 400.89)	0 per 1,000	20 more per 1,000 (40 fewer to 90 more) [d]
Recurrence of the previous anxiety disorder. Protocol outcome: increase in symptoms for which the medication was originally prescribed follow up: 16 months	87 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	HR 1.04 (0.53 to 2.06)	444 per 1,000 [c]	13 more per 1,000 (177 fewer to 258 more)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
c. Study only provides HR summary statistics and % of people with the outcome. Numbers in each group calculated from these percentages (assumed all people analysed). d. Calculated from risk difference due to zero events in the control arm.					

Table 54: Clinical evidence summary: Mixed antidepressants: Mindfulness-based cognitive therapy + taper vs placebo substitution taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo substitution taper	Risk difference with Mindfulness-based cognitive therapy (MBCT) + taper
Relapse (recurrence of major depressive episode): protocol outcome: increase in symptoms for which the medication was originally prescribed assessed with: DSM-IV major depressive episode, using the depression module of the SCID follow up: 18 months	56 (1 RCT)	⨁⨁◯◯ LOW [a,b]	RR 0.64 (0.36 to 1.13)	600 per 1,000	216 fewer per 1,000 (384 fewer to 78 more)
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).					

Table 55: Clinical evidence summary: Mixed antidepressants: advice to GP to discontinue person's antidepressants vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Advice to GP to discontinue patient's antidepressants
Antidepressant discontinuation follow up: 1 years [a]	146 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	RR 1.23 (0.67 to 2.27)	197 per 1,000	45 more per 1,000 (65 fewer to 251 more)
Antidepressant restart. Protocol outcome: relapse into medication use follow up: 1 years	146 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	RR 1.74 (0.60 to 5.06)	66 per 1,000	49 more per 1,000 (26 fewer to 267 more)
Relapse (depressive or anxiety disorder during follow-up). Protocol outcome: increase in symptoms for which the medication was originally prescribed. assessed with: CIDI follow up: 1 years	146 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	RR 1.95 (0.97 to 3.94)	132 per 1,000	125 more per 1,000 (4 fewer to 387 more)

a. Regardless of intention to comply with the recommendation to discontinue or not in the intervention group

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

c. Downgraded for comparison indirectness: the study included a control group who received usual care/no intervention. Unclear if there was any intention to withdraw from antidepressants in this group.

d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).

See full GRADE tables in Appendix G, section G.4.

1.5.4 Economic evidence

1.5.4.1 Included studies

One health economic study with the relevant comparison was included in this review.[69] This is summarised in the health economic evidence profile below (Table 56) and the health economic evidence table in H.4.

1.5.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.5.5 Summary of included economic evidence

Table 56: Health economic evidence profile: Antidepressant cessation advice vs usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Eveleigh 2014[69] (Netherlands)	Partially applicable [(a)]	Potentially serious limitations[(b)]	Within-RCT analysis (PANDA trial [177]) Population: Inappropriate long-term antidepressants users Comparators: Antidepressant cessation advice vs usual care Time horizon: 12 months	Usual care costs £49[(c)] more than antidepressant cessation advice	Usual care gives 0.02 more QALYs than cessation advice	Usual care costs an extra £2,450 per QALY gained compared with cessation advice	Probabilistic analysis only conducted on the societal perspective results. No one-way sensitivity analyses were conducted.

Abbreviations: QALY= quality-adjusted life years; RCT= randomised controlled trial
(a) Cost perspective is the Netherlands health service.
(b) The time horizon might be too short. Effectiveness data come from a single RCT rather than a systematic review.
(c) 2013 Euro converted to UK pounds.[196]

1.5.6 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.5.7 Evidence statements

1.5.7.1 Economic

- One cost-utility analysis found that usual care was cost-effective compared to cessation advice (ICER: £2,450 per QALY gained). The analysis was assessed as partially applicable with potentially serious limitations.

1.6 Mixed medicines

1.6.1 Effectiveness evidence

1.6.1.1 Included studies

Thirteen papers reporting nine RCTs were included in the review;[16, 21, 90, 96, 139, 219, 263, 265, 268, 269, 293-295] these are summarised in **Table 57** below.

The studies included participants taking a variety of mixed medicines: the most common being benzodiazepines and Z-drugs.[16, 90, 139, 219, 263, 265, 268, 269, 293, 294] Other studies included participants who were taking benzodiazepines, antidepressants, opioids or other medicines (for those taking other medicines not listed on the protocol, this was <20%),[96] benzodiazepines, Z-drugs or antidepressants[21] and opioids, anxiolytics, hypnotics and sedatives (in this study, breakdown of the specific medicines was not provided, only described as anxiolytics, hypnotics and sedatives).[295]

Interventions and comparisons included: CBT plus taper versus taper,[21, 96] mindfulness-based relapse prevent plus a psychoeducation session plus voluntary gradual withdrawal versus a psychoeducation session plus voluntary gradual withdrawal,[16] patient advice and education versus usual care,[90] melatonin versus placebo,[139, 219] prescriber education via an intensive support programme versus a written manual,[263] a structured intervention with follow-up visits versus a structured intervention with written instructions compared to usual care,[265, 268, 269] electroacupuncture versus sham acupuncture,[293, 294] motivational interviewing versus a booklet on health behaviour.[295]

Evidence from these studies is summarised in the clinical evidence summaries below in **Table 58** to **Table 67**. See also the study selection flow chart in Appendix C. Other relevant Appendices include study evidence tables in section E.5, forest plots in section F.5 and GRADE tables in section G.5.

1.6.1.2 Excluded studies

See the excluded studies list in Appendix I.

1.6.2 Summary of studies included in the effectiveness evidence

Table 57: Summary of studies included in the evidence review (Mixed medicines)

Study	Intervention and comparison	Population	Outcomes	Comments
Barros 2021[16]	Mindfulness-based relapse prevention (MBRP) + initial psychoeducation group session (based on principles of motivational interviewing) + individualised guidance on gradual voluntary withdrawal Vs Initial psychoeducation group session (based on principles of motivational interviewing) + individualised guidance on gradual voluntary withdrawal. 8-week intervention	Women using hypnotic medication (benzodiazepines and Z-drugs) for sleep induction at least 4 times a week for a minimum of 90 days. N=70 Mean age (SD): 53 (13) years Brazil	Equivalent hypnotic dose (defined daily dose/diazepam mg equivalent (DDD/DME); protocol outcome: reduction in prescribed drug use) Insomnia (Insomnia severity index (ISI); protocol outcome: symptoms for which the medication was originally prescribed) All at post-intervention (8 weeks) and 6 months	Hypnotics (benzodiazepines (61%) and non-benzodiazepines (Z-drugs; 39%) Downgraded for indirect population: breakdown of benzodiazepines not reported, unclear if on guideline medicine list. 86.8% had been prescribed hypnotics (>80% so no downgrade for this reason) The possibility of gradual withdrawal was discussed in a psychiatric consultation and individualised guidance on gradual withdrawal was given. The psychiatrist informed participants the tapering would be voluntary and should only occur after the group psychoeducation session.
Belleville 2007[21]	CBT plus taper Participants were given self-help materials in the form of five booklets for treatment for	Chronic users of hypnotics (benzodiazepines and Z-drugs). Two participants were also taking antidepressants.	HRQOL Cessation of prescribed drug use	

Study	Intervention and comparison	Population	Outcomes	Comments
	insomnia, each of which covered a specific component of the CBT of insomnia. Participants were sent the booklets throughout the 8-week intervention period and asked to follow the guidelines as closely as possible. The booklets covered: self-management, stimulus control, cognitive therapy for changing dysfunctional beliefs and attitudes, education, and evaluation. Participants were also asked by therapists regarding their adherence to the CBT guidance during weekly telephone calls. Vs Tapered withdrawal alone Participants received taper programme only. No additional services were received. Taper (all patients) All patients were given a step-by-step withdrawal programme. Dose was reduced by 25% every two weeks with the aim to achieve complete drug withdrawal by the end of week 8. Participants met with a physician to provide an individualized withdrawal schedule, and offer support and encouragement, and to adjust the withdrawal schedule if necessary.	N= 53 Mean age (SD): 55.3 years (11.4) Canada	Daily hypnotic dose Withdrawal symptoms: Depression, anxiety and Clinical Institute Withdrawal Assessment (CIWA-B) Increase in symptoms: Insomnia Severity Index (ISI) All at post-intervention (8 weeks) and 6 months	

Study	Intervention and comparison	Population	Outcomes	Comments
	8-week intervention			
Giblin 1983[90]	Patient advice/education Psychological treatment: Relaxation technique - This was a form of the autogenic relaxation procedure. The technique was taught in the first session and practised at the start of all the other sessions. Information - Information was given in simple written form and discussed in the treatment sessions. The information was concerned with sleep, insomnia, hypnotics and their effects on sleep, and sleep-preventing behaviour. General advice - Subjects were encouraged to view their problems in a systematic and logical way, to adopt a positive optimistic attitude to their difficulties, and to use the techniques every night. They were told that there might be a number of effects as a result of drug-withdrawal, but that these would soon end. A lot of reinforcement, in other words, approval, from the therapist was given when anyone reported any success. All participants were asked to stop taking hypnotics. Vs	People who were currently using hypnotics (Benzodiazepines and Z-drugs) nightly and had been doing so for six months or more. N=20 Mean age (range): 71.3 years (56-83) UK	Number of people who haven't used hypnotics during the previous 4-week period (post intervention) No hypnotic use during the previous 4-week period (at 12 weeks) Resumption of nightly hypnotic post intervention Resumption of nightly hypnotic at 12 weeks Sleep latency post intervention Sleep latency at 12 weeks	

Study	Intervention and comparison	Population	Outcomes	Comments
	Usual care No psychological intervention was available. All participants were asked to stop taking hypnotics. 20 weeks			
Gorenstein 2005[96]	CBT plus medical management taper (CBT-MM): 13 concurrent weekly CBT sessions (50 minutes each). The principal methods involved progressive muscle relaxation, diaphragmatic breathing, cognitive restructuring, worry-behaviour prevention, problem-solving, interoceptive exposure, strategies for coping with medication withdrawal, daily activity structuring, in vivo exposure and sleep hygiene. Vs Medical management (MM) involved 13 weekly sessions lasting about 10-15 minutes each. Sessions dealt with the patient's clinical state, medication efficacy, side effects, the next medication step and prescription of medication. Both groups had tapering of medication by approximately 20%	Elderly people who were getting unsatisfactory results from anxiolytics. Mixed population: Benzodiazepines (60%), antidepressants (about 20%) and other anxiolytics (meprobamate, opiate, valerian, diphenhydramine) N= 42 Age: >60 years USA	Cessation of benzodiazepine Reduction of benzodiazepine Responders: Clinical Global Impression Scale; 'much improved' or 'very much improved' (protocol outcome: Increase in symptoms for which the medication was originally prescribed) Average proportion of medication taken post-treatment relative to pre-treatment All at post-intervention (13 weeks)	Other outcomes: Anxiety scores, Penn State worry questionnaire Beck Depression Inventory, Symptoms Checklist 90-R 6-month follow-up for CBT-MM only. Post-intervention scores for these outcomes are not reported with the n numbers.

Study	Intervention and comparison	Population	Outcomes	Comments
	reduction each week for benzodiazepines. 13 weeks			
Lahteenmaki 2014[139]	Melatonin + psychological support + taper Vs Placebo + psychological support + taper 6 months	Men and women aged 55 years or older who were long term users of Benzodiazepines as hypnotics, and also Z-drugs. N=92 Age: median (IQR) 65.7 (10.5) years Finland	Cessation of prescribed drug at post intervention and 6 months Benzodiazepine usage at 6 months	Withdrawal symptoms: Benzodiazepine Withdrawal Symptom Questionnaire: BWSQ reported as medians only – unable to analyse
Puustinen 2018[219]	As above	As above	Cessation of prescribed drug at 3 years	Follow- up of Lahteenmaki 2014 (see above)
van de Steeg-van Gompel 2009[263]	Prescriber Intensive support programme Included an educational manual consisting of information about the project, step by step instructions for managing the project, schedules for the reduction of benzodiazepine use, an electronic example of the discontinuation letter, background information regarding long term benzodiazepine use and publications on the effectiveness of the intervention. It also included an interactive educational meeting and one or more telephone calls by a coach	Community pharmacies receiving prescriptions for long-term benzodiazepines from GPs. Participants were taking benzodiazepines and Z-drugs. N= 43 pharmacies (25673 patients) Age (mean): 65 years (15.3) The Netherlands	Cessation of benzodiazepine Reduction of benzodiazepine At 0-3 months and at 4-6 months	Cluster randomised Indirect population- unclear if included drugs not on guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs Written manual for prescribers Pharmacies only received the written educational manual, and no further implementation support was given. Up to 8 month follow up			
Vicens 2014[265] Vicens 2016[268] Vicens 2011[269]	Structured intervention with follow-up visits. Based on a structured educational interview comprising: 1) information on benzodiazepine dependence, abstinence and withdrawal symptoms 2) the risks of long-term use, memory and cognitive impairment, accidents and falls 3) reassurance about reducing medication 4) a self-help leaflet to improve sleep quality if patients were taking benzodiazepines for insomnia. Follow-up appointments every 2-3 weeks until the end of the dose reduction. Taper: 10-25% reduction in the daily dose of the benzodiazepine every 2-3 weeks. Vs	People aged 18-80 years taking benzodiazepines or related drugs (zopiclone, zolpidem, or zaleplon) daily for at least 6 months for anxiety, depression, insomnia or pain. Note: baseline information shows that at least 13.9% were on Z-drugs. N= 532 (75 GPs) Age 64 years (median) IQR 55-72 Spain	Mortality at 36 months Cessation of benzodiazepine at 6, 12 and 36 months Withdrawal symptoms (tremor, irritability, insomnia, anxiety, convulsions): all reported separately. Note: in study these were reported as a breakdown of mild, moderate, severe. These were combined for the purpose of this review as all people who had the outcome. At 6 and 12 months Suicide attempt (protocol outcome: self-harm or harm to others) at 12 months	Cluster randomised (adjusted analysis reported for some of the cessation outcome comparisons, but not other outcomes). Indirect population- unclear if included drugs not on guideline medicine list Indirect comparison: usual group may not have involved deprescribing benzodiazepines

Study	Intervention and comparison	Population	Outcomes	Comments
	Structured intervention with written instructions. As per the structured intervention with follow-up visits group except patients received written instructions reinforcing educational information at their first and only contact with their GP. No follow- up visit was scheduled, although patients could request an appointment with their GP when needed. Taper: 10-25% reduction in the daily dose of the benzodiazepine every 2-3 weeks. Vs Usual care Patients received routine care; their GPs could provide brief advice but did not receive any specific recommendation about the management of long-term benzodiazepine use from the study trainers. 12 month follow up (Vicens 2016 – 36-month follow-up)			
Yeung 2019[294] Yeung 2017[293]	Electroacupuncture Electroacupuncture combined with gradual tapering. Electroacupuncture twice per week for 4 consecutive weeks. Participants were needled by	Long-term benzodiazepine and z drug users. N= 144	Cessation of benzodiazepine Benzodiazepine dose usage	Indirect population- unclear if included drugs not on guideline medicine list

Study	Intervention and comparison	Population	Outcomes	Comments
	sterile, disposable acupuncture needles at preselected acupoints until an indicator of 'effective needling' in Traditional Chinese medicine theory was obtained. The inserted needles were retained for 30 minutes, and 4 pairs of needles were connected to an electric stimulator to deliver continuous and constant electrical stimulation at 4Hz. Taper: 25% reduction of daily benzodiazepine consumption in the first and second weeks, followed by 25% reduction for the remaining 50% of benzodiazepine every 3-4 days. Vs. Sham acupuncture Sham acupuncture+ taper. Sham acupuncture used placebo needles, a non-invasive sham device, after the same sterilisation procedure as the electroacupuncture group. The placebo needles ensured the appearance of skin penetration without creating real skin penetration when the needles were pressed. Needles were placed 1 inch away from the acupoints and connected with an electric stimulator without any supply of electrical stimulation.	Age 57.5 (10.6) years Hong Kong	Withdrawal symptoms (BWSQ, insomnia, anxiety, depression) All at 6 and 16 weeks	Dichotomous outcomes: adjusted OR (logistic regression analysis) Continuous outcomes: adjusted MD (linear regression analysis)

Study	Intervention and comparison	Population	Outcomes	Comments
	Taper: 25% reduction of daily benzodiazepine consumption in the first and second weeks, followed by 25% reduction for the remaining 50% of benzodiazepine every 3-4 days. 16-week follow-up			
Zahradnik 2009[295]	Motivational interviewing Two counselling sessions based on motivational interviewing plus individualised written feedback. The first intervention took place in the hospital and was targeted to last 30-45 minutes; the second intervention, 4 weeks later, was conducted by telephone. Core constructs of the Transtheoretical Model of behaviour change was assessed and an individualised feedback letter was developed. This was sent to study participants 8 weeks after the first intervention. When appropriate, strategies for improving self-efficacy and maintaining changes were included in the feedback letter. In each step of the intervention, it was pointed out that it was necessary to discontinue or reduce the medication only with help from professionals, e.g., the GP or medical specialist. Vs	People regularly using or with dependence or abuse of prescription drugs (opioids, anxiolytics, hypnotics and sedatives) N= 126 Age (mean): 55.13 years (11.59) Germany	Mortality Cessation of benzodiazepine Reduction of benzodiazepine Mean defined daily dosage difference (protocol outcome: reduction of prescribed drug use) All at 3 months	Cluster randomised Indirect population- unclear if included drugs not on guideline medicine list 84.2% were taking 1 type of medication 55.6% opioids 11.1% hypnotics 16.7% sedatives Population included people with dependence or who misused prescription drugs Study also reports results from logistic regression analysis for the effect of the intervention for different drug classes, but this was only reported for hypnotics and sedatives combined and opioids separately. Overall data have been used.

Study	Intervention and comparison	Population	Outcomes	Comments
	Booklet on health behaviour with general information on prescription drugs. 3-month follow-up			

1.6.3 Summary of the effectiveness evidence

Table 58: Clinical evidence summary: MBRP + initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal vs initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MBRP
Equivalent hypnotic dosage (DDD/DME); protocol outcome: reduction in prescribed medication use; at post-intervention (8 weeks)	70 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean hypnotic dosage (DDD/DME); was 1.97	MD 1.01 lower (2.29 lower to 0.27 higher)
Equivalent hypnotic dosage (DDD/DME); protocol outcome: reduction in prescribed medication use; at 6 months follow-up	70 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	-	The mean hypnotic dosage (DDD/DME); was 0.76	MD 0.2 higher (0.48 lower to 0.88 higher)
Insomnia (Insomnia Severity Index; range 0-28; higher values = worse outcome); protocol outcome: symptoms for which the medication was originally prescribed; at post-intervention (8 weeks)	70 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean Insomnia Severity Scale was 15.43	MD 1.28 lower (3.95 lower to 1.39 higher)
Insomnia (Insomnia Severity Index; range 0-28; higher values = worse outcome); protocol outcome: symptoms for which the medication was originally prescribed; at 6 months follow-up	70 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean Insomnia Severity Scale was 15.7	MD 4.82 lower (7.45 lower to 2.19 lower)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded for population indirectness: breakdown of benzodiazepines used not provided and unclear if on guideline medicine list

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MBRP
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of intervention and control groups). Calculated MIDs for continuous outcomes were as follows: hypnotic dosage: 1.45; ISI: 2.94					

1 **Table 59: Clinical evidence summary: CBT + taper vs taper**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
HRQOL (SF-36- physical) assessed with: SF-36-Physical health component score Scale from: 0 to 100 follow up: 8 weeks	48 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean SF-36 physical component score in the control group was 79.42	The mean SF-36 physical component score in the intervention group was 10.42 lower (20.9 lower to 0.06 higher)
HRQOL assessed with: SF-36-physical health component follow up: 6 months	43 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean SF-36 physical component score in the control group was 78.17	The mean SF-36 physical component score in the intervention group was 8.32 lower (19.52 lower to 2.88 higher)
HRQOL assessed with: SF-36-mental health component follow up: 8 weeks	48 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean SF-36 mental component score in the control group was 69.67	The mean SF-36 mental component score in the intervention group was 3.72 lower (12.91 lower to 5.47 higher)
HRQOL assessed with: SF-36-mental health component follow up: 6 months	43 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean SF-36 mental component score in the control group was 74.09	The mean SF-36 mental component score in the intervention group was 1.09 lower

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
					(10.82 lower to 8.64 higher)
Cessation of drug post intervention follow up: 8/13 weeks	75 (2 RCTs)	⊕◯◯◯ VERY LOW [a,c]	RR 2.50 (1.39 to 4.49)	256 per 1,000	385 more per 1,000 (100 more to 895 more)
Cessation of drug follow up: 6 months	43 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 0.87 (0.48 to 1.59)	542 per 1,000	70 fewer per 1,000 (282 fewer to 320 more)
Benzodiazepine usage (daily hypnotic dose) post intervention, lorazepam equivalent, mg. Protocol outcome: reduction of prescribed drug use assessed with: Daily hypnotic dose follow up: 8 weeks	48 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean benzodiazepine usage post intervention in the control group was 0.09	The mean benzodiazepine usage in the intervention group was 0.08 higher (0.1 lower to 0.26 higher)
Benzodiazepine usage (daily hypnotic dose), lorazepam equivalent, mg. Protocol outcome: reduction of prescribed drug use assessed with: Daily hypnotic dose follow up: 6 months	43 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	The mean benzodiazepine usage in the control group was 0.37	The mean benzodiazepine usage in the intervention group was 0.04 lower (0.47 lower to 0.39 higher)
Decrease in prescribed drug use follow up: 13 weeks	28 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.30 (0.91 to 1.87)	714 per 1,000	214 more per 1,000 (64 fewer to 621 more)
'Responder' Clinical Global Impressions Scale ‘much improved’ or ‘very much improved’ Protocol outcome: increase in symptoms for which the medication was originally prescribed. follow up: 13 weeks	28 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.80 (0.81 to 4.02)	357 per 1,000	286 more per 1,000 (68 fewer to 1,079 more)
Average proportion of medication taken post-treatment relative to pre-treatment. Protocol outcome: reduction of prescribed drug use.	28 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	-	The mean proportion of medication taken (post-treatment dose divided by pre-	MD 0.12 lower (0.72 lower to 0.49 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
Follow-up: 13 weeks				treatment dose) was 0.583	
Depression post intervention. Protocol outcome: withdrawal symptoms assessed with: BDI Scale from: 0 to 36 follow up: 8 weeks	48 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean depression score in the control group was 4.21	The mean depression score in the intervention group was 3.11 higher (0.16 higher to 6.06 higher)
Depression. Protocol outcome: withdrawal symptoms assessed with: BDI Scale from: 0 to 36 follow up: 6 months	43 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean depression score in the control group was 4.78	The mean depression score in the intervention group was 0.43 lower (2.81 lower to 1.95 higher)
Anxiety post intervention. Protocol outcome: withdrawal symptoms assessed with: STAI-state Scale from: 20 to 80 follow up: 8 weeks	48 (1 RCT)	⨁◯◯◯ LOW [a,b]	-	The mean anxiety score in the control group was 37.04	The mean anxiety score in the intervention group was 0.86 lower (7.31 lower to 5.59 higher)
Anxiety Protocol outcome: withdrawal symptoms assessed with: STAI-state Scale from: 20 to 80 follow up: 6 months	43 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean anxiety score in the control group was 35.48	The mean anxiety score in the intervention group was 4.13 lower (9.65 lower to 1.39 higher)
Withdrawal symptoms post intervention (CIWA-B) assessed with: CIWA-B Scale from: 0 to 100 follow up: 8 weeks	48 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean withdrawal symptoms score in the control group was 23.53	The mean withdrawal symptoms score in the intervention group was 1.18 higher (7.37 lower to 9.73 higher)
Withdrawal symptoms assessed with: CIWA-B Scale from: 0 to 100 follow up: 6 months	43 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean withdrawal symptoms score in the control group was 17.33	The mean withdrawal symptoms score in the intervention group was 1.62 higher

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with taper	Risk difference with CBT + taper
					(5.51 lower to 8.75 higher)
Insomnia post intervention. Protocol outcome: increase in symptoms for which the medication was originally prescribed (ISI) assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 8 weeks	48 (1 RCT)	⨁⨁◯◯ LOW [a,b]	-	The mean insomnia score in the control group was 14.25	The mean insomnia score in the intervention group was 2.52 lower (5.69 lower to 0.65 higher)
Insomnia. Protocol outcome: increase in symptoms for which the medication was originally prescribed (ISI) assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 6 months	43 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	-	The mean insomnia score in the control group was 11.48	The mean insomnia score in the intervention group was 0.78 lower (4.81 lower to 3.25 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of intervention and control groups for continuous outcomes). Calculated MIDs for continuous outcomes were as follows: daily hypnotic dose 0.65, BDI 3.28, STAI 5.39, CIWA-B 4.99, Insomnia Severity Scale 2.13. Published MIDs were: SF-36 physical 2, SF-36: mental 3.
c. The majority of the evidence had an indirect population (the specific benzodiazepine used by patients was not reported)

Table 60: Clinical evidence summary: Patient advice plus relaxation vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with patient advice/education
No hypnotic use during previous 4 weeks. Protocol outcome: cessation of drug follow up: 4 weeks	20 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 7.00 (1.04 to 46.95)	100 per 1,000	600 more per 1,000 (4 more to 4,595 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with patient advice/education
No hypnotic use during previous 4 weeks. Protocol outcome: cessation of drug follow up: 12 weeks	20 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	RR 6.00 (0.87 to 41.21)	100 per 1,000	500 more per 1,000 (13 fewer to 4,021 more)
Resumption of nightly hypnotic use. Protocol outcome: relapse into medication use. follow up: 4 weeks	20 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	RR 0.14 (0.02 to 0.96)	700 per 1,000	602 fewer per 1,000 (686 fewer to 28 fewer)
Resumption of nightly hypnotic use. Protocol outcome: relapse into medication use. follow up: 12 weeks	20 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	RR 0.25 (0.07 to 0.90)	800 per 1,000	600 fewer per 1,000 (744 fewer to 80 fewer)
Sleep latency. Protocol outcome: increase in symptoms for which the medicine was originally prescribed. follow up: 4 weeks	20 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	-	The mean sleep latency score in the control group was 27	The mean sleep latency score in the intervention group was 43 higher (17.29 higher to 68.71 higher)
Sleep latency. Protocol outcome: increase in symptoms for which the medicine was originally prescribed. follow up: 12 weeks	20 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	-	The mean sleep latency score in the control group was 32	The mean sleep latency score in the intervention group was 2 lower (24.39 lower to 20.39 higher)

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Possibly indirect population- no breakdown of drugs was provided.
c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of the intervention and control groups for continuous outcomes). MID for sleep latency was calculated to be 19.

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Table 61: Clinical evidence summary: Melatonin + support + taper compared to placebo + support + taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + support + taper	Risk difference with melatonin + support + taper
Cessation post intervention follow up: 1 months	90 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	RR 0.88 (0.74 to 1.04)	911 per 1,000	109 fewer per 1,000 (237 fewer to 36 more)
Cessation follow up: 6 months	89 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	RR 0.72 (0.42 to 1.23)	444 per 1,000	124 fewer per 1,000 (258 fewer to 102 more)
Cessation follow up: 3 years	83 (1 RCT)	⨁⨁◯◯ LOW [a]	RR 0.84 (0.44 to 1.59)	341 per 1,000	55 fewer per 1,000 (191 fewer to 201 more)
Benzodiazepine usage at 6 months. Protocol outcome: reduction of prescribed drug use	89 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	OR 2.50 (1.12 to 5.58)	Unable to calculate	Unable to calculate
a. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crosses 2 MIDs (0.8 and 1.25 for dichotomous outcomes)					

Table 62: Clinical evidence summary: Prescriber education vs written manual for prescribers

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with written manual	Risk difference with intensive support
Cessation follow up: 0-3 months	19398 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.06 (0.96 to 1.16)	83 per 1,000	5 more per 1,000 (3 fewer to 13 more)
Cessation follow up: 4-6 months	19398 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 0.97 (0.89 to 1.06)	102 per 1,000	3 fewer per 1,000 (11 fewer to 6 more)
50% reduction in benzodiazepine use follow up: 0-3 months	19398 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.06 (0.99 to 1.14)	148 per 1,000	9 more per 1,000 (1 fewer to 21 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with written manual	Risk difference with intensive support
50% reduction in benzodiazepine use follow up: 4-6 months	19398 (1 RCT)	⊕◯◯◯ VERY LOW a,b	RR 0.95 (0.89 to 1.02)	167 per 1,000	8 fewer per 1,000 (18 fewer to 3 more)
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias. b. Downgraded by 1 increment as the population may have been indirect (no breakdown of drugs provided.)					

Table 63: Clinical evidence summary: Structured intervention with follow-up vs usual care

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with follow-up
Cessation of drug follow up: 6 months	364 (1 RCT)	⊕◯◯◯ VERY LOW a,b	RR 2.59 (1.78 to 3.75)	Unable to calculate[e]	Unable to calculate[e]
Cessation of drug follow up: 12 months	364 (1 RCT)	⊕◯◯◯ VERY LOW a,b	RR 3.00 (2.04 to 4.41)	Unable to calculate[e]	Unable to calculate[e]
Cessation of drug follow up: 36 months	364 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	RR 1.59 (1.15 to 2.19)	Unable to calculate[e]	Unable to calculate[e]
Mortality follow up: 36 months	308 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c	RR 0.47 (0.04 to 5.11)	13 per 1,000	7 fewer per 1,000 (13 fewer to 55 more)
Tremor (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⊕◯◯◯ VERY LOW a,b	RR 3.05 (1.49 to 6.23)	53 per 1,000	109 more per 1,000 (26 more to 277 more)
Irritability (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⊕◯◯◯ VERY LOW a,b	RR 2.56 (1.47 to 4.44)	88 per 1,000	138 more per 1,000 (41 more to 304 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with follow-up
Insomnia (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.65 (1.85 to 3.80)	176 per 1,000	291 more per 1,000 (150 more to 494 more)
Anxiety (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 3.13 (2.02 to 4.86)	124 per 1,000	263 more per 1,000 (126 more to 477 more)
Convulsions (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 2.74 (0.29 to 26.11)	6 per 1,000	10 more per 1,000 (4 fewer to 148 more)
Tremor (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	348 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	RR 1.05 (0.49 to 2.29)	67 per 1,000	3 more per 1,000 (34 fewer to 87 more)
Irritability (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	348 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.16 (0.67 to 2.00)	122 per 1,000	20 more per 1,000 (40 fewer to 122 more)
Insomnia (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	348 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.25 (0.92 to 1.71)	287 per 1,000	72 more per 1,000 (23 fewer to 203 more)
Anxiety (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	348 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.30 (0.88 to 1.91)	201 per 1,000	60 more per 1,000 (24 fewer to 183 more)
Convulsions (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	348 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) [d]
Attempted suicide. Protocol outcome: self-harm or harm to others follow up: 12 months	340 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) [d]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing benzodiazepines.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with follow-up
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed 2 MIDs (0.8 and 1.25 for dichotomous outcomes). d. Calculated from risk difference due to zero events in both arms. e. Unable to calculate control group risk and absolute effect as adjusted risks reported by the study.					

1 **Table 64: Clinical evidence summary: Structured intervention with written instructions vs usual care**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with written instructions
Cessation of drug follow up: 6 months	341 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.97 (2.09 to 4.23)	Unable to calculate[f]	Unable to calculate[f]
Cessation of drug follow up: 12 months	341 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 3.01 (2.03 to 4.45)	Unable to calculate[f]	Unable to calculate[f]
Cessation of drug at 36 months follow up: 36 months	341 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.51 (1.11 to 2.06)	Unable to calculate[f]	Unable to calculate[f]
Mortality follow up: 36 months	294 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.06 (0.38 to 11.05)	13 per 1,000	14 more per 1,000 (8 fewer to 135 more)
Tremor(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	329 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 2.14 (0.99 to 4.62)	53 per 1,000	60 more per 1,000 (1 fewer to 192 more)
Irritability(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	329 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.99 (1.73 to 5.18)	88 per 1,000	176 more per 1,000 (64 more to 369 more)
Insomnia (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	329 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 2.96 (2.07 to 4.23)	176 per 1,000	346 more per 1,000 (189 more to 570 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with written instructions
Anxiety (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	329 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	RR 3.26 (2.09 to 5.07)	124 per 1,000	279 more per 1,000 (135 more to 503 more)
Convulsions (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	329 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.07 (0.07 to 16.95)	6 per 1,000	0 fewer per 1,000 (5 fewer to 94 more)
Tremor (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	323 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.03 (0.46 to 2.31)	67 per 1,000	2 more per 1,000 (36 fewer to 88 more)
Irritability (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	323 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.19 (0.68 to 2.07)	122 per 1,000	23 more per 1,000 (39 fewer to 130 more)
Insomnia (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	323 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.16 (0.84 to 1.61)	287 per 1,000	46 more per 1,000 (46 fewer to 175 more)
Anxiety (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	323 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	RR 1.47 (1.00 to 2.17)	201 per 1,000	95 more per 1,000 (0 fewer to 235 more)
Convulsions(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	323 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) [d]
Attempted suicide. Protocol outcome: self-harm or harm to others Follow up: 12 months	317 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	Peto OR 7.53 (0.15 to 379.64)	0 per 1,000	10 more per 1,000 (10 fewer to 20 more) [e]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing benzodiazepines.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed 2 MIDs (0.8 and 1.25 for dichotomous outcomes).
d. Calculated from risk difference due to zero events in both arms.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with Structured intervention with written instructions
e. Calculated from risk difference due to zero events in the control arm f. Unable to calculate control group risk and absolute effect as adjusted risks reported by the study.					

1 **Table 65: Clinical evidence summary: Structured intervention with follow-up vs structured intervention with written instructions**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Structured intervention with written instructions	Risk difference with Structured intervention with follow-up visits
Cessation of drug follow up: 6 months	359 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.87 (0.67 to 1.12)	429 per 1,000	56 fewer per 1,000 (141 fewer to 51 more)
Cessation of drug follow up: 12 months	364 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	RR 1.00 (0.98 to 1.02)	Unable to calculate[f]	Unable to calculate[f]
Cessation of drug follow up: 36 months	359 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.05 (0.82 to 1.36)	393 per 1,000	20 more per 1,000 (71 fewer to 141 more)
Mortality follow up: 36 months	304 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.23 (0.03 to 2.02)	28 per 1,000	21 fewer per 1,000 (27 fewer to 28 more)
Tremor (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	345 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.42 (0.83 to 2.46)	113 per 1,000	48 more per 1,000 (19 fewer to 165 more)
Irritability(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	345 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.85 (0.59 to 1.24)	264 per 1,000	40 fewer per 1,000 (108 fewer to 63 more)
Insomnia (mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	345 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.90 (0.72 to 1.11)	522 per 1,000	52 fewer per 1,000 (146 fewer to 57 more)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Structured intervention with written instructions	Risk difference with Structured intervention with follow-up visits
Anxiety(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	345 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.96 (0.74 to 1.25)	403 per 1,000	16 fewer per 1,000 (105 fewer to 101 more)
Convulsions(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 6 months	356 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 2.74 (0.29 to 26.11)	6 per 1,000	10 more per 1,000 (4 fewer to 148 more)
Tremor(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	343 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.02 (0.47 to 2.22)	69 per 1,000	1 more per 1,000 (37 fewer to 84 more)
Irritability(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	343 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.98 (0.58 to 1.64)	145 per 1,000	3 fewer per 1,000 (61 fewer to 93 more)
Insomnia(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	343 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.08 (0.80 to 1.44)	333 per 1,000	27 more per 1,000 (67 fewer to 147 more)
Anxiety(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	343 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 0.88 (0.63 to 1.24)	296 per 1,000	35 fewer per 1,000 (109 fewer to 71 more)
Convulsions(mild/moderate/severe). Protocol outcome: withdrawal symptoms follow up: 12 months	343 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	not estimable	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more)[d]
Attempted suicide. Protocol outcome: self-harm or harm to others Follow- up: 12 months	337 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Peto OR 0.12 (0.00 to 5.95)	6 per 1,000	10 fewer per 1,000 (from 20 fewer to 10 more)[e]

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing benzodiazepines.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Structured intervention with written instructions	Risk difference with Structured intervention with follow-up visits
c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5* median baseline SDs of the intervention and control groups for continuous outcomes). d. Calculated from risk difference due to zero events in both arms. e. Calculated from risk difference due to zero events in the intervention arm f. Unable to calculate control group rate absolute effect as adjusted risks reported by the study.					

1 **Table 66: Clinical evidence summary: Motivational interviewing vs information booklet**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with information booklet	Risk difference with motivational interview
Mortality follow up: 3 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	Peto OR 0.15 (0.00 to 7.69)	16 per 1,000	20 fewer per 1,000 (from 60 fewer to 30 more)[d]
Cessation follow up: 3 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.88 (0.73 to 4.83)	97 per 1,000	85 more per 1,000 (26 fewer to 371 more)
Reduction>25% follow up: 3 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	RR 1.56 (1.01 to 2.39)	339 per 1,000	190 more per 1,000 (3 more to 471 more)
Mean defined daily dosage difference Protocol outcome: reduction of prescribed drug use follow up: 3 months	117 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	-	The mean defined daily dosage difference in the control group was 0.12	The mean defined daily dosage difference in the intervention group was 0.3 higher (0.49 lower to 1.09 higher)
a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias. b. Downgraded by 2 increments as the population may have been indirect (no breakdown of drugs provided) and the comparison group was indirect (no specific aim to decrease medication in the control group).					

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with information booklet	Risk difference with motivational interview
c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of the intervention and control groups for continuous outcomes). MID for daily dosage difference was calculated to be 1.18 d. Calculated from risk difference due to zero events in the intervention arm.					

Table 67: Clinical evidence summary: Electroacupuncture+ taper vs sham acupuncture+ taper

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham acupuncture	Risk difference with electroacupuncture
Cessation of drug assessed with: 14-day prospective daily record follow up: 6 weeks	144 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	OR 1.03 (0.26 to 4.06)	Unable to calculate[c]	Unable to calculate[c]
Cessation at 16 weeks assessed with: with 14-day prospective daily record follow up: 16 weeks	144 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	OR 0.87 (0.29 to 2.61)	Unable to calculate[c]	Unable to calculate[c]
Equivalent dose of usage in diazepam mg/d follow up: 6 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean equivalent dose of usage in diazepam mg/d was 4.9	MD 0.06 lower (0.37 lower to 0.25 higher)
Equivalent dose of usage in diazepam mg/d follow up: 16 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean equivalent dose of usage in diazepam mg/d was 5.0	MD 0.1 lower (0.4 lower to 0.2 higher)
Withdrawal symptoms (BWSQ) assessed with: Benzodiazepine Withdrawal Symptom Questionnaire Scale from: 0 to 40 follow up: 6 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean BWSQ in the control group was 4.5	MD 0.21 higher (0.1 lower to 0.52 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham acupuncture	Risk difference with electroacupuncture
Withdrawal Symptoms (BWSQ) assessed with: Benzodiazepine Withdrawal symptom Questionnaire Scale from: 0 to 40 follow up: 16 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean BWSQ in the control group was 5.8	MD 0.11 higher (0.21 lower to 0.43 higher)
Insomnia (ISI) Protocol outcome: withdrawal symptoms assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 6 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean Insomnia Severity Scale in the control group was 11.2	MD 0.04 higher (0.29 lower to 0.37 higher)
Insomnia (ISI) Protocol outcome: withdrawal symptoms assessed with: Insomnia Severity Index Scale from: 0 to 28 follow up: 16 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean Insomnia Severity Scale in the control group was 10.5	MD 0.06 lower (0.3 lower to 0.18 higher)
Anxiety (HADS anxiety) Protocol outcome: withdrawal symptoms assessed with: Hospital Anxiety and Depression Scale- Anxiety subset Scale from: 0 to 21 follow up: 6 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean HADS anxiety in the control group was 3.7	MD 0.03 lower (0.45 lower to 0.39 higher)
Anxiety (HADS anxiety) Protocol outcome: withdrawal symptoms assessed with: Hospital Anxiety and Depression Scale- anxiety subset Scale from: 0 to 21 follow up: 16 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean HADS anxiety in the control group was 4.3	MD 0.09 higher (0.28 lower to 0.46 higher)
Depression (HADS depression) Protocol outcome: withdrawal symptoms assessed with: Hospital Anxiety and Depression Scale- depression subset	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean HADS depression in the control group was 3.7	MD 0.06 higher (0.22 lower to 0.34 higher)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham acupuncture	Risk difference with electroacupuncture
Scale from: 0 to 21 follow up: 6 weeks					
Depression (HADS depression) Protocol outcome: withdrawal symptoms assessed with: Hospital Anxiety and Depression Scale- depression subset Scale from: 0 to 21 follow up: 16 weeks	144 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-	The mean HADS depression in the control group was 4.5	MD 0.14 higher (0.18 lower to 0.46 higher)
a. Downgraded as the population may have been indirect (no breakdown of drugs provided) b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of the intervention and control groups). MID for the equivalent dose of usage was 4.46, 2.55 for BWSQ, 2.55 for ISI, 1.27 for HADS anxiety, and HADS depression c. Unable to calculate control group rate and absolute effect as adjusted risks reported by the study.					

See full GRADE tables in Appendix G, section G.5.

1.6.4 Economic evidence

1.6.4.1 Included studies

No health economic studies on mixed medicines were included.

1.6.4.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix D.

1.6.5 Summary of included economic evidence

None.

1.6.6 Economic model

This area was not prioritised for a new cost-effectiveness analysis.

1.6.7 Evidence statements

1.6.7.1 Economic

- No relevant economic evaluations were identified.

1.7 The committee's discussion and interpretation of the evidence

1.7.1 The outcomes that matter most

The critical outcomes for this review were health-related quality of life, cessation/reduction of the prescribed medicine, withdrawal symptoms, and mortality. A more effective intervention or strategy will result in more people discontinuing their prescribed medicine. However, reduction in the prescribed medicine was also agreed as an outcome that needed to be considered, as for people on very high initial doses of prescribed medicines, a reduction to safer levels is also a positive outcome. The importance of considering cessation/reduction of the prescribed medicine in context with other outcomes such as withdrawal symptoms was highlighted. This is because, a concurrent intervention to aid withdrawal may encourage people to adhere to a tapering schedule, even if the schedule is too quick for the individual. Therefore, even if an intervention is effective in increasing the number of people discontinuing their medication, if there is an unacceptable negative impact due to more withdrawal symptoms being experienced from a taper that was too fast, this must be taken into account. The committee highlighted that it is important to assess quality of life. It was noted that withdrawal could be initially unpleasant for the individual and result in a short-term negative impact on quality of life. However, in the longer term, it may be beneficial for the person to discontinue a medicine associated with dependence. Longer-term follow-up of quality of life will therefore be more representative of the effectiveness of the withdrawal intervention.

Important outcomes for this review were agreed as: relapse into medication use, use of illicit drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose, reduced tolerance, patient satisfaction, self-harm or harm to others, symptoms for which the medication was originally prescribed, and distress.

Evidence was identified in people prescribed opioids, benzodiazepines, z-drugs, antidepressants, or in a mixed stratum for studies with no breakdown of results according to medicine. No evidence was identified in people prescribed gabapentinoids.

1.7.1.1 Opioids

For opioids, the critical outcome reduction/cessation of prescribed drugs was reported for all comparisons. Critical outcomes of health-related quality of life and withdrawal symptoms were also reported for some comparisons. Reduction/cessation of prescribed drugs corresponded to study outcomes of discontinuation, mean daily dose in the past week or opioid consumption at the end of treatment and/or follow-up, and dose reduction of 50% or more. Withdrawal symptoms were reported as overall severity of withdrawal symptoms, not specific or individual symptoms.

Important outcomes were, use of illicit or over-the-counter drugs or alcohol as a replacement to prescribed drugs, an increase in symptoms for which the medication was originally prescribed, and improvements in adverse effects commonly associated with long-term prescribed substance use. Increase in symptoms for which the medication was originally prescribed corresponded to study outcomes of pain severity or intensity of the highest pain, the intensity of the average pain or pain duration. Improvements in adverse effects commonly associated with long-term prescribed medication use were reported in the studies as insomnia severity, the number of opioid medication-related adverse events and severity of opioid medication-related adverse events.

No evidence was identified for mortality, relapse into medication use, non-fatal overdose, reduced tolerance, patient satisfaction, self-harm or harm to others, or distress.

1.7.1.2 Benzodiazepines

For benzodiazepines, the critical outcome of reduction/cessation of prescribed drugs was reported for all comparisons with the exception of 2: valproate substitution plus taper versus taper alone, and patient advice, education, and support plus gradual withdrawal versus patient advice, education, and support plus abrupt withdrawal. The critical outcomes of health-related quality of life, mortality and withdrawal symptoms were reported for some comparisons. Reduction/cessation of prescribed drugs corresponded to study outcomes of discontinuation, mean dose, dose reduction of 50% or more, reduction in benzodiazepines, weekly use, and 50% reduction in plasma level. Withdrawal symptoms were reported as both the overall severity of withdrawal symptoms and specific/individual symptoms. The individual symptoms were either specified as withdrawal symptoms in the study, or classified as withdrawal symptoms by the reviewer if it was a symptom reported that was not the same as the initial indication in the study (for example, if a study in a population given benzodiazepines for a mixture of indications reported a symptom of anxiety, this was classified in the review as a withdrawal symptom, and not an increase in symptoms for which the medication was originally prescribed).

Important outcomes available were, relapse into medication use, use of illicit or over-the-counter drugs or alcohol as a replacement to prescribed drugs, psychological distress, and increase in symptoms for which the medication was originally prescribed. For the latter, this was classified by the reviewer if, for example, insomnia was reported in a study where the original population was people taking benzodiazepines for insomnia.

No evidence was identified for: non-fatal overdose, reduced tolerance, patient satisfaction, self-harm or harm to others, or adverse effects commonly associated with prescribed medication use.

1.7.1.3 Z-drugs

For Z-drugs, the critical outcomes of reduction/cessation of prescribed drugs and withdrawal symptoms were reported only for the comparison of acupuncture versus CBT. Withdrawal symptoms were reported as the individual symptoms of anxiety and depression. These were classified as withdrawal symptoms by the reviewer, as the original indication of the population for taking z-drugs was for insomnia.

The only important outcome reported was symptoms for which the medication was originally prescribed. This outcome was insomnia severity, and was therefore classified as this protocol outcome as the original indication of the population for taking Z-drugs was for insomnia.

No evidence was identified for: health-related quality of life, mortality, relapse into medication use, use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose, reduced tolerance, patient satisfaction, self-harm or harm to others, adverse effects commonly associated with prescribed medication use or distress.

1.7.1.4 Mixed medicines

For mixed medicines, the critical outcomes of reduction/cessation of prescribed drugs, health-related quality of life, mortality, and withdrawal symptoms were reported for some comparisons. Withdrawal symptoms were reported as both the overall severity of withdrawal symptoms and specific/individual symptoms. Important outcomes reported were, the increase in symptoms for which the medication was originally prescribed, relapse into medication use, and self-harm or harm to others.

No evidence was identified for use of illicit or over-the-counter drugs or alcohol as a replacement for prescribed drugs, non-fatal overdose, reduced tolerance, patient satisfaction, adverse effects commonly associated with prescribed medication use or distress.

1.7.1.5 Antidepressants

For antidepressants, the critical outcomes of reduction/cessation of prescribed drugs, mortality/suicide, and withdrawal symptoms were reported for some of the comparisons. Withdrawal symptoms were reported as both the overall severity of withdrawal symptoms and specific/individual symptoms.

Important outcomes reported were, an increase in symptoms for which the medication was originally prescribed, self-harm or harm to others, patient satisfaction, and relapse into medication use.

No evidence was identified for health-related quality of life, use of illicit or over-the-counter drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose,

reduced tolerance, adverse effects commonly associated with prescribed medication use or distress.

1.7.2 The quality of the evidence

A number of comparisons were identified throughout the review with a control arm of 'usual care'. These studies provided little detail on the composition of 'usual care', and whether an attempt was made to withdraw prescribed medicines in this group. Studies comparing interventions to usual care providing an unclear description on the composition of usual care were included and downgraded for indirectness, as per the protocol. These were not excluded, as medicines associated with dependence are widely recommended to be used for short-term use only, so the assumption was made that usual care may constitute a certain amount of deprescribing. If it was clear from the study that there was not an attempt to withdraw medicines in either arm, for example, if a study stated that people were continued on their medication, then the study was excluded.

1.7.2.1 Opioids

The majority of the evidence across all comparisons was of low or very low quality due to risk of bias for all outcomes, and also due to imprecision lowering confidence in the effect estimate for the majority of outcomes. Evidence was downgraded due to risk of bias for various reasons, including selection bias, lack of blinding, incomplete outcome reporting (missing data), and outcome reporting (e.g., the outcome reported incompletely or as a P value only). Multicomponent taper support plus taper program versus usual prescribing was also downgraded for indirectness for all outcomes. This was due to the control group receiving opioid prescriptions from their usual prescribers, with no specific aim to taper. However, this was not a completely inactive control, as, at the screening visit, both intervention and control arms were shown a 14-minute video of interviews with people who have successfully tapered off opioids concerning what they had gained from this.

There were a few exceptions where evidence was of moderate quality due to only being downgraded for risk of bias and not imprecision. This included the outcomes of opioid consumption and non-opioid medication dosage, for electroacupuncture plus taper versus sham electroacupuncture plus taper. One of these studies was a 3-arm trial and also compared both the electroacupuncture and sham arms to taper as part of a pain medication management (PMM). The majority of evidence from these comparisons was also of moderate quality. For the comparisons versus PMM, outcomes were only extracted post-intervention, as participants in this group were given the opportunity to receive electroacupuncture during the follow-up period.

1.7.2.2 Benzodiazepines

The majority of evidence across all comparisons was of low to very low quality due to risk of bias and imprecision. The main reasons for downgrading for risk of bias were selection bias, blinding, and incomplete outcome reporting. Alongside this, a number of outcomes were downgraded for either population or comparison indirectness. A number of the included studies described an indirect population for whom the specific benzodiazepine used was not reported. The review protocol excluded people taking 'non-NHS prescribed medicines' and set to include only those taking one of the benzodiazepines from a setlist (so long as >80% of people were using a benzodiazepine from this list). The committee considered that the inclusion of studies not reporting the specific benzodiazepine being used by included participants could lead to results that were not generalisable to the UK setting and may impact the

effectiveness of interventions to safely withdraw from the prescribed benzodiazepine. A number of studies also included an indirect comparison of participants who were randomised to continue receiving usual care.

There were a few exceptions where evidence was of moderate quality, this included evidence for cessation of benzodiazepines with CBT and taper versus taper alone and a number of outcomes in studies of patient information alongside taper. The evidence for patient information reported moderate-quality evidence for a reduction in benzodiazepine use, and relapse into medication use for the comparisons of psychological intervention, education and training with tapered withdrawal versus psychological intervention, education and advice with tapered withdrawal, for benzodiazepine dose with patient advice and information versus usual care and for the comparison of brief advice, education, and support versus usual care. One study compared patient advice, education and support, with a gradual withdrawal to the same intervention with an abrupt withdrawal. The only reported outcome of relapse into medication use was of moderate quality.

Evidence for benzodiazepine dose was of high quality for the comparison of patient advice and information versus patient advice.

1.7.2.3 Z-drugs

One comparison was identified for Z-drugs, comparing acupuncture to CBT, with both interventions being performed in a group setting. People in both arms of the trial were asked to discontinue their medication 3-5 days prior to the acupuncture or CBT intervention, but there are no details of whether any instruction on tapering or abrupt discontinuation were given. All the outcomes were of low quality due to imprecision and risk of bias, with the exception of insomnia (symptoms for which the medication was originally prescribed) outcome at the post-intervention time point, which was moderate quality. The main reasons for downgrading due to risk of bias were blinding and incomplete outcome reporting.

1.7.2.4 Mixed medicines

The quality of evidence was very low for all the outcomes for a number of comparisons: mindfulness-based relapse prevention plus psychoeducation group session plus individualised guidance on gradual voluntary withdrawal versus a psychoeducation group session plus individualised guidance on gradual voluntary withdrawal, patient advice and relaxation versus usual care, prescriber education versus a written manual for prescribers, structured intervention with follow-up visits versus structured education with written instructions (and both of these interventions versus usual care), and motivational interviewing versus an information booklet. Most of the evidence was downgraded due to risk of bias and imprecision, however, comparisons comparing to a control group of usual care were also downgraded for indirectness, due to the composition of ‘usual care’ being unclear as to whether withdrawal was attempted. The evidence for the mindfulness-based relapse prevention intervention was downgraded for population indirectness due to it being unclear which benzodiazepines the population were taking, and whether these were included in the guideline medicines list.

The quality of evidence for the comparison of CBT plus a taper versus taper alone was predominantly of low and very low quality, mainly due to risk of bias and imprecision. This was with the exception of the outcomes of daily dose (reduction in medication use) and depression (withdrawal symptoms), which were not downgraded for imprecision and were of moderate quality. Some outcomes were also

downgraded for indirectness because the specific benzodiazepine taken by the study population was unclear.

For melatonin, support and taper versus placebo, support and taper, the evidence was of moderate quality for cessation of medication at 1 and 6 months, but of low quality for this outcome at 3 years follow-up.

For electroacupuncture plus taper versus sham acupuncture plus taper, the evidence was of very low quality for the cessation of medication outcomes, but of moderate quality for reduction of medication and for all the withdrawal symptoms outcomes.

1.7.2.5 Antidepressants

The majority of evidence across all comparisons was of low to very low quality due to risk of bias and imprecision. The main reasons for downgrading for risk of bias were selection bias, blinding, and incomplete outcome reporting. Alongside this, some outcomes were downgraded for comparison indirectness, as in the usual care group it was unclear if there was an intention to withdraw antidepressants. One comparison of a 14-day taper versus a 3-day taper was downgraded for population indirectness as people were discontinuing antidepressants in order to switch to another antidepressant.

There were a few exceptions where evidence was of moderate quality, this included evidence for: antidepressant cessation and symptoms for which the medication was originally prescribed, for the comparison of a 1-week taper versus abrupt discontinuation; and 2 of the withdrawal symptoms outcomes (headaches and increased dreaming/nightmares) for the comparison of desvenlafaxine 50mg for 7 days followed by placebo for 7 days versus abrupt discontinuation.

1.7.3 Benefits and harms

Evidence was identified in people prescribed opioids, benzodiazepines, z-drugs, antidepressants, and in people receiving a variety of these medicines from studies with no breakdown of results. No evidence was identified in people prescribed gabapentinoids.

The committee noted that some comparisons were compared to a control arm of ‘usual care’ and that the included studies provided little or no detail on the composition of ‘usual care’. The committee discussed the limitations of the usual care comparisons included, specifically that, just because people are on medicines for which long-term use is not advised, this does not always mean people will be discontinued from the medicines if left to usual care. Therefore, usual care could encompass anything from ‘little or no intervention to support withdrawal’ to ‘a comprehensive support for withdrawing from the prescribed medicine’. As such, the committee agreed that studies comparing interventions to a usual care arm with an unclear description on the composition of usual care were not as helpful as comparisons where there was an aim of withdrawal in the control group. It was agreed that, if the usual care arm continued on their prescribed medicines, it was not a meaningful comparison in order to assess the effectiveness of withdrawal interventions. The committee cited this lack of clarity as a significant issue when reviewing the evidence available and was unable to base any firm conclusions on the comparisons of interventions to usual care, as discussed below.

For the majority of comparisons identified in the review, the evidence could not be pooled, and therefore the committee’s interpretation of the effectiveness of interventions was based on single studies and their consensus. Issues relating to

comparisons available within the review relevant to each drug class is discussed in more detail below.

1.7.3.1 Opioids

Varenicline plus Interdisciplinary Treatment Program (ITP)versus Placebo plus ITP

Evidence from 1 study suggested there was a clinically important benefit of varenicline combined with a taper program compared to placebo combined with the taper program, in terms of withdrawal symptoms following the intervention, but there was uncertainty around the effect. There was also no clinically important difference between the intervention and control in the number of people who discontinued opioid use, and there was no evidence for any of the other protocol outcomes. The committee discussed that the evidence for use of varenicline with a taper program for withdrawal of opioids, was very limited, with only very low-quality evidence from one outcome showing a clinical benefit. They also noted that varenicline is being used off-license in this context and so would require good evidence on which to base a recommendation. The committee, therefore, agreed there was insufficient evidence to inform a recommendation in this case.

Acupuncture plus standard outpatient medication management with opioid weaning versus standard outpatient medication management with opioid weaning

One study assessed the effectiveness of an additional acupuncture intervention given alongside the standard medication management with opioid weaning. There was a clinically important benefit of acupuncture on the morphine equivalent dose (MED) post-intervention. However, the difference in dose at baseline was highlighted as a factor contributing to the risk of bias for this outcome and therefore the committee agreed that this wasn't a reliable result to inform decision making. There was a potential clinical benefit of acupuncture on pain, although this was borderline and no clinically important difference was observed between groups for withdrawal symptoms.

It was noted that completion of opioid weaning in the study was determined by reducing MED to below 90mg and individual functionality as determined by the treating provider, rather than aiming for complete withdrawal. The study reported that not everyone completely ceased opioid use, but the number of people ceasing opioids was not reported. It was also noted that as part of the standard medication management, both groups could be given adjuvant non-opioid medicines (such as antidepressants or NSAIDs) and other therapies (such as non-pharmacological therapies). The number of people receiving these adjuvant therapies in each group was not reported, but the committee noted this could influence the effectiveness if this was unbalanced between the groups. The committee discussed these concerns, contributing to the low and very low quality of this evidence, as well as the small number of participants in the study. Due to the low quality of the evidence and the fact that the outcome of cessation of opioids was not reported, the committee agreed there was insufficient evidence to make a recommendation for acupuncture to aid withdrawal from opioids.

However, the committee raised that acupuncture has been used for the management of dependence on illicit substances in addiction services for some time, but recent evidence (not relevant to this review protocol) has meant it is no longer used by some services. The committee was aware of anecdotal evidence to support the use of acupuncture for dependence. Due to the limited evidence available here and use

in substance misuse settings, the committee agreed further research would be beneficial to determine whether the potential benefits of acupuncture in people with illicit drug use would translate to people withdrawing from prescribed opioids. Therefore, they made a recommendation for future research into the effectiveness of acupuncture to aid withdrawal from opioids in this population.

Multicomponent taper support with taper for opioid withdrawal versus usual prescribing

As described above, comparisons to usual care, where there was uncertainty about how much deprescribing would occur in the usual care arm, were difficult to interpret and therefore did not inform recommendations. For this comparison, although the control arm was usual prescribing, both arms were shown a video of people who had successfully tapered off opioids and what they had gained from this. This could be considered an intervention in the control group that may influence the decision to withdraw from opioids. The committee, therefore, considered this evidence to have more credibility than some of the other comparisons to usual care alone.

The evidence from 1 study suggested there was a clinically important benefit of the multicomponent taper support intervention combined with a taper program compared to usual prescribing for quality of life and opioid dose reduction of 50% or more at 22 weeks (intervention completion). Both of these benefits were maintained at 34 weeks, where a benefit in pain severity was also observed. However, there was considerable uncertainty around these effects due to imprecision. No clinically important difference between groups was found for opioid discontinuation and mean daily opioid dose in the past week at 22 and 34 weeks, pain severity at 22 weeks, and insomnia severity at 22 and 34 weeks.

The mean (between group) difference in daily opioid dose in the past week at 22 weeks was 42.9 mg, with a lower mean dose in the intervention arm. The committee discussed whether this could potentially be considered clinically important. However, it was noted that the starting opioid dose was high for both groups and that the mean difference in opioid dose noted at 22 weeks corresponded to only a 20% reduction from baseline. The committee agreed that this would not reflect a reduction to a safe dose in this population and that the reduction did not appear to be sustained at 34 weeks. The committee also noted that the lower pain severity score observed at 34 weeks with the multicomponent taper support intervention combined with a taper program, which was deemed clinically important, could be attributed to the aforementioned increase in the mean daily opioid dose in the past week at 34 weeks compared to 22 weeks (i.e., to the lack of maintenance of the dose reduction noted at 22 weeks), with a higher opioid dose lowering the pain experienced.

No clinically important difference was found for opioid discontinuation, but there was a clinically important benefit of the multicomponent taper support intervention combined with a taper program for opioid dose reduction of 50% or more. The committee discussed that a dose reduction to a safer level in people who have been on high opioid doses for a long time can often be the initial aim, as opposed to a complete discontinuation, so this observation may be important.

The committee noted that, despite the absence of a clinically important effect in some outcomes, results appeared to be in a helpful direction favouring the multicomponent taper support intervention combined with a taper program. Furthermore, the committee noted that the fact that the evidence showed no increase in pain scores with the taper intervention (at 22 weeks, when a large opioid dose reduction was also noted with the intervention) supports the effectiveness of the multicomponent taper

support intervention. Nevertheless, they noted that pain reduction may not be as indicative of withdrawal as often, factors other than pain, drive opioid use.

Looking at the multicomponent taper support intervention offered in the contributing study in detail, the committee noted that it was an intensive intervention with many components and had a strong focus on CBT. Aspects of the intervention which aimed to reduce chronic pain appeared to involve alternative methods of pain management, as participants were also given antidepressants (tricyclics and SSRIs). That, along with the multiplicity of its components, complicated the evaluation of the interventions' effectiveness and any conclusions regarding which intervention components clinical effectiveness could be attributed to. The committee raised that in their experience the intervention did resemble the way pain is currently managed in primary care, with support being provided while pharmacology is being reduced.

It was also noted that the acceptability of the intervention may have been low, with the study only recruiting 35 people over 3 years. This can be typical for this population, as many people believe that the medication is helpful for their pain and are fearful of reducing medication due to withdrawal symptoms or re-emergence of pain. Therefore, without effective education first, people may want to stay on their medication. It was also discussed that people can have multiple physical and mental health conditions. For these reasons, the committee also agreed that a multifaceted approach is often required in this population, involving targeting behavioural changes and it is not as simple as just reducing the person's dose.

Although evidence of clinical effectiveness of the multicomponent taper support intervention had limitations, as discussed above, the committee agreed a combined approach involving tapering and multicomponent support appears promising. However, the committee agreed there was not sufficient evidence on which to base recommendations. In order for withdrawal to be achieved, the committee agreed that more than one intervention may be required. The committee agreed that it would be useful to have more evidence on the key components of an effective multicomponent intervention to support withdrawal of opioids, and therefore a recommendation for future research was made.

Electroacupuncture plus taper, sham electroacupuncture plus taper or taper

Two studies compared electroacupuncture plus a taper versus sham acupuncture plus a taper. For one of these studies, the taper was in the form of an opioid reduction schedule alone. For the other study, the taper was part of pain medication management (PMM), consisting of education and an opioid medication reduction schedule. However, for each study, the taper was the same in both arms, and therefore the comparison is of electroacupuncture versus sham acupuncture.

The evidence suggested there was a clinically important benefit of electroacupuncture compared to sham electroacupuncture for two quality of life domains on the SF-36: general health and mental health. However, there was considerable uncertainty about these effects due to serious imprecision in the effect estimates. No clinically important difference was found between the two groups in: quality of life assessed as physical health, opioid consumption (mg/week) post-intervention or at 12-week follow-up, the number of people with 50% opioid medication reduction at the end of treatment, non-opioid medication dosage, the intensity of the highest pain, average pain, duration of pain (hr/day), weekly opioid medication-related adverse events per person and severity of opioid medication-related adverse events.

Evidence from one of these studies compared electroacupuncture plus PMM, and sham electroacupuncture plus PMM to PMM alone. Both of these comparisons

demonstrated some benefit of electroacupuncture and sham electroacupuncture for quality of life, but not for the other outcomes reported.

Despite the absence of a clinically important effect in the majority of outcomes, the committee noted that results appeared to favour the electroacupuncture intervention. The committee noted that there were baseline differences in opioid dose between the groups that could impact the interpretation of results. Baseline doses were higher in the intervention arm, which could potentially obscure an important benefit foropioid dose post-intervention. It was also noted that the additional patient contact time and the tactile component of both the electroacupuncture and sham acupuncture arms may be having some benefit and that there may be some benefit also observed in the sham arm from the non-specific treatment effects. The committee agreed that with the evidence supporting the effectiveness of electroacupuncture being very limited and of very low quality, they could not make a recommendation for its use. However, as described above, the committee was interested in whether the benefit of acupuncture sometimes seen in the treatment of people dependent on illicit opioids, would extend to withdrawal of prescribed opioids. Therefore, a recommendation for future research on the effectiveness of acupuncture for withdrawal of opioids was made. The committee agreed that this research recommendation should include electroacupuncture.

The committee also noted that across comparisons there was a reduction in opioid consumption with PMM alone. Looking at the components of PMM, which involved the provision of pain management information, an individualised opioid medication reduction schedule, and follow-up telephone calls, the committee agreed based on their clinical experience that similar taper interventions are offered in current practice. The committee noted the multiplicity of PMM and how it was difficult to pinpoint the active components that contribute to dose reduction. They agreed that in order to be able to recommend PMM they needed to know the method by which dose reduction was achieved. They agreed that this evidence again reiterated the importance of further research into multicomponent interventions.

1.7.3.2 Benzodiazepines

CBT

CBT plus tapered withdrawal versus CBT plus abrupt withdrawal

Evidence from 2 studies suggested that providing CBT and an abrupt withdrawal programme resulted in a clinically important benefit on cessation of benzodiazepines at both post-intervention and 12-month follow-up, relative to providing CBT alongside a tapered withdrawal programme. No clinically important difference was found between the intervention and comparison groups in the number of people achieving reduced benzodiazepine use at post-intervention, as measured by a >50% reduction in benzodiazepine plasma level, however, CBT plus a taper showed a clinically important benefit for this outcome at 12-month follow-up when compared to CBT with abrupt withdrawal.

The evidence also suggested that those receiving a tapered withdrawal had both fewer and less severe withdrawal symptoms at post-intervention, and were less likely to have relapsed into taking benzodiazepine medication. These outcomes all demonstrated a clinically important benefit of CBT and a tapered withdrawal relative to CBT and an abrupt withdrawal.

As both groups received the CBT intervention, this provides evidence for the comparison of abrupt versus tapered withdrawal when alongside CBT, but does not assess the effectiveness of CBT in isolation. The committee noted that the evidence

provided for this comparison was from a single RCT with a small dataset (of~40 participants) and evidence was of very low quality and so was unable to base any recommendations on the evidence alone. However, the committee agreed by consensus that benzodiazepines should not be abruptly withdrawn due to a risk of withdrawal-associated seizures and delirium tremens.

CBT plus tapered withdrawal versus tapered withdrawal

Evidence suggested that group CBT provided alongside a tapered withdrawal programme provided a clinically important benefit for quality of life at 18 months compared to receiving a tapered withdrawal alone. The committee noted this benefit but highlighted that a change in quality of life would need to be considered within the context of medical management and benzodiazepine use at that time to ascertain if the change in quality of life was due to maintenance or withdrawal of the prescribed medication. This information was not available at the 18-month follow-up for this study population, but pooled data from 3 trials showed a clinically important benefit of CBT and tapered withdrawal at 12 to 15 months follow-up for the rate of successful cessation of benzodiazepine. Evidence from 1 study also showed a clinically important benefit with CBT combined with a tapered withdrawal in the number of people who had successfully reduced their benzodiazepine use at both post-intervention and 12-month follow-up up. It was highlighted that cessation of benzodiazepines might not always signify a benefit if the person discontinued or reduced their BZs too quickly (for example if a patient on a taper who is also undertaking structured CBT was more likely to adhere to a tapering plan, even if that plan is too quick), which can lead to harm through more severe and longer withdrawal symptoms. However, there was no clinically important difference between groups in the withdrawal symptoms outcome at 3 months. No clinically important difference was found for the outcomes of symptoms for which the medication was originally prescribed at post-intervention or 12 months, relapse into medication use at 24 months, or alcohol use at 3 months, between groups receiving CBT and a tapered withdrawal and those receiving a tapered withdrawal alone.

The committee agreed that the evidence was supportive of group CBT given alongside a taper for the withdrawal of benzodiazepines. Although the majority of this evidence was of low or very low quality, the committee agreed that their experience was that psychological support alongside a withdrawal schedule can be beneficial for many people. They agreed this was an important area to further explore with cost-effectiveness modelling, in order to inform a recommendation.

The committee also discussed that although the evidence indicated a clinical benefit of CBT, CBT may not be a helpful or suitable intervention for everyone, and it may also depend on the type of CBT and the timing that it is offered. It was noted that CBT, along with other psychological interventions, can require the person to do a lot of ‘homework’, and from experience, some people are just not well enough and need to focus on more simple goals. For example, someone who is in the midst of withdrawal may not be in the mindset to cope with a CBT intervention and might not benefit from it at this time. The committee agreed in these instances, as with all recommended approaches, the person should be supported to find a withdrawal intervention or reduction schedule that suits them. The committee discussed that CBT may be more helpful at the start of the withdrawal process, or afterward to prevent returning to medication use. However, there was not sufficient evidence to inform this, and it was agreed that this might be individualised depending on circumstances. Therefore, it was agreed that the recommendation should specify that the timing of the referral for CBT should be agreed with the individual. The committee agreed that the most effective model of CBT was unclear from the evidence, as CBT models from individual studies varied. It was noted this may need to be determined

on an individualised basis according to what is most suitable for the person concerned, however, the committee also made a recommendation for future research to investigate the most effective model of CBT to support withdrawal from benzodiazepines, including the most appropriate timing.

Group CBT plus a tapered withdrawal versus group work plus tapered withdrawal

One study compared group CBT to group work, in which both intervention and comparison groups received the same tapered withdrawal programme. Those receiving CBT had a clinically important benefit in terms of discontinuing benzodiazepines at the end of the intervention compared to those allocated to group work. However, no clinically important difference was found between groups for quality of life at 3 months follow-up. Benefits were also not observed in withdrawal symptoms at either follow up, rate of relapse into medication use at 11 months, psychological distress at post-intervention, or anxiety (for which the medication was originally prescribed) at the end of the intervention. There was a possible clinical benefit of CBT on anxiety at 3 months, but this was only evident for one out of the two anxiety outcomes. There was also a possible clinical benefit of CBT on psychological distress at 3 months.

Although there was a benefit of CBT with taper on the number of people discontinuing their benzodiazepines after the intervention, this outcome was not reported at later follow-up time points. It was highlighted by the committee that people may be more likely to stick to a tapering schedule whilst having an intervention such as CBT, even if the taper is too quick for that individual. Therefore, this outcome alone does not always signify a benefit and it is not clear whether this effect would still have been observed if the information were available from longer follow-up. However, as there was no clinical difference in the outcomes of quality of life or withdrawal symptoms, the committee agreed this suggests that there were no negative consequences of more people discontinuing benzodiazepines in the CBT arm.

In this comparison, CBT was in the form of group sessions over a 20-week period. The CBT arm and the group work arm met at the same regularity and followed the same taper regimens. The principal difference was in the lack of any specific directions for changing thoughts and behaviours or any CBT strategies in the group work arm. The committee considered that this comparison may assess the effectiveness of CBT whilst controlling for any benefit of an additional therapeutic relationship as a result of the group sessions (i.e., to be able to draw conclusions that any difference in outcomes observed is due to the CBT, and not additional contact with healthcare professionals). The committee agreed that this provides a small amount of evidence that CBT is beneficial in helping people withdraw from benzodiazepines, even when controlled for therapeutic contact time. They noted that this, alongside the evidence discussed above, warranted further exploration with a de novo economic model on the use of group CBT to support withdrawal.

CBT plus tapered withdrawal or tapered withdrawal alone versus usual care

The data provided a comparison between CBT alongside a tapered withdrawal to usual care as well as tapered withdrawal alone compared to usual care. The usual care group did not receive any help with benzodiazepine reduction. As noted above, the committee expressed concerns about the inferences that could be made from usual care comparisons where it was not clear whether any encouragement to reduce medicine use was given. The evidence reported mixed results with improvements in quality of life favouring usual care, but cessation of

benzodiazepines was better with CBT and a tapered withdrawal or tapered withdrawal alone at 3 and 15 months. The committee considered that the reduction in quality of life for some domains may have demonstrated an initial negative consequence of successfully discontinuing the prescribed benzodiazepines and that the usual care arm may have had a better quality of life due to the fact that they remained on their medication. It was discussed that withdrawal from benzodiazepines can be unpleasant for some time and people can feel subjectively worse, but in the long term it is better for the person not to be on medication associated with dependence for which they are not deriving any therapeutic benefit. The committee discussed that if there were longer follow-up timepoints of perhaps 3 years or longer, we might see more benefit in people who managed to discontinue the long-term use of medication. The study also reported no clinically important difference between groups for withdrawal symptoms or the number of people using alcohol. Due to the comparison group being usual care, the committee agreed this evidence was less informative for decision making than the CBT comparisons already discussed.

Pharmacological interventions

The committee discussed the evidence from a number of studies comparing pharmacological interventions to support withdrawal from benzodiazepines. The committee highlighted that the evidence available for these comparisons was often from smaller studies and provided low and very low-quality evidence with high levels of uncertainty (imprecision) around the point estimates.

Lorazepam substitution + taper versus diazepam substitution + taper

One study compared lorazepam substitution alongside a tapered withdrawal to diazepam substitution with tapered withdrawal. There was a clinically important benefit of diazepam for the outcomes of mortality (suicide) and cessation of benzodiazepines. The committee noted that there was only a single case of suicide from the small dataset and considered that this would likely have been influenced by factors outside of the allocated intervention. The committee discussed that it is common practice to convert to a benzodiazepine with a longer half-life such as diazepam prior to a taper. This appears to be reflected in the evidence, although evidence was from one small study and was of low quality.

The committee noted that the practice of converting people on benzodiazepines to one with a longer half-life prior to tapering is common. This is because it is considered that benzodiazepines with a longer half-life are likely to have advantages for tapering by allowing better management of the pace of reduction. It can also lead to fewer fluctuations in benzodiazepine levels, and therefore potentially fewer withdrawal symptoms. Withdrawing from short-acting benzodiazepines, such as lorazepam, can be difficult as the withdrawal symptoms can occur very quickly. There are also more options for smaller doses with diazepam pills than with some other benzodiazepines. Converting to diazepam is also often done if people are on more than one benzodiazepine, to convert them to one benzodiazepine prior to tapering. However, it was also mentioned that whenever you switch from one medication to another, you run the risk of new complications with the new medication. The speed of the taper, and the support given were also discussed as potentially being more important considerations than introducing new medications. The committee agreed there was little evidence in the review on the effectiveness of converting to diazepam prior to tapering, with only the one study described above comparing diazepam substitution plus taper to lorazepam substitution plus taper. However, ideally, the comparison needed from the evidence would have been people to be converted to diazepam prior to tapering versus those not converted to diazepam (staying on their

original benzodiazepine) prior to tapering. This comparison was not identified in the evidence. The committee was also mindful of the BNF, the Orange Book, and the Ashton manual, which are all widely used, and recommend converting to diazepam prior to tapering benzodiazepines. This, along with the perceived benefits described above, the widespread practice of converting to a benzodiazepine with a longer half-life and the view that patients favour this method, led to the committee making a recommendation, partially formed by consensus, to consider converting to a longer half-life benzodiazepine prior to tapering. The committee agreed further research was also required, and made a research recommendation, looking at whether converting to a benzodiazepine with a longer half-life is beneficial compared to not converting (staying on the original benzodiazepine).

Other pharmacological intervention comparisons

The following interventions alongside a taper were compared to placebo plus a taper: buspirone, imipramine, dothiepin, and melatonin. Buspirone and imipramine were also compared to each other. Valproate alongside a taper was compared to a taper alone. And finally, propranolol plus an abrupt withdrawal was compared to a taper alone.

For the comparison of buspirone substitution with a tapered withdrawal to imipramine substitution with a tapered withdrawal, one study found clinically important harm with buspirone substitution relative to imipramine for cessation of benzodiazepines. Buspirone with a tapered withdrawal compared to placebo with a tapered withdrawal showed inconsistent directions of effect for cessation of benzodiazepines, with both a benefit and harm of intervention reported at varying time-points (harm at post-intervention and 12 months follow-up and benefit at 3 months follow-up). The committee considered that this was likely due to the small size of the studies. The study also demonstrated clinically important harm with buspirone substitution for withdrawal symptoms of anxiety, insomnia, giddiness, and gastrointestinal symptoms, but a benefit of buspirone for the withdrawal symptom of headache. Evidence from two separate studies reported clinically important benefit for the cessation of benzodiazepines at 3-month follow-up with imipramine and melatonin, but no difference was observed between melatonin and placebo groups at 12-month follow-up. Another study demonstrated placebo to be more effective than dothiepin for cessation of benzodiazepines, but a clinically important benefit of dothiepin for patient satisfaction. For valproate alongside a taper versus a taper alone, no difference was found between groups for withdrawal symptoms or use of illicit drugs. For propranolol plus an abrupt withdrawal versus a taper alone, there was a clinically important benefit of the taper alone for cessation of benzodiazepines and withdrawal symptoms. The committee noted that it is difficult to unpick whether any difference in outcomes would be due to the propranolol or the abrupt/gradual nature of the withdrawal.

The committee discussed that pharmacological interventions in the evidence described above (valproate, buspirone, propranolol, imipramine, dothiepin, and melatonin) were most likely being used with the aim of being an alternative treatment for the underlying condition (for example, anxiety or insomnia). The committee discussed the evidence for these pharmacological interventions and agreed that there was not enough evidence of a benefit for any of the interventions, and for some, there was even a benefit of the control arm. In addition, introducing a new medication comes with a risk of complications or side effects with the new medication. The committee acknowledged that treatment of the underlying condition was out of scope for this guideline, and there may be specific instances where alternative medicine is used appropriately to treat the underlying condition, but the committee agreed there was no evidence here to recommend that these should be

used to aid withdrawal. For valproate, the committee highlighted that there are additional considerations due to the potential harms of the use of this medicine in women of childbearing age. The committee agreed that this, along with the evidence of no difference in outcomes with valproate, warranted a 'do not' recommendation due to potential harms of the drug with no evidence of effect. For buspirone, the committee noted that there was evidence of a benefit for the placebo for cessation of benzodiazepines and the majority of withdrawal symptoms outcomes. This, along with the fact that buspirone can lead to dependence or abuse, and that it would be used off licence for this indication, led to the committee making a 'do not' recommendation for buspirone as well. The committee agreed that this recommendation would only apply to benzodiazepines as these medicines weren't used for withdrawal for the other drug classes.

Information provision

The committee discussed the evidence from a number of studies reviewing the effectiveness of information provision for people withdrawing from benzodiazepine use. Information, education, and support were provided in varying formats, including letters advising participants to withdraw from their prescribed benzodiazepine, self-help booklets, and GP consultations with the provision of information about benzodiazepines and benefits to reduced medication. In most cases, the intervention of information provision was delivered as the sole intervention, however in a small number of cases, information was provided alongside a structured tapering programme or psychological interventions such as visualising withdrawal symptoms, and imagery to address anxiety.

The committee agreed that the majority of the evidence available on information provision, education, and support was from small studies and generally low-quality evidence with high levels of uncertainty (imprecision) around the point estimates.

Evidence from one study compared the efficacy of a standard letter used to inform people about benzodiazepines and tailored letters designed to increase the participants' perceptions of discontinuing benzodiazepine use and increase self-efficacy. Although very low quality, the evidence showed a clinically important benefit of both single and multiple tailored letters relative to standard information letters for cessation of benzodiazepine at 1-year follow-up. The committee expressed the view that this evidence supported their consensus view that more, tailored information can be beneficial in engaging people in withdrawal strategies.

There was low and moderate-quality evidence for patient advice and information compared to usual care. These data showed a clinically important benefit of information provision for the reduction and cessation of prescribed benzodiazepines. The committee also noted clinically important harm as recorded by one study for psychiatric morbidity at 6 months with brief advice, education and support compared to usual care, but highlighted that the evidence was of very low quality. No difference was found between groups receiving advice, education, and support, and usual care for withdrawal symptoms. However, as previously stated, the committee agreed that for all the comparisons of information/advice versus usual care, it was not possible to make any firm conclusions due to the lack of clarity about the composition of the usual care arm, and how much deprescribing occurred.

One study also compared patient advice, education, and support with an abrupt withdrawal to that with a tapered withdrawal and found a clinically important benefit with a gradual withdrawal programme for the rate of relapse into benzodiazepine use following the intervention. This supported the previously discussed committee consensus that tapering benzodiazepines should not be abrupt and should follow a

gradual tapering programme. The committee, therefore, agreed to include this within the recommendations.

The committee agreed that the evidence available was of insufficient quality and quantity to determine the composition or mode of delivery of advice, education, and support. However, the committee agreed that in general there was a benefit of improved reduction and cessation of benzodiazepine with the provision of patient information with little to no observed harmful effect. The committee considered that providing people with information on the benefits of benzodiazepine withdrawal can be an inexpensive but effective tool to empower the person withdrawing to successfully discontinue.

The committee discussed that some of the evidence was for information provided in written format. However, it was agreed that this is not always appropriate and highlighted the need to consider low literacy groups. The committee agreed this reinforced evidence reported in the information and support review included within this guideline. The committee also agreed from personal experiences, that it is best to provide information in a number of formats and in a way that is appropriate for the individual. For example, in both verbal and written format to reinforce the information. The committee also discussed that it can be beneficial to repeat this information at subsequent appointments. Therefore, the committee made a recommendation across all drug classes, based on both the evidence from benzodiazepines and mixed drug classes, but also based on consensus, that people should be provided with information relevant to their individual preferences to support withdrawal.

1.7.3.3 Z-drugs

CBT versus acupuncture

A clinical benefit of CBT compared to acupuncture for cessation of Z-drug use after the intervention and for symptoms for which the medicine was originally prescribed (insomnia) at both follow-up time points was reported from one study. There was no clinical difference between groups for the withdrawal symptoms of anxiety or depression at any time point. It was highlighted to the committee that people in both arms of the study were asked to discontinue their medication 3-5 days prior to the intervention, but there were no details of whether any instruction on tapering or abrupt discontinuation was given. The committee commented that the withdrawal could have been abrupt and inappropriate for Z-drugs, limiting the usefulness of these results on decision-making. The benefit seen in terms of insomnia may reflect the focus of the CBT intervention on cognitive restructuring, with sessions containing information regarding sleep physiology, different ways of coping with sleeping problems, sleep restriction, maintaining factors, stimulus control, and relaxation techniques, and was therefore aimed at treating insomnia rather than targeted at withdrawal per se. The committee agreed that although there was some benefit of CBT over acupuncture, this evidence alone did not support a recommendation for CBT for the withdrawal of Z-drugs.

1.7.3.4 Mixed medicines

The population in these studies included people on at least one of a variety of ‘hypnotics’ or ‘anxiolytics’, as termed by the studies. The majority of these studies combined people on either benzodiazepines or Z-drugs, but some studies also had a mixed population with people on antidepressants or opioids.

Mindfulness-based relapse prevention (MBPR), psychoeducation and guidance on gradual voluntary withdrawal vs psychoeducation and guidance on gradual voluntary withdrawal

For this comparison, both arms received the psychoeducation group session (based on principles of motivational interviewing) along with the individualised guidance on gradual voluntary withdrawal. The evidence from 1 study, therefore, reflects the effectiveness of the mindfulness-based relapse prevention (MBRP) intervention specifically. There was a clinically important benefit of MBRP for insomnia (for which the medicine was prescribed) at 6 months, but not directly after the intervention. However, no clinical difference was observed for an equivalent hypnotic dose at either post-intervention or 6 months.

It was noted that the psychoeducation group session received by the control group (based on the principles of motivational interviewing) was a very active control group, which might explain why more benefit wasn't observed from MBPR. This brief intervention involved feedback, advice, empathy, and discussion of a menu of possibilities for change. It was agreed that this intervention comprised many of the elements the committee agreed should be considered prior to withdrawal from medicines, and reflected many of the recommendations included in this guideline. It was also noted that the evidence was of very low quality and there was no evidence for the number of people who managed to successfully withdraw from hypnotic medication. The committee agreed that there was not enough evidence of a clinical benefit to recommend MBRP, but they agreed in their experience mindfulness may be of benefit to people wishing to withdraw from medicines.

The committee discussed that psychological support could come in many forms, but that the majority of evidence in this review across drug classes was for CBT. The committee noted that CBT has developed a large quantitative research base over the past few decades, more so than any other model of psychotherapy. They considered that this is partly because of its design and approach (usually manualised and time-limited), so it is possible to replicate CBT in different forms, where other therapies usually cannot be replicated in the same way. This also allows efficacy to be evaluated in RCTs. CBT has shown to be generalisable and available to the entire population through the IAPT model, it is currently the most widely available form of psychotherapy in this country. Despite this, people wishing to withdraw from their prescribed medicines may benefit from other types of counselling or psychological intervention. Therefore, the committee agreed it was also important to make a recommendation for future research to investigate the effectiveness of other psychological interventions to support withdrawal. It was agreed that this research recommendation should be made across all the medicine classes.

CBT plus tapered withdrawal versus tapered withdrawal

Evidence from 2 studies showed a clinically important benefit of CBT plus taper for cessation of medication at post-intervention, but at 6 months follow-up this effect was reversed, showing a clinically important benefit of the taper alone. There was also a clinically important benefit of CBT plus taper for one out of the three reductions in medication use outcomes, with the other two outcomes showing no difference between CBT plus taper and taper alone. Taper alone was beneficial for quality of life reported on the SF-36 physical and mental scales at post-intervention and SF-36 physical at 6 months, but no difference between the groups for SF-36 mental health at 6 months. There was a clinically important benefit of CBT plus taper for symptoms for which the medication was originally prescribed at post-intervention, but no difference at 6 months. There was no difference between groups for the withdrawal symptoms outcomes of anxiety, depression, or total withdrawal symptoms score, with

the exception of depression at post-intervention which showed a clinically important benefit of taper alone. The committee considered that the benefit of taper alone on the majority of quality of outcomes reflected prior discussions on the evidence for benzodiazepines, that the timing of CBT is important, and it may not be appropriate at all stages of withdrawal. Another potential explanation for this effect was that CBT can raise awareness of the person's discomfort during withdrawal and the impact of this on their quality of life. The population in the study contributing to this evidence was chronic users of hypnotics (benzodiazepines or z-drugs). Although there was evidence of the effectiveness of CBT for people withdrawing from benzodiazepines (as described above), this does not seem to be reflected in a mixed population including people on Z-drugs. Overall, the committee agreed that the variation in direction of effect across the outcomes made it difficult to make any recommendations from this evidence in a mixed population and that the economic model and recommendation for CBT should focus on benzodiazepines only. They noted that the limited and unconvincing evidence for CBT for all the other drug classes also supported the need for a research recommendation for psychological therapies to aid withdrawal more generally.

Patient advice plus relaxation versus usual care

Evidence from one study showed a clinically important benefit of patient advice plus relaxation for cessation of medication and relapse into medication use at both post-intervention and follow-up time points. However, the converse was true for symptoms for which the medication was originally prescribed at post-intervention and no difference between groups in this outcome at 12 weeks follow-up. The committee again agreed that concerns on what usual care comprised of limited inferences that could be made from this comparison.

Melatonin, support and taper versus placebo, support and taper

The focus of this comparison was melatonin versus placebo, as both arms received the same additional support. Evidence from one study showed a clinically important benefit of placebo for cessation of medication at 1 month, 6 months, and 3 years. The majority of this evidence was of moderate quality, but there was only evidence for one outcome and the committee agreed that no recommendation could be made for the use of melatonin based on this limited evidence.

Prescriber education versus written manual for prescribers

Evidence from one study showed no clinical difference in cessation or reduction of medicine at any follow-up time point. The committee agreed that this comparison did not assess the effectiveness of providing information/education for prescribers, only the format in which the information/education is given. Therefore, information and education for prescribers may still be of benefit, but there is no evidence to support a recommendation for the use of intensive prescriber education.

Structured intervention with follow-up versus Structured intervention with written instructions

One study compared a structured educational interview and GP-tailored stepped dose reduction with follow-up visits to the same intervention and dose reduction but with written instructions only. The follow-up intervention included follow-up appointments with their GP every 2-3 weeks until the end of the dose reduction. The written instructions intervention included reinforcing educational information at their first and only contact with their GP, along with a tailored gradual dose reduction until benzodiazepine cessation. No follow-up visit was scheduled, although patients could request an appointment with their GP when needed. Therefore, this comparison was

assessing the effectiveness of the GP follow-up visits, and not the effectiveness of providing an initial education intervention alongside a taper.

Results were mixed in terms of the direction of effect and whether they were sustained at longer follow-up timepoints. The committee agreed that due to the variation in the direction of effect favouring different interventions for different outcomes, and due to the very low quality of this evidence, no specific recommendation could be made on the use of follow-up with GP visits or written instructions. The committee also commented that an individualised approach would be required, depending on the amount of information and follow-up visits a person may need during a dose reduction, and that this is something that is difficult to generalise from an RCT.

Motivational interviewing versus an information booklet

One study compared motivational interviewing versus an information booklet. There was a clinically important benefit of motivational interviewing for mortality, cessation of medication, and reduction of medication by at least 25%. There was no difference between groups for mean-defined daily dosage. The committee discussed that it was unclear whether the control group received any specific aim to taper medication. This taken alongside the very low quality and the limited amount of evidence meant the committee agreed they could not make a recommendation for the use of motivational interviewing to aid withdrawal, but considered this may fall within psychological therapies considered within the research recommendation.

Electroacupuncture plus taper versus sham acupuncture plus taper

One study compared electroacupuncture plus taper to sham acupuncture plus taper. There was no clinically important difference between groups for any of the outcomes. The committee discussed that the therapeutic contact time in the sham group may have been just as important as the electroacupuncture intervention and again highlighted the importance of forming a good therapeutic relationship and supporting people through withdrawal.

1.7.3.5 Antidepressants

CBT plus tapered withdrawal versus clinical management plus tapered withdrawal

Two studies in people on tricyclic antidepressants compared CBT plus a taper to clinical management plus a taper in people with major depressive disorder or recurrent depression who had been successfully treated with antidepressants and were in remission but also had residual symptoms of depression. The aim of the studies was to assess the effectiveness of CBT on these residual symptoms. The committee agreed that this study was well controlled for the therapeutic contact time.

There was a clinically important benefit of CBT plus taper for symptoms for which the medication was originally prescribed, as shown by a lower occurrence of episodes of major depression during subsequent 2 years follow-up. However, no clinical difference was seen in the cessation of antidepressants or residual symptoms of depression score at 20 weeks. The committee commented that the majority of people in the control clinical management group discontinued antidepressants, and therefore may be why there is little added benefit of the CBT. The committee discussed that, because the aim of the studies was to look at the effect of the CBT on the residual symptoms, the CBT intervention would be targeting the underlying condition and not withdrawal per se. The committee also noted that people in one of the studies had recurrent depression and that recurrent depression and/or residual symptoms may

be a reason to continue antidepressant treatment or consider psychological interventions, and therefore this population may not be completely applicable to those withdrawing from antidepressants in clinical practice.

The committee agreed that this provides some evidence that CBT interventions can help prevent relapse, although there wasn't evidence to suggest CBT helps with the successful withdrawal of antidepressants. The committee noted that NICE guidelines on depression covered psychological interventions for relapse prevention, and cross-referred to the CG90 NICE guideline for depression in adults.

Taper length comparisons

One study in people on desvenlafaxine was included in the 'other antidepressants' stratum and compared abrupt discontinuation (people switched straight to placebo) with a 1-week taper (people reduced from 50mg/day to 25mg/day for 1 week and then switched to placebo). There was a clinically important benefit of the 1-week taper on the outcomes of self-harm (suicide attempt) and withdrawal symptoms (taper/post-therapy emergent adverse events). There was no clinical difference between groups for mortality, cessation of antidepressants, symptoms for which the medication was originally prescribed, and withdrawal symptoms (when assessed by the DESS total score, number of people with discontinuation syndrome, or number of people with suicidal ideation).

Another study in people receiving desvenlafaxine compared 4 withdrawal taper lengths: abrupt discontinuation (switch straight to placebo); desvenlafaxine 50 mg/d for 7 days, and then 25 mg/d for 7 days (desvenlafaxine 50-25 taper); desvenlafaxine 50 mg/d every other day for 14 days (desvenlafaxine 50-eo taper); and desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (desvenlafaxine 50-placebo taper). It was noted that the population was women who were taking antidepressants due to menopausal vasomotor symptoms, and may have received as little as 5 weeks of treatment with antidepressants at the time of discontinuation. The committee noted this is shorter than seen in clinical practice in people taking antidepressants for depression or anxiety. There was a clinical benefit of all three tapers in comparison to the abrupt discontinuation for withdrawal symptoms but no clinical difference for patient satisfaction for the 50-25 taper or 50-placebo taper, and a clinical benefit of abrupt discontinuation on patient satisfaction for the 50-eo taper. However, it was noted that, unlike the other outcomes which were taken at differing timepoints for each arm relative to the last dose of desvenlafaxine (withdrawal symptoms outcomes taken at 1-week drug-free wash-out), the patient satisfaction outcome was taken at week 3 for all arms. Therefore, the abrupt discontinuation group had been medicine-free for 3 weeks by this point, whereas the taper arms had been medicine-free for only 1 or 2 weeks which may have favoured the abrupt discontinuation group as they may have started to adapt to being off the antidepressants.

For the head-to-head comparisons of the different taper lengths, there tended to be a clinical benefit of the two 2-week tapers when compared to the 1-week taper on the occurrence of some of the individual withdrawal symptoms, but no clinical difference for other individual withdrawal symptoms or for the DESS total scores. Patient satisfaction showed the opposite effect, with a clinical benefit of the 1-week taper when compared to the two 2-week tapers. The head-to-head comparison of the two 2-week tapers demonstrated a clinical benefit of desvenlafaxine 50-eo for the occurrence of 3 of the individual withdrawal symptoms, but with no clinical difference for the other 5 individual withdrawal symptoms and for the DESS total score. Patient satisfaction showed the opposite effect, with a clinical benefit of the desvenlafaxine 50-25 taper.

One further study in a mixed population on different classes of antidepressants compared a 14-day taper with a 3-day taper. There was no clinical difference between the 3-day and the 14-day taper in withdrawal symptoms. It was noted that even in the 14-day taper arm, almost half of the people experienced a discontinuation syndrome, and the committee agreed that 14 days would be too short a duration for withdrawal of antidepressants in clinical practice. The committee discussed that this population may differ from those in other included studies, as it included people who were discontinuing antidepressants in order to switch to another antidepressant, and therefore may still have a clinical indication for continuing antidepressants. It was also noted that people could have been taking antidepressants for as little as 6 weeks. Again, this is a much shorter duration than seen in clinical practice when people can be on antidepressants for months or years at the point of withdrawal. This may underestimate the withdrawal symptoms observed upon discontinuation.

The committee discussed that the evidence above shows in general that a taper is beneficial over an abrupt withdrawal. This evidence, along with committee experience and consensus, reinforced the committee's previous discussion about not withdrawing medicines abruptly, and agreed this should apply across all medicine classes.

The committee noted that this was the only evidence comparing different tapering speeds or schedules to each other across all medicine classes considered in this guideline. Although this evidence tended to show that a longer taper has benefits over a shorter taper, the committee was in agreement that the people in the majority of the studies hadn't been on antidepressants very long (as little as 5 weeks) much shorter than would be seen in clinical practice. This may underestimate the withdrawal symptoms experienced. In addition, there was a strong committee consensus that all taper durations seen in the evidence were shorter than would be acceptable in clinical practice. From the experience of both the clinical and patient representatives on the committee, tapering should be much slower than those tapering speeds for which there is evidence. The minimum period for a taper that would be considered in practice is 4 weeks, and only then if there are no problems or distressing withdrawal symptoms. The committee's experience is that people can need 12-18 months to withdraw from antidepressants, but it is very variable, and some people can withdraw in shorter time frames. The committee was also aware of other evidence such as case studies showing short- and longer-term harms of withdrawing these medicines too quickly. The committee agreed that the most important aspect of a taper schedule is that it is at a rate tolerable for the individual, which in most cases is a slow and stepwise reduction, and made a consensus recommendation across all medicine classes to reflect this.

The committee discussed that there are long-term risks and harms of taking antidepressants, such as increased risk of falls and fractures, and increased risk of bleeds (especially in combination with other medicines such as NSAIDs). Therefore, if someone is able to withdraw in the shorter durations within this spectrum (closer to 4 weeks), then this would be beneficial to the person in order to take away these risks of long-term use, however, they agreed the limitations in the evidence available within this review meant a specific duration couldn't be recommended, and an individualised approach would allow a shorter taper duration where it was suitable for the person. Therefore, the experience of the committee contributed to the recommendation made across all drug classes to balance the risk of adverse events from continued exposure to the medicines with minimising risk of withdrawal symptoms by slow dose reduction and withdrawal.

The committee agreed that a slow and stepwise reduction is often the best approach, and recommended this for all medicine classes. The committee agreed that this

stepwise reduction should be in decrements proportionate to the existing dose. This means that each decrement would be a percentage of the current dose, and therefore decrements would be smaller as the person gets down to lower doses. This is often referred to as hyperbolic tapering. The committee noted, from experience, that the final and smallest dose is often the hardest to withdraw, no matter how low the dose gets. The exception to this hyperbolic tapering is for gabapentinoids. From experience and considering the current clinical practice, the committee agreed that gabapentinoids can be reduced by a fixed amount at each decrement and made a recommendation to reflect this. Despite the lack of evidence comparing longer taper durations, the committee did not make a research recommendation as they agreed this would need to be individualised. The committee was also aware of research currently underway to help determine this.

It was discussed that it is difficult with some antidepressant formulations to get down to lower doses/smaller dose reductions due to the pill dosages available. In these cases, it might be helpful to switch to an antidepressant available in smaller dosages or to one which is available in liquid formulation, if it is not possible to do smaller dose reductions using pills. However, it was agreed that a recommendation along these lines should not be made, as it is very much dependent on the individual circumstances and the doses and formulations available for each antidepressant. It was also discussed that 'tapering strips' might make it easier for the person to decrease their dose and withdraw from antidepressants. Tapering strips are a strip of pouches containing consecutively slightly lower doses to be taken each day. However, tapering strips are not currently licenced in the UK and no evidence was identified. Therefore, the committee agreed that their future research recommendation to investigate the effectiveness of aids and technologies to support withdrawal could include research into the effectiveness of using tapering strips. It was agreed that different aids and technologies could be used across drug classes, and therefore this research recommendation was made for all medicines considered.

In addition to the recommendation made across all medicine classes, regarding the factors to consider when planning withdrawal (such as duration of use, dose and history of withdrawal symptoms). The committee agreed by consensus that there are factors of certain antidepressants that can make it more difficult to withdraw, including those with a shorter half-life such as paroxetine or venlafaxine, and those with anticholinergic properties such as TCAs or duloxetine. Therefore, a recommendation was made to consider these factors when planning withdrawal of antidepressants.

CBT plus tapered withdrawal versus tapered withdrawal

One study in a mixed population receiving different classes of antidepressants compared CBT plus taper to a tapered withdrawal. CBT was delivered in group sessions and included elements of targeting withdrawal symptoms, as well as the underlying condition. The control group received individualised sessions with a psychiatrist. At 16 months there was a clinical benefit in the control group for mortality, due to one suicide in the CBT arm. There was no clinical difference between groups for symptoms for which the medication was originally prescribed (reoccurrence of the previous anxiety disorder) at 16 months. The committed commented that CBT interventions can sometimes be beneficial in preventing a relapse of the original condition, but that the relatively active control group in this comparison may have contributed to the lack of clinical benefit observed. They agreed this was insufficient evidence to inform a recommendation for CBT for withdrawal of antidepressants.

Mindfulness-based cognitive therapy and taper versus placebo substitution taper

One study in a mixed population receiving different classes of antidepressants compared mindfulness-based cognitive therapy and a taper to a placebo substitution taper. There was a clinically important benefit of mindfulness-based cognitive therapy and taper for symptoms for which the medication was originally prescribed (reoccurrence of an episode of major depression) at 16 months follow-up, however, no other evidence was available. The committee discussed that this provides some evidence that mindfulness-based interventions may help prevent relapse, although there wasn't evidence to suggest mindfulness-based interventions help with successful withdrawal. The committee agreed to cross-refer to the CG90 NICE guideline for depression in adults where recommendations for psychological interventions for relapse prevention were available.

The committee discussed that mindfulness interventions can play a role in helping withdrawal, by distracting from unpleasant withdrawal symptoms even if they do not affect the severity of withdrawal symptoms. However, there was not enough evidence to make a recommendation. The committee agreed this should be included within the future research recommendation on the effectiveness of psychological interventions to aid withdrawal, as discussed previously.

Advice to GP to discontinue patient's antidepressants versus usual care

One study in a mixed population of people on different classes of antidepressants compared a letter sent to the GP advising them to discontinue the patient's antidepressants versus usual care. At 1-year follow-up, there was no clinical difference in the outcomes of cessation of antidepressants or relapse into medication use, and a clinical benefit of usual care for symptoms for which the medicine was originally prescribed (relapse of a depressive or anxiety disorder).

This study states that no baseline diagnostics were disclosed to the GPs in the control arm, and therefore the expectation was that prescribing would continue in most cases. The committee agreed, as with other usual care comparisons, this was not informative for drawing inferences on effectiveness of withdrawal interventions from.

1.7.4 Considerations across all medicine classes

The committee agreed that there are a number of overarching themes for withdrawal from all medicine classes and made a number of general recommendations to cover these. These are discussed above, but some additional considerations that were informed by committee consensus and evidence from related reviews in this guideline are discussed below.

The committee discussed the importance of setting expectations with the person. It was discussed that people are not always informed about how unpleasant withdrawal can be, and this could set the wrong expectations. It was agreed by consensus that people should be informed that withdrawal symptoms are common but do not affect everyone, and that it is not always possible to predict who will suffer from withdrawal symptoms. People can often be concerned about re-emergence of the original symptoms or condition, and it is important to reassure the person from the outset that this will be assessed and managed if it occurs.

The committee agreed that it should be emphasised within the recommendations that people often need to be reassured that they will be supported throughout the process. For some people this might just be support from the prescriber through a

supportive therapeutic relationship, for others it might be through psychological interventions. People may have been on the medicines for a long time, and the medicine may also be acting as a 'comfort blanket' for the individual. The committee agreed people should be reassured about the support they will get if they feel like this comfort blanket is being taken away. There was some qualitative evidence (see evidence review on Patient Information and Support) that support groups can be beneficial and the committee agreed from experience that peer support can be very helpful for people initiating and going through withdrawal, and therefore made a recommendation to consider providing details of sources of peer support. From committee experience, support from national and local support groups and helplines can also be helpful and should be considered. The committee also discussed that there are many examples of local and national helplines, for example those offered by charities.

The committee acknowledged that withdrawal is a very individualised experience. Some people find withdrawal extremely difficult and experience severe withdrawal symptoms and long-term harms if the medicine is withdrawn too quickly. Other people may not experience withdrawal symptoms and find it easier to discontinue treatment. It was agreed that it is not always possible to predict the ability to tolerate medicine taper and that many factors can affect the withdrawal experience (withdrawal incidence, severity and duration). The committee discussed that many people report that withdrawal is more difficult the longer someone has been on a medicine, and therefore the initial reduction should be less in these situations, but this rule does not always reflect what happens in current practice. Likewise, there is a view that people on higher doses tend to do worse, but again this is not always the case. It was also highlighted in discussions that people on higher doses tend to have more complexities in terms of co-morbidities or previous adverse life events, so this may confound the picture. Therefore, the committee made consensus recommendations that factors such as dose and length of time on the medication should be taken into account when planning the taper, with the caveat that the ability to tolerate medicine taper is variable and unpredictable.

Another consideration for tolerance of medicine tapering is whether someone is on multiple medicines, and the committee discussed that the experience of withdrawal can be modified by other medicines. An example was given that people can get an emergence of side effects from one medicine, perhaps that the medicine being withdrawn had been masking. This can also add to the complexity of distinguishing between withdrawal symptoms, re-emergence of symptoms of the original condition and side effects of the medicine. Therefore, a consensus recommendation was made to take into account whether someone is on multiple medicines. Although many factors can affect tolerance of medicine tapering, it was agreed that previous experience of withdrawal should be taken into account, as this might give an indication of an individual's ability to tolerate medicine taper. The plan for withdrawal should also take into account the urgency of withdrawal. For example, the committee agreed a gradual withdrawal is appropriate when a medicine is no longer effective or necessary. However, if a medicine is causing significant harm, a more rapid withdrawal may be necessary. It is also important when planning withdrawal to consider the timing of the start of the dose reduction, and any personal circumstances which could impact on the success of dose reduction, and which may need to be considered. It was the committee's view that this should be discussed and agreed with the individual, for example to coincide with or avoid other significant events occurring in the individual's life. Significant life events can dramatically impact the success of withdrawing from these medicines. However, this may not always be possible, as some personal circumstances can last for long periods, such as unemployment or relationship problems.

As discussed above, a recommendation was made not to withdraw medicines abruptly, however, the committee noted that abrupt withdrawal of opioids, whilst it can be unpleasant and lead to indirect harms, does not have the same direct harms as those of benzodiazepines and the severity of risks of rapidly withdrawing opioids is different to the other drug classes. From the experience of the committee, some people can show a preference towards abruptly stopping their opioids. However, the committee agreed that abrupt withdrawal of opioids can still be dangerous due to the indirect harms such as profound craving and risk of relapse and overdose. It was discussed that prescribers have the responsibility to inform and avoid this risk, and that the person might not understand what this means for them. Therefore, opioids should still be included under this recommendation not to abruptly withdraw, rather than be an exception. The committee did agree there are some exceptional circumstances when an abrupt withdrawal may be necessary; if the risk of harm far outweighs the risk of withdrawal symptoms, for example, if someone experiences a serious side effect of the medicine, such as upper GI bleeding in people taking antidepressants, serotonin syndrome in people taking SSRIs, respiratory depression from an opioid or severe ataxia from a gabapentinoid. This was included within the recommendation. In the committee's experience, this would usually be done within a controlled hospital environment, due to the seriousness of the side effect.

It was discussed that people should not be on medicines with the potential for dependence and long-term harms any longer than required, therefore if the individual did not have any problems with withdrawal or any distressing withdrawal symptoms, then there may be benefits in using a shorter time frame for withdrawal, in order to remove the harms of long-term use of the medicine. The recommendation was made to balance the risk of adverse events from continued exposure to the medicines with minimising risk of withdrawal symptoms by slow dose reduction and withdrawal. It was discussed that people who are given responsibility for their dose reductions can do better. Examples were given from the committee from experiences of people who benefited from being given trust to control their dose reductions (patient-led reductions), and that these people often had better outcomes in terms of successfully withdrawing. Therefore, the committee made the consensus recommendation to consider giving people an element of control over the process. Giving the person their normal prescription, but asking them to try and reduce their dose over that set period, and therefore return to their next appointment with medicine leftover, is a good example of giving people control over the process. Still having their usual amount of medicine can people feel secure, and giving them this control can empower the person to do it themselves. The committee discussed that, although suggested medicine-specific reduction/withdrawal schedules exist in various current guidance, there is huge variation in how someone responds to withdrawal and how someone reacts if very individual. It was the view of the committee that individual assessment is an important factor. Therefore, one of the most important aspects of agreeing a reduction schedule is that it is flexible and can be informed by any response to the early stages of dose reduction. The consensus recommendation was made to review the taper schedule regularly and revise as required.

As described above, switching to a benzodiazepine with a longer half-life before withdrawal may have some benefits. It was discussed from experience that for opioids, converting to long-acting medications used to be common practice, but it is now no longer favourable as it is thought immediate release preparations can give quicker relief of pain and people may only use them when needed, therefore the overall daily dose may be lower than with longer acting preparations. From clinical experience, when tapering opioids people don’t tend to switch to opioids with a long half-life (as with benzodiazepines), as there is some evidence that this can lead to higher daily doses in people. In fact, with opioids it can sometimes help to switch to

an immediate-release preparation to allow a greater flexibility in dosing and allow a dose reduction overall. This is because, with immediate release preparations people tend to take the medicine only when needed and get quicker relief of pain, which can lead to overall daily dose being lower. If a patient is taking a combination of slow release and immediate release opioids, it can be useful to discuss which of these gives the person the most benefit and begin dose reduction with the preparation they find least helpful. As no evidence was identified, and the situation may differ depending on the individual's circumstances, the committee decided that a recommendation could not be made, but that their discussion about the possibility of switching to an immediate release preparation before withdrawal should be documented. In terms of antidepressants, again there was no evidence, and the committee drew on their experience. This reflected that it is often easier to withdraw from an antidepressant with a longer half-life. However, it is not common practice to switch to an antidepressant with a longer half-life such as fluoxetine just for withdrawal, as introduction of a new antidepressant can have its complications. Only occasionally people may switch to fluoxetine if they have particular problems with withdrawal. The committee agreed that it would be useful to have more evidence in the case of antidepressants, and made a recommendation for further research, looking at whether converting to an antidepressant with a longer half-life is beneficial compared to not converting (staying on the original antidepressant).

It was the view of the committee that if symptoms occur or worsen after a dose reduction, it is important to try to determine whether they are withdrawal symptoms or a re-emergence of symptoms of the original condition. If these are thought likely to be withdrawal symptoms (see also Chapter on Withdrawal Symptoms), the committee agreed by consensus that the next dose reduction may need to be delayed, or the person may need to revert to the previous dose. It was the committee's view that the individual concerned can often say whether what they are experiencing feels like the symptoms they had before or whether the symptoms are new, unfamiliar symptoms, or alongside new physical symptoms.

The committee discussed that there is no evidence from the review for pharmacological interventions specifically given to manage the symptoms of withdrawal. Evidence from the benzodiazepines and opioids sections suggested a lack of benefit for a range of pharmacological interventions given alongside withdrawal, in most cases presumably given with the aim of being an alternative treatment for the underlying condition. The committee was aware of some commonly used medicines which can provide short-term immediate symptomatic relief of physical withdrawal symptoms (examples include clonidine, buscopan, or mebeverin for stomach cramps, antihistamines for sleep problems). However, introduction of new medicines during withdrawal can complicate the process and comes with a risk of complications or side effects with the new medication. There was a strong consensus from both the patient and healthcare professional perspective that new medicines (especially those associated with dependence or withdrawal) should be avoided during withdrawal. Therefore, the recommendation was made to avoid the use of these medicines to treat the symptoms of withdrawal.

As no evidence was identified for gabapentinoids, the committee made a recommendation for future research on the most effective withdrawal strategies or interventions to aid the withdrawal of gabapentinoids.

Finally, a future research recommendation was made to investigate the most effective service models for supporting people to withdraw from these medicines.

1.7.5 Cost effectiveness and resource use

1.7.5.1 All drug classes

Three papers were included in the health economics review for the review question on safe withdrawal strategies. Two of these studies were about safe withdrawal from benzodiazepines and the other looked at antidepressants. There was no health economic evidence on opioids, Z drugs and Gabapentinoids.

The committee made recommendations to improve information and support for people who may be anxious about discontinuing their medication. In addition, based on the clinical evidence on opioids and benzodiazepines, the committee recommended a gradual, stepwise dose reduction instead of an abrupt discontinuation to minimize withdrawal symptoms. Finally, the committee made recommendations to raise awareness of withdrawal symptoms to help prescribers to plan dose reduction. These recommendations should help clinicians to adopt best practice in the management of people trying to discontinue from opioids, gabapentinoids, z drugs, benzodiazepines and antidepressants, thus potentially preventing the onset of withdrawal symptoms and adverse events. Currently, only a few centres within the NHS provide services to people willing to discontinue prescribed drugs, so the recommendations are expected to increase the provision of these services, potentially leading to an additional cost for the NHS. However, any resource needed should be at least partially offset by savings caused by the reduction of people taking these drugs and the drug-related adverse events.

1.7.5.2 Benzodiazepines

Two analyses on safe withdrawal from benzodiazepines were included.

A first cost comparison analysis looked at the costs associated with usual care, discontinuation letter, and GP medicine review, from the perspective of the UK NHS. The analysis was considered directly applicable with potentially serious limitations, as, although it assumed no difference in health outcome, SF-36 mental score was found to be higher in people reducing benzodiazepine medication. The results suggest that discontinuation letter is cost-saving compared with the other two strategies.

A second cost utility analysis was conducted in the Netherlands and compared usual care with tapering alone and tapering plus CBT. The analysis was considered partially applicable as it was conducted in a setting different from the UK NHS and with potentially serious limitations as it was based on a single RCT which had unbalanced baseline characteristics and baseline costs in the three arms. The cost-utility analysis found usual care to be less expensive and associated with a higher utility gain, hence dominating the other two strategies. However, tapering alone and CBT were associated with a higher probability of discontinuation, with tapering plus CBT costing £1,300 for every extra successful discontinuation compared to usual care, and tapering off alone costing £2,400 for every extra successful discontinuation compared to tapering plus CBT. The committee noted that the cost-utility analysis seemed to favour usual care even though the discontinuation strategies achieved a higher reduction in benzodiazepine consumption. This implies that while group CBT or tapering were successful in helping more people discontinue benzodiazepines, they were also causing a loss of utility probably due to withdrawal effects, which made those strategies not cost-effective in a short-term cost-utility analysis. The study was a within-trial comparison and, as such, could only capture costs and benefits occurring during the short duration of the trial. The committee noted that most of the adverse effects of benzodiazepines (e.g., mental impairment) occur only

later in life, so any analysis not including an adequately long-time horizon would likely fail to capture any significant benefits of benzodiazepine cessation. Therefore, it was proposed to develop an original economic evaluation on benzodiazepines cessation strategies using a life-long time horizon and the meta-analysis conducted for the clinical review to derive treatment effectiveness.

A third study was excluded as it assumed the same efficacy between benzodiazepines and no drugs and did not include any withdrawal symptoms.

The guideline cost-utility analysis looked at 3 different strategies: group cognitive behavioural therapy alongside tapering off, tapering off only, and usual care. A probabilistic Markov model was developed including several adverse events which were found to be correlated with long-term benzodiazepines consumption: hip fractures, fall injuries, dementia onset, and road traffic accidents. The probabilistic results showed that cognitive behavioural therapy alongside tapering off dominated the other 2 strategies, thus being the most cost-effective strategy. Tapering alone was cost-effective compared to usual care but it was dominated by CBT. Following the discussion of the results, the committee decided to recommend that clinicians consider group CBT to support people discontinuing benzodiazepines. The number of people who may seek withdrawal services, is currently uncertain. One UK study estimated that around 120,000 people may be willing to use withdrawal services if available,[54] but the committee noted that the study was highly selective, as it was based on a single centre in a relatively deprived area with a high prescription rate, and therefore likely to overestimate the number of people willing to discontinue. Nevertheless, as people taking benzodiazepines in the UK are around 1.4 million,[255] even if a small proportion of them seek withdrawal services, this will represent a significant cost for the NHS. As stated previously, there is currently limited provision within the NHS to support withdrawal from prescribed medicines, so the recommendations are expected to increase provision of these services, including group cognitive behavioural therapy. Additional resources will be needed in the short term to provide these services in the areas where they are not widely available, although this should be balanced by savings accrued from a reduction in adverse drug events.

1.7.5.3 Antidepressants

One cost-utility analysis conducted in the Netherlands looked at the cost-effectiveness of antidepressant cessation advice, to discontinue medication in long-term inappropriate antidepressant users. The analysis was considered partially applicable with potentially serious limitations as it used a time horizon considered to be too short to capture benefits of antidepressant cessation. The study found the intervention to reduce costs, while resulting in a very small loss of QALYs. The calculated cost per QALY gained was £2,450 for usual care compared to cessation advice. The committee did not consider the difference in QALYs between the two strategies (0.02) to be statistically or clinically significant and therefore concluded that the intervention was cost saving. No specific recommendation was made for people with inappropriate long-term antidepressant usage as the evidence was too limited. However, the committee made general recommendations to consider withdrawing a medicine if the medicine is no longer benefiting the person. This should include people with inappropriate long-term antidepressant usage. It is likely that the recommendations will lead to cessation or dose reduction advice by the prescribers to those using inappropriate medication. This should lead to savings for the NHS and no significant harm for the patient, particularly if best practice of gradual withdrawal and monitoring withdrawal symptoms recommended by the committee is widely followed.

1.7.6 Other factors the committee took into account

The committee agreed that it should be highlighted in the recommendations that healthcare professionals should be aware that people can often have different views to them in terms of the benefits and harms of their medicines. The decision to withdraw medicines should be a shared decision between the person and the prescriber, but there may be some instances where a person may not want to reduce or withdraw their medicines, and the healthcare professional believes the medicine is doing that person harm. In some cases, it may take time to come to a shared decision to reduce or withdraw and this will be aided by building a good relationship between the prescriber and the individual. It was also discussed that people may have been prescribed medicines historically, in line with the evidence available at the time and in good faith of the healthcare professional and the committee stressed the importance of not apportioning blame, to either party. The committee agreed that explaining to a person that dependence is an expected effect of these medicines can help reassure them that they are not to blame. In addition, the person may not have been fully aware of the harms associated with the medicine. The importance of assessing and discussing the balance between any ongoing benefits and harms was highlighted, as was the importance of a supportive and ongoing relationship between the patient and the prescriber. The prescriber should also explore the ongoing clinical indications and whether that is still what the medication is being prescribed for now, for example, is the medication still treating the symptoms of the condition, or is it acting as a blanket against other difficulties in life and to alleviate distress. The use of these medicines is often associated with other contributory factors such as trauma or adverse childhood events. Therefore, it may be necessary to consider whether the person will need other types of intervention, either for the underlying condition, if still present or for any distress caused by contributory factors.

The committee strongly agreed that every effort should be made to reach a shared decision, however, there are instances when agreement cannot be reached, and the healthcare professional believes the prescribing is particularly unsafe and is not in the person's best interest. The committee noted that the prescriber has a professional obligation to not continue something which is unsafe. It was agreed that guidance should be in line with advice on 'handling patient requests for medicines you don't think will benefit them' in the General Medical Council guidance: good practice in prescribing and managing medicines and devices. The reasons for the decision should be explained to the person and documented, and the person should be offered a second opinion. The committee discussed some exceptional circumstances when it may be necessary to initiate a reduction or a more rapid reduction than the person agrees to. These circumstances may include instances when very unsafe levels of medicine prescribing are identified or in environments where continued use may be hazardous, such as in secure settings (prison). The committee discussed the responsibilities of the prescriber in these situations. The committee agreed that in these exceptional circumstances there should be a more frequent review of the withdrawal or reduction, and that medicines may be required to treat physical symptoms of withdrawal. The committee agreed these medicines were not required for everyone when withdrawing because the other recommendations to support individualised taper at a rate the person was comfortable with should negate the need for additional medicines.

The committee discussed that situations occur when, despite best efforts, it may have been impossible for a person to reduce their dose. There are a small minority of people who are not able to reduce or withdraw. In these cases, although continued prescribing is not ideal due to the potential harms, the alternative may be unbearable for the person. The committee agreed from experience that it is sometimes

necessary for the person to continue the medicine as it can take time to get to a point where reduction or withdrawal can be considered, but that this should be continually monitored to ensure this is safe. In these cases, the committee recommended by consensus that the aim should be to stop any further escalation in dose. The committee explored other longer-term support which may help in these instances, such as harm reduction messages, and best interest meetings.

1.7.7 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1, 1.5.2, 1.5.3, 1.5.4, 1.5.5, 1.5.6, 1.5.7, 1.5.8, 1.5.10, 1.5.11, 1.5.12, 1.5.15, 1.5.16, 1.5.17, 1.5.18, 1.5.19, 1.5.20, 1.5.21 and the research recommendations on multicomponent withdrawal interventions; psychological interventions to support withdrawal; service models for withdrawal interventions; converting to a medicine with a different half-life to aid withdrawal; CBT to support withdrawal from benzodiazepines; acupuncture to support withdrawal from opioids; withdrawal interventions for gabapentinoids; aids to support withdrawal. Other evidence supporting these recommendations can be found in the evidence reviews on: A Patient Information and Support, and D Withdrawal Symptoms.

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Appendices

Appendix A Review protocols

A.1 Review protocol for Safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms

Field	Content
PROSPERO registration number	CRD42020167778
Review title	Pharmacological and non-pharmacological strategies for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms
Review question	What are the most clinically and cost effective pharmacological and non-pharmacological strategies, for example tapered withdrawal or education and support, for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids and antidepressants)?
Objective	To identify the most clinically and cost effective pharmacological and non-pharmacological strategies for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids and antidepressants).
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • Health and Evidence • HTA

	Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. For full search strategies see Appendix B
Condition or domain being studied	Dependence and/or withdrawal symptoms associated with prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants
Population	Inclusion: adults (≥18 years) taking prescribed medicines* that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants). NB. for this question, include prescription medicines which can also be bought over the counter (e.g., codeine, co-codamol). *Note: for a study to be included, the medicine should be listed on the guideline medicine list (see 0). See also decision rule below. **Stratification** Drug class • Opioids • Benzodiazepines, • Z-drugs • Gabapentinoids • Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others).

	Rationale: effectiveness of withdrawal methods expected to differ due to the different mechanisms of action of each drug class, and within class for antidepressants. If any studies are identified in a mixed population (people on different drug classes above) without a breakdown of results by the above strata, these studies will be reported separately under a mixed stratum. No other population strata. **Exclusions:** Children and young people (<18 years) People taking opioids for end-of-life care, acute pain, cancer pain will be excluded. However, people who were originally prescribed the medicines for acute pain or for cancer pain (for which they have recovered) but might have difficulty stopping the medicines, will be included. Use of gabapentinoids when prescribed for epilepsy. People taking the above drugs that have not been prescribed for their own use (with the exception of prescription medicines which can also be bought over the counter (these will be included in this question)). **Decision rules for inclusion of primary studies** If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old. If the study includes mixed populations, some taking prescribed drugs and some taking illicit drugs, the study will only be included if at least 80% of people were taking prescribed drugs. If the study includes people on medicines NOT listed on the guideline medicines list, the study will be included if at least 80% of the population are on medicines listed on the guideline medicines list. If there is no breakdown reported, but some people were on medicines not listed on the guideline medicines list, the study will be included but the population will be downgraded for indirectness.
Intervention	*Note: some of the specific interventions may overlap as to whether they are considered under one or more of the given headings, and the interventions given are examples.* **Approaches to treatment of dependence, discontinuation/withdrawal:**

	Dose reduction Tapered withdrawal strategies (e.g., versus rapid or abrupt withdrawal) Managed withdrawal (e.g., the Ashton manual) **Pharmacological interventions:** Opioid substitutes or other opioids (e.g., methadone, buprenorphine, lofexidine, gabapentin, pregabalin, naltrexone, codeine, slow-release morphine) For benzodiazepine withdrawal, switching to a long-acting benzodiazepine like diazepam, or substitutes (e.g., antidepressants, anticonvulsants). **Non-pharmacological interventions:** Psychosocial interventions, for example: - Behavioural couples therapy - Contingency management - Group-work/recovery groups - Peer support Psychological interventions, for example: - Mindfulness based approaches - Cognitive behavioural therapy (CBT) Patient advice/education and support Prescriber education Brief intervention and advice Motivational interviewing Counselling Acupuncture

	Relaxation yoga Collaborative Care Model Shared decision-making tools and decision aids for withdrawal *Note: individual interventions (e.g., CBT) will be analysed separately and will not be combined under the above headings*
Comparator	Compared to each other or usual care for withdrawal Exclude: no intervention/continuation on medication *Note: if the comparison is 'usual care' and it is unclear whether the usual care involved an element of deprescribing, the study will be included and downgraded for indirectness.*
Types of study to be included	Randomised controlled trials Systematic review of randomised controlled trials. (For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will be used for citation searching). Published NMAs and IPDs will be considered for inclusion. Non-randomised comparative studies will only be considered for any drug class stratifications for which no RCT evidence is identified (NRSs accounting for confounding using multivariate analysis will be given preference). **Exclusions:** Non comparative studies
Other exclusion criteria	Non-NHS prescribed medicines (for the full list of medicines to be included in the guideline see 0) Antipsychotic and stimulant medicines. Use of medicines prescribed in specialist settings for specific conditions (such as gabapentinoids when prescribed for epilepsy). Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs). Withdrawal from illicit drugs (e.g., heroin).

	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available and non-randomised comparative studies will be included in the absence of evidence.
Context	Review will aim to identify the most clinically and cost effective pharmacological and non-pharmacological strategies for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms. It's noted that guidance already exists on this topic for illicit drug misuse. However, the context and reasons for dependence on prescription medications are very different and therefore similar effectiveness cannot be assumed without a review and input from expert committee.
Primary outcomes (critical outcomes)	Validated HRQOL (continuous outcome), including: - Physical health - Psychological health - Social functioning Mortality (dichotomous or time-to-event outcome, all-cause mortality and breakdown of overdose or suicide related mortality) Reduction/cessation of prescribed drug use (dichotomous outcome) Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome (dichotomous or continuous outcome, as defined by the study) ***Report outcomes at post-intervention and longest follow-up***
Secondary outcomes (important outcomes)	Relapse into medication use (dichotomous outcome, as reported by the study) Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs (dichotomous outcome) Non-fatal overdose (dichotomous outcome) Reduced tolerance (dichotomous outcome) Patient Satisfaction (dichotomous or continuous outcome)

	Self-harm or harm to others (dichotomous outcome) Increase in symptoms for which the medication was originally prescribed (dichotomous or continuous outcome, as reported by the study e.g., numerical rating scale or visual analogue scale for pain) Improvements in adverse effects commonly associated with long-term prescribed substance use such as cognitive deficits or constipation associated with opioids (dichotomous or continuous outcome, as reported by the study) Distress (e.g., CORE10) ***Report outcomes at post-intervention and longest follow-up***
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. An in-house developed database; EviBase, will be used for data extraction. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Nonrandomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:

	• papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Strategy for data synthesis	Drugs will be pooled within classes with the exception of antidepressants. Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50%, indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
Analysis of sub-groups	Sub-groups that will be investigated if heterogeneity is present: • Inpatient vs outpatient setting for withdrawal.

	• Addiction support service vs no addiction support service • Gabapentin and pregabalin will be pooled in the analysis as 'gabapentinoids' unless heterogeneity is observed. • Higher potency/shorter half-life and lower potency/longer half-life benzodiazepines will be pooled unless heterogeneity is observed.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Review team members	From the National Guideline Centre: Serena Carville, Guideline lead Emily Terrazas-Cruz, Senior systematic reviewer Melina Vasileiou, Senior systematic reviewer Alfredo Mariani, Health economist Elizabeth Pearton, Information specialist Tamara Diaz, Project Manager	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	

Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10141
Other registration details	n/a
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020167778
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Details of existing review of same topic by same authors	None
Additional information	None
Details of final publication	www.nice.org.uk

1

A.2 Review protocol health economic evidence

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix D below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[181] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

	• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

This literature search strategy was used for the following review:

- Pharmacological and non-pharmacological strategies for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[181]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 68: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 15 June 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 – 15 June 2021	Randomised controlled trials

Database	Dates searched	Search filter used
		Systematic review studies Observational studies Exclusions (animal studies, letters, comments)
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 6 of 12 CENTRAL to 2021 Issue 6 of 12	None
Epistemonikos (The Epistemonikos Foundation)	Inception - 15 June 2021	English
Health and Evidence	Inception – 15th June 2021	None

1 **Medline (Ovid) search terms**

1.	*substance-related disorders/ or *narcotic-related disorders/
2.	*Substance Withdrawal Syndrome/
3.	exp Inappropriate Prescribing/
4.	*Medical Overuse/
5.	exp Prescription Drug Misuse/
6.	exp Deprescriptions/
7.	Medication Therapy Management/
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
10.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
11.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
12.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
13.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
14.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
15.	or/1-14
16.	((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab.
17.	Opiate Substitution Treatment/ or *Opioid-related disorders/
18.	or/16-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.

27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or mouse or mice or rodent*).ti.
36.	or/29-35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	15 not (36 or 37)
39.	limit 38 to English language
40.	18 not (36 or 37)
41.	limit 40 to English language
42.	exp Narcotics/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	Zolpidem/ or Eszopiclone/
47.	(generation adj3 hypnotic*).ti,ab.
48.	exp Benzodiazepines/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp Antidepressive Agents/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	exp Flupenthixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.

55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	gabapentin/ or pregabalin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/42-57
59.	39 and 58
60.	41 or 59
61.	randomized controlled trial.pt.
62.	controlled clinical trial.pt.
63.	randomi#ed.ab.
64.	placebo.ab.
65.	randomly.ab.
66.	clinical trials as topic.sh.
67.	trial.ti.
68.	or/61-67
69.	Meta-Analysis/
70.	Meta-Analysis as Topic/
71.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
72.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
73.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
74.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
75.	(search* adj4 literature).ab.
76.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
77.	cochrane.jw.
78.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
79.	or/69-78
80.	Epidemiologic studies/
81.	Observational study/
82.	exp Cohort studies/
83.	(cohort adj (study or studies or analys* or data)).ti,ab.
84.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
85.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
86.	Controlled Before-After Studies/
87.	Historically Controlled Study/
88.	Interrupted Time Series Analysis/
89.	(before adj2 after adj2 (study or studies or data)).ti,ab.
90.	exp case control study/
91.	case control*.ti,ab.
92.	Cross-sectional studies/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/80-93

95.	60 and (68 or 79 or 94)

1 **Embase (Ovid) search terms**

1.	*drug dependence/
2.	*withdrawal syndrome/
3.	exp inappropriate prescribing/
4.	deprescription/
5.	exp prescription drug misuse/
6.	medication therapy management/
7.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
9.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
10.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
11.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
12.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
13.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
14.	or/1-13
15.	((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)).ti,ab.
16.	*benzodiazepine dependence/
17.	Opiate Substitution Treatment/
18.	or/15-17
19.	letter.pt. or letter/
20.	note.pt.
21.	editorial.pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/19-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/26-33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	14 not (34 or 35)
37.	limit 36 to English language

38.	18 not (34 or 35)
39.	limit 38 to English language
40.	*narcotic agent/
41.	*alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/
42.	*alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	*zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/
47.	(generation adj3 hypnotic*).ti,ab.
48.	*benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp *antidepressant agent/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	*flupentixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	*pregabalin/ or *gabapentin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/40-57
59.	37 and 58

60.	39 or 59
61.	random*.ti,ab.
62.	factorial*.ti,ab.
63.	(crossover* or cross over*).ti,ab.
64.	((doubl* or singl*) adj blind*).ti,ab.
65.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
66.	crossover procedure/
67.	single blind procedure/
68.	randomized controlled trial/
69.	double blind procedure/
70.	or/63-71
71.	systematic review/
72.	Meta-Analysis/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/73-82
82.	Clinical study/
83.	Observational study/
84.	family study/
85.	longitudinal study/
86.	retrospective study/
87.	prospective study/
88.	cohort analysis/
89.	follow-up/
90.	cohort*.ti,ab.
91.	89 and 90
92.	(cohort adj (study or studies or analys* or data)).ti,ab.
93.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
94.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
95.	(before adj2 after adj2 (study or studies or data)).ti,ab.
96.	exp case control study/
97.	case control*.ti,ab.
98.	cross-sectional study/
99.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
100.	or/82-88,91-99
101.	60 and (70 or 81 or 100)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Substance-Related Disorders] this term only
#2.	MeSH descriptor: [Narcotic-Related Disorders] this term only
#3.	MeSH descriptor: [Substance Withdrawal Syndrome] this term only
#4.	MeSH descriptor: [Inappropriate Prescribing] explode all trees
#5.	MeSH descriptor: [Medical Overuse] this term only
#6.	MeSH descriptor: [Deprescriptions] 1 tree(s) exploded
#7.	MeSH descriptor: [Prescription Drug Misuse] explode all trees
#8.	MeSH descriptor: [Medication Therapy Management] this term only
#9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) NEAR/2 (drug* or medicine* or medicat* or medical* or pharm*)):ti,ab
#10.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) NEAR/3 (prescription* or prescrib*)):ti,ab
#11.	(addict* NEAR/3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)):ti,ab
#12.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*):ti,ab
#13.	((therap* or treat*) NEAR/2 (manag* or substit*)):ti,ab
#14.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) NEAR/2 symptom*):ti,ab
#15.	((drug* or medic*) NEAR/2 (prescription* or prescrib*)):ti,ab
#16.	(OR #1-#15)
#17.	((withdraw* or prescription* or prescrib*) near/2 (opioid* or opiate*)):ti,ab
#18.	MeSH descriptor: [Opiate Substitution Treatment] this term only
#19.	MeSH descriptor: [Opioid-Related Disorders] this term only
#20.	MeSH descriptor: [Narcotics] explode all trees
#21.	(OR #17-#20)
#22.	((analgesic* NEAR/3 narcotic NEAR/3 agent*) or (opioid* or opiate*)):ti,ab
#23.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*):ti,ab
#24.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon):ti,ab
#25.	MeSH descriptor: [Zolpidem] this term only
#26.	MeSH descriptor: [Eszopiclone] this term only
#27.	(generation NEAR/3 hypnotic*):ti,ab
#28.	MeSH descriptor: [Benzodiazepines] explode all trees
#29.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam):ti,ab
#30.	MeSH descriptor: [Antidepressive Agents] explode all trees
#31.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or

	NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*):ti,ab
#32.	MeSH descriptor: [Flupenthixol] explode all trees
#33.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine):ti,ab
#34.	(5 Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine):ti,ab
#35.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine):ti,ab
#36.	MeSH descriptor: [Gabapentin] this term only
#37.	MeSH descriptor: [Pregabalin] this term only
#38.	(gabapentin* or pregabalin*):ti,ab
#39.	(OR #22-#38)
#40.	#16 AND #39
#41.	#21 or #40

1 **Epistemonikos search terms**

1.	(advanced_title_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)))) OR advanced_abstract_en:((advanced_title_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) OR advanced_abstract_en:(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses))))) AND (advanced_title_en:((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR

	Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*)) OR advanced_abstract_en:((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*)))

1 **Health and evidence**

1.	[(("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses) OR abstract:("over prescribe" OR "over prescribes" OR "over prescribing" OR "appropriate prescribing" OR "inappropriate prescribing" OR "safe prescribing" OR withdraw* OR depend* OR "inappropriate medication" OR misuse OR misuses OR overuse OR overuses)) AND ((opioid* OR opiate* OR narcotic* OR alfentanil* OR alphaprodine* OR buprenorphine* OR butorphanol* OR codeine* OR co-codamol* OR dextromoramide* OR dextropropoxyphene* OR diamorphine* OR dihydrocodeine* OR dihydromorphine* OR dipipanone* OR ethylmorphine* OR fentanyl* OR heroin* OR hydrocodone* OR hydromorphone* OR levorphanol* OR meperidine* OR meptazinol* OR methadone* OR morphine* OR oxycodone* OR oxymorphone* OR papaveretum* OR pentazocine* OR pethidine* OR phenazocine* OR promedol* OR remifentanil* OR sufentanil* OR tapentadol* OR tilidine* OR tramadol* OR z drug* OR z hypnotic* OR non-benzodiazepin* OR nonbenzodiazepin* OR imidazopyridines OR cyclopyrrolones OR pyrazolopyrimidines OR zolpidem OR zopiclone OR eszopiclone OR zaleplon OR benzodiazepin* OR bzd OR Alprazolam OR Chlordiazepoxide OR Clobazam OR Clonazepam OR Diazepam OR Flurazepam OR Loprazolam OR Lorazepam OR Lormetazepam OR Midazolam OR Nitrazepam OR Olanzapine OR Oxazepam OR Temazepam OR antidepress* OR anti depress* OR thymoanaleptic* OR thymoleptic* OR MAOI* OR NDRI* OR SSRI* OR SNRI* OR SNORI* OR SARI* OR RIMA* OR tricyclic* OR TCA* OR tetracyclic* OR TeCA* OR Agomelatine OR Aripiprazole OR Benactyzine OR Clorgyline OR Deanol OR Desvenlafaxine* OR Duloxetine* OR Flupentixol OR Iproniazid OR Isocarboxazid OR Levomilnacipran OR Lithium* OR Mirtazapine OR Moclobemide OR Nialamide OR Phenelzine OR Pizotyline OR

	Quetiapine* OR Reboxetine OR Rolipram OR Selegiline OR Sertraline OR Tranylcypromine OR Vilazodone* OR Vortioxetine OR 5-Hydroxytryptophan OR Amisulpride OR Bupropion OR Citalopram OR Escitalopram OR Fluoxetine OR Fluvoxamine OR Maprotiline OR Mianserin OR Paroxetine OR Quipazine OR Ritanserin OR Sulpiride OR Trazodone OR Tryptophan OR Venlafaxine OR Viloxazine OR Amitriptyline OR Amoxapine OR Clomipramine OR Desipramine OR Dothiepin OR Dosulepin OR Doxepin OR Imipramine OR Iprindole OR Lofepramine OR Nefazodone OR Nortriptyline OR Opipramol OR Protriptyline OR Trimipramine OR gabapentin* OR pregabalin*))]

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches with the terms used in the clinical search for prescription withdrawal and drug types. The NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015) and the Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) were searched via the Centre for Research and Dissemination (CRD). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for economic modelling and quality of life studies.

Table 69: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 17 June 2021	Health economics studies Quality of life studies Modelling studies Exclusions (animal studies, letters, comments)
	Quality of Life 1946 – 17 June 2021	
	Modelling 1946 – 17 June 2021	
Embase	Health Economics 1 January 2014 – 17 June 2021	Health economics studies Quality of life studies Modelling studies Exclusions (animal studies, letters, comments)
	Quality of Life 1974 – 17 June 2021	
	Modelling 1974 – 17 June 2021	
Centre for Research and Dissemination (CRD)	NHSEED Inception –31 March 2015	None
	HTA Inception – 31 March 2018	

Medline (Ovid) search terms

1.	*substance-related disorders/ or *narcotic-related disorders/
2.	*Substance Withdrawal Syndrome/
3.	exp Inappropriate Prescribing/
4.	*Medical Overuse/
5.	exp Prescription Drug Misuse/
6.	exp Deprescriptions/

7.	Medication Therapy Management/
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
9.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
10.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
11.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
12.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
13.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
14.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
15.	or/1-14
16.	((withdraw* or prescription* or prescrib*) adj2 opi*).ti,ab.
17.	Opiate Substitution Treatment/ or *Opioid-related disorders/
18.	or/16-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or mouse or mice or rodent*).ti.
36.	or/29-35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	15 not (36 or 37)
39.	limit 38 to English language
40.	18 not (36 or 37)
41.	limit 40 to English language
42.	exp Narcotics/
43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or

	dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	Zolpidem/ or Eszopiclone/
47.	(generation adj3 hypnotic*).ti,ab.
48.	exp Benzodiazepines/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp Antidepressive Agents/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	exp Flupenthixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	gabapentin/ or pregabalin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/42-57
59.	39 and 58
60.	41 or 59
61.	quality-adjusted life years/
62.	sickness impact profile/
63.	(quality adj2 (wellbeing or well being)).ti,ab.
64.	sickness impact profile.ti,ab.
65.	disability adjusted life.ti,ab.
66.	(qal* or qtime* or qwb* or daly*).ti,ab.
67.	(euroqol* or eq5d* or eq 5*).ti,ab.
68.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
69.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
70.	(hui or hui1 or hui2 or hui3).ti,ab.
71.	(health* year* equivalent* or hye or hyes).ti,ab.
72.	discrete choice*.ti,ab.

73.	rosser.ti,ab.
74.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
75.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
76.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
77.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
78.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
79.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
80.	or/61-79
81.	exp models, economic/
82.	*Models, Theoretical/
83.	*Models, Organizational/
84.	markov chains/
85.	monte carlo method/
86.	exp Decision Theory/
87.	(markov* or monte carlo).ti,ab.
88.	econom* model*.ti,ab.
89.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
90.	or/81-89
91.	economics/
92.	value of life/
93.	exp "costs and cost analysis"/
94.	exp Economics, Hospital/
95.	exp Economics, medical/
96.	Economics, nursing/
97.	economics, pharmaceutical/
98.	exp "Fees and Charges"/
99.	exp budgets/
100.	budget*.ti,ab.
101.	cost*.ti.
102.	(economic* or pharmaco?economic*).ti.
103.	(price* or pricing*).ti,ab.
104.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
105.	(financ* or fee or fees).ti,ab.
106.	(value adj2 (money or monetary)).ti,ab.
107.	or/91-106
108.	60 and (80 or 90 or 107)

1 **Embase (Ovid) search terms**

1.	*drug dependence/
2.	*withdrawal syndrome/
3.	exp inappropriate prescribing/
4.	deprescription/
5.	exp prescription drug misuse/
6.	medication therapy management/

7.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)).ti,ab.
8.	((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)).ti,ab.
9.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
10.	(deprescription* or de-prescription* or deprescrib* or de-prescrib*).ti,ab.
11.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
12.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
13.	((drug* or medic*) adj2 (prescription* or prescrib*)).ti,ab.
14.	or/1-13
15.	((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)).ti,ab.
16.	*benzodiazepine dependence/
17.	Opiate Substitution Treatment/
18.	or/15-17
19.	letter.pt. or letter/
20.	note.pt.
21.	editorial.pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/19-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or mouse or mice or rodent*).ti.
34.	or/26-33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	14 not (34 or 35)
37.	limit 36 to English language
38.	18 not (34 or 35)
39.	limit 38 to English language
40.	*narcotic agent/
41.	*alphaprodine/ or *buprenorphine/ or *codeine/ or *dextromoramide/ or *dextropropoxyphene/ or *diamorphine/ or *dihydrocodeine/ or *dihydromorphine/ or *dipipanone/ or *ethylmorphine/ or *hydrocodone/ or *hydromorphone/ or *levorphanol/ or *methadone/ or *morphine/ or *oxycodone/ or *pethidine/ or *tapentadol/ or *tilidine/
42.	*alfentanil/ or *butorphanol/ or *cocodamol/ or *fentanyl/ or *meptazinol/ or *oxymorphone/ or *opiate/ or *pentazocine/ or *phenazocine/ or *remifentanil/ or *sufentanil/ or *tramadol/ or *trimeperidine/

43.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
44.	(alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*).ti,ab.
45.	(z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon).ti,ab.
46.	*zolpidem/ or *zopiclone/ or *eszopiclone/ or *zaleplon/
47.	(generation adj3 hypnotic*).ti,ab.
48.	*benzodiazepine derivative/ or *alprazolam/ or *benzodiazepine/ or *chlordiazepoxide/ or *clobazam/ or *clonazepam/ or *diazepam/ or *flurazepam/ or *loprazolam/ or *lorazepam/ or *lormetazepam/ or *midazolam/ or *nitrazepam/ or *olanzapine/ or *oxazepam/ or *temazepam/
49.	(benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam).ti,ab.
50.	exp *antidepressant agent/
51.	(antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or "monoamine oxidase inhibit*" or "Norepinephrine and dopamine reuptake inhibit*" or NDRI* or "Selective serotonin reuptake inhibit*" or SSRI* or "Serotonin and norepinephrine reuptake inhibit*" or SNRI* or SNORI* or "Serotonin antagonist and reuptake inhibit*" or SARI* or "Reversible Monoamine Oxidase Inhibit*" or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*).ti,ab.
52.	*flupentixol/
53.	(Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine).ti,ab.
54.	(5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine).ti,ab.
55.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine).ti,ab.
56.	*pregabalin/ or *gabapentin/
57.	(gabapentin* or pregabalin*).ti,ab.
58.	or/40-57
59.	37 and 58
60.	39 or 59
61.	quality-adjusted life years/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.

69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/61-81
83.	statistical model/
84.	exp economic aspect/
85.	83 and 84
86.	*theoretical model/
87.	*nonbiological model/
88.	stochastic model/
89.	decision theory/
90.	decision tree/
91.	monte carlo method/
92.	(markov* or monte carlo).ti,ab.
93.	econom* model*.ti,ab.
94.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
95.	or/85-94
96.	health economics/
97.	exp economic evaluation/
98.	exp health care cost/
99.	exp fee/
100.	budget/
101.	funding/
102.	budget*.ti,ab.
103.	cost*.ti.
104.	(economic* or pharmaco?economic*).ti.
105.	(price* or pricing*).ti,ab.
106.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
107.	(financ* or fee or fees).ti,ab.
108.	(value adj2 (money or monetary)).ti,ab.
109.	or/96-108
110.	60 and (82 or 95 or 109)

NHS EED and HTA (CRD) search terms

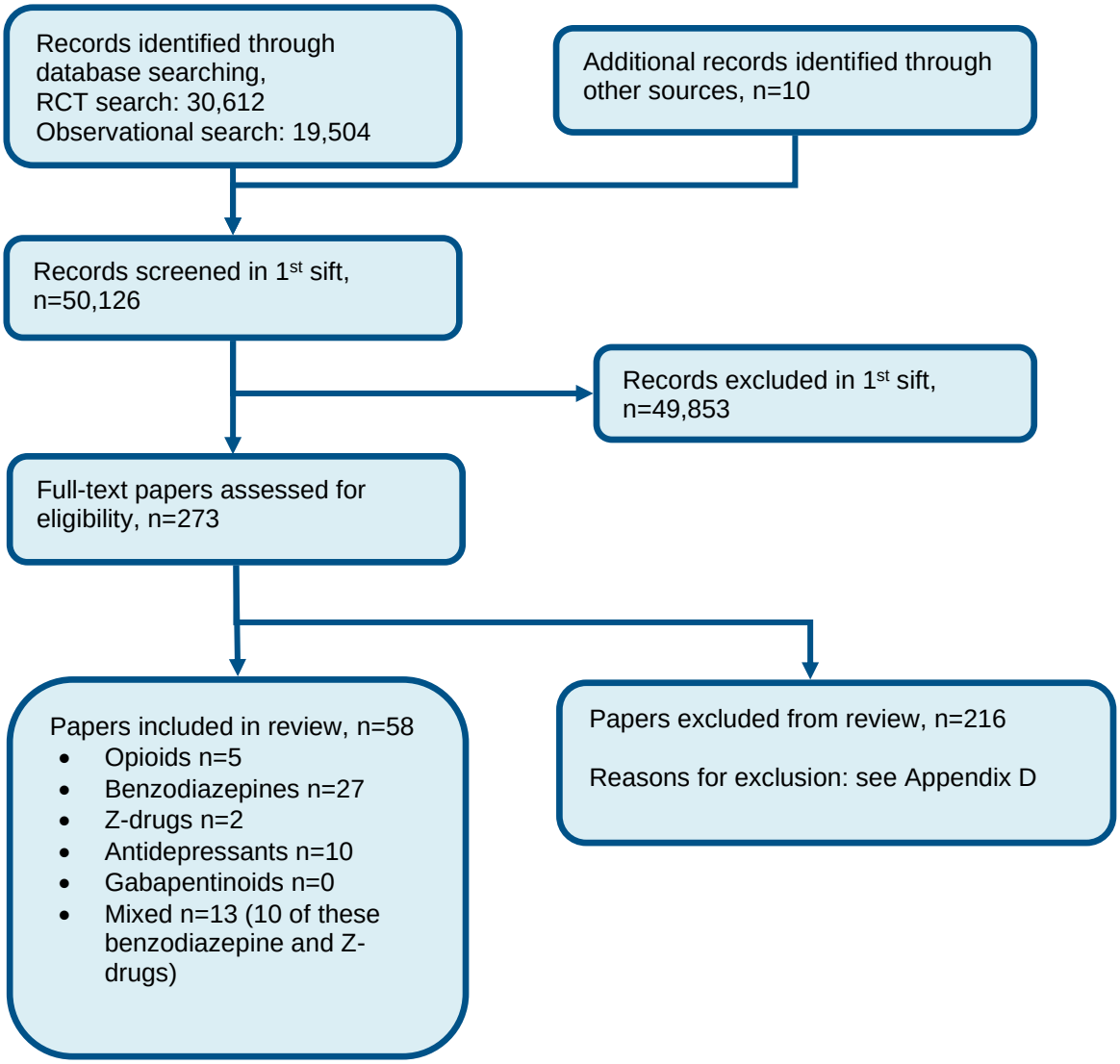
#1.	(MeSH DESCRIPTOR Substance-Related Disorders)
#2.	(MeSH DESCRIPTOR Substance Withdrawal Syndrome)
#3.	(MeSH DESCRIPTOR Inappropriate Prescribing EXPLODE ALL TREES)
#4.	(MeSH DESCRIPTOR Medical Overuse)
#5.	(MeSH DESCRIPTOR Deprescriptions EXPLODE ALL TREES)
#6.	(MeSH DESCRIPTOR Prescription Drug Misuse EXPLODE ALL TREES)
#7.	(MeSH DESCRIPTOR Medication Therapy Management)
#8.	(((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw* or depend*) adj2 (drug* or medicine* or medicat* or medical* or pharm*)))
#9.	(((over* or inappropriate or misus* or abuse* or abusing or long* term or longterm or short* term or short term or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* or safe* or manag* or withdraw*) adj3 (prescription* or prescrib*)))
#10.	((addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)))
#11.	((deprescription* or de-prescription* or deprescrib* or de-prescrib*))
#12.	(((therap* or treat*) adj2 (manag* or substit*)))
#13.	(((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*))
#14.	MeSH DESCRIPTOR Narcotic-Related Disorders
#15.	(((drug* or medic*) adj2 (prescription* or prescrib*)))
#16.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17.	(MeSH DESCRIPTOR narcotics EXPLODE ALL TREES)
#18.	(((analgesic* adj3 narcotic adj3 agent*) or (opioid* or opiate*)))
#19.	((alfentanil* or alphaprodine* or buprenorphine* or butorphanol* or codeine* or co-codamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphine* or dipipanone* or ethylmorphine* or fentanyl* or heroin* or hydrocodone* or hydromorphone* or levorphanol* or meperidine* or meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*))
#20.	((z drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon))
#21.	(MeSH DESCRIPTOR Eszopiclone)
#22.	((generation adj3 hypnotic*))
#23.	(MeSH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES)
#24.	((benzodiazepin* or bzd or Alprazolam or Chlordiazepoxide or Clobazam or Clonazepam or Diazepam or Flurazepam or Loprazolam or Lorazepam or Lormetazepam or Midazolam or Nitrazepam or Olanzapine or Oxazepam or Temazepam))
#25.	(MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES)
#26.	((antidepress* or anti depress* or thymoanaleptic* or thymoleptic* or MAOI* or NDRI* or SSRI* or SNRI* or SNORI* SARI* or RIMA* or tricyclic* or TCA* or tetracyclic* or TeCA*))
#27.	(("monoamine oxidase inhibit*"))
#28.	((Norepinephrine adj2 dopamine))
#29.	(("Selective serotonin reuptake inhibit*"))
#30.	((Serotonin adj2 norepinephrine))

#31.	((Serotonin antagonist))
#32.	(("Reversible Monoamine Oxidase Inhibit*"))
#33.	(MeSH DESCRIPTOR Flupenthixol EXPLODE ALL TREES)
#34.	((Agomelatine or Aripiprazole or Benactyzine or Clorgyline or Deanol or Desvenlafaxine* or Duloxetine* or Flupentixol or Iproniazid or Isocarboxazid or Levomilnacipran or Lithium* or Mirtazapine or Moclobemide or Nialamide or Phenelzine or Pizotyline or Quetiapine* or Reboxetine or Rolipram or Selegiline or Sertraline or Tranylcypromine or Vilazodone* or Vortioxetine))
#35.	((5-Hydroxytryptophan or Amisulpride or Bupropion or Citalopram or Escitalopram or Fluoxetine or Fluvoxamine or Maprotiline or Mianserin or Paroxetine or Quipazine or Ritanserin or Sulpiride or Trazodone or Tryptophan or Venlafaxine or Viloxazine))
#36.	((Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opipramol or Protriptyline or Trimipramine))
#37.	(MeSH DESCRIPTOR pregabalin)
#38.	((gabapentin* or pregabalin*))
#39.	(#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#40.	#16 AND #39
#41.	(((withdraw* or prescription* or prescrib*) adj2 (opioid* or opiate*)))
#42.	MeSH DESCRIPTOR Opiate Substitution Treatment
#43.	MeSH DESCRIPTOR Opioid-Related Disorders
#44.	#41 OR #42 OR #43
#45.	#40 OR #44

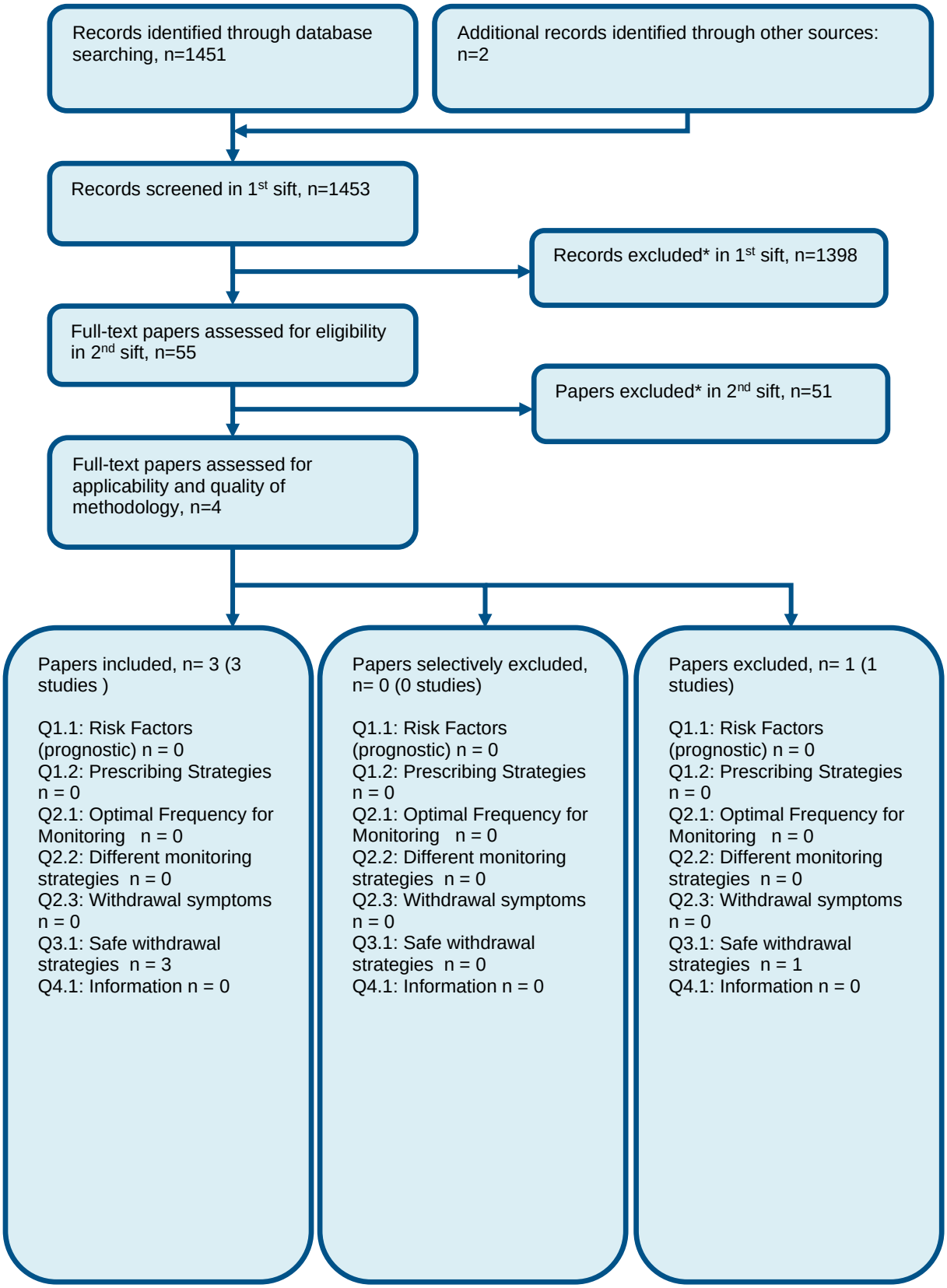
1
2

Appendix C Effectiveness evidence study selection

Figure 3: Flow chart of clinical study selection for the review of Withdrawal Interventions



Appendix D Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix E Effectiveness evidence:

E.1 Opioids

Study	Hooten 2015[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in USA; Setting: Comprehensive Pain Rehabilitation Centre Interdisciplinary Treatment Program (ITP) at Mayo Clinic Rochester MA.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 15 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Urine toxicology screening
Stratum	Opioids
Subgroup analysis within study	Not applicable:
Inclusion criteria	Age≥ 21 years, daily morphine equivalent dose ≥ 60mg and non-cancer chronic pain >6 months duration
Exclusion criteria	Current use of varenicline, history of major cardiovascular, pulmonary, surgical or psychiatric condition that would limit full participations in the ITP
Recruitment/selection of patients	Unclear; patients were recruited at the time of admission to the Interdisciplinary Treatment Program (ITP)
Age, gender and ethnicity	Age - Median (IQR): Varenicline: 49 (36-60) Placebo 46 (29-53). Gender (M:F): 13:5. Ethnicity: Caucasian
Further population details	Chronic pain patients undergoing opioid detoxification in an interdisciplinary pain program

Extra comments	N/A
Indirectness of population	No indirectness
Interventions	Both interventions were alongside a taper program: medically directed opioid detoxification as part of an interdisciplinary pain treatment program. Opioid detoxification is a well-established component of the ITP, with the opioid medication identified at admission determining each individual's taper schedule, all aiming to eliminate opioid use by the conclusion of the ITP. All opioid tapers were medically directed. The ITP is of 3-week duration and a cognitive behavioural model served as the basis for treatment. Admissions occur on a revolving basis with patients attending 8h daily for 15 consecutive working days. The primary goal of treatment was functional restoration. (n=10) Intervention 1: Varenicline plus Interdisciplinary Treatment Program (ITP) based on a cognitive behavioural model and including medically directed opioid taper. Varenicline 0.5 mg once daily for days 1 to 3, twice daily for days 4 to 7, then 1 mg twice daily for days 8 to 15plus ITP: Patients attend 8 hours/day for 15 consecutive working days. Duration 15 days. Concurrent medication/care: Not specified. Indirectness: No indirectness (n=11) Intervention 2: Placebo plus Interdisciplinary Treatment Program (ITP) based on a cognitive behavioural model and including medically directed opioid taper. Identically appearing tablets with varenicline plus ITP: Patients attend 8 hours/day for 15 consecutive working days. Duration 15 days. Concurrent medication/care: Not specified. Indirectness: No indirectness
Funding	Academic or government funding (The Mayo Foundation, Rochester MN)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANAGED WITHDRAWAL; INTERDISCIPLINARY TREATMENT PROGRAM BASED ON A COGNITIVE BEHAVIOURAL MODEL AND INCLUDING MEDICALLY DIRECTED OPIOID TAPER PLUS VERENICLINE versus MANAGED WITHDRAWAL; INTERDISCIPLINARY TREATMENT PROGRAM BASED ON A COGNITIVE BEHAVIOURAL MODEL AND INCLUDING MEDICALLY DIRECTED OPIOID TAPER PLUS PLACEBO

Protocol outcome 1: Reduction/cessation of prescribed drug use

-Actual outcome 1: Number of people who discontinued (assessed each working day from baseline during detoxification; assumed to be three weeks i.e., duration of ITP program); Group 1: 7/7, Group 2: 11/11; Comments: these numbers are inferred from the outcome 'median time to completion of tapering' which is taken to imply that all participants who completed the treatment program discontinued opioids.

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Vague outcome, especially due to no follow-up; Indirectness of outcome: No indirectness; Baseline details: Between group difference in the morphine equivalent dose at baseline of 60 mg/day (45%), difference in BMI of 8.4 kg/m (25%); Group 1 Number missing: 3, Reason: Withdrew from study; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Opioids: Decrease in severity of withdrawal symptoms- Clinical Opiate Withdrawal scale (COWS) at Assessed each working day from baseline during detoxification (assumed to be 3 weeks); Group 1: 5/7, Group 2: 4/11; Comments: Study assessed the linear regression for each person over time and analysed the slope – a negative regression indicates a decrease in COWS score over time. The slope of the regression being negative in 5/7 people in the varenicline group and 4/11 in the placebo group was interpreted to Indicate that opioid withdrawal symptoms tended to decrease over time in those treated with varenicline and increase over time in those treated with placebo Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Outcome results were inferred from papers' regression analysis of severity of withdrawal symptoms outcome from the number of patients for which the slope was negative in each group taken to indicate a decrease in severity. Also, COWS baseline scores were not available.; Indirectness of outcome: No indirectness; Baseline details: Between group difference in the morphine equivalent dose at baseline of 60 mg/day (45%), difference in BMI of 8.4 kg/m (25%); baseline scores were not available.; Group 1 Number missing: 3, Reason: Withdrew from study; Group 2 Number missing: 0, Reason: N/A The paper also reported outcomes of time to completion of tapering and pain severity which met the review protocol but were reported in an unusable format for analysis.	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

Study	**Jackson 2021[118]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in USA; Setting: Outpatient
Line of therapy	1st line
Duration of study	Not clear: for duration of weaning regimen (different in each person)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic pain patients referred to the pain management clinic for opioid weaning and/or discontinuation
Stratum	Opioids:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Males or females aged 18-65 years; referred to the pain management clinic for opioid weaning and/or discontinuation; English speaking
Exclusion criteria	Pregnancy or nursing mothers; significant psychologic disease requiring ongoing treatment
Recruitment/selection of patients	Informational flyers provided to chronic pain patients who met inclusion criteria by their treating pain specialist provider.
Age, gender and ethnicity	Age - Mean (SD): 56.5 (17.3) years. Gender (M:F): 8/7 (for 15 people followed up). Ethnicity: White 14 (93.3%); Black 1 (6.7%)
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Acupuncture + standard outpatient medication management with opioid weaning. Acupuncture sessions included with each office visit. National Acupuncture Detoxification Association (NADA) protocol for auricular acupuncture. Administered on 5 bilateral points of the participants' ear, in accordance with NADA protocol. The depth of the 25mm sterile spring style acupuncture needle was dependent on the anatomical structure of the participant and position of each acupoint with around 5mm. Administration was

	performed without a guide or rotation. In accordance with NADA protocol, needles remained in place for 35 minutes. Once a month until opioid weaning was complete. Both groups received standard outpatient medication management with opioid weaning. This entailed monthly visits with gradual reductions (10-20% overall MED) in combination with adjuvant non-opioid medications and therapies. Completion of the weaning regimen was determined by overall MED (<90 MED) and individual patient functionality as determined by the treating provider. Further reductions in MED were encouraged but are often not attainable depending on each patient's chronic pain symptomatology. Duration Until opioid weaning complete. Concurrent medication/care: Adjuvant non-opioid medications and therapies as part of the standard medication management could include antidepressants, muscle relaxants, NSAIDs, acetaminophen, anticonvulsants, and alpha-2 adrenergic agonists. Additional therapies included physical therapy and psychological support. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=7) Intervention 2: Standard medication management + opioid weaning regimen: This entailed monthly visits with gradual reductions (10-20% overall MED) in combination with adjuvant non-opioid medications and therapies. Completion of the weaning regimen was determined by overall MED (<90 MED) and individual patient functionality as determined by the treating provider. Further reductions in MED were encouraged but are often not attainable depending on each patient's chronic pain symptomatology. Duration Until opioid weaning complete. Concurrent medication/care: Adjuvant non-opioid medications and therapies as part of the standard medication management could include antidepressants, muscle relaxants, NSAIDs, acetaminophen, anticonvulsants, and alpha-2 adrenergic agonists. Additional therapies included physical therapy and psychological support. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPUNCTURE + STANDARD MEDICATION MANAGEMENT + OPIOID WEANING REGIMEN versus STANDARD MEDICATION MANAGEMENT + OPIOID WEANING REGIMEN

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Opioids: Morphine equivalent dose (MED) at post-intervention (completing of weaning); Group 1: mean 78 (SD 44); n=9, Group 2: mean 125 (SD 124); n=6
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness; Baseline details: Difference in the outcome at baseline is greater than the effect estimate; Blinding details: Dose reductions determined by the caregiver who was blinded; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: lost to follow-up Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Opioids: Subjective withdrawal symptoms (Clinical Institute Narcotic Assessment (CINA)) at post-intervention (completing of weaning); Group 1: mean 6.4 (SD 3.6); n=9, Group 2: mean 7.1 (SD 3.8); n=6, CINA range unclear Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Difference in the outcome at baseline is greater than the effect estimate; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: lost to follow-up Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed - Actual outcome for Opioids: Pain (numerical rating scale (NRS)) at post-intervention (completing of weaning); Group 1: mean 5.2 (SD 1.7); n=9, Group 2: mean 6.9 (SD 1.5); n=6; NRS range unclear Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: lost to follow-up	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

Study	**Sullivan 2017[253]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=35)
Countries and setting	Conducted in USA; Setting: UW Medicine centre for Pain Relief in Seattle, Washington.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 34 weeks

Method of assessment of guideline condition	Unclear method of assessment/diagnosis: In-person screening visit with study physician assistant
Stratum	Opioids
Subgroup analysis within study	Not applicable:
Inclusion criteria	CNCP, defined as pain on more than half of the days in the past six months; use of opioid medication on more than half of the previous 90 days; willingness to taper opioid dose by at least 50% (or 120 mg MED, whichever was less); daily MED > 50 mg; recent urine drug test with no aberrancy; and future visits scheduled at the Centre for Pain Relief. After enrolment began, the requirement for a 50% (or 120 mg) taper goal, recent urine drug test, and future visits scheduled at the Centre for pain Relief were removed and the required opioid dose at study entry was lowered to >25 mg MED in order to increase enrolment.
Exclusion criteria	Currently receiving treatment for cancer (other than non-melanoma skin cancer); medical comorbidity with life expectancy less than one year or otherwise considered medically unstable (as judged by the referring physician); use of parental transdermal or transmucosal opioids or naltrexone within the previous month; currently residing in a skilled nursing or long-term care facility; currently using any implanted device for pain control (e.g. intrathecal pump, spinal cord stimulator, peripheral nerve stimulator); surgery within the previous month or planned during the next 6 months; report of suicide attempt or psychiatric hospitalisation in the past 10 years or current suicidal ideation with specific plan or intent; significant cognitive impairment as assessed using the 6-item screener; report of psychotic symptoms on the Modified MINI Interview and report of current abuse of substances other than nicotine or marijuana according to the National Institute on Drug Abuse Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (marijuana was allowed because it is legal under Washington State Law). The exclusion for psychiatric hospitalizations within the past 10 years was changed to within the past year after study enrolment began in order to increase enrolment.
Recruitment/selection of patients	Participants were recruited through clinician or self-referrals and clinic advertisement at the UW Medicine Centre for Pain Relief and via referrals from other UW medicine specialty and primary care clinics and other Seattle pain clinics.
Age, gender and ethnicity	Age - Mean (SD): 54.4 (10.1). Gender (M:F): 10/25. Ethnicity: 83% white
Further population details	Mean (SD) duration of pain was 13.8 (8.2) years; mean (SD) duration of current opioid use was 10.2 (4.3) years; mean (SD) daily opioid dose at baseline was 207.2 mg MED (269.3) in the taper support group and

	245.2 mg (347.3) in the usual care group. At baseline, 11/18 (61%) of the taper support group and 9/17 (53%) of the usual care group scored 10 or more on the PHQ-9 (moderate or greater depressive symptoms). Patients agreed not to initiate buprenorphine treatment while enrolled in the study. All other concurrent pain treatment was allowed.
Extra comments	N/A
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Multicomponent psychological opioid taper support (including motivational interviewing and CBT) + taper. At the screening visit, patients had been shown a 14-minute video of interviews with patients who has successfully tapered off opioids concerning what they had gained by this. The intervention began with a visit to the principal investigator, an experienced pain medicine/psychiatry physician, to evaluate whether adjustment or initiation of non-opioid psychotropic medication was indicated. This physician then adjusted or provided a prescription for new medication as indicated and supervised the study physician assistant (PA) in monitoring patient response over the course of the intervention period. Next, patients met with the study PA for a Motivational Interview-based sessions concerning opioid tapering that included: 1) eliciting the patients' history related to pain, opioid therapy and related difficulties; 2) eliciting change talk related to tapering; 3) education about dose-related health risks; 4) identifying practical and psychological barriers to tapering opioid dose and problem-solving ways to overcome these; and 5) developing a commitment to change with respect to opioid therapy. Patients were also show a short video of interviews with the same patients who were in the first video they had seen prior to randomisation, concerning coping with challenges of tapering off opioids. The taper support protocol included an additional 17 weekly 30-minute sessions with the PA. Patients were provided with an opioid medication prescription for the week at each visit. Patients were encouraged to attend all sessions in person but were allowed to complete up to every other session by telephone. At the sessions, patients reported on pain, withdrawal, and mood/anxiety symptoms. Each session included pain self-management training modelled after empirically supported cognitive-behavioural therapy (CBT) interventions for chronic pain. The sessions included: 1) rationale for pain self-management and education about the neurophysiology of pain and the role of cognitive and behavioural variable in chronic pain and adjustment to it; 2) behavioural goal setting; 3) education about, training in, and practice of various relaxation techniques (diaphragmatic breathing, progressive muscle relaxation, body scans, applied

	relaxation); 4) behavioural activation techniques, activity scheduling and instruction in activity pacing; 5) education regarding the role of cognitions in negative affective responses to pain and instruction in positive pain coping self-statements and distraction techniques; 6)sleep hygiene education; and 7) education about and training in ways to maintain gains, reduce the risk of pain flare-ups, and cope with pain flare-ups if they do occur. Motivational Interviewing was used periodically to address ambivalence about tapering as needed. Patients completed 'personal action plans' at each session for home activities to perform between sessions (e.g., practice of relaxation techniques, personal goal-related activities. The intervention protocol also included booster phone calls from the PA at 24, 28 and 32 weeks after randomization. At each call, patients were asked to review their experiences with their personal action plans for pain self-management and activity participation and with relapse prevention plans they had created. These plans were modified, and pain management skills were reviewed as needed. A detailed protocol for each session was developed for the PA to follow and a patient workbook for the 18-weekly sessions that included educational content related to each session. Participants were given this workbook and asked to read each session's section between sessions and bring the workbook to each session. They were also given CDs with relaxation exercises for home practice and a book about pain self-management (D.C. Turk and F. Winter, The Pain Survival Guide, American Psychological Association, 2005) and were asked to read specific chapters in the book between sessions. Duration 22 weeks. Concurrent medication/care: The PA assumed all opioid medication prescribing during the intervention taper period. For those remaining on opioid medication at the end of this period, their prior prescriber resumed prescribing. The opioid taper protocol specified a 10% reduction of the original dose per week until 30% of the original dose was reached. At that point, the 10% was recalculated on the basis of this dose and the taper then proceeded by 10% of this new dose per week. Patients were allowed to pause the taper and hold their opioid dose steady at any point. They were not allowed to increase their opioid dose; those wishing to do so were withdrawn from the visits with the PA but retained in the study for data collection. Indirectness: No indirectness Comments: Prior to seeing patients the PA was trained by two clinical psychologists in motivational interviewing adapted for use with patients considering opioid tapering and, in the pain, self-management training intervention; and was supervised in intervention delivery in regular sessions with the pain medicine/psychiatry physician and the psychologists.

	(n=17) Intervention 2: Usual care (usual prescribing). Patients received care for their pain, including opioid prescriptions from their usual prescribers, as they would as if they were not in the study, with no restrictions other than avoiding buprenorphine for the duration of the study. Also at the screening visit, patients had been shown a 14-minute video of interviews with patients who has successfully tapered off opioids concerning what they had gained by this. Duration 22 weeks. Concurrent medication/care: Not applicable. Indirectness: Serious indirectness; Indirectness comment: There was no tapering aim
Funding	Academic or government funding (The National Institute on drug abuse)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTICOMPONENT OPIOID TAPER SUPPORT + TAPER versus USUAL CARE (USUAL PRESCRIBING)

Protocol outcome 1: Quality of life

- Actual outcome for Opioids: Patient global Impression of Change (PGIC) at 22 weeks post randomization; Group 1: 9/16, Group 2: 3/13; Comments: Number of people rating themselves as at least moderately better since the study begun; number of people analysed was not clear and was inferred from descriptive results for this outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments -; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 4, Reason: did not complete follow-up

- Actual outcome for Opioids: Patient Global Impression of Change (PGIC) at 34 weeks post randomization; Group 1: 10/15, Group 2: 6/16; Comments: The number analysed was unclear and was inferred from descriptive results given for the outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments -; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 3, Reason: did not complete follow-up; Group 2 Number missing: 2, Reason: did not complete follow-up

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Opioids: Opioid dose (mean daily opioid dose in the past week) at 22 weeks post randomization; adjusted MD -42.90mg (95% CI -92.42 to 6.62). Group 1: n=18, Group 2: n=17; Comments: Assessed via self-report or obtained through electronic medical records if self-report data were unavailable.

Opioid use was converted to MED using the Washington State Agency Medical Directors' Group Opioid Dose Calculator. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments -; Indirectness of outcome: No indirectness; Baseline details: Baseline mean (SD) Intervention vs Control group : 207.17 (269.38) vs 245.19 (347.35); Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 2, Reason: did not complete follow-up

- Actual outcome for Opioids: Opioid dose (mean daily opioid dose in the past week) at 34 weeks post randomization; adjusted MD -26.71mg (95%CI -83.04 to 29.62). Group 1: n=18, Group 2: n=17; Comments: Assessed via self-report or obtained through electronic medical records if self-report data were unavailable. Opioid use was converted to MED using the Washington State Agency Medical Directors' Group Opioid Dose Calculator. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments -; Indirectness of outcome: No indirectness; Baseline details: Baseline mean (SD) Intervention vs Control group : 207.17 (269.38) vs 245.19 (347.35); Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 1, Reason: did not complete follow-up

- Actual outcome for Opioids: Opioid discontinuation at 22 weeks post randomization; Group 1: 1/16, Group 2: 1/15; Comments: Unclear how this was measured; likely to have been self-reported. Outcome was not part of the protocol but was extracted as it was reported in the results section.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 2, Reason: did not complete follow-up

- Actual outcome for Opioids: Opioid discontinuation at 34 weeks post randomization; Group 1: 2/16, Group 2: 2/16; Comments: Unclear how this was measured; likely to have been self-reported. Outcome was not part of the protocol but was extracted as it was reported in the results section.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 1, Reason: did not complete follow-up

Actual outcome for Opioids: Number of people who reduced opioids by 50% or more at 22 weeks post randomization; Group 1: 7/18, Group2: 2/16; Comments: Unclear how this was measured; likely to have been self-reported. Outcome was not part of the protocol but was extracted as it was reported in the results section.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: did not complete follow-up.

Actual outcome for Opioids: Number of people who reduced opioids by 50% or more at 34 weeks post randomization; Group 1: 9/16, Group 2: 5/16; Comments: Unclear how this was measured; likely to have been self-reported. Outcome was not part of the protocol but was extracted as it was reported in the results section. Exact number of people analysed for this outcome at 34 weeks was unclear.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 1, Reason: did not complete follow-up

Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Opioids: Pain severity at 22 weeks post randomization; adjusted MD -0.68 (95%CI -2.01 to 0.64)Group 1: n=18, Group 2: n=17; Brief pain Inventory (BPI) 0-10 Top=High is poor outcome. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 2, Reason: did not complete follow-up

- Actual outcome for Opioids: Pain severity at 34 weeks post randomization; adjusted MD -0.91 (95%CI -2.30 to 0.48) Group 1: n=18, Group 2: n=17; Brief Pain Inventory (BPI) 0-10 Top=High is poor outcome. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose; Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 1, Reason: did not complete follow-up Protocol outcome 4: Improvements in adverse effects commonly associated with long-term prescribed medication use - Actual outcome for Opioids: Sleep difficulties (Insomnia severity) at 22 weeks post randomization; adjusted MD -3.13 (95%CI -7.22 to 0.96) Group 1: n=18, Group 2: n=17. Insomnia Severity Index (ISI) 0-28 Top=High is poor outcome. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose plus potential difference in outcome at baseline intervention vs control group mean (SD): 15.56 (7.52) vs 17.12 (6.62); Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 2, Reason: did not complete follow-up - Actual outcome for Opioids: Sleep difficulties (Insomnia severity) at 34 weeks post randomization; adjusted MD -1.19 (95%CI -5.49 to 3.11)Group 1: n=18, Group 2: n=17; Insomnia Severity Index (ISI) 0-28 Top=High is poor outcome. Using ITT and a series of linear regression analyses, with separate models for each outcome at each time point, to test whether the two study groups differed at 22 and 34 weeks on the outcome measures, adjusting for the baseline value of the outcome measure. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in MED baseline dose plus potential difference in outcome at baseline intervention vs control group mean (SD): 15.56 (7.52) vs 17.12 (6.62); Blinding details: Opioid prescribing was not assumed by PA in the usual care group as was done in the intervention group.; Group 1 Number missing: 2, Reason: did not complete follow-up; Group 2 Number missing: 1, Reason: did not complete follow-up	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Distress

Study	**Zheng 2008[298]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=35)
Countries and setting	Conducted in Australia; Setting: Primary care; the Barbara Walker Centre for Pain Management (BWCPM) at the St Vincent's Hospital, Melbourne, Australia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6-week intervention + 12-week follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All volunteer participants were assessed by pain physicians according to the Classification of Chronic Pain Definitions published by the International Association for the Study of Pain (IASP)
Stratum	Opioids
Subgroup analysis within study	Not applicable
Inclusion criteria	Pain patients aged between 18 and 80 years (inclusive), suffering from non-malignant pain for more than 3 months, and using opioid like medication (OLM)
Exclusion criteria	Not specified
Recruitment/selection of patients	not specified
Age, gender and ethnicity	Age - Mean (SD): 49.71 (11.86). Gender (M:F): 18:17. Ethnicity: not specified
Further population details	1. Gabapentinoids: not applicable 2. Half-life of benzodiazepines: not applicable 3. Setting: outpatient
Extra comments	REA vs sham electroacupuncture group pain history (Mean years) (SD): 19.8 (24.5) vs 13 (11.1) years; OLM use: Codeine (n=24), Methadone (n=1), Oxydocodone (n=9), Morphine (n=7), Tramadol (n=10)

Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Non-pharmacological interventions - Acupuncture. Real electroacupuncture (with concurrent OLM reduction schedule): two pairs of acupuncture points, Shousanli LI10/Hegu LI4 and Zusanli ST36/Fenglong ST40 were selected unilaterally and alternated from side to side in different treatment sessions for invasive EA (Myer 501, Meyer Medical Electronics, Australia) at an alternative frequency of 2 and 100 Hz. Up to five supplementary acupuncture points were chosen according to the side effects of OLM that participants experienced during that week. The intervention was given twice a week, each treatment lasting 30 min with a 20-min EA stimulation time. Duration 6 weeks. Concurrent medication/care: The pain physicians developed OLM reduction schedules for the participants, based on summaries of the weekly OLM consumption. A researcher who was blinded to the treatment allocation phoned each participant to inform them of the schedule and encouraged them to reduce OLM consumption. In total three telephone calls were made to each participant during the 20 weeks of the study. Indirectness: No indirectness Further details: 1. Addiction support services: not stated (n=18) Intervention 2: Non-pharmacological interventions - Acupuncture. Sham acupuncture (with concurrent OLM reduction schedule): acupuncture needles were superficially inserted to non-classical acupuncture points with no stimulation and connected to a mock EA stimulator. The intervention was given twice a week, each treatment lasting 30 min with a 20-min mock EA stimulation time. Duration 6 weeks. Concurrent medication/care: The pain physicians developed OLM reduction schedules for the participants, based on summaries of the weekly OLM consumption. A researcher who was blinded to the treatment allocation phoned each participant to inform them of the schedule and encouraged them to reduce OLM consumption. In total three telephone calls were made to each participant during the 20 weeks of the study. Indirectness: No indirectness Further details: 1. Addiction support services: not stated
Funding	Academic or government funding (Faculty of Life Sciences, RMIT university; one author also supported by an Australian Postgraduate Award (APA) and an Australian Acupuncture and Chinese Medicine Association)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REAL ELECTROACUPUNCTURE (REA) versus Sham Electroacupuncture (SEA) Protocol outcome 1: Reduction/cessation of prescribed drug use	

- Actual outcome for Opioids: OLM consumption (mg/week) at Post-intervention (study week 8); Group 1: mean 281.4 (SD 401.9); n=17, Group 2: mean 219.1 (SD 293); n=18; OLM dosage was converted to morphine equivalent (MED).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Self-reported; Indirectness of outcome: No indirectness; Baseline details: Mean (SD) baseline REA vs sham electroacupuncture OLM consumption (mg/week): 461.6 (462.6) vs 295.5 (288); Blinding details: Due to the nature of the treatment, person administering care could not be blinded; Group 1 Number missing: 8, Reason: n=5 dropped out (1 could not tolerate the sensation of needling, 1 had aggravation of symptoms, 1 had transportation problems, 1 reason unclear, 1 had baby-sitting problems); n=3 unable to be contacted at follow-up; Group 2 Number missing: 4, Reason: n=4 dropped out (2 due to transportation problems, 1 had to go back to work, 1 had a family issue)

-Actual outcome for Opioids: OLM consumption (mg/week) at follow-up (study week 20, i.e. 12 weeks post intervention); Group 1: mean 344.7 (SD 396.8); n=17, Group 2: mean 239.0 (SD 294.5); n=18; OLM dosage was converted to morphine equivalent (MED).

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Self-reported; Indirectness of outcome: No indirectness; Baseline details: Mean (SD) baseline REA vs sham electroacupuncture OLM consumption (mg/week): 461.6 (462.6) vs 295.5 (288); Blinding details: Due to the nature of the treatment, person administering care could not be blinded; Group 1 Number missing: 8, Reason: n=5 dropped out (1 could not tolerate the sensation of needling, 1 had aggravation of symptoms, 1 had transportation problems, 1 reason unclear, 1 had baby-sitting problems); n=3 unable to be contacted at follow-up; Group 2 Number missing: 4, Reason: n=4 dropped out (2 due to transportation problems, 1 had to go back to work, 1 had a family issue)

Protocol outcome 2: Increase in symptoms for which the medication was originally prescribed
- Actual outcome for Opioids: Average pain at Post-intervention (study week 8); Group 1: mean 3.8 (SD 2); n=17, group 2: 4.8 (1.9); VAS 0-10, Top=High is Poor outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - Self-reported; Although from pre-specified primary outcome measures and results it looks like the VAS scores were reported for this outcome, this is not clearly stated and the study also appeared to have measured pain using the McGill questionnaire; Indirectness of outcome: No indirectness; Baseline details: Baseline average pain comparable REA vs SEA: 4.6 (1.6) vs 5.5 (1.7); but differences in baseline OLM consumption, incidents of side-effects; Blinding details: Due to the nature of the treatment, person administering care could not be blinded; Group 1 Number missing: 8, Reason: n=5 dropped out (1 could not tolerate the sensation of needling, 1 had aggravation of symptoms, 1 had transportation problems, 1 reason unclear, 1 had baby-sitting problems); n=3 unable to be contacted at follow-up; Group 2 Number missing: 4, Reason: n=4 dropped out (2 due to transportation problems, 1 had to go back to work, 1 had a family issue)

- Actual outcome for Opioids: Duration of pain (hr/day) at Post-intervention (study week 8); Group 1: mean 16.4 (SD 5.8); n=17, Group 2: mean 14.6 (SD 4.5); n=18

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - Self-reported; Indirectness of outcome: No indirectness; Baseline details: Baseline average duration of pain comparable REA vs SEA: 16.8 (5.3) vs 15.6 (4.6); but differences in baseline OLM consumption, incidents of side-effects; Blinding details: Due to the nature of the treatment, person administering care could not be blinded; Group 1 Number missing: 8, Reason: n=5 dropped out (1 could not tolerate the sensation of needling, 1 had aggravation of symptoms, 1 had transportation problems, 1 reason unclear, 1 had baby-sitting problems); n=3 unable to be contacted at follow-up; Group 2 Number missing: 4, Reason: n=4 dropped out (2 due to transportation problems, 1 had to go back to work, 1 had a family issue)	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Distress

Study	**Zheng 2019[297]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=108)
Countries and setting	Conducted in Australia; Setting: Pain Services Unit of the Royal Melbourne Hospital, the Caulfield Pain Management and Research Centre of the Caulfield Hospital, the Sunshine Hospital, RMIT Clinical Trial Laboratory and one site in Geelong, in Victoria, Australia.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks + 3 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were screened following a three-step process by a research assistant, a researcher and then by medical doctors via telephone, pro forma and via face-to-face interview.
Stratum	Opioids
Subgroup analysis within study	Not applicable

Inclusion criteria	Participants aged between 18 and 85 years at entry, confident in conversational and reading English, suffering from chronic musculoskeletal pain, regardless of pain locations, and who had taken OM regularly for more than two months without dose limitation.
Exclusion criteria	Active abuse of OM as judged by pain specialists, severely depressed with suicidal tendency as judged by pain specialists, unstable hear condition, pregnancy or intent to become pregnant, breastfeeding women, epilepsy, brain tumour, current cancer haemophilia or wearing cardiac pacemakers, no general practitioner available for liaison, acupuncture treatment in the last 12 months, or unwilling to reduce OM.
Recruitment/selection of patients	Participants were recruited from three hospital-based outpatient pain clinics, six medical centres and the community.
Age, gender and ethnicity	Age - Mean (SD): 56.32 (12.49). Gender (M:F): 47:61. Ethnicity: not specified
Further population details	1. Gabapentinoids: not applicable 2. Half-life of benzodiazepines: not applicable 3. Setting: outpatient
Extra comments	Patients with chronic musculoskeletal pain, consuming opioid medication (OM). Mean (SD) baseline morphine equivalent OM dose was 463.3 (438.6) in the EA group, 620.8 (792.5) in the sham electroacupuncture group and 871.4 (1,772.3) in the PMM group
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Non-pharmacological interventions - Acupuncture. Electroacupuncture (EA) + PMM: an acupuncture treatment manual was developed for training acupuncturists. The selection of acupuncture points was semi structured. In total, up to 12 needles were used for each session, consisting of four formula points for EA, including unilateral Shousanli LI10 and Hegu LI4, Zusanli ST36 and Fenglong ST40, and eight supplementary points chosen according to the adverse effects of OM that participants experienced during that week. Disposable acupuncture needles of 0.25-mm diameter and 30 mm or 40-mm length were used. Those points were selected for their proven analgesia and opioid-sparing effects. The protocol was designed by experienced and registered acupuncturists on the team with an intention to focus on opioid reduction. The acupuncture procedures followed those described in Zheng 2008 study. A battery-operated electroacupuncture instrument was connected to the handles of four needles in the main acupuncture points in the extremities to deliver electrical stimulation for 20 minutes at an alternating frequency of 2 and 100 Hz every three seconds. The

	intensity of stimulation was strong but comfortable and was adjusted once during the treatment. The treatment was given twice a week for four weeks, followed by once a week for two weeks. In total 12 sessions were delivered within 10 weeks. These were provided by registered acupuncturists with at least three years of clinical experience. Duration 10 weeks. Concurrent medication/care: During the run-in period, the general practitioners of the participants were notified. Their assistance in prescribing OMs and not introducing nonessential therapy during the trial was sought. Co-interventions were discouraged. Participants using other therapies for chronic pain such as herbal medicine, physiotherapy, chiropractic and osteopathy were required to either discontinue them before the trial or consistently maintain their use during the trial and record use in their diaries. All participants received PMM which was provided by pain specialists in the fifth week assisted by a standard manual. PMM intervention is described below. They then received EA for 10 weeks. Indirectness: No indirectness Further details: 1. Addiction support services: not stated (n=29) Intervention 2: Non-pharmacological interventions - Acupuncture. Sham electroacupuncture + PMM: a set of sham points was developed to match each real point for Sham Electroacupuncture and was stimulated with a manufacture-modified non-functioning EA stimulator. The treatment was given twice a week for four weeks, followed by once a week for two weeks. In total 12 sessions were delivered within 10 weeks. Duration 10 weeks. Concurrent medication/care: During the run-in period, the general practitioners of the participants were notified. Their assistance in prescribing OMs and not introducing nonessential therapy during the trial was sought. Co-interventions were discouraged. Participants using other therapies for chronic pain such as herbal medicine, physiotherapy, chiropractic and osteopathy were required to either discontinue them before the trial or consistently maintain their use during the trial and record use in their diaries. All participants received PMM which was provided by pain specialists in the fifth week assisted by a standard manual. PMM intervention is described below. They then received SA for 10 weeks. Indirectness: No indirectness Further details: 1. Addiction support services: not stated (n=31) Intervention 3: Non-pharmacological interventions - Patient advice/education and support (PMM alone). A pain and medication management information brochure was developed to standardize PMM across all study centres. Before randomization, pain specialists used the manual to explain to participants the impact of chronic pain, the potential problems associated with opioid medication, and individualised opioid medication reduction schedules with rapid-acting OMs reduced first, then the long-acting (slow/modified-release)OMs. Participants were asked to reduce their OM dosage by 30% in week 8, 50% by week 11 and 75%

	to 100% by week 14, as long as their pain did not get worse. Non-OM medications were either prescribed or increased for pain relief. Patients were allowed to modify those medications. The types and dosages of all non-OM pain relief medications were recorded. Pain specialists provided pain and medication education to each participant once in the whole trial. PMM was delivered by pain specialists at the pain clinics and followed up by a trained researcher who made regular calls to all participants to remind them of the OM reduction schedule. After the 10-week waiting period during which they received PMM, participants were given the opportunity to have EA treatment. Duration 10 weeks. Concurrent medication/care: During the run-in period, the general practitioners of the participants were notified. Their assistance in prescribing OMs and not introducing nonessential therapy during the trial was sought. Co-interventions were discouraged. Participants using other therapies for chronic pain such as herbal medicine, physiotherapy, chiropractic and osteopathy were required to either discontinue them before the trial or consistently maintain their use during the trial and record use in their diaries. Indirectness: No indirectness Further details: 1. Addiction support services: not stated
Funding	Academic or government funding (National Health and Medical Research Council (NHMRC), partial funding by the Helen McPherson Smith Trust)

Across comparisons, SDs were calculated using the standard error reported in the study for all continuous outcomes except for: 'Number of OM-related AEs per person' and 'Severity of OM-related AEs' outcomes for which SDs were available.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ELECTROACUPUNCTURE (EA) + PMM versus Sham Electroacupuncture +PMM
Protocol outcome 1: Quality of life
- Actual outcome for Opioids: QoL (SF-36- Total) at End of treatment (average of weeks 11-14); Group 1: mean 41.6 (SD 18); n=48, Group 2: mean 39.3 (SD 16.16); n=29; SF-36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

- Actual outcome for Opioids: QoL (SF-36- Physical health) at End of treatment (average of weeks 11-14); Group 1: mean 35 (SD 16.63); n=48, Group 2: mean 34.3 (SD 15.08); n=29; SF-36 Physical health 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

- Actual outcome for Opioids: QoL (SF-36- Mental health) at End of treatment (average of weeks 11-14); Group 1: mean 48.5 (SD 20.78); n=48, Group 2: mean 44.9 (SD 17.77); n=29; SF-36 Mental health 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

Protocol outcome 2: Reduction/cessation of prescribed drug use
- Actual outcome for Opioids: OM dosage at End of treatment (average of weeks 11-14); Group 1: adjusted mean 526.6 mg (SD 166.28); n=48, Group 2: adjusted mean 537.4 mg (SD 165.32); n=29; Comments: Recorded daily in the Medication and Pain Diaries. OM dosages were converted into oral morphine equivalent dosages

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in the outcome; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline morphine equivalent OM dose (mg/week) was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

- Actual outcome for Opioids: OM dosage at End of three-month follow-up (week 26); Group 1: adjusted mean 410.4 mg (SD 127.5); n=25, Group 2: adjusted mean 475.5 mg (SD 127.9); n=20; Comments: Recorded daily in the Medication and Pain Diaries. OM dosages were converted into oral morphine equivalent dosages

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline morphine equivalent OM dose (mg/week) was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 23, Reason: withdrew before treatment completion: due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); n=12 withdrew at follow-up; Group 2 Number missing: 9, Reason: withdrew before treatment completion due to allocated treatment not being effective or change of mind; withdrew at follow-up (n=7)
- Actual outcome for Opioids: 50% OM reduction at End of treatment (average of weeks 11-14); Group 1: 9/48, Group 2: 8/29

Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in the outcome; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline morphine equivalent OM dose (mg/week)
was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

Protocol outcome 3: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs
- Actual outcome for Opioids: Non-OM dosage at End of treatment (average of weeks 11-14); Group 1: mean 9.6 (SD 6.93); n=48 Group 2: mean 9.3 (SD 7); n=29 Medication quantification Scale version III was used to quantify consumption of non-OMs for pain. Non-OMs included simple analgesics, such as Panadol Osteo; nonsteroidal ani-inflammatory medication such as Nurofen, antidepressants and anticonvulsants used for pain relief.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

Protocol outcome 4: Increase in symptoms for which the medication was originally prescribed
- Actual outcome for Opioids: Intensity of the highest pain at End of treatment (average of weeks 11-14); Group 1: mean 6 (SD 2.08); n=48, Group 2: mean 5.9 (SD 2.15); n=29; VAS 0-10 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score
was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

- Actual outcome for Opioids: Intensity of the average pain at End of treatment (average of weeks 11-14); Group 1: mean 5.1 (SD 2.08); n=48, Group 2: mean 5.4 (SD 2.69); n=29; VAS 0-10 Top=High is poor outcom

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score
was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

Protocol outcome 5: Improvements in adverse effects commonly associated with long-term prescribed medication use

- Actual outcome for Opioids: Number of OM-related AEs per person at End of treatment (average of weeks 11-14); Group 1: mean 1.4 (SD 2.7); n=48, Group 2: mean 3.2 (SD 4); n=29

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

- Actual outcome for Opioids: Severity of OM-related AEs at End of treatment (average of weeks 11-14); Group 1: mean 5.6 (SD 10.4); n=48, Group 2: mean 12.9 (SD 20.1); n=29

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score
was 463.3 (438.6) in the EA group, 620.8 (792.5) in the Sham Electroacupuncture group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 2, Reason: withdrew due to allocated treatment not being effective or change of mind

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ELECTROACUPUNCTURE (EA) + PMM versus PAIN MEDICATION MANAGEMENT (PMM)
Protocol outcome 1: Quality of life

- Actual outcome for Opioids: QoL (SF-36- Total) at End of treatment (average of weeks 11-14); Group 1: mean 41.6 (SD 18.01); n=48, Group 2: mean 35.8 (SD 20.04); n=31; SF-36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score
was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; difference in baseline QoL scores 36.7 (22.6) vs 31 (21.6) is comparable to follow-up score difference; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: QoL (SF-36- Physical health) at End of treatment (average of weeks 11-14); Group 1: mean 35 (SD 16.63); n=48, Group 2: mean 30.6 (SD 17.26); n=31; SF-36- Physical health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; difference in baseline QoL scores 36.7 (22.6) vs 31 (21.6) is comparable to follow-up score difference; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: QoL (SF-36- Mental health) at End of treatment (average of weeks 11-14); Group 1: mean 48.5 (SD 20.78); n=48, Group 2: mean 41.1 (SD 23.38); n=31; SF-36-Mental health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint
Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Opioids: OM dosage at End of treatment (average of weeks 11-14); Group 1: adjusted mean 526.6 mg (SD 166.28); n=48, Group 2: adjusted mean 585.2 mg (SD 166.48); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group.; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: 50% OM reduction at End of treatment (average of weeks 11-14); Group 1: 9/48, Group 2: 4/31

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group.; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

Protocol outcome 3: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs

- Actual outcome for Opioids: Non-OM dosage at End of treatment (average of weeks 11-14); Group 1: mean 9.6 (SD 6.93); n=48, Group 2: mean 10.1 (SD 6.68); n=31; Medication quantification Scale version III was used to quantify consumption of non-OMs for pain. Non-OMs included simple analgesics, such as Panadol Osteo; nonsteroidal ani-inflammatory medication such as Nurofen, antidepressants and anticonvulsants used for pain relief. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated

treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

Protocol outcome 4: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Opioids: Intensity of the highest pain at End of treatment (average of weeks 11-14); Group 1: mean 6 (SD 2.08); n=48, Group 2: mean 6.6 (SD 2.23); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective or change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: Intensity of the average pain at End of treatment (average of weeks 11-14); Group 1: mean 5.1 (SD 2.08); n=48, Group 2: mean 5.8 (SD 2.23); n=31; VAS 0-10 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective or change of mind, difficulty travelling or time constraint

Protocol outcome 5: Improvements in adverse effects commonly associated with long-term prescribed medication use
- Actual outcome for Opioids: Number of OM-related AEs per person at End of treatment (average of weeks 11-14); Group 1: mean 1.4 (SD 2.7); n=48, Group 2: mean 2.5 (SD 3.3); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: Severity of OM-related AEs at End of treatment (average of weeks 11-14); Group 1: mean 5.6 (SD 10.4); n=48, Group 2: mean 11.4 (SD 18.9); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 463.3 (438.6) in the EA group, 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 12, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=3), worsening of symptoms n=2, difficulty with traveling (n=1), not satisfied with group allocation (n=1), had other pain-related treatment, accidentally randomized (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Sham Electroacupuncture +PMM versus PAIN MEDICATION MANAGEMENT (PMM)

Protocol outcome 1: Quality of life

- Actual outcome for Opioids: QoL (SF-36- Total) at End of treatment (average of weeks 11-14); Group 1: mean 39.3 (SD 16.16); n=29, Group 2: mean 35.8 (SD 20.04); n=31; SF-36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3); baseline QoL between score difference: 39.5 (25.3) vs 31 (21.6) was larger than Qol difference at follow up; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective or change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: QoL (SF-36- Physical health) at End of treatment (average of weeks 11-14); Group 1: mean 34.3 (SD 15.01); n=29, Group 2: mean 30.6 (SD 17.26); n=31; SF-36- Physical health 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM only group; baseline QoL between score difference: 39.5 (25.3) vs 31 (21.6) was larger than Qol difference at follow up; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: QoL (SF-36- Mental health) at End of treatment (average of weeks 11-14); Group 1: mean 44.9 (SD 17.7); n=29, Group 2: mean 41.1 (SD 23.38); n=31; SF-36- Mental health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM only group; baseline QoL between score difference: 39.5 (25.3) vs 31 (21.6) was larger than Qol difference at follow up; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1; Group 2 Number missing: 4Reason: withdrew due to allocated treatment not being effective change of mind, difficulty travelling or time constraint

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Opioids: OM dosage at End of treatment (average of weeks 11-14); Group 1: adjusted mean 537.4 mg (SD 165.32); n=29, Group 2: adjusted mean 585.2 mg (SD 166.48); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1),; Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: 50% OM reduction at End of treatment (average of weeks 11-14); Group 1: 8/29, Group 2: 4/31
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High Outcome reporting - Low, Measurement - Low, Crossover

- Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score
was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM group; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1),; Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

Protocol outcome 3: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs

- Actual outcome for Opioids: Non-OM dosage at End of treatment (average of weeks 11-14); Group 1: mean 9.3 (SD 7); n=29, Group 2: mean 10.1 (SD 6.68); n=31; Medication quantification Scale version III was used to quantify consumption of non-OMs for pain. Non-OMs included simple analgesics, such as Panadol Osteo; nonsteroidal ani-inflammatory medication such as Nurofen, antidepressants and anticonvulsants used for pain relief.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean

(SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

Protocol outcome 4: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Opioids: Intensity of the highest pain at End of treatment (average of weeks 11-14); Group 1: mean 5.9 (SD 2.15); n=29, Group 2: mean 6.6 (SD 2.23); n=31; VAS 0-10 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4 Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: Intensity of the average pain at End of treatment (average of weeks 11-14); Group 1: mean 5.4 (SD 2.69); n=29, Group 2: mean 5.8 (SD 2.23); n=31; VAS 0-10 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint
Protocol outcome 5: Improvements in adverse effects commonly associated with long-term prescribed medication use

- Actual outcome for Opioids: Number of OM-related AEs per person at End of treatment (average of weeks 11-14); Group 1: mean 3.2 (SD 4); n=29, Group 2: mean 2.5 (SD 3.3); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint

- Actual outcome for Opioids: Severity of OM-related AEs at End of treatment (average of weeks 11-14); Group 1: mean 12.9 (SD 20.1); n=29, Group 2: mean 11.4 (SD 18.9); n=31

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - High risk of bias due to the baseline differences in OM dose; Indirectness of outcome: No indirectness; Baseline details: mean (SD) baseline OM weekly score was 620.8 (792.5) in the Sham Electroacupuncture group vs 871.4 (1,772.3) in the PMM; Group 1 Number missing: 2, Reason: withdrew due to allocated treatment not being effective (n=1), change of mind (n=1); Group 2 Number missing: 4, Reason: withdrew due to allocated treatment not being effective, change of mind, difficulty travelling or time constraint	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Distress

E.2 Benzodiazepines

Study	Ashton 1990[6]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in United Kingdom; Setting: Treatment supplied by hospital pharmacy
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥18 years, had been on continuous benzodiazepine therapy for ≥6 months, wished to withdraw from benzodiazepine therapy, were not taking psychotropic medication nor abusing alcohol or drugs, and free from any psychiatric or physical disease.
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients referred by GPs for help in benzodiazepine withdrawal.
Age, gender and ethnicity	Age - Mean (SD): 41.8 (10.6). Gender (M:F): 9/14. Ethnicity: not reported

Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: People on long half-life benzodiazepines (Diazepam). 3. Setting: Outpatient
Extra comments	Any patients on benzodiazepines other than diazepam were switched to diazepam before the start of the trial.
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Buspirone substitution + tapered withdrawal. At the start of the second four-week block, patients were given buspirone (5mg t.d.s.). At the start of the fifth four-week block, buspirone was replaced with placebo tablets. Duration 20 weeks. Concurrent medication/care: Diazepam treatment was administered in four-week treatment blocks. For the first week, all patients were maintained on their usual dose, administered as a syrup. At the start of the third four-week block (weeks 9-12), diazepam was slowly withdrawn reducing the concentration of the syrup by 25% each week until it was zero. For the fourth four-week block all patients continued on a placebo syrup. At the start of the fifth four-week cycle all patients syrup administration was stopped. Concurrent medication: Diphenhydramine for night sedation, paracetamol for pain, propranolol for tremor and palpitations where indicated. Free to attend tranquilliser support groups if desired. Indirectness: No indirectness Further details: 1. Addiction support services: (n=12) Intervention 2: Placebo substitution + tapered withdrawal. At the start of the second four-week block patients received additional placebo tablets, taken t.d.s until the end of the fifth four-week block. Duration 20 weeks. Concurrent medication/care: Diazepam treatment was administered in four-week treatment blocks. For the first week, all patients were maintained on their usual dose, administered as a syrup. At the start of the third four-week block (weeks 9-12), diazepam was slowly withdrawn reducing the concentration of the syrup by 25% each week until it was zero. For the fourth four-week block all patients continued on a placebo syrup. At the start of the fifth four-week cycle all patients syrup administration was stopped. Concurrent medication: Diphenhydramine for night sedation, paracetamol for pain, propranolol for tremor and palpitations where indicated. Free to attend tranquilliser support groups if desired. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Equipment/drugs provided by industry (Drugs and facilities provided by Bristol Myers CNS)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO BUSPIRONE. versus PLACEBO

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Remained off benzodiazepines at 12 months; Group 1: 6/11, Group 2: 11/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Significant difference in baseline diazepam dose; Group 1 Number missing: 0, Reason: 7 participant did not complete trial. Data reported for all participants (completers and non-completers); Group 2 Number missing: 0, Reason: 1 participant did not complete trial. Data reported for all participants (completers and non-completers) Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Benzodiazepines: Withdrawal symptoms at 16 weeks (visit 13); Group 1: mean 24.75 (SD 6.07); n=4, Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Significant difference in baseline diazepam dose; Group 1 Number missing: 7; Group 2 Number missing: 1 - Actual outcome for Benzodiazepines: HADS (anxiety) at 16 weeks (visit 13); Group 1: mean 14.5 (SD 5.25); n=4, Group 2: mean 11.75 (SD 3.1); n=8; HADS 0-21 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Significant difference in baseline diazepam dose; Group 1 Number missing: 7; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Baillargeon 2003[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in Canada; Setting: Community - outpatients

Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 50 years or older; daily benzodiazepine use at bedtime for the past 3 months or more; and diagnosis of chronic insomnia, defined as insomnia for a period of 6 months or more in accordance with the American Sleep Disorders Association. Inability to refrain from taking sleeping pills at night because of fear of a bad night's sleep or sleep efficiency of less than 80% over a 2-week period. Participants also had to be experiencing impaired daytime functioning, irritability or mood disturbances.
Exclusion criteria	People with cognitive impairment, severe psychiatric problems or physical problems possibly related to insomnia were excluded, as were those taking a benzodiazepine during the daytime or drinking more than 3 alcoholic beverages per day.
Recruitment/selection of patients	Recruited people with chronic insomnia through referral by family physicians and media advertisements
Age, gender and ethnicity	Age - Mean (SD): 67.4 (6.8). Gender (M:F): 27/38. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear (Not reported). 3. Setting: Outpatient
Indirectness of population	Serious indirectness: Specific benzodiazepine used not reported
Interventions	(n=35) Intervention 1: Non-pharmacological interventions - CBT + tapered withdrawal. Cognitive-behavioural treatment involved behavioural, cognitive and educational components. The behavioural component included instructions for stimulus control and procedures for sleep restriction. The goal of stimulus control was to reinforce the bed as a cue for sleep and to regularise sleep rhythm. The cognitive component addressed irrational thinking that could exacerbate the sleep disorder through emotional arousal. The educational component included sleep hygiene education and information on the adverse effects of benzodiazepines on health. The cognitive-behavioural treatment was provided in small groups of 5 to 7 participants,

	who underwent 8 weekly group sessions. One month after the last session, participants were invited to a “booster” session to reinforce the skills acquired during group therapy. Gradual tapering began concurrently with the initiation of cognitive behavioural therapy and was supervised by a physician who met with each participant weekly over an 8-week period. The proposed schedule was a 25%reduction of dosage at 1- or 2-week intervals. At each visit, the physician looked for withdrawal symptoms and prescribed either the same or a lower dosage, depending on the patient’s symptoms. Duration 8 weeks. Concurrent medication/care: The physicians were not permitted to give advice on nonpharmacological treatments of insomnia. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=30) Intervention 2: Tapered withdrawal alone. Gradual tapering was supervised by a physician who met with each participant weekly over an 8-week period. The proposed schedule was a 25%reduction of dosage at 1- or 2-week intervals. At each visit, the physician looked for withdrawal symptoms and prescribed either the same or a lower dosage, depending on the patient’s symptoms. Duration 8 weeks. Concurrent medication/care: The physicians were not permitted to give advice on nonpharmacological treatments of insomnia. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Academic or government funding (National Health Research and Development Program, Health Canada)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) + TAPER versus TAPERED WITHDRAWAL STRATEGIES ALONE

Protocol outcome 1: Reduction/cessation of prescribed drug use
- Actual outcome for Benzodiazepines: Benzodiazepine free at Post-intervention; Group 1: 26/34, Group 2: 11/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Lost to follow up; Group 2 Number missing: 1, Reason: Lost to follow up
- Actual outcome for Benzodiazepines: Benzodiazepine free at 12 months; Group 1: 23/33, Group 2: 7/29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 1, Reason: Lost to follow up
- Actual outcome for Benzodiazepines: Daily dose (mg diazepam eqv) at Post intervention; Mean; CBT + taper: 2.84; Taper: 4.72 (p value: 0.196) mg/day (diazepam equivalent), Comments: SD not reported);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Lost to follow up; Group 2 Number missing: 1, Reason: Lost to follow up - Actual outcome for Benzodiazepines: Benzodiazepine >50% reduction at Post-intervention; Group 1: 33/34, Group 2: 20/29 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Lost to follow up; Group 2 Number missing: 1, Reason: Lost to follow up - Actual outcome for Benzodiazepines: Benzodiazepine >50% reduction at 12 months; Group 1: 26/32, Group 2: 15/29 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Lost to follow up; Group 2 Number missing: 1, Reason: Lost to follow up	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Distress

Study	**Bashir 1994[17]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=109)
Countries and setting	Conducted in United Kingdom; Setting: General practices
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable

Inclusion criteria	A chronic user was defined as someone who had been on benzodiazepines for at least a year and who took tablets at least three times weekly.
Exclusion criteria	Those with acute serious illness; anyone currently receiving psychiatric treatment or with a history of psychosis; anyone currently dependent on alcohol or illicit drugs; patients taking benzodiazepines for a medical problem such as epilepsy; patients unable to attend the surgery because of physical infirmity; and individuals unable to complete questionnaires for any reason.
Recruitment/selection of patients	General practitioners were asked to recruit all chronic benzodiazepine users by writing to patients receiving repeat prescriptions and asking them to attend the surgery.
Age, gender and ethnicity	Age - Mean (range): 62 (32-86). Gender (M:F): 42/67. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: At the start of the study 30 patients were taking diazepam,24 nitrazepam, 44 temazepam, 13 lorazepam, three oxazepam and one triazolam). 3. Setting: Outpatient
Extra comments	At the start of the study 30 patients were taking diazepam,24 nitrazepam, 44 temazepam, 13 lorazepam, three oxazepam and one triazolam. Data missing for one patient. No mention of length of time of being on a stable dose
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Non-pharmacological interventions - Brief intervention and advice. Patients were allocated by their doctor to receive minimal intervention, consisting of general practitioner advice on coming off benzodiazepines plus a self-help booklet which patients took away to read. Duration Not reported. Concurrent medication/care: Not reported. Unclear if single or multiple consultations. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=58) Intervention 2: Usual care. Patients received no study intervention (detail not provided). Duration Not reported. Concurrent medication/care: Not reported. Unclear if single or multiple consultations. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Academic or government funding (Supported by a grant from the Royal College of General Practitioners)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BRIEF INTERVENTION AND ADVICE versus USUAL CARE

Protocol outcome 1: Reduction/cessation of prescribed drug use
- Actual outcome for Benzodiazepines: Reduced benzodiazepine intake at 6 months; Group 1: 20/46, Group 2: 11/44; Comments: Prescribed benzodiazepine prescription: intervention 9/50, control 3/55
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 14

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: Withdrawal symptom score at 6 months; Group 1: mean 7.3 (SD 6.2); n=46, Group 2: mean 5.7 (SD 5.9); n=47; Score used unclear Range unclear Top=High is poor outcome; Comments: Quantitative symptoms (median): intervention 0, control 0.5

Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: 16 non respondents at 6 months – 2 died, one who had spent much time in hospital, 8 who declined to fill in the second or third questionnaires and five who were
not contactable. Unclear who was in which group.; Group 2 Number missing: 11, Reason: 16 non respondents at 6 months – 2 died, one who had spent much time in hospital, 8 who declined to fill in the second or third questionnaires and five who were
not contactable. Unclear who was in which group.

Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Benzodiazepines: Prevalence of psychiatric morbidity at 6 months; Group 1: 24/46, Group 2: 19/47; Comments: Measured by a score of 2+ on the GHQ.

Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: 16 non respondents at 6 months – 2 died, one who had spent much time in hospital, 8 who declined to fill in the second or third questionnaires and five who were not contactable. Unclear who was in which group.; Group 2 Number missing: 11, Reason: 16 non respondents at 6 months – 2 died, one who had spent much time in hospital, 8 who declined to fill in the second or third questionnaires and five who were not contactable. Unclear who was in which group.

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced

	tolerance; Patient Satisfaction ; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Busto 1986[35]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Canada; Setting: Community practice
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18 to 69 years with daily use of benzodiazepine for at least three months, with cumulative benzodiazepine exposure above 2700 mg of diazepam or equivalent, and problems attributed to the use of benzodiazepine or inability to stop taking the drug because of subsequent symptoms.
Exclusion criteria	Active medical and psychiatric conditions, abuse of multiple drugs during the preceding six months, or use of a centrally active medication other than the benzodiazepine within 30 days of the trial.
Recruitment/selection of patients	Participants were self-referred for assessment, referred by physicians or responded to advert.

Age, gender and ethnicity	Age - Mean (SD): 41 years (11.9). Gender (M:F): 20/20. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: Diazepam (22), Lorazepam (11), Oxazepam (3), Flurazepam (2), Triazolam (1), Chlordiazepoxide (1), Nitrazepam (1)). 3. Setting: Outpatient
Extra comments	Diazepam (22), Lorazepam (11), Oxazepam (3), Flurazepam (2), Triazolam (1), Chlordiazepoxide (1), Nitrazepam (1)
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: CBT + tapered withdrawal. Following baseline period of continued use of benzodiazepine, switched to receive equivalent dose of diazepam. At the first therapy session goals were set for dose reduction of 1 to 5 mg per week of the study drug. The goal was to reduce the dose to zero within five to six weeks. Duration 8 weeks. Concurrent medication/care: All patients also received weekly CBT sessions provided by two psychologists. Indirectness: No indirectness Further details: 1. Addiction support services: (n=19) Intervention 2: CBT + abrupt withdrawal. Following baseline period of continued use of benzodiazepine, switched to receive equivalent dose of placebo. At the first therapy session goals were set for dose reduction of 1 to 5 mg per week of the placebo. The goal was to reduce the dose to zero within five to six weeks. Duration 8 weeks. Concurrent medication/care: All patients also received weekly CBT sessions provided by two psychologists. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SWITCHING TO A LONG-ACTING BENZODIAZEPINE DIAZEPAM + CBT versus COGNITIVE BEHAVIOURAL THERAPY (CBT) + ABRUPT WITHDRAWAL

Protocol outcome 1: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: No. of symptoms experienced (per patient) at 8 weeks; Group 1: mean 3.5 (SD 2.8); n=21, Group 2: mean 9.7 (SD 5.6); n=19

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2 from original allocation. Not included in data reported, Reason: Relocated; Group 2 Number missing: 0

- Actual outcome for Benzodiazepines: Severity of symptoms experienced at 8 weeks; Group 1: mean 3.7 (SD 3.2); n=21, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2 from original allocation. Not included in data reported, Reason: Relocated; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Cantopher 1990[39]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=31)
Countries and setting	Conducted in United Kingdom; Setting: Community setting - general practice.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable

Inclusion criteria	Aged 18-70 years, had been taking benzodiazepine for at least 6 months for anxiety, and were receiving at least 15 mg diazepam daily or equivalent.
Exclusion criteria	Present alcoholism or illicit drug use, psychosis, epilepsy or mental handicap, asthma, heart disease, abnormal kidney or liver function, current treatment with other psychotropic drugs, and likely pregnancy during study period.
Recruitment/selection of patients	Patients recruited from general practices in Portsmouth and Southampton for repeat prescriptions.
Age, gender and ethnicity	Age - Mean (SD): 45.9 (13.2). Gender (M:F): 9/22. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Systematic review: mixed (Prior to switch, participants took: diazepam (18), lorazepam (9), chlordiazepoxide (3), temazepam (3), nitrazepam (2), clobazam (1), triazolam (1), flurazepam (1)). 3. Setting: Outpatient
Extra comments	All patients not taking diazepam were switched to diazepam before entering the trial. Prior to switch, participants took diazepam (18), lorazepam (9), chlordiazepoxide (3), temazepam (3), nitrazepam (2), clobazam (1), triazolam (1), flurazepam (1)
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Pharmacological interventions - Propranolol substitution + abrupt withdrawal. Diazepam was replaced with placebo. Propranolol (40 mg t.d.s) supplemented abrupt withdrawal. Active drugs were stopped at week 10 and placebo stopped at week 12. Visits were continued until week 16. Duration 12 weeks. Concurrent medication/care: No other medication was permitted during the study period. Indirectness: No indirectness Further details: 1. Addiction support services: (n=16) Intervention 2: Tapered withdrawal alone. Diazepam + propranolol placebo. Diazepam placebo was added in a stepwise manner from week 0 to week 10. Active drugs were stopped at week 10 and placebo stopped at week 12. Visits were continued until week 16. Duration 12 weeks. Concurrent medication/care: No other medication was permitted during the study period. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Equipment/drugs provided by industry (Trial materials provided by Chemical Industries PLC and Roche UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABRUPT WITHDRAWAL + PROPRANOLOL versus TAPERED WITHDRAWAL STRATEGIES ALONE Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Successful withdrawal at 6 months; Group 1: 4/15, Group 2: 11/16 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline symptom score significantly higher in propranolol group.; Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Benzodiazepines: Withdrawal symptoms at 6 months; Group 1: 14/15, Group 2: 11/16 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline symptom score significantly higher in propranolol group.;

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Cappell 1987[40]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=42)
Countries and setting	Conducted in Canada; Setting: Community.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 weeks

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic users of benzodiazepines, being a daily user for at least 3 months, and a cumulative benzodiazepine exposure higher than 2700mg diazepam or equivalent, and an inability to discontinue because of symptoms resulting from abstinence.
Exclusion criteria	Pregnancy, significant psychiatric, hepatic, renal, cardiovascular, or pulmonary disease, multiple drug abuse, excessive use of alcohol within 30 days of trial start.
Recruitment/selection of patients	Most presented in response to public advertisement, and a smaller number were self-reported or referred by professionals in the community.
Age, gender and ethnicity	Age - Mean (range): 41 (20-59). Gender (M:F): 21/21. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: Diazepam (10), Lorazepam (5), Oxazepam (3), Flurazepam (1)). 3. Setting: Outpatient
Extra comments	Diazepam (10), Lorazepam (5), Oxazepam (3), Flurazepam (1)
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Advice education and support + abrupt withdrawal. Behavioural intervention + Benzodiazepine placebo. At baseline, diazepam was switched with a placebo drug. Patients received behavioural treatment sessions, an hour in length, conducted by qualified psychiatrists. Sessions provided information on symptoms of withdrawal and set goals to reduce dose of the study drug. Up to 8 sessions were offered. Reassurance and encouragement were provided. Duration 8 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=21) Intervention 2: Advice education and support + tapered withdrawal. Behavioural intervention. Patients received

	behavioural treatment sessions, an hour in length, conducted by qualified psychiatrists. Sessions provided information on symptoms of withdrawal and set goals to reduce dose of the study drug. Up to 8 sessions were offered. Reassurance and encouragement were provided. Duration 8 weeks. Concurrent medication/care: At the conclusion of each weekly treatment, daily and weekly goals for diazepam use were agreed, targeting a gradual dose reduction. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PATIENT ADVICE/EDUCATION AND SUPPORT + ABRUPT WITHDRAWAL versus PATIENT ADVICE/EDUCATION AND SUPPORT + GRADUAL WITHDRAWAL Protocol outcome 1: Relapse into medication use - Actual outcome for Benzodiazepines: Unauthorized benzodiazepine use during trial period at 8 weeks; Group 1: 16/19, Group 2: 7/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Cormack 1994[48]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=209)
Countries and setting	Conducted in United Kingdom; Setting: Community setting - General Practices

Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Long-term regular users of benzodiazepines.
Exclusion criteria	The patient was in a current crisis or with an illness for which the drugs were required at the time, had a current diagnosis of psychosis or dementia, was in a position where a hospital doctor or a carer could administer medication, was known to abuse alcohol or was unable to read.
Recruitment/selection of patients	Ten general practitioners with personal lists in the three practices were asked to identify long-term regular users of benzodiazepines. Individuals were identified from their repeat prescribing records, either manually recorded or computer generated.
Age, gender and ethnicity	Age - Mean (range): 69 (34-102). Gender (M:F): 43/166. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Indirectness of population	Serious indirectness: Specific benzodiazepine used not reported
Interventions	(n=65) Intervention 1: Non-pharmacological interventions - Patient advice/education and support. Patients received a letter from their general practitioner asking them to try to reduce or stop their benzodiazepine medication and advising that this should be done gradually. Duration n/a - single letter. Concurrent medication/care: Background treatment unclear. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=75) Intervention 2: Non-pharmacological interventions - Patient advice/education and support. Patients received a letter

	from their general practitioner asking them to try to reduce or stop their benzodiazepine medication and advising that this should be done gradually, followed at monthly intervals by four information sheets giving advice about reducing medication, including practical suggestions for coping without drugs. Duration 6 months. Concurrent medication/care: Background treatment unclear. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=69) Intervention 3: Usual care. Control group received no information or advice. Duration 6 months. Concurrent medication/care: Background treatment unclear. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable Comments: Usual care not defined
Funding	Academic or government funding (Grant from the Devon Northcott Medical Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LETTER FROM GP versus USUAL CARE

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Patients who reduced their benzodiazepine use at 6 months; Group 1: 24/65, Group 2: 11/69

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant;

- Actual outcome for Benzodiazepines: Patients with no benzodiazepine prescription at 6 months; Group 1: 15/65, Group 2: 4/69
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant;

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LETTER FROM GP + INFORMATION SHEETS versus LETTER FROM GP

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Patients who reduced their benzodiazepine use at 6 months; Group 1: 37/75, Group 2: 24/65
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant. - Actual outcome for Benzodiazepines: Patients with no benzodiazepine prescription at 6 months; Group 1: 10/75, Group 2: 15/65 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant; RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LETTER FROM GP + INFORMATION SHEETS versus USUAL CARE Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Patients who reduced their benzodiazepine use at 6 months; Group 1: 37/75, Group 2: 11/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant. - Actual outcome for Benzodiazepines: Patients with no benzodiazepine prescription at 6 months; Group 1: 10/75, Group 2: 4/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: users were allocated to the three groups, roughly matched for age and sex to ensure a representative spread between groups. Beyond this, allocation to groups was random and was performed by the research assistant;	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Elliott 2005[67]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	(n=53)
Countries and setting	Conducted in United Kingdom; Setting: Community setting
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Illicit drug users undergoing mandatory reduction in prescribed diazepam
Exclusion criteria	Not reported
Recruitment/selection of patients	Sample drawn from all illicit drug users placed on a prescribed diazepam tapered reduction program.
Age, gender and ethnicity	Age - Mean (SD): 30.6 years (6.5). Gender (M:F): 26/27. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: People on long half-life benzodiazepines (Diazepam). 3. Setting: Outpatient
Extra comments	Those agreeing to randomisation had been prescribed diazepam for a mean of 2.9 years (mean baseline dose 28.9mg). 52/53 were prescribed methadone during the study. 7/53 were prescribed antidepressant medication during the study.
Indirectness of population	No indirectness

Interventions	(n=24) Intervention 1: Non-pharmacological interventions - Psychological intervention, education and training + tapered withdrawal. Patients received fortnightly psychological intervention and an information booklet with elements of behavioural intervention covering a) provision of information and education about effects of withdrawal, anxiety, and sleep patterns; b) visualising withdrawal symptoms; c) diaphragmatic breathing, progressive muscle relaxation exercises, and guided imagery to address anxiety; d) sleep planning and encouraging good sleeping habits. After six fortnightly visits, participants were given further skills training to practice and develop the basic techniques to aid withdrawal, anxiety, and sleep problems. These visits continued for six months. Duration 6 months. Concurrent medication/care: All participants were placed on a diazepam reduction plan, with monthly prescription reduction set at 10%. Indirectness: No indirectness Further details: 1. Addiction support services: (n=29) Intervention 2: Non-pharmacological interventions - Psychological intervention, education and advice + tapered withdrawal. Patients received fortnightly psychological intervention and an information booklet with elements of behavioural intervention covering a) provision of information and education about effects of withdrawal, anxiety, and sleep patterns; b) visualising withdrawal symptoms; c) diaphragmatic breathing, progressive muscle relaxation exercises, and guided imagery to address anxiety; d) sleep planning and encouraging good sleeping habits. After six fortnightly visits, participants were given verbal advice only on request and referred back to information booklet. These visits continued for six months. Duration 6 months. Concurrent medication/care: All participants were placed on a diazepam reduction plan, with monthly prescription reduction set at 10%. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Academic or government funding (Funded by the Chief Scientist Office)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PATIENT ADVICE/EDUCATION AND SUPPORT (ENHANCED) versus PATIENT ADVICE/EDUCATION AND SUPPORT (LIMITTED)

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Change in diazepam dose (mg) at 6 months; Group 1: mean -7.9 mg (SD 9.3); n=24, Group 2: mean -12.3 mg (SD 6.5); n=29

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

	- Actual outcome for Benzodiazepines: HADS depression at 6 months; Group 1: mean -2.8 (SD 6.6); n=19, Group 2: mean 2.3 (SD 4.6); n=20; HADS depression 0-21 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 9 - Actual outcome for Benzodiazepines: HADS anxiety at 6 months; Group 1: mean -0.8 (SD 4.6); n=19, Group 2: mean 1.6 (SD 4.8); n=20; HADS anxiety 0-21 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 9 - Actual outcome for Benzodiazepines: Pittsburgh sleep quality index (PSQI) at 6 months; Group 1: mean -0.4 (SD 4.2); n=19, Group 2: mean 2.3 (SD 4.7); n=20; PSQI 0-21 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 9 Protocol outcome 3: Relapse into medication use - Actual outcome for Benzodiazepines: No. of weeks in suspension of diazepam reduction at 6 months; Group 1: mean 10.4 (SD 6.2); n=24, Group 2: mean 8.2 (SD 5.6); n=29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Protocol outcome 4: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs - Actual outcome for Benzodiazepines: Participants using illicit benzodiazepines at follow-up at 6 months; Group 1: 10/19, Group 2: 12/20; Comments: At baseline: enhanced (18), limited (9) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 9
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was

	originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Gnjidic 2019[93]**
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=42)
Countries and setting	Conducted in Australia; Setting: In-hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 65 years of age and admitted to cardiology, renal, endocrine, general medicine, rheumatology or surgical orthopaedic wards were screened. Patients who were prescribed one or more benzodiazepines on the inpatient medication chart were invited into the study.
Exclusion criteria	Participants were excluded from the study if they were: (a)unable to speak, understand and complete the interview in English; (b)identified as cognitively impaired by clinical staff; (c) isolated due to infection; or (d) refused to participate.
Recruitment/selection of patients	Inpatients recruited from the Royal North Shore Hospital, Sydney, Australia

Age, gender and ethnicity	Age - Median (IQR): 71.5 (69-80.3). Gender (M:F): 19/23. Ethnicity: White (90.5%), Middle Eastern (7.1%), Aboriginal (2.4%)
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: Diazepam (7), Oxazepam (3), Temazepam (28), Lorazepam (1), Clonazepam (1), Nitrazepam (2)). 3. Setting: Inpatient
Extra comments	Type of benzodiazepine used n(%) Diazepam 7 (16.7) Oxazepam 3 (7.1) Temazepam 28 (66.7) Lorazepam 1 (2.4) Clonazepam 1 (2.4) Nitrazepam 2 (4.8)
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Non-pharmacological interventions - Brief intervention and advice. Intervention participants received the patient-empowerment booklet. Information in the booklet aimed to cause cognitive dissonance using self-administered true-or-false questions on effects associated with benzodiazepine use, with feedback to correct myths and wrong beliefs. It also used the social comparison theory by showing a successful cessation example and a tapering protocol as a guide to help stop use of benzodiazepine. Participants were asked to read the booklet in their own time and discuss any concerns about their benzodiazepine medications with their doctor or pharmacist following hospital discharge. Duration Hospital admission. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: (n=22) Intervention 2: Usual care. Patients in the control group received usual care (no more information). Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Academic or government funding (Australian National Health and Medical Research, and Australian Research Council Dementia Research Development Fellowship)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PATIENT ADVICE/EDUCATION AND SUPPORT (INFORMATION BOOKLET) versus USUAL CARE (NOT REPORTED)	

Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Benzodiazepine cessation at 1 month; Group 1: 6/11, Group 2: 7/11; Comments: 7 of 29 patients presenting at follow up ceased benzodiazepine before discharge and not included in analysis Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 6; Group 2 Number missing: 7	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Heather 2004[111]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=284)
Countries and setting	Conducted in United Kingdom; Setting: General practices
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6-month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines

Subgroup analysis within study	Not applicable
Inclusion criteria	Long-term benzodiazepine users were defined in our study as patients of any age or gender who had taken benzodiazepines continuously for at least six months (i.e., had received at least one prescription for benzodiazepines every two months during the previous six).
Exclusion criteria	Currently experiencing an acute serious illness; currently receiving specialist psychiatric treatment or with a history of psychosis; currently dependent on alcohol or illicit drugs; taking benzodiazepines for a medical condition such as epilepsy; unable to attend the surgery because of physical infirmity; unable to complete questionnaires for any reason. GPs were also permitted to exclude patients if they felt that requesting a reduction in benzodiazepine intake might be harmful for any reason.
Recruitment/selection of patients	General practices in Newcastle and North Tyneside were selected at random and a letter sent to all GPs in the sampled practices inviting them to participate in the study. Practice Managers retrieved lists of long-term benzodiazepine users from computerised repeat prescription records
Age, gender and ethnicity	Age - Mean (SD): 69.16 (11.52). Gender (M:F): 74/210. Ethnicity:
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Extra comments	Over half (55%) were prescribed temazepam, 22% diazepam and 14% nitrazepam.
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Non-pharmacological interventions. Patients were sent a letter inviting them to see their GP for a medication review. Before the trial began, the researcher met participating GPs to give guidance on how the consultation should be carried out. Consultations were scheduled to last for 12min. Written guidelines were produced consisting of information for patients about benzodiazepines, reasons why it might be beneficial to reduce medication and a timetable that could be used to plan withdrawal. These guidelines were attached to patients' notes so that the GP could refer to them during the consultation. GPs were allowed discretion as to how the consultation was conducted. Copies of a self-help booklet, entitled Helping you Cope: A Guide to Starting and Stopping Tranquillisers and Sleeping Tablets, were supplied by The Mental Health Foundation and given to patients during the consultation, along with a leaflet about sleeping problems. Duration 12 minutes. Concurrent medication/care: Not reported. Indirectness: No indirectness

	Further details: 1. Addiction support services: (n=93) Intervention 2: Non-pharmacological interventions. Patients were sent an amended version of the letter used in the study by Cormack and colleagues. The letter was produced by the research team on practice-headed paper and signed by the patient's usual GP. Patients in the Letter group were not sent the self-help booklet or leaflet. Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: (n=93) Intervention 3: Usual care. Patients received usual care but no interventions. Definition of usual care not provided. Duration n/a. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Academic or government funding (Funded by the Northern and Yorkshire Regional Health Authority R&D Programme.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP CONSULTATION versus GP LETTER

Protocol outcome 1: Quality of life

- Actual outcome for Benzodiazepines: SF-36 at 6 months; There were no significant differences between study groups in changes on any of the nine SF-36 sub-scores;

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness;

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Dose reduction at 6 months; Group 1: mean 121.01 (SD 88.5); n=95, Group 2: mean 123.17 (SD 98.96); n=88; Comments: benzodiazepine intake (in 10 mg diazepam equivalents)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5

- Actual outcome for Benzodiazepines: Stopped benzodiazepine intake at 6 months; Group 1: 10/95, Group 2: 9/88
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP CONSULTATION versus USUAL CARE Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Dose reduction at 6 months; Group 1: mean 121.01 (SD 88.5); n=95, Group 2: mean 126.76 (SD 111.31); n=89; Comments: benzodiazepine intake (in 10 mg diazepam equivalents) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 4 - Actual outcome for Benzodiazepines: Stopped benzodiazepine intake at 6 months; Group 1: 10/95, Group 2: 6/89 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 4 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP LETTER versus USUAL CARE Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Dose reduction at 6 months; Group 1: mean 123.17 (SD 98.96); n=88, Group 2: mean 126.76 (SD 111.31); n=89; Comments: benzodiazepine intake (in 10 mg diazepam equivalents) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 4 - Actual outcome for Benzodiazepines: Stopped benzodiazepine intake at 6 months; Group 1: 9/88, Group 2: 6/89 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Lader 1987[137]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in United Kingdom; Setting: Outpatients
Line of therapy	Not applicable
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Referred by general practitioners and consultant psychiatrists and reassessed before inclusion. Pre-treatment assessment included mental state assessment and physical examination. Blood was taken for full blood count and liver function tests and urinalysis was performed for sugar, protein and microscopy. The urine was also screened for benzodiazepine and other drugs, and an electrocardiogram was done
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients on long-term (more than 6 months) therapeutic dose benzodiazepine medication, who at mental state assessment were deemed not to require any further benzodiazepine medication.
Exclusion criteria	Abuse of alcohol or other drugs
Recruitment/selection of patients	Patients were referred by general practitioners and consultant psychiatrists for help in discontinuing their long-term normal dose benzodiazepine usage
Age, gender and ethnicity	Age - Mean (SD): 39.1 (not specified). Gender (M:F): 10:14. Ethnicity: not specified
Further population details	1. Gabapentinoids: 2. Half-life of benzodiazepines: 3. Setting:

Extra comments	All participants had been assessed as being free from symptoms of the anxiety which had originally led to the prescription of benzodiazepines, but problems on attempting to lower the dosage of their medication had been encountered previously. Thus, they were regarded as physically dependent. Mean duration of benzodiazepine use was 8.4 years. Dosage of benzodiazepines were all within the usual therapeutic ranges. 11 patients were on diazepam, of whom two were taking 20 to 30 mg/day. For eight patients on lorazepam, dosages ranged from 1.25 to 5 mg/day
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Pharmacological interventions - Buspirone substitution + withdrawal. Both groups were maintained on their pre withdrawal benzodiazepine medication and dosage for the first 2 weeks (1 and 2). Then, they were withdrawn stepwise from these medications over 4 weeks: during the first of these 2 weeks (3 and 4), buspirone was substituted for the benzodiazepine in an initial dosage of 5 mg (one capsule) twice daily, followed by 10 mg (two capsules) twice daily during the second phase when the patient had stopped benzodiazepine medication. Duration 10 weeks. Concurrent medication/care: If symptoms were severe, the dosage could be increased to a maximum daily dosage of 30 mg of buspirone. Side effects to the trial medication resulted in reduction of dosage. At the end of the 4-week withdrawal, both groups were administered placebo in dosages corresponding to the preceding week for another 2 weeks (7 and 8). Both groups were free of all medication in the last 2 weeks of the trial (9 and 10). Indirectness: No indirectness Further details: 1. Addiction support services: (n=11) Intervention 2: Placebo substitution + withdrawal. Both groups were maintained on their pre withdrawal benzodiazepine medication and dosage for the first 2 weeks (1 and 2). Then, they were withdrawn stepwise from these medications over 4 weeks: during the first of these 2 weeks (3 and 4), placebo was substituted for the benzodiazepine in an initial dosage of 5 mg (one capsule) twice daily, followed by 10 mg (two capsules) twice daily during the second phase when the patient had stopped benzodiazepine medication. Duration 10 weeks. Concurrent medication/care: If symptoms were severe, the dosage could be increased to a maximum daily dosage of six capsules of placebo. Side effects to the trial medication resulted in reduction of dosage. At the end of the 4-week withdrawal, both groups were administered placebo in dosages corresponding to the preceding week for another 2 weeks (7 and 8). Both groups were free of all medication in the last 2 weeks of the trial (9 and 10). Indirectness: No indirectness Further details: 1. Addiction support services:

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUSPIRONE SUBSTITUTION + WITHDRAWAL versus PLACEBO + WITHDRAWAL

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Successful completion of withdrawal at 10 weeks; Group 1: 5/13, Group 2: 6/11; Comments: Following the first week of buspirone and placebo substitution for the benzodiazepines, the attrition rate was faster for patients on buspirone than for the placebo group. 2/13 on buspirone dropped out the week following the reduction of their benzodiazepine by half (week 3). 3/13 dropped out after cessation of their benzodiazepines (week 5) despite receiving a mean of 20 mg of buspirone per day. Subsequent rate of dropout was one patient per week, giving a total of eight dropouts on buspirone. The rate of drop out on placebo was more gradual. 5/11 on placebo dropped out at a rate of one patient per week between the 3rd and 7th weeks. Patients in both groups dropped out because of severe withdrawal symptoms and recommenced their benzodiazepine medication.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Differences in various factors including anxiety and other outcome rating scales;

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Distress

Study (subsidiary papers)	**Morin 2004[170] (Morin 2005[171])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=76)
Countries and setting	Conducted in Canada; Setting: Outpatient - community
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were chronic users of benzodiazepines for insomnia who wished to discontinue. Aged 55, history of using benzodiazepine for more than 50% of the nights over previous 3 months, difficulties sleeping for 3 nights a week for at least 6 months, distress or impaired daytime function
Exclusion criteria	Insomnia related to medical or psychiatric condition, presence of sleep apnoea, currently participating in psychotherapy, use of psychotropic drugs other than benzodiazepine, cognitive impairment.
Recruitment/selection of patients	recruited through newspaper advertisements and physician referrals.
Age, gender and ethnicity	Age - Mean (SD): 62.5 (6.3). Gender (M:F): 38/38. Ethnicity: Caucasian
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: short 1.3%; intermediate 55%; long 20%). 3. Setting: Outpatient
Extra comments	Study also included a third arm which was CBT for insomnia without the taper. This comparison was not included in the review as per the review protocol, as there was no aim to withdrawal in this arm. The study states that patients who received CBT alone were 'not expected to change their medication use and were not provided guidance about reducing their medication intake'. lorazepam - 41%; temazepam - 12.8%; bromazepam - 11.5%; oxazepam - 5.1%; alprazolam - 2.6%; flurazepam/clonazepam 25.7%; triazolam - 1.28%
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Non-pharmacological interventions - Cognitive behavioural therapy (CBT) + taper. Patients in the combined CBT + Taper condition received both the tapering program and CBT. Patients in the CBT group attended 10 weekly 90-min. therapy sessions conducted in small groups of four to six individuals and led by a licensed clinical psychologist. Treatment consisted of a structured, multifaceted, intervention involving

	behavioural, cognitive, and educational components that targeted different facets of insomnia. The behavioural component incorporated sleep restriction therapy and stimulus control procedures. The cognitive therapy component was designed to alter faulty beliefs and attitudes that often serve to exacerbate insomnia. Discussion of behavioural sleep management strategies was restricted to CBT sessions to minimize overlap across conditions. Duration 10 weeks. Concurrent medication/care: Patients received no additional care. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=25) Intervention 2: Tapered withdrawal. Subjects enrolled in the medication taper condition met weekly with a physician for 10 brief consultation sessions (15–20 min). The content of those sessions focused on (a) reviewing the written taper schedule,(b) documenting changes in insomnia symptoms, and (c) monitoring withdrawal effects and any other adverse events. Patients were provided with a step-by-step withdrawal plan, with the goal of eliminating benzodiazepine use by the 8thweek of treatment. The following principles were used in designing those schedules: setting goals, stabilization on a single benzodiazepine for patients using more than one benzodiazepine, reduction of about 25% of the initial dosage every two weeks until the lowest available dosage of the benzodiazepine was reached, introduction of an increasing number of drug-free nights, and scheduled hypnotic use rather than usage on a as needed basis. Support and encouragement to follow the written withdrawal schedule were provided, but no specific behavioural recommendations for improving sleep were given during those sessions. Duration 10 weeks. Concurrent medication/care: No additional care was provided. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Academic or government funding (Supported by NIMH grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TAPERED WITHDRAWAL STRATEGIES ALONE versus COGNITIVE BEHAVIOURAL THERAPY (CBT) + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Drug-free subjects at Post-treatment; Group 1: 12/25, Group 2: 23/27

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Benzodiazepines: Drug-free subjects at 12 months; Group 1: 13/20, Group 2: 16/23

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 4, Reason: Lost to follow-up

- Actual outcome for Benzodiazepines: weekly benzodiazepine used (diazepam equivalent mg) at Post intervention; Group 1: mean 11.4 mg (SD 6.72); n=25, Group 2: mean 1.3 mg (SD 6.34); n=27; Comments: values are mean and SE

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Benzodiazepines: weekly benzodiazepine used (diazepam equivalent mg) at 12 months; Group 1: mean 13.28 mg (SD 7.09); n=25, Group 2: mean 4.43 mg (SD 6.62); n=27; Comments: Values are mean and SE

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 4, Reason: Lost to follow-up

Protocol outcome 2: Relapse into medication use

- Actual outcome for Benzodiazepines: Relapse into drug use at 24 months; Group 1: 4/13, Group 2: 7/21

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: Lost to follow-up; Group 2 Number missing: 6, Reason: Lost to follow-up

Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Benzodiazepines: Insomnia severity index at Post intervention; Group 1: mean 12.72 (SD 1.12); n=25, Group 2: mean 11.18 (SD 1.06); n=27; Insomnia Severity Index 0-28 Top=High is poor outcome; Comments: values are mean and SE

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Benzodiazepines: Insomnia severity index at 12 months; Group 1: mean 9.97 (SD 1.18); n=25, Group 2: mean 11.06 (SD 1.11); n=27; Insomnia Severity Index 0-28 Top=High is poor outcome; Comments: values are mean and SE

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 4

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

Study	**Morton 1995[172]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=24)
Countries and setting	Conducted in United Kingdom; Setting: Benzodiazepine Withdrawal Clinic within Maudsley Hospital.
Line of therapy	1st line
Duration of study	Intervention + follow up: 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Normal dose (<30mg/day of diazepam or equivalent) taken long-term (over 6 months).
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-70 years and within 20% of normal body weight limit.
Exclusion criteria	Major physical or psychiatric illness; drug abuse; women of childbearing age unless taking effective contraceptive measures.
Recruitment/selection of patients	Consultant psychiatrist/GP referral for help with stopping benzodiazepines.
Age, gender and ethnicity	Age - Range: 25-69 (mean 46). Gender (M:F): 16F/ 8M. Ethnicity: NR

Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: People on long half-life benzodiazepines (Diazepam and lorazepam). 3. Setting: Outpatient (benzodiazepine withdrawal clinic).
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Pharmacological interventions - Buspirone + taper. Two baseline weeks on current BZD dose. Then patients were given buspirone in flexible dosage according to the usual criteria of clinical need, at a minimum of 15mg/day in divided doses. After 4 weeks of stabilisation BZD medication was tapered off, with reduction to zero in 6 weeks. At week16, after 4 weeks BZD abstinence, the buspirone was halved in dosage and then stopped 2 weeks later. After 2 drug free weeks, the patients returned for their final visit. Duration 20 weeks. Concurrent medication/care: No additional medication was allowed. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=12) Intervention 2: Placebo + taper. Two baseline weeks on current benzodiazepine dose. Then patients were given placebo in flexible dosage according to the usual criteria of clinical need, at a minimum of 15mg/day in divided doses. After 4 weeks of stabilisation benzodiazepine medication was tapered off, with reduction to zero in 6 weeks. At week16, after 4 weeks benzodiazepine abstinence, the placebo was halved in dosage and then stopped 2 weeks later. After 2 drug free weeks, the patients returned for their final visit. Duration 20 weeks. Concurrent medication/care: No additional medication was allowed. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Study funded by industry (The study was supported by a grant from Bristol- Myers Squibb UK to the Institute of Psychiatry.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUSIPIRONE + TAPER versus PLACEBO + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Completion of withdrawal at 16 weeks; Group 1: 6/12, Group 2: 6/12

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 6, Reason: dropped out of study due to inefficacy in controlling benzodiazepine withdrawal symptoms.; Group 2 Number missing: 6, Reason: dropped out of study due to inefficacy in controlling benzodiazepine withdrawal symptom

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Benzodiazepines: Adverse event: giddiness at 20 weeks; Group 1: 7/12, Group 2: 4/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Benzodiazepines: Adverse event: GI symptoms at 20 weeks; Group 1: 6/12, Group 2: 3/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Benzodiazepines: Adverse event: headache at 20 weeks; Group 1: 1/12, Group 2: 2/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Benzodiazepines: Insomnia at 20 weeks; Group 1: 3/12, Group 2: 1/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; symptoms for which the medication was originally prescribed; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Murphy 1991[176]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45 (68 in total including study arm not included))
Countries and setting	Conducted in United Kingdom; Setting: Outpatients

Line of therapy	1st line
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Regular benzodiazepine use ≥6 months at a dosage of 2-16mg
Stratum	Benzodiazepines:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who: had taken a prescribed benzodiazepine in regular dosage for ≥6 months; were unable to reduce or stop their drug because of apparent withdrawal symptoms; were taking no other psychotropic drugs; were taking their benzodiazepine in a daily dosage of 2-16mg of diazepam (or equivalent dosage of another benzodiazepine); were taking their drugs for anxiety or insomnia or related neurotic symptomatology; wished to stop their benzodiazepines and were willing to take part in the study as outpatients.
Exclusion criteria	NR
Recruitment/selection of patients	All patients attending psychiatric outpatient clinics between November 1985 and January 1988.
Age, gender and ethnicity	Age - Mean (SD): Diazepam group: 49.5 (12.6) Lorazepam group: 42.1 (9.1). Gender (M:F): Diazepam group: 19F/3M Lorazepam group: 17F/4M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed (lorazepam and diazepam). 3. Setting:
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Diazepam + taper. Patients were provided with diazepam tablets in roughly equivalent dosage to their original benzodiazepine. The change was made to the appropriate number of tablets, each containing 5mg of diazepam. Each patient remained on this dosage until the end of the fourth week, after which the dosage was reduced in 25% aliquots at 2-week intervals until complete withdrawal by the end of the tenth week. If patients were unable to reduce their drugs at the appropriate time they were regarded as dropouts for the purpose of this study. Duration 14 weeks. Concurrent medication/care: NR. Indirectness: No

	indirectness; Indirectness comment: 2/68 were taking drugs not on protocol at baseline (group not reported) Further details: 1. Addiction support services: Not stated/Unclear (n=23) Intervention 2: Lorazepam + taper. Patients were provided with lorazepam tablets in roughly equivalent dosage to their original benzodiazepine. The change was made to the appropriate number of tablets, each containing 1mg of lorazepam. Each patient remained on this dosage until the end of the fourth week, after which the dosage was reduced in 25% aliquots at 2-week intervals until complete withdrawal by the end of the tenth week. If patients were unable to reduce their drugs at the appropriate time they were regarded as dropouts for the purpose of this study. Duration 14 weeks. Concurrent medication/care: NR. Indirectness: No indirectness; Indirectness comment: 2/68 patients were taking drugs not on the protocol at baseline (group not reported) Further details: 1. Addiction support services: Not stated/Unclear
Funding	Study funded by industry (Hofmann La Roche, Basel)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LORAZEPAM + TAPER versus DIAZEPAM + TAPER

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Benzodiazepines: Suicide at 14 weeks; Group 1: 1/23, Group 2: 0/22; Comments: Committed suicide after 12 weeks' treatment.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Study completers at 14 weeks; Group 1: 13/23, Group 2: 16/22; Comments: Examination of serum benzodiazepine levels showed that all had probably complied with the withdrawal regime.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcomes not reported by the study	Quality of life; Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Nathan 1986[180]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=7)
Countries and setting	Conducted in USA; Setting: Outpatient.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III diagnosis of GAD; daily benzodiazepine dose>6 months
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Females between the ages of 25 and 50; a DSM-III diagnosis of GAD; daily benzodiazepine use of over 6 months; absence of physical problems requiring the use of benzodiazepines; no concurrent use of any other psychoactive medications.
Exclusion criteria	NR
Recruitment/selection of patients	Newspaper advertisement.

Age, gender and ethnicity	Age - Range: inclusion criteria was 25-50 years; actual age range NR. Gender (M:F): All female. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed 3. Setting: Outpatient
Indirectness of population	Serious indirectness: Full breakdown of benzodiazepines used was not provided.
Interventions	(n=4) Intervention 1: Non-pharmacological interventions - Biofeedback assisted stress management + taper. Patients were seen individually by a psychologist. The treatment included taped relaxation training twice daily at home, EMG and skin temperature biofeedback in the office as well GSR-II at home, and limited, supportive stress management counselling. A small galvanic skin response and temperature unit, the GSR-II was given to patients for home practice. Duration 10 weekly sessions. Concurrent medication/care: All patients were advised to decrease benzodiazepine use by 20% of their original dose every 2 weeks. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=3) Intervention 2: Non-pharmacological interventions - Brief withdrawal counselling +taper. Patients were seen individually for weekly 10-minute sessions to simulate counselling and encouragement of traditional medical care. However, given the small number of patients recruited and the availability of highly trained clinicians, brief but intensive, individual psychoanalytic psychotherapy was offered to decrease further attrition and yield more information about the withdrawing patient. The psychotherapy was conducted by a psychiatrist and a psychiatric social worker. Duration 10 weekly sessions. Concurrent medication/care: All patients were advised to decrease benzodiazepine use by 20% of their original dose every 2 weeks. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIOFEEDBACK-ASSISTED STRESS MANAGEMENT TREATMENT+ TAPER versus SUPPORTIVE WITHDRAWAL/ INTENSIVE PSYCHOANALYTIC PSYCHOTHERAPY + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Complete withdrawal from benzodiazepine at 10 weeks; Group 1: 1/3, Group 2: 0/3; Comments: Biofeedback group: 1 patient dropped out of the study at week 4; 1 patient completely stopped their benzodiazepine dose; 1 reduced dose from 15 to 8 mg/day (<50%); 1 reduced

dose from 30-3mg/day (>50%). All three in the control group 'decreased medications by approximately 50% by the end of treatment'. Numbers completely withdrawing from benzodiazepines determined from this information. Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: patient dropped out of study; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**O'Connor 2008[194]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Canada; Setting: Hospital outpatients
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 20-week intervention plus up to 11 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines:

Subgroup analysis within study	Not applicable:
Inclusion criteria	Age 21-64 years; taking benzodiazepine for at least 2 years; having a diagnosis of benzodiazepine dependence for at least 2 months; presenting an anxiety problem and/ or insomnia for at least 3 months and meeting DSM IV criteria for one of the following: insomnia, panic with agoraphobia, generalised anxiety disorder, social phobia, specific phobia and adaptational problems with anxious mood.
Exclusion criteria	Taking any other psychotropic medication; substance or alcohol abuse; presence of any other axis I diagnosis (except insomnia); presence over the course of the last year of a major medical or physical problem; receiving any other psychotherapy for at least 3 months and not intending to consult for other therapy.
Recruitment/selection of patients	Media announcements, clinic publicity and referrals.
Age, gender and ethnicity	Age - Mean (SD): CBT, group support + taper: 47.35 (9.9) Group support + taper: 48.19 (9.8). Gender (M:F): 24:21. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed: 61% on short half-life, 39% on long half-life; no breakdown in results). 3. Setting: Not stated/Unclear
Indirectness of population	Serious indirectness: Did not state names of benzodiazepines patients were using- may include ones not on protocol
Interventions	(n=23) Intervention 1: Non-pharmacological interventions - CBT + tapered withdrawal. The PASS programme (Programmed'Aideau Succèsdu Sevrage; Programme Aimed at Successful Severance of benzodiazepines) attempts to boost confidence in the initial phase of withdrawal regardless of diagnosis. The PASS group programme and the group support programme were both delivered in a manualized form to be administered in group format over a 20-week period. Both manuals were divided into three sections covering (a) preparation; (b) severance; (c) maintaining abstinence. The PASS programme was built around insights gained from the previous studies, and the literature, on the psychosocial profiles likely to influence outcome.

The therapy aimed to enhance self-efficacy principally through normalising expectancies of withdrawal and attributions of withdrawal; through boosting confidence in (a) coping without benzodiazepine, (b)coping with anxious inhibiting situations; and through developing a belief in capacity to function autonomously from benzodiazepine. The PASS programme began with a 4-week period of preparation which preceded the tapered withdrawal schedule. The preparation period involved psychoeducation and cognitive restructuring through providing realistic information on withdrawal and addressing personal or subcultural beliefs or myths about cessation.

The taper programme was explained, and perceived difficulties were discussed together with individual motivations to cease benzodiazepine, withdrawal expectancies, and the future vision of obstacles impeding functioning. Developing a positive preparation involved basing anticipation on the consideration of resources and abilities of the person by improving self-efficacy to cope with difficult everyday situations without benzodiazepine. As well as confronting anticipations, interpretations and prejudices about the risk of failure, other exercises addressed the importance of the attribution of sensations and their significance.

In particular, the role of extreme vigilance to unusual physical sensations in amplifying discomfort was discussed, as was the tendency to misinterpret any discomfort experienced during discontinuation as due to withdrawal or rebound. Discontinuation began at the fifth week, and passed through four stages, each of 4 weeks duration: getting started; keeping going; nearly there; staying there. As well as the weekly group meetings, participants also attended at three weekly intervals for a consultation with a treating physician who controlled the taper regime. In order to help coping with getting started, the participants had recourse to 10 resource documents which could be discussed in the PASS group under the direction of the facilitators.

The resource documents included cognitive–behavioural strategies to deal with withdrawal symptoms; normalizing reactions and anxiety sensitivities; stress and mood management; muscle relaxation; problem resolution; regulating lifestyle; quality of life; sleep hygiene; social support; motivation; self-efficacy. These resources were employed on an as-needed basis and their use in the PASS context was to deal with specific difficulties encountered during withdrawal. Each participant, with the aid of the resource document, group discussion and therapist input, decided on a plan of action for the following week.

Upon the return, the following week, the effectiveness of the plan and its consequences were evaluated in the group. In the second step of keeping going, the progress and lessons learned so far were consolidated and

	medium-term difficulties in adaptation were addressed, for example, social support; poor life quality; changing lifestyle; and reinforcing confidence in functioning in daily activities. The third step, nearly there, focused on overcoming thoughts or feelings likely to sabotage abstinence, again working on confidence and coping skills in the group with the aid of the resource documents. At this stage, participants set the date for their final severance. In the final stage, staying there, the participants dealt with the initial stages of complete severance. In particular, they revised and rehearsed useful coping strategies, envisioned how they would deal with new difficult situations, and reviewed how they had so far successfully adapted to and tolerated symptoms. Specific strategies to deal with relapse were rehearsed, such as thinking ahead, learning from mistakes; not jumping to conclusions; making future decisions consistent with a non-benzodiazepine user. Successful completers received a PASS-PORT at follow-up to signal their autonomy from benzodiazepine use. Duration 20 weeks. Concurrent medication/care: Taper: procedure involved a weekly reduction in 25% of the initial dose over 16 weeks, up to a maximum of 113 days and depending on the half-life of the medication. where tablets did not allow precise dose reduction, either tablets were cut in half or spaced over days as required. Participants consulted treating physicians at the 6th, 8th, 11th, 14th, 17th and 20th group treatment session. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=22) Intervention 2: Non-pharmacological interventions - Group work + tapered withdrawal. The Group Support (GS) Programme. The GS group met at the same regularity as the PASS group and followed identical taper regimes. The principal difference was in the lack of any specific directions for changing thoughts and behaviours. In this GS condition, no CBT strategies were presented, and exchanges took the form of open-ended discussion on themes such as ‘What is anxiety? ’No direct action or strategy to deal with any problems was suggested. Any requests for specific help were deflected back to the group. Following open discussion, participants noted the key points of discussion and also continued to reflect on the themes throughout the following week. Each week a different theme was discussed and any personal request for a strategy was referred for group discussion. Duration 20 weeks. Concurrent medication/care: Taper as per CBT group. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service

Funding	Academic or government funding (Fonds de la Recherche en Sante du Quebec and the Conseil Quebecois de la Recherche Sociale (grant 961227))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT), GROUP SUPPORT+ TAPER versus GROUP-WORK+ TAPER

Protocol outcome 1: Quality of life

- Actual outcome for Benzodiazepines: Systematic Quality of Life Inventory- current state at 3 months follow-up; Group 1: mean 8.4 (SD 1.88); n=11, Group 2: mean 8.35 (SD 0.72); n=10; Systematic Quality of Life Inventory- current state subscale scale unclear Top=High is good outcome; Comments: Baseline values
CBT- 6.13 (4.04) n=18
Group support 6.75 (3.15) n=17

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 13, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Succeeder- ceased medication at 20 weeks post taper; Group 1: 15/23, Group 2: 11/22

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 6, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 11, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: Number of withdrawal symptoms at the end of the treatment period. at 20 weeks post taper; Group 1: mean 7.57 (SD 4.48); n=14, Group 2: mean 8.64 (SD 4.12); n=12; Benzodiazepine Withdrawal Symptom Questionnaire 0-40 Top=High is poor outcome; Comments: Baseline values: CBT 7.17 (5.78)
GS 10.82 (6.56)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 10, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; did not complete questionnaire.; Group 2 Number missing: 12, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; did not complete questionnaire.

- Actual outcome for Benzodiazepines: Number of withdrawal symptoms at 3 month follow up. at 3 month follow up; Group 1: mean 7.67 (SD 5.32); n=11, Group 2: mean 7.22 (SD 3.15); n=10; Benzodiazepine Withdrawal Symptom Questionnaire 0-40 Top=High is poor outcome; Comments: Baseline value: CBT: 7.17 (5.78)
GS: 10.82 (6.56)

Risk of bias: All domain – Very High, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 13, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

Protocol outcome 4: Relapse into medication use

- Actual outcome for Benzodiazepines: Defined as retaking medication of any dose at follow-up. at 11 month follow-up; Group 1: 1/10, Group 2: 1/10; Comments: number analysed was those who completed the treatment and had ceased benzodiazepine by the end of the study and who were followed up at 11 months.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in

the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete 11 month follow up; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete 11 month follow up.

Protocol outcome 5: Increase in symptoms for which the medication was originally prescribed
- Actual outcome for Benzodiazepines: Spielberger: state at 20 weeks post taper; Group 1: mean 43.29 (SD 12.15); n=14, Group 2: mean 43.18 (SD 9.66); n=12; Spielberger State-Trait Anxiety questionnaire 0-80 Top=High is poor outcome; Comments: Baseline values
CBT: 43.5 (10.11)
GS:43.06 (11.87)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 10, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 12, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

- Actual outcome for Benzodiazepines: Spielberger: state at 3-month follow-up; Group 1: mean 35.33 (SD 10.14); n=11, Group 2: mean 41.9 (SD 9.55); n=10; Spielberger State and Trait Anxiety questionnaire 0-80 Top=High is poor outcome; Comments: Baseline values
CBT: 43.5 (10.11)
GS:43.06 (11.87)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 13, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

- Actual outcome for Benzodiazepines: Spielberger: trait at 20 weeks post taper; Group 1: mean 42.07 (SD 11.74); n=14, Group 2: mean 45.4 (SD 9.29); n=12; Spielberger state and trait anxiety questionnaire 0-80 Top=High is poor outcome; Comments: Baseline values
CBT: 45.56 (10.03)

GS:49.71 (11.01)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 10, Reason: abandoned trial; dropped out before baseline assessment; abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; did not complete questionnaire.; Group 2 Number missing: 12, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview;; did not complete questionnaire.

- Actual outcome for Benzodiazepines: Spielberger: trait at 3 month follow up; Group 1: mean 39 (SD 11.22); n=11, Group 2: mean 42.56 (SD 7.75); n=10; Spielberger state and trait questionnaire 0-80 Top=High is poor outcome; Comments: Baseline values
CBT: 45.56 (10.03)
GS:49.71 (11.01)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 13, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.

Protocol outcome 6: Distress

- Actual outcome for Benzodiazepines: Psychological distress inventory at 20 weeks post taper; Group 1: mean 52.57 (SD 14.08); n=14, Group 2: mean 49.5 (SD 6.09); n=12; Psychological Distress Inventory 0-100 Top=High is poor outcome; Comments: Baseline values
CBT:54.06 (13.29)
GS: 58.31 (18.35)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 10, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; did not complete questionnaire.; Group 2 Number missing: 12, Reason:

abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; did not complete questionnaire. - Actual outcome for Benzodiazepines: Psychological distress inventory at 3 month follow up; Group 1: mean 44.44 (SD 12.7); n=11, Group 2: mean 54.4 (SD 12.74); n=10; Psychological Distress Inventory 0-100 Top=High is poor outcome; Comments: Baseline values CBT:54.06 (13.29) GS: 58.31 (18.35) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: It is quite possible that patients would be able to deduce their group allocation based on the information contained in the group sessions.; Group 1 Number missing: 13, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.; Group 2 Number missing: 14, Reason: abandoned trial by ceasing to discontinue and participate in the group at any time following evaluation; dropped out prior to initial interview; non succeeder; did not complete questionnaire.	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use

Study (subsidiary papers)	**Oude voshaar 2006[201] (Oude voshaar 2003[202], Oude voshaar 2006[203])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=180)
Countries and setting	Conducted in Netherlands
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 15 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with long-term use of benzodiazepine who were unable to quit their usage benzodiazepines by themselves after receiving a discontinuation letter from their GP.
Exclusion criteria	Current psychiatric treatment; current treatment for drug or alcohol dependence; medical history of psychosis; epilepsy; insufficient mastery of the Dutch language; or terminal illness. Some potential participants were excluded by their GP's request due to severe comorbidity or for psychosocial reasons.
Recruitment/selection of patients	People who met inclusion criteria were sent a letter by their general practitioner advising them to quit gradually and inviting them to the surgery 3 months later to evaluate the effect of the letter. At this consultation the doctor enquired whether the patient had been able to achieve complete abstinence and if not, whether the patient would participate in this study.
Age, gender and ethnicity	Age - Mean (SD): 63 (12). Gender (M:F): 54/126. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Extra comments	'Long-term use' was defined as benzodiazepine use for at least 3 months with a prescribed amount sufficient for at least 60 days of consumption in accordance with the recommended dosage.
Indirectness of population	Serious indirectness: Specific benzodiazepine used not reported
Interventions	(n=73) Intervention 1: Non-pharmacological interventions - CBT+ tapered withdrawal. Attended five weekly 2-h sessions of group CBT in addition to the dose reduction visits to their general practitioner. The sessions started halfway through the tapering-off period and finished 2 weeks after the conclusion of the withdrawal programme. The aim of the group therapy was to support the participants during the tapering-off process and to prevent relapse thereafter. The therapy programme included: (a) psychoeducation concerning the advantages and disadvantages of long-term benzodiazepine use;

	(b) teaching and practising relaxation exercises by means of progressive relaxation; (c) cognitive restructuring of the interpretation of withdrawal symptoms. The sessions were led by registered psychologists, experienced in CBT, who received training and a detailed manual of the therapy. Duration 4 weeks. Concurrent medication/care: Participants who were not using diazepam were transferred to an equivalent dose of diazepam for 2 weeks by their own doctor. For participants taking more than one benzodiazepine, the dosages were added together. The daily dose of diazepam was reduced by 25% a week during four weekly visits. Participants had the opportunity to divide the last step into two steps of 12.5%for 4 days. Indirectness: No indirectness Further details: 1. Addiction support services: (n=73) Intervention 2: Tapered withdrawal. Participants who were not using diazepam were transferred to an equivalent dose of diazepam for 2 weeks by their own doctor. For participants taking more than one benzodiazepine, the dosages were added together. The daily dose of diazepam was reduced by 25% a week during four weekly visits. Participants had the opportunity to divide the last step into two steps of 12.5%for 4 days. Duration 4 weeks. Concurrent medication/care: No additional therapy. Indirectness: No indirectness Further details: 1. Addiction support services: (n=34) Intervention 3: Usual care. Participants in the usual care control group were informed about the randomisation by letter. They did not receive any help with benzodiazepine reduction. Duration 4 weeks. Concurrent medication/care: No additional therapy. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Academic or government funding (Dutch Health Care Insurance Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) versus DOSE REDUCTION ALONE

Protocol outcome 1: Quality of life

- Actual outcome for Benzodiazepines: SF-36: Physical function at 18 months; Group 1: mean 68 (SD 26); n=58, Group 2: mean 65 (SD 26); n=59; SF-36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Social function at 18 months; Group 1: mean 68 (SD 22); n=58, Group 2: mean 64 (SD 26); n=59; SF-36 Social function 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Role limitation (physical) at 18 months; Group 1: mean 57 (SD 44); n=58, Group 2: mean 54 (SD 42); n=59; SF-36 Role limitation (physical) 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Role limitation (emotional) at 18 months; Group 1: mean 67 (SD 41); n=58, Group 2: mean 76 (SD 39); n=59; SF-36 Role limitation (emotional) 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Mental health at 18 months; Group 1: mean 71 (SD 17); n=58, Group 2: mean 76 (SD 39); n=59; SF-36 mental health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Vitality at 18 months; Group 1: mean 63 (SD 20); n=58, Group 2: mean 61 (SD 20); n=59; SF-36: vitality 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: Pain at 18 months; Group 1: mean 67 (SD 26); n=58, Group 2: mean 61 (SD 27); n=59; SF-36: pain 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

- Actual outcome for Benzodiazepines: SF-36: General health perception at 18 months; Group 1: mean 62 (SD 19); n=58, Group 2: mean 57 (SD 20); n=59; SF-36: general health perception 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 14

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Successful discontinuation at 3 months; Group 1: 33/57, Group 2: 37/60

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 16; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: Failure to discontinue median % dose reduction
at 3 months; Of the 66 individuals who completed the study but failed to discontinue, the median dose reduction was:
Tapering with CBT: 53%
Tapering: 35%
Usual care: -5%;

Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:; Group 2 Number missing:

- Actual outcome for Benzodiazepines: Successful discontinuation at 15 months; Group 1: 20/68, Group 2: 25/69

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 4

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)
at 3 months; Group 1: mean 6.8 (SD 7.5); n=73, Group 2: mean 6.2 (SD 6.8); n=73; BWSQ 0-40 Top=High is poor outcome; Comments: Scale unclear - to review

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 11

Protocol outcome 4: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs

- Actual outcome for Benzodiazepines: Patients using alcohol at 3 months; Group 1: 40/73, Group 2: 42/73

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 11

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) versus USUAL CARE

Protocol outcome 1: Quality of life

- Actual outcome for Benzodiazepines: SF-36: Physical function at 18 months; Group 1: mean 68 (SD 26); n=58, Group 2: mean 72 (SD 26); n=26; SF-36 Physical function 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Social function at 18 months; Group 1: mean 68 (SD 22); n=58, Group 2: mean 69 (SD 19); n=26; SF-36 Social function 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Role limitation (physical) at 18 months; Group 1: mean 57 (SD 44); n=58, Group 2: mean 76 (SD 36); n=26; SF-36 Role limitation (physical) 0-100 Top=High is good outcome; Comments: Significant baseline differences between groups

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Role limitation (emotional) at 18 months; Group 1: mean 67 (SD 41); n=58, Group 2: mean 81 (SD 29; n=26; SF-36 role limitation (emotional) 0-100 Top=High is good outcome; Comments: Significant differences between baseline values

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Mental health at 18 months; Group 1: mean 71 (SD 17); n=58, Group 2: mean 81 (SD 29); n=26; SF-36 mental health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Vitality at 18 months; Group 1: mean 63 (SD 20); n=58, Group 2: mean 63 (SD 24); n=26; SF-36: vitality 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: Pain at 18 months; Group 1: mean 67 (SD 26); n=58, Group 2: mean 69 (SD 22); n=26; SF-36: pain 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

- Actual outcome for Benzodiazepines: SF-36: General health perception at 18 months; Group 1: mean 62 (SD 19); n=58, Group 2: mean 55 (SD 22); n=26; SF-36: general health perception 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 8

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Successful discontinuation at 3 months; Group 1: 33/57, Group 2: 5/34

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 16 Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: Successful discontinuation at 15 months; Group 1: 20/68, Group 2: 5/33

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 1

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) at 3 months; Group 1: mean 6.8 (SD 7.5); n=73, Group 2: mean 5.8 (SD 7.3); n=34; BWSQ 0-40 Top=Unclear

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 13

Protocol outcome 4: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs

- Actual outcome for Benzodiazepines: Patients using alcohol at 3 months; Group 1: 40/73, Group 2: 18/34

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 13

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOSE REDUCTION ALONE versus USUAL CARE

Protocol outcome 1: Quality of life

- Actual outcome for Benzodiazepines: SF-36: Physical function at 18 months; Group 1: mean 65 (SD 26); n=59, Group 2: mean 72 (SD 26); n=26; SF-36 Physical function 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Social function at 18 months; Group 1: mean 64 (SD 26); n=59, Group 2: mean 69 (SD 19); n=26; SF-36 Social function 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Role limitation (physical) at 18 months; Group 1: mean 54 (SD 42); n=59, Group 2: mean 76 (SD 36); n=26; SF-36 Role limitation (physical) 0-100 Top=High is good outcome; Comments: Significant differences between baseline scores

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Role limitation (emotional) at 18 months; Group 1: mean 76 (SD 39); n=59, Group 2: mean 81 (SD 29); n=26; SF-36 role limitation (emotional) 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Mental health at 18 months; Group 1: mean 76 (SD 39); n=59, Group 2: mean 81 (SD 29); n=26; SF-36 mental health 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Vitality at 18 months; Group 1: mean 61 (SD 20); n=59, Group 2: mean 63 (SD 24); n=26; SF-36: vitality 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: Pain at 18 months; Group 1: mean 61 (SD 27); n=59, Group 2: mean 69 (SD 22); n=26; SF-36: pain 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

- Actual outcome for Benzodiazepines: SF-36: General health perception at 18 months; Group 1: mean 57 (SD 20); n=59, Group 2: mean 55 (SD 22); n=26; SF-36: general health perception 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 13

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Successful discontinuation at 3 months; Group 1: 37/60, Group 2: 5/34

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 13; Group 2 Number missing: 0

- Actual outcome for Benzodiazepines: Successful discontinuation at 15 months; Group 1: 25/69, Group 2: 5/33

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4; Group 2 Number missing: 1

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) at 3 months; Group 1: 6.2 (SD 6.8); n=73, Group 2: mean 5.8 (SD 7.3); n=34; BWSQ 0-40 Top=Unclear

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing: 13 Protocol outcome 4: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs - Actual outcome for Benzodiazepines: Patients using alcohol at 3 months; Group 1: 42/73, Group 2: 18/34 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 13; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

Study	**Rickels 2000[225]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=107)
Countries and setting	Conducted in USA; Setting: Outpatient - community
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	To be enrolled in the program, patients were required to have a diagnosis of generalized anxiety disorder according to DSM-III-R, to beat least 21 years old, and to have been taking diazepam, lorazepam, or alprazolam in therapeutic doses continuously for the past 12 months (5 mg diazepam was considered equivalent to 1 mg lorazepam and 0.5 mg alprazolam).
Exclusion criteria	Patients with a primary panic disorder diagnosis were excluded from this report.

Recruitment/selection of patients	Patients were recruited by physician referrals and notices in local media
Age, gender and ethnicity	Age - Mean (SD): 48 (14). Gender (M:F): 59/48. Ethnicity: not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear (Mixed population: diazepam, lorazepam, oralprazolam - breakdown not provided). 3. Setting: Outpatient
Indirectness of population	Serious indirectness: Breakdown of people on each study drug not provided. Unclear in>80% were on relevant study drug
Interventions	(n=23) Intervention 1: Imipramine substitution + tapered withdrawal. During the screening phase, patients were kept on a stable dose of their benzodiazepine within the therapeutic range for 2–4 weeks. They were then assigned to double-blind treatment with imipramine, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of approximately 25% per week. The taper phase was followed by a 5-week Benzodiazepine-free phase during which the patient's clinical status in the initial period without benzodiazepines was prospectively assessed. Duration 15-19 weeks. Concurrent medication/care: After participation in the benzodiazepine discontinuation program, patients were returned to the care of their family physicians. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable Comments: Of the 107 patients who entered the program, 32 patients did not complete the pre-taper treatment phase, leaving 75 patients to enter the taper phase. (n=28) Intervention 2: Buspirone substitution + tapered withdrawal. During the screening phase, patients were kept on a stable dose of their benzodiazepine within the therapeutic range for 2–4 weeks. They were then assigned to double-blind treatment with buspirone, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of approximately 25% per week. The taper phase was followed by a 5-week benzodiazepine-free phase during which the patient's clinical status in the initial period without benzodiazepines was prospectively assessed. Duration 15-19 weeks. Concurrent medication/care: After participation in the benzodiazepine discontinuation program, patients were returned to the care of their family physicians. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable Comments: Of the 107 patients who entered the program, 32 patients did not complete the pre-taper treatment phase, leaving 75 patients to enter the taper phase.

	(n=24) Intervention 3: Placebo substitution + tapered withdrawal. During the screening phase, patients were kept on a stable dose of their benzodiazepine within the therapeutic range for 2–4 weeks. They were then assigned to double-blind treatment with placebo, while the daily benzodiazepine intake was not altered. Four weeks later, patients entered a taper phase that lasted 4–6 weeks. During the taper phase, daily benzodiazepine intake was reduced at a rate of approximately 25% per week. The taper phase was followed by a 5-week benzodiazepine-free phase during which the patient's clinical status in the initial period without benzodiazepines was prospectively assessed. Double-blind study treatment was continued for the first 3 weeks of the benzodiazepine-free phase; placebo was substituted, single blind, for imipramine and buspirone for the final 2 weeks. Patients were seen weekly. Duration 15-19 weeks. Concurrent medication/care: After participation in the benzodiazepine discontinuation program, patients were returned to the care of their family physicians. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable Comments: Of the 107 patients who entered the program, 32 patients did not complete the pre-taper treatment phase, leaving 75 patients to enter the taper phase.
Funding	Academic or government funding (Supported by NIMH grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO A SUBSTITUTE (IMIPRAMINE) + TAPER. versus FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO A SUBSTITUTES (BUSPIRONE) + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use
- Actual outcome for Benzodiazepines: Benzodiazepine free at 3 months; Group 1: 19/23, Group 2: 19/28
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 2

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO A SUBSTITUTE (IMIPRAMINE) + TAPER. versus PLACEBO + TAPERED WITHDRAWAL STRATEGIES ALONE

Protocol outcome 1: Reduction/cessation of prescribed drug use
- Actual outcome for Benzodiazepines: Benzodiazepine free at 3 months; Group 1: 19/23, Group 2: 9/24
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 1

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO A SUBSTITUTES (BUSPIRONE) + TAPER versus PLACEBO + TAPERED WITHDRAWAL STRATEGIES ALONE Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Benzodiazepines: Benzodiazepine free at 3 months; Group 1: 19/28, Group 2: 9/24 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 1

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Sanchez-craig 1987[235]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Canada; Setting: Outpatients
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Long-term users of therapeutic doses of benzodiazepine. Mean (SD) daily dose: 16.2 (11.5) for CBT + gradual tapering group and 13.9 (8.1) for CBT + placebo group.
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable

Inclusion criteria	18-69 years of age; daily use of a benzodiazepine for at least3 months prior to study entry; cumulative benzodiazepine exposure (defined as the product of the average daily dose in milligrams and the total duration of use in days) above 2700mg of diazepam (or the equivalent); reported inability to discontinue use because of symptoms that occurred during attempts at discontinuation.
Exclusion criteria	Pregnancy, significant psychiatric, hepatic, renal, cardiovascular or pulmonary disease; multiple drug abuse during the 6 months prior to entry; use of centrally active substances other than benzodiazepine during the 30-days prior to entry (excepting nicotine, caffeine, and alcohol in moderate amounts i.e., ≤30g per day.
Recruitment/selection of patients	Self-referral (54%), referral by professionals in the community (10%),presented in response to public advertisements offering assessment and treatment to people concerned with their long-term use of benzodiazepine (36%).
Age, gender and ethnicity	Age - Mean (range): CBT + gradual tapering: 40.1 (20-59) CBT + placebo: 41.8 (21-57). Gender (M:F): CBT + gradual tapering: M:F 48% CBT + placebo: 53% male. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed: approximately 75% on long acting, no breakdown in results). 3. Setting: Not stated/Unclear
Indirectness of population	Serious indirectness: 4/9 dose equivalences reported in study are for drugs not in protocol.
Interventions	(n=23) Intervention 1: CBT + tapered withdrawal. Subjects received active diazepam during the withdrawal regime. Subjects were treated by the psychologists in weekly sessions of approximately 60 minutes. During the weekly visits they were also seen by other members of the research team meaning they spent about 2 hours per week in the clinic. Baseline period (2 weeks)- subjects monitored drug and alcohol use on forms which were presented to the therapist at the first treatment session. They continued their prescribed benzodiazepine in their normal dosage. Initiation of treatment and explanation of objectives- subjects were told they would be guided to set goals of reduction, to identify the circumstances of drug use and to develop skills for coping with those circumstances without using tranquillizers. Information from the self-monitoring forms was used as the starting point for the agreement of dose reduction. Basic information about what symptoms might be expected during withdrawal was given and general information on the pharmacology and known effects of benzodiazepine was also

	provided. At the end of the session, a filled prescription for the upcoming week was issued (drug or placebo). Identification of functions served by benzodiazepine- subjects considered reasons for their benzodiazepine usage in a questionnaire and responses were used to explore factors in maintaining benzodiazepine use and developing alternatives. Goal setting and feedback. subjects selected a goal which they felt confident of attaining. In most cases the weekly goal was a reduction not great than 5mg of diazepam or its placebo equivalent per day. They had to continue to monitor their alcohol consumption to avoid compensating for a reduction in tranquillizer use. The importance of keeping self-monitoring records and of bringing completed forms to treatment sessions was emphasised. Coping with expected withdrawal symptoms- information was provided and it was emphasized that the main feature would be discomfort rather than a threat to health. They were taught cognitive coping strategies to aid this. Emphasis was placed on formulating self-statements that were believable, simply stated, and easy to remember. Coping with negative emotions, inability to sleep etc- subjects were taught to deal with anxiety provoking circumstances using both cognitive and behavioural techniques. Termination of treatment- the plan was to complete treatment by mutual agreement when drug intake had been reduced to zero and the subject was confident of maintaining gains achieved during treatment. All subjects were advised to contact the clinic (24-hour helpline) in the event of unacceptable discomfort before taking independent action. Patients were repeatedly and strongly urged to use the service as necessary. Duration 5 therapy sessions. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=19) Intervention 2: CBT + abrupt withdrawal. Subjects received inert tablets and were monitored weekly as per the gradual withdrawal group. Subjects were treated by the psychologists in weekly sessions of approximately 60 minutes. During the weekly visits they were also seen by other members of the research team meaning they spent about 2 hours per week in the clinic. Baseline period (2 weeks)- subjects monitored drug and alcohol use on forms which were presented to the therapist at the first treatment session. They continued their prescribed benzodiazepine in their normal dosage. Initiation of treatment and explanation of objectives- subjects were told they would be guided to set goals of reduction, to identify the circumstances of drug use and to develop skills for coping with those circumstances without using tranquillizers. Information from the self-monitoring forms was used as the starting point for the agreement of dose reduction. Basic information about what symptoms might be expected during withdrawal was given and general information on the pharmacology and known effects of benzodiazepine was also provided. At the end of the session, a filled prescription for the upcoming week was issued (drug or placebo). Identification of functions served by benzodiazepine- subjects considered reasons for their benzodiazepine

	usage in a questionnaire and responses were used to explore factors in maintaining benzodiazepine use and developing alternatives. Goal setting and feedback. subjects selected a goal which they felt confident of attaining. they had to continue to monitor their alcohol consumption to avoid compensating for a reduction in tranquillizer use. Coping with expected withdrawal symptoms- information was provided and it was emphasized that the main feature would be discomfort rather than a threat to health. They were taught cognitive coping strategies to aid this. Coping with negative emotions, inability to sleep etc- subjects were taught to deal with anxiety provoking circumstances using both cognitive and behavioural techniques. Termination of treatment- the plan was to complete treatment by mutual agreement when drug intake had been reduced to zero and the subject was confident of maintaining gains achieved during treatment. All subjects were advised to contact the clinic (24-hour helpline) in the event of unacceptable discomfort before taking independent action. Patients were repeatedly and strongly urged to use the service as necessary. Duration 5 sessions. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT+ GRADUAL TAPER versus CBT+ ABRUPT TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Cessation of drug- no evidence of use of a benzodiazepine upon analysis of a blood and urine sample at End of treatment; Group 1: 9/23, Group 2: 11/19; Comments: Calculated from % provided in study.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

- Actual outcome for Benzodiazepines: Cessation of drug- no evidence of use of a benzodiazepine upon analysis of a blood and urine sample at 12 months; Group 1: 5/23, Group 2: 8/19; Comments: Calculated from % provided in study.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

- Actual outcome for Benzodiazepines: 'improved'-reduction on plasma benzodiazepine level over 50% of level determined during baseline. at End of treatment; Group 1: 3/23, Group 2: 3/19; Comments: Calculated from % provided in study.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome for Benzodiazepines: 'improved'-reduction on plasma benzodiazepine level over 50% of level determined during baseline. at 12 months; Group 1: 4/23, Group 2: 1/19; Comments: Calculated from % provided in study. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Protocol outcome 2: Relapse into medication use - Actual outcome for Benzodiazepines: Patients requesting a shift from the medication issued in the study back to their own supplies. at During treatment period; Group 1: 1/23, Group 2: 7/19; Comments: Calculated from % provided in study. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Ten Wolde 2008[256]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=861)
Countries and setting	Conducted in Netherlands; Setting: General practices in the Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Mean duration of use 8.1 years (10.6) weekly dose diazepam equivalent 49.3mg (70.8)
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable:
Inclusion criteria	Chronic benzodiazepine user. No further details
Exclusion criteria	Not reported
Recruitment/selection of patients	GPs were selected randomly from an electronic version of the Dutch telephone directory and received E200 compensation for participating.
Age, gender and ethnicity	Age - Mean (SD): 62.3 (14.2). Gender (M:F): 68.1%F 31.9%M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Systematic review: mixed (Oxazepam/ Temazepam/Diazepam). 3. Setting: Outpatient
Indirectness of population	Serious indirectness: 67.9% were taking oxazepam/temazepam/ diazepam
Interventions	(n=278) Intervention 1: Non-pharmacological interventions - Patient advice/education and support. A pre-test questionnaire that had been sent out to all participants was used to produce the tailored letter. Each letter was based on an individual assessment. The individual data were fed into a computer program in which an individually tailored letter was composed on the basis of rules about what information would be appropriate to include given a specific response on the individual assessment. Each letter began with an introduction explaining the goal and rationale of the information. Subsequently the 3 main determinants were addressed. The information was designed to 1) increase the perceptions of the positive outcome expectations of discontinuing benzodiazepine use 2) lower the perceptions of the positive outcome expectations of the use of benzodiazepine and 3)increase self-efficacy expectations with regard to discontinuing usage (by offering several skills to reach abstinence, such as making a plan to cut down benzodiazepines and by offering alternatives in order to cope with worrying thoughts). the intervention consisted of one letter of 5-6 pages of information (approx. 1200 words) in which all of these 3 psychological determinants were addressed in the above order of presentation. Duration Single letter. Concurrent medication/care: NR. Indirectness: No indirectness

	Further details: 1. Addiction support services: Not stated/Unclear (n=310) Intervention 2: Non-pharmacological interventions - Patient advice/education and support. A pre-test questionnaire that had been sent out to all participants was used to produce the first tailored letter. The additional two subsequent letters were each based on a separate individual assessment made by means of a standardised telephone interview of a maximum of 10 minutes. Each letter was based on an individual assessment. The individual data were fed into a computer program in which an individually tailored letter was composed on the basis of rules about what information would be appropriate to include given a specific response on the individual assessment. Each letter began with an introduction explaining the goal and rationale of the information. Subsequently the 3 main determinants were addressed. The information was designed to 1) increase the perceptions of the positive outcome expectations of discontinuing benzodiazepine use 2) lower the perceptions of the positive outcome expectations of the use of benzodiazepines and 3)increase self-efficacy expectations with regard to discontinuing usage (by offering several skills to reach abstinence, such as making a plan to cut down benzodiazepines and by offering alternatives in order to cope with worrying thoughts). The intervention consisted of three letters of about three pages each (approx. 400 words) sent at intervals of 1 month. The first tailored letter was designed to increase the perceptions of the positive outcome expectations of discontinuing benzodiazepine usage and to lower the perceptions of the positive outcome expectations of the use of benzodiazepines. The second tailored letter was designed to increase self-efficacy expectations with regard to discontinuing usage, while the content of the third letter provided more skills for discontinuing usage, or provided a summary of the information in the first two letters, depending on the individual needs detected in the third assessment. In addition, participants were provided with progress feedback: individual changes in benzodiazepine use were mentioned. The tailoring included three working mechanisms that have the potential to be effective: personalisation, feedback and adaptation. Duration 3 letters. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=273) Intervention 3: Advice, education and support. Standard letter used by GPs in the Netherlands to inform patients about benzodiazepine. The same for all patients, it pinpointed only the disadvantages of benzodiazepine use (such as the risk of becoming addicted) and contained brief advice on how to discontinue use. The letter consisted of approximately 200 words. Duration Single letter. Concurrent medication/care: NR. Indirectness: No

	indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (Dutch Council for Health Insurance)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SINGLE TAILORED LETTER versus GP LETTER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Cessation of benzodiazepine at 12 months; Group 1: 40/163, Group 2: 23/159; Comments: Calculated from percentages reported in paper.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 115, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.; Group 2 Number missing: 114, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIPLE LETTERS versus SINGLE TAILORED LETTER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Cessation of benzodiazepine at 12 months; Group 1: 44/186, Group 2: 40/163; Comments: Calculated from percentages reported in study.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 124, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.; Group 2 Number missing: 115, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIPLE LETTERS versus GP LETTER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Cessation of benzodiazepine at 12 months; Group 1: 44/186, Group 2: 23/159; Comments: Calculated from percentages provided by the study.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 124, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.; Group 2 Number missing: 114, Reason: dropped out of study; did not fill in baseline questionnaire properly; did not complete follow-up questionnaire.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	Tyrer 1996[261]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=87)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People who had taken a benzodiazepine for at least 6 months and had tried unsuccessfully to reduce or stop because of apparent withdrawal symptoms.
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	People who had taken a benzodiazepine for at least 6 months and had tried unsuccessfully to reduce or stop because of apparent withdrawal symptoms. Patients were taking benzodiazepines alone.
Exclusion criteria	Hypertension, major depressive disorder, a psychotic disorder or melancholia (after administration of SCID).
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Other: NR. Gender (M:F): NR. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Indirectness of population	Serious indirectness: No breakdown of benzodiazepines used- may have included those not on protocol.
Interventions	(n=41) Intervention 1: Pharmacological interventions - Dothiepin substitution + tapered withdrawal. Weeks 1-4: Dothiepin tablets in flexible increasing dosage, up to 150mg/day. Weeks 5-12 : Taper involving a reduction of the initial benzodiazepine dosage by 20% every 2 weeks. Final assessment at 14 weeks. Duration 14 weeks. Concurrent medication/care: NR. Indirectness: No indirectness

	Further details: 1. Addiction support services: Not stated/Unclear (n=46) Intervention 2: Pharmacological interventions - Placebo substitution + tapered withdrawal. Weeks 1-4: Placebo tablets in flexible increasing dosage. Weeks 5-12 : Taper involving a reduction of the initial benzodiazepine dosage by 20% every 2 weeks. Final assessment at 14 weeks. Duration 14 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Study funded by industry (Research department of Boots Drug Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Dothiepin+ TAPER versus PLACEBO + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Taking no benzodiazepine at 14 weeks; Group 1: 11/36, Group 2: 17/41

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 5, Reason: unclear

Protocol outcome 2: Patient Satisfaction

- Actual outcome for Benzodiazepines: Satisfaction analogue rating scale at 14 weeks; Group 1: mean 70.5 mm (SD 23.8); n=19, Group 2: mean 47.6 mm (SD 38.7); n=21; Satisfaction scale 0-100 Top=High is good outcome

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 22, Reason: full recovery (3), adverse events (7), non-compliance (2), failure to attend/ lack of efficacy/ unknown reasons (9), did not complete questionnaire (1).; Group 2 Number missing: 25, Reason: full recovery (1), adverse events (5), non-compliance (7), failure to attend/ lack of efficacy/ unknown reasons (11), did not complete questionnaire (1).

- Actual outcome for Benzodiazepines: Global outcome scale (withdrawal symptoms, success in benzodiazepine withdrawal, satisfaction with treatment received). Poor outcome at 14 weeks; Group 1: 13/38, Group 2: 21/41

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 5, Reason: unclear

- Actual outcome for Benzodiazepines: Global outcome scale (withdrawal symptoms, success in benzodiazepine withdrawal, satisfaction with treatment received). Fair outcome at 14 weeks; Group 1: 13/38, Group 2: 11/41 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 5, Reason: unclear - Actual outcome for Benzodiazepines: Global outcome scale (withdrawal symptoms, success in benzodiazepine withdrawal, satisfaction with treatment received). Good outcome at 14 weeks; Group 1: 12/38, Group 2: 9/41 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 5, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Vicens 2006[266]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=139)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 14-75 years; taking Benzodiazepines at least 5 times a week for >1 year.
Exclusion criteria	Severe depression or anxiety, psychotic or markedly symptomatic personality disorders, illegal drug or severe alcohol intake; those under the care of a psychiatrist; increase in anxiety or insomnia at the time of recruitment; inpatients; those with cognitive impairment or advanced disease.
Recruitment/selection of patients	All eligible patients were asked for their consent.
Age, gender and ethnicity	Age - Mean (SD): Standardised advice: 60 years (12.3), usual care: 58 years (10.4). Gender (M:F): Standardised advice group: 13M/60F; usual care group: 12M/54F. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed (Standardised advice group: 62 short, 11 long; usual care group: 50 short, 15 long). 3. Setting: Outpatient
Indirectness of population	No indirectness: Inclusion criteria was 14-75 years, but average age suggests that the majority of included participants were adults.
Interventions	(n=73) Intervention 1: Advice education and support. The intervention consisted of an interview with a standardised message that had been developed previously through a qualitative study on 4 focal groups of 8-12 chronic benzodiazepine users. On the first visit, issues that were discussed included: what benzodiazepines are and what they are used for, treatment of symptoms vs treatment of their cause, untoward effects of benzodiazepines, problems of long-term use (dependence, tolerance and abstinence syndrome) and information on how to withdraw benzodiazepines through a stepwise reduction in dose. Follow-up surgery-based consultations lasting 10 minutes involved stressing the issues discussed on the first visit, evaluating possible abstinence or withdrawal symptoms and positive reinforcement of achievements. Taper: gradual reduction of benzodiazepine dose, with control visits every 15 days. The dose was reduced between 10 and 25% of the initial dose fortnightly. Participating physicians received training on the administration of questionnaires, the structured interview and the guidelines for tapering off doses. Duration Average 2.6 months, range 1-7. Concurrent medication/care: NR.

	Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=66) Intervention 2: Usual care. Managed according to usual practice and informed of the convenience of reducing the use of benzodiazepines. Duration Average 2.6 months, range 1-7. Concurrent medication/care: NR. Indirectness: Serious indirectness; Indirectness comment: Unclear if usual care involves deprescribing of benzodiazepines. Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (Spanish Society of Family and Community Medicine, Gerencia d'Atencio Primaria de Mallorca and Primary Care Preventative and Health Promotion Activities Network (redIAPP).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STANDARDISED ADVICE + TAPER versus USUAL CARE

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Success- no use/ no more than once every 15 days at 6 months; Group 1: 29/73, Group 2: 2/64

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: Person had moved/ could not be contacted.

- Actual outcome for Benzodiazepines: Success- no use/ no more than once every 15 days at 12 months; Group 1: 33/71, Group 2: 6/64
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Person had moved/ could not be contacted.; Group 2 Number missing: 2, Reason: Person had moved/ could not be contacted.

- Actual outcome for Benzodiazepines: Reduced- at least a 50% reduction in initial dose at 12 months; Group 1: 16/71, Group 2: 11/64

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: Person had moved/ could not be contacted.; Group 2 Number missing: 2, Reason: Person had moved/ could not be contacted.

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-

	fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Vissers 2007[270]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Netherlands; Setting: Community - general practice
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients who used benzodiazepine as a sleeping medication for more than three months (defined as long-term use) with a minimum use of three days per week.
Exclusion criteria	Exclusion criteria were the use of more than one benzodiazepine at the same time, use of another type of sleep medication, use of stimulants and, according to their GP, alcohol misuse, serious mental/somatic disease or unfit to participate.
Recruitment/selection of patients	Patients were selected via their GPs
Age, gender and ethnicity	Age - Other: <50 years: 6; 50-59 years: 6; 60-69 years: 13; 70-79 years: 11; >80 years: 2. Gender (M:F): 16/22. Ethnicity: not reported

Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: People on long half-life benzodiazepines (Participants had their benzodiazepine converted to an equivalent dose of diazepam at the start of the trial. 3. Setting: Outpatient
Extra comments	Benzodiazepine used before study entry not reported. Participants' benzodiazepine prescriptions were converted to an equivalent dose of diazepam at the trial start
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Pharmacological interventions - Melatonin substitution + tapered withdrawal. Participant benzodiazepine was converted to an equivalent dose of diazepam and stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose. 5 mg melatonin was added which had to be taken 4 h before patients went to bed. After stopping diazepam, the use of melatonin was continued for six more weeks. Duration 18 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=18) Intervention 2: Placebo substitution + tapered withdrawal. Participant benzodiazepine was converted to an equivalent dose of diazepam and stabilized for two weeks and then further converted every two weeks to 75%, 50%, 25%, 12.5% and 0% of the original dose. 5 mg placebo was added which had to be taken 4 h before patients went to bed. After stopping diazepam, the use of placebo was continued for six more weeks. Duration 18 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FOR BENZODIAZEPINE WITHDRAWAL, SWITCHING TO A SUBSTITUTES (MELATONIN) + TAPER. versus TAPERED WITHDRAWAL STRATEGIES ALONE + PLACEBO

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: Benzodiazepine discontinuation at post intervention (18 weeks); Group 1: 12/20, Group 2: 9/18

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Benzodiazepines: Benzodiazepine discontinuation at 1 year; Group 1: 8/19, Group 2: 7/17 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: stopped participation after taper-off; Group 2 Number missing: 1, Reason: stopped participation after taper-off.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction ; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

Study	**Vorma 2011[271]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Finland; Setting: inpatient
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Benzodiazepines
Subgroup analysis within study	Not applicable:

Inclusion criteria	Patients had to meet DSM IV-R criteria for opioid dependence and benzodiazepine dependence.
Exclusion criteria	Pregnancy; active medical illness; severe mental disorder; history of convulsions; unable to speak Finnish.
Recruitment/selection of patients	Consecutively admitted
Age, gender and ethnicity	Age - Mean (SD): Valproate: 32 (6.7), taper alone 32 (5.3). Gender (M:F): 22:8. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Inpatient
Extra comments	Not reported if prescribed or illicit BZs, but talks about the daily dose so suggests prescribed.
Indirectness of population	Serious indirectness: 2 out of the 7 benzodiazepines listed (that people could be on) are not included in review protocol list, but no breakdown provided
Interventions	(n=14) Intervention 1: Pharmacological interventions - Valproate substitution + tapered withdrawal. Valproate 20mg/kg per day for 2 weeks, with a reduction during the 3rd week. All subjects received gradual benzodiazepine tapering, where the subjects' reported dosage was converted into an equivalent dose of diazepam, with a maximum of 80mg per day. After the initial dose, dosages were reduced by 10mg daily until 40mg per day was reached, after which reductions were 5 mg daily. Duration 3 weeks. Concurrent medication/care: The patients were maintained during benzodiazepine detoxification on methadone 20-50mg or buprenorphine 2-16mg to prevent most opioid withdrawal symptoms. If symptoms occurred, lofexidine was used. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=16) Intervention 2: Tapered withdrawal. Gradual benzodiazepine tapering, where the subjects' reported dosage was converted into an equivalent dose of diazepam, with a maximum of 80 mg per day. After the initial dose, dosages were reduced by 10mg daily until 40mg per day was reached, after which reductions were 5 mg daily. Duration 3 weeks. Concurrent medication/care: The patients were maintained during benzodiazepine detoxification on methadone 20-50mg or buprenorphine 2-16mg to prevent most opioid withdrawal symptoms. If symptoms occurred, lofexidine was used. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear

Funding	Academic or government funding (Annual EVO Financing from the Department of Psychiatry, Helsinki University Central Hospital.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VALPROATE + GRADUAL TAPER versus GRADUAL TAPER ALONE

Protocol outcome 1: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Benzodiazepines: weekly Clinical Institute Withdrawal Assessment Scale - Benzodiazepines (CIWA-B) at Days 15-20; Group 1: mean 5.2 (SD 3.7); n=14, Group 2: mean 6.3 (SD 3.9); n=15; CIWA-B short version 0-18 Top=High is poor outcome; Comments: Last observation carried forward used by authors as 8 subjects discontinued participation in CIWA-B ratings but stayed in treatment.
Days 1-7 CIWA-B scores- mean (SD)
valproate group: 5.1 (2.7)
control group: 6.2 (3.5)

Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Valproate group benzodiazepine dose at baseline 60mg (20-160), placebo 30 (8-75) median plus range; Group 1 Number missing: 5, Reason: 4 discontinued ratings, 1 discharged prior to completing treatment; Group 2 Number missing: 5, Reason: 3 discontinued ratings, 1 discharged prior to completing treatment, 1 no CIWA-B ratings

Protocol outcome 2: Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs

- Actual outcome for Benzodiazepines: Discharged for using illicit drugs in hospital at during 3-week study period; Group 1: 1/14, Group 2: 1/16

Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Valproate group benzodiazepine dose at baseline 60mg (20-160), placebo 30 (8-75) median plus range;

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Relapse into medication use; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use ; Distress

E.3 Z-drugs

Study (subsidiary papers)	Bergdahl 2016[24] (Bergdahl 2017[23])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=67)
Countries and setting	Conducted in Sweden; Setting: Outpatient clinics and secondary care
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Z-drugs
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women (18–75 years) with insomnia disorder, diagnosed according to the DSM-5 [2], who had been using nonbenzodiazepine hypnotics at least three times a week for six months or more but still had maintained insomnia symptoms. They also had a wish to end their usage of sleep medication. Participants were required to comprehend and speak the Swedish language.
Exclusion criteria	Substance dependence (alcohol or drugs), patients with severe psychiatric disorder, severe somatic disease, pharmacological treatment with antipsychotic drugs and/or morphine/morphine-like drugs, patients who had initiated antidepressant or anxiolytic treatment within the past 3 months, or pregnancy.
Recruitment/selection of patients	Participants were recruited by advertisement in the local newspaper and from an outpatient sleep clinic. Regarding the recruitment by the advertisement, the subjects initiated the first contact.
Age, gender and ethnicity	Age - Mean (SD): 60.5 (9.4). Gender (M:F): 49/155 (of cohort assessed for eligibility) 50F/9M (of those randomised). Ethnicity: Not reported

Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Non-pharmacological interventions - Acupuncture. Auricular acupuncture - twice a week for 4 weeks. All treatments were performed in hospital facilities with 2-6 participants per group session. During each session, the participants were treated with five acupuncture needles in each of the outer ears for 45 minutes; no needle stimulation was performed. During the treatment the participants sat in chairs and were instructed by the acupuncturist to close their eyes and to focus on keeping their breathing calm and regular. The acupuncturists aimed to have the same attitude and behaviour in order to make the treatment as similar as possible for all participants. When the needles had been inserted the acupuncturist left the room. Participants were instructed to discontinue their hypnotic drug treatment 3-5 days before the intervention. 54% of the group discontinued before treatment started. Duration 4 weeks. Concurrent medication/care: No information on concomitant treatment. Indirectness: No indirectness Further details: 1. Addiction support services: (n=35) Intervention 2: Non-pharmacological interventions - Cognitive behavioural therapy (CBT). The CBT-i group received manual-based group treatment, focused on cognitive restructuring, once a week for six weeks. There were 2-6 participants per group session. The sessions contained information regarding sleep physiology, different ways of coping with sleeping problems, sleep restriction, maintaining factors, stimulus control, and relaxation techniques. Each session lasted for 90 minutes. Three registered psychologists who all had undergone CBT training and were experienced in giving CBT-i treatment carried out the treatments. All sessions were performed in hospital facilities. Participants were instructed to discontinue their hypnotic drug treatment 3-5 days before the intervention. 62% of the group discontinued before treatment started. Duration 6 weeks. Concurrent medication/care: No information on concomitant treatment. Indirectness: No indirectness Further details: 1. Addiction support services:

Funding	Academic or government funding (Ekhagastiftelsen provided financial support)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPUNCTURE versus COGNITIVE BEHAVIOURAL THERAPY (CBT)

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Z-drugs: Discontinuation of hypnotic drug at end of treatment (6 months); Group 1: 17/24, Group 2: 21/25

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: declined to participate: 4, excluded: 1, declined further participation: 2, adverse event: 1; Group 2 Number missing: 10, Reason: declined to participate: 6, declined further participation: 4

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Z-drugs: Hospital Anxiety and Depression Scale (HADS)-Anxiety at Post-treatment (4 and 6 weeks); Group 1: mean -0.9 (SD 0.46); n=25, Group 2: mean -0.68 (SD 0.54); n=25; HADS 0-21 Top=High is poor outcome; Comments: Variance is SE not SD

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: declined to participate: 4, excluded: 1, declined further participation: 1, adverse event: 1; Group 2 Number missing: 10, Reason: declined to participate: 3, declined further participation: 6, did not complete questionnaires: 1

- Actual outcome for Z-drugs: HADS-Anxiety at 6 months; Group 1: mean -0.36 (SD 0.54); n=22, Group 2: mean -0.61 (SD 0.56); n=23; HADS 0-21 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10, Reason: declined to participate: 4, excluded: 1, declined further participation: 3, adverse event: 1, did not complete questionnaires: 1; Group 2 Number missing: 12, Reason: declined to participate: 3, declined further participation: 8, did not complete questionnaires: 1

- Actual outcome for Z-drugs: HADS-Depression at Post-treatment (4 and 6 weeks); Group 1: mean -0.39 (SD 0.4); n=25, Group 2: mean -0.49 (SD 0.63); n=25; HADS 0-21 Top=High is poor outcome; Comments: Variance is SE not SD

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: declined to participate: 4, excluded: 1, declined further participation: 1, adverse event: 1; Group 2 Number missing: 10, Reason: declined to participate: 3, declined further participation: 6, did not complete questionnaires: 1

- Actual outcome for Z-drugs: HADS-Depression at 6 months; Group 1: mean -0.7 (SD 0.37); n=22, Group 2: mean -0.99 (SD 0.49); n=23; HADS 0-21 Top=High is poor outcome; Comments: Variance is SE not SD Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10, Reason: declined to participate: 4, excluded: 1, declined further participation: 3, adverse event: 1, did not complete questionnaires: 1; Group 2 Number missing: 12, Reason: declined to participate: 3, declined further participation: 8, did not complete questionnaires: 1 Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed - Actual outcome for Z-drugs: Insomnia at Post-treatment (4 and 6 weeks); Group 1: mean -2.07 (SD 0.78); n=25, Group 2: mean -8.16 (SD 1.18); n=25; Insomnia Severity Scale (insomnia severity index) 0-28 Top=High is poor outcome; Comments: Variance is SE not SD Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: declined to participate: 4, excluded: 1, declined further participation: 1, adverse event: 1; Group 2 Number missing: 10, Reason: declined to participate: 3, declined further participation: 6, did not complete questionnaires: 1 - Actual outcome for Z-drugs: Insomnia at 6 months; Group 1: mean -3.27 (SD 0.84); n=22, Group 2: mean -6.09 (SD 1.33); n=23; Insomnia Severity Scale 0-28 Top=High is poor outcome; Comments: Variance is SE not SD Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10, Reason: declined to participate: 4, excluded: 1, declined further participation: 3, adverse event: 1, did not complete questionnaires: 1; Group 2 Number missing: 12, Reason: declined to participate: 3, declined further participation: 8, did not complete questionnaires: 1	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

E.4 Antidepressants

Study (subsidiary papers)	PANDA trial: Eveleigh 2018[70] (Muskens 2013[177])
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=146)
Countries and setting	Conducted in Netherlands; Setting: 45 General Practices
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Long-term users of antidepressants. Eligible patients underwent a structured psychiatric interview by telephone using the Composite International Diagnostic Interview (CIDI, version 3.0), conducted by trained interviewers. Patients were excluded if they had appropriate use of long-term antidepressants according to the Dutch guidelines for depressive and anxiety disorders.
Stratum	Antidepressants: Mixed antidepressants: 73% were on SSRIs; 12% on SNRIs; 6% on TCAs; 8% on other non-TCAs
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Long-term antidepressant use (≥9 months). All antidepressants were included, except monoamine oxidase inhibitors. 2. Written informed consent.
Exclusion criteria	1. Current treatment in a psychiatric inpatient or outpatient clinic. 2. Appropriate use of long-term antidepressants according to the Dutch guidelines for depressive and anxiety disorders (that is, a history of recurrent depression (≥3 episodes) and/or a recurrent psychiatric disorder with at least two relapses after antidepressant discontinuation). 3. History of psychosis, bipolar disorder, or obsessive-compulsive disorder. 4. Current diagnosis of substance use disorder, excluding tobacco, because of the necessity of specialised

	treatment. 5. Non-psychiatric indication for long-term antidepressant usage, for example neuropathic pain. 6. Hearing impairment and/or insufficient understanding of the Dutch language. Age was not an exclusion criterion.
Recruitment/selection of patients	Long-term antidepressant users (≥9 months) selected from GP prescription databases. To prevent contamination between intervention and control group, a cluster randomisation was performed with the general practice as the unit of clustering. A practice was either an intervention practice or a control practice.
Age, gender and ethnicity	Age - Mean (SD): Intervention: 56 (12.9); control: 56 (14.3). Gender (M:F): 44/102. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses of antidepressants not reported Study also reports the outcome of the proportion of participants who successfully discontinued their long-term antidepressant use after 1 year. Successful discontinuation is defined as no antidepressant use during the preceding 6 months (prior to 1 year follow up) and the absence of a depressive or anxiety disorder during the 1-year follow-up, as assessed by the CID. This outcome was not extracted due to the overlap with the protocol outcomes of total number of people who discontinued and the total number of people who relapsed.
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Non-pharmacological interventions - Prescriber education. A patient-specific letter was sent to the GP with the recommendation to discontinue the antidepressant. Information was provided on antidepressant tapering and the discontinuation syndrome. A gradual tapering programme was recommended. The GP invited the patient to discuss the recommendation. No treatment restrictions were imposed in case of a relapse or the onset of a new psychiatric disorder after discontinuation. In the intervention group, the recommendation to discontinue was rejected in 34/70 (by the patient in 14, by the GP in 1 and by both in 16; 3 cases were missing). Duration of taper not specified (gradual taper). Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=76) Intervention 2: Usual care. GPs were unaware which patients participated in this study and

	continued usual care. The control condition will consist of usual care and do not impose restrictions on GPs to deliver care or to refer to specialised mental health care, including the continuation or discontinuation of psychotropic drugs. Since baseline psychiatric diagnostics will not be disclosed for patients who have given informed consent in a control practice, we expect continuation of antidepressant drug treatment in most cases. Duration 1 year follow up on usual care. Concurrent medication/care: Not reported. Indirectness: Serious indirectness; Indirectness comment: usual care group had no aim to taper or discontinue. Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LETTER TO GP WITH RECOMMENDATION TO DISCONTINUE THE PATIENT versus USUAL CARE

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Antidepressants: others: Antidepressant discontinuation (regardless of intention to comply with recommendation to discontinue or not in the intervention group) at 1 year; Group 1: 17/70, Group 2: 15/76; Comments: Adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias)

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: No missing data, as antidepressant discontinuation was calculated from prescription database (although unclear if any data missing).; Group 2 Number missing: 0

Protocol outcome 2: Relapse into medication use

- Actual outcome for Antidepressants: others: Antidepressant restart at 1 year; Group 1: 8/70, Group 2: 5/76; Comments: Adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias)

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: No missing data, as antidepressant discontinuation was calculated from prescription database (although unclear if any data missing); Group 2 Number missing: 0

Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Antidepressants: others: Relapse: depressive or anxiety disorder during the 1-year follow-up, as assessed by the CIDI (regardless of whether the participant discontinued antidepressants or not) at 1 year; Group 1: 18/70, Group 2: 10/76; Comments: Adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias) Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness; Group 1 Number missing: 20, Reason: unreachable n=1, CIDI interview too bothersome n=1, refused CIDI interview n=5, mental health problems n=1, no time n=2, no reason given n=10; Group 2 Number missing: 10, Reason: unreachable n=3, CIDI interview too bothersome n=2, refused CIDI interview n=1, deceased n=1, no benefit for participant n=1, physical illness n=1, no reason given n=1.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Fava 1994[71]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in Italy; Setting: Outpatients who had been referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine, Bologna, Italy.
Line of therapy	1st line
Duration of study	Intervention time: 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People with major depressive disorder successfully treated with antidepressants (full remission - see inclusion criteria for more details). Diagnoses were established by the consensus of a psychiatrist and a clinical psychologist independently using the Schedule for Affective Disorders and Schizophrenia.

Stratum	Antidepressants: tricyclics: All on TCAs (8 people (20%) on desipramine - not on guideline medicine list).
Subgroup analysis within study	Not applicable
Inclusion criteria	Current diagnosis of primary major depressive disorder according to the Research Diagnostic Criteria; no history of manic, hypomanic, or cyclothymic features; no history of active drug or alcohol abuse or dependence or of personality disorder according to DSM-III-R criteria; no history of antecedent dysthymia; no active medical illness; successful response to antidepressant drugs administered by the same psychiatrist according to a standardised protocol; after drug treatment all patients were assessed by the same clinical psychologist who had evaluated them on intake, but who did not take part in the treatment. Only the patients rated as 'better' or 'much better' according to Kellner's global rating scale of improvement and as in full remission were included in the study; subjects had to show no evidence of depressed mood after treatment, according to a modified version of Paykel's Clinical Interview for Depression and thus be in stage 3 of primary unipolar depression.
Exclusion criteria	No residual symptoms after treatment with antidepressants - all patients were treated for at least 3 months but no more than 5 months with full doses of antidepressant drugs, after which the modified version of the Paykel Clinical Interview for Depression was administered (covering 19 symptom areas) - to evaluate prodromal and residual symptoms. Only 6 of the 49 patients screened had no residual symptoms and they were excluded from further participation.
Recruitment/selection of patients	Consecutive outpatients satisfying inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): CBT + taper: 43.7 (3.2); clinical management + taper: 48.5 (3.3). Gender (M:F): 13/27. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses: CBT group: 7 patients on amitriptyline 200mg/day, 6 on desipramine 200mg/day, 5 on imipramine 200mg/day, 2 on mianserin 60mg/day, 1 not reported; taper group: 12 patients on amitriptyline 200mg/day, 2 on desipramine 200mg/day, 4 on imipramine 200mg/day, 2 on mianserin 60mg/day, 2 not reported.

	The aim of the study was to explore the feasibility of a psychotherapeutic approach to the residual symptoms of depression after successful treatment with antidepressant drugs. A later study [72, 196] also included in this review looked at the same intervention, but in a different population with recurrent depression.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Non-pharmacological interventions - Cognitive behavioural therapy (CBT) + taper. Ten 40-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline or its equivalent every other week, and then the drugs were withdrawn completely. Discontinuation of antidepressant drug use was not feasible for 3 patients (1 in the CBT group and 2 in the CM group), and they were excluded from the study at that point. CBT was conducted as described by Beck et al. The psychiatrist, an experienced therapist, used strategies and techniques designed to help depressed patients correct their distorted views and maladaptive beliefs. Whenever appropriate, as in the case of residual symptoms related to anxiety, exposure strategies were planned with the patient. Duration 20 weeks. Concurrent medication/care: 6 people in the intervention groups were also taking benzodiazepines, 2 of which discontinued during the study. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=22) Intervention 2: Clinical management (CM) + taper. Ten 40-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline or its equivalent every other week, and then the drugs were withdrawn completely. Discontinuation of antidepressant drug use was not feasible for 3 patients (1 in the CBT group and 2 in the CM group), and they were excluded from the study at that point. Clinical management consisted of monitoring medication tapering, reviewing the patient's clinical status, and providing the patient with support and advice if necessary. In clinical management, specific interventions such as exposure strategies, diary work, and cognitive restructuring were proscribed. Duration 20 weeks. Concurrent medication/care: 6 people in the control group were also taking benzodiazepines, 2 of which discontinued during the study. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) + TAPER versus CLINICAL MANAGEMENT	

+ TAPER Protocol outcome 1: Reduction/cessation of prescribed drug use - Actual outcome for Antidepressants: tricyclics: Discontinuation of antidepressants (states the number of people in whom discontinuation was not feasible, and these people were excluded from further analysis) at Post-treatment (20 weeks); Group 1: 20/21, Group 2: 20/22; Comments: Calculated from the comment that discontinuation was not feasible in 1 person in the CBT group and in 2 people in the CM group. These people were excluded from further analysis, so only the 20 people in each group who discontinued treatment were analysed further. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Increase in symptoms for which the medication was originally prescribed - Actual outcome for Antidepressants: tricyclics: Relapse (occurrence of a Research Diagnostic Criteria-defined episode of major depression during follow up) at 2 years; Group 1: 4/21, Group 2: 9/22; Comments: Including the people who were unable to discontinue during the taper stage, as it specifically states that these people were withdrawn because of relapse during the medication tapering phase. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Antidepressants: tricyclics: Residual symptoms score (people in the study had residual symptoms after successful treatment with antidepressants (baseline) - this score was assessed again after CBT or CM + taper) at Post-treatment 20 weeks; Group 1: mean 24.25 (SD 2.9); n=20, Group 2: mean 26.25 (SD 2.07); n=20; Total score on the modified version of the Paykel Clinical Interview for Depression – range of values not reported, assumed to be 133 (based on 19 symptom areas and a 1-7 point scale) Top=High is poor outcome; Comments: Notes that a residual symptom was scored as present when a rating of at least 3 of the 7-point scale was assigned, but does not report the range of values for the total score. 19 symptom areas were assessed, so assumed to be 19x7 total possible score. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: unable to discontinue during taper phase; Group 2 Number missing: 2, Reason: unable to discontinue during taper phase	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	Fava 1998[72]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Italy; Setting: Outpatients who had been referred to and treated in the Affective Disorders Program of the University of Bologna School of Medicine, Bologna, Italy.
Line of therapy	1st line
Duration of study	Intervention time: 20 weeks (both groups had ten sessions once every other week when the taper intervention was performed)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People taking antidepressant medication (successfully treated - see inclusion criteria for more details). The patients' diagnoses were established by the consensus of a psychiatrist and a clinical psychologist independently using the Schedule for Affective Disorders and Schizophrenia.
Stratum	Antidepressants: tricyclics: 35 were on TCAs (11 on desipramine, not on guideline medicine list); 5 were on SSRIs. Patients who could not tolerate tricyclic antidepressant drugs were switched to selective serotonin reuptake inhibitors.
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with recurrent depression (≥3 episodes of depression) who had been successfully treated with antidepressant drugs. (1) a current diagnosis of major depressive disorder according to the Research Diagnostic Criteria for a Selected Group of Functional Disorders; (2) 3 or more episodes of depression, with the immediately preceding episode being no more than 2 and a half years before the onset of the present episode (3) a minimum 10-week remission according to Research Diagnostic Criteria (≤2 symptoms present to no more than a mild degree with absence of functional impairment) between the index episode and the immediately preceding episode; (4) a minimum global severity score of 7 for the current episode of depression; (5) no history of manic, hypomanic, or cyclothymic features; (6) no history of active drug or

	alcohol abuse or dependence or of personality disorder according to DSM-IV criteria; (7) no history of antecedent dysthymia; (8) no active medical illness; and (9) successful response to antidepressant drugs administered by 2 psychiatrists according to a standardized protocol. After drug treatment, all patients were assessed by the same psychologist who had evaluated them on intake but who did not take part in the treatment. Only patients rated as “better” or “much better” according to a global scale of improvement and as being in full remission were included in the study. Patients also had to show no evidence of depressed mood after treatment according to a modified version of the Paykel Clinical Interview for Depression. Patients fit the criteria for stage 3 (the residual phase) of unipolar depression.
Exclusion criteria	None reported (does not state that people with no residual symptoms were excluded, as the previous study does [71, 196])
Recruitment/selection of patients	Consecutive outpatients
Age, gender and ethnicity	Age - Mean (SD): CBT + taper: 45.1 (10.3); Clinical management + taper: 48.7 (12.1). Gender (M:F): 16/24. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses: CBT group: 7 patients on amitriptyline 150-200mg/day, 5 on desipramine 150-200mg/day, 5 on imipramine 150-200mg/day, 2 on fluoxetine 20-40mg/day, 2 on sertraline 150mg/day; taper group: 7 patients on amitriptyline 150-200mg/day, 6 on desipramine 150-200mg/day, 5 on imipramine 150-200mg/day, 2 on fluoxetine 20-40mg/day. All patients were treated for 3 to 5 months with full doses of antidepressant drugs, after which the modified version of the CID (covering 19 symptom areas) was administered by the clinical psychologist - to assess the residual symptoms. The aims of the study included the effect of CBT on the residual symptoms after successful treatment with antidepressant drugs. An earlier study [71, 196] also included in this review looked at the same intervention, but in a different population (major depressive disorder, not recurrent depression).
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Non-pharmacological interventions - Cognitive behavioural therapy (CBT) + taper. "CBT and pharmacotherapy" (CBT + taper): Both groups had ten 30-minute sessions once every other week.

	Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week and then the drugs were withdrawn completely (in the last 2 sessions, all patients were drug free). Discontinuation of antidepressant drug use was not feasible for 5 patients (3 in the CBT group and 2 in the CM group), and they were excluded from the study at that point. Cognitive behavioural treatment consisted of the following 3 main ingredients: (1) CBT of residual symptoms of major depression. The psychiatrist, an experienced therapist, used strategies and techniques designed to help depressed patients correct their distorted views and maladaptive beliefs, particularly regarding symptoms concerned with anxiety and irritability, which constitute the bulk of residual symptoms in patients with depression. Whenever appropriate, as in the case of residual symptoms related to anxiety, exposure strategies were planned with the patient, e.g., in the case of phobic external cues in agoraphobia or social phobia. (2) Lifestyle modification. Patients were instructed that depression is merely the consequence of a maladaptive lifestyle, which does not take life stress, interpersonal friction, excessive work, and inadequate rest into proper account. Antidepressant drugs restore normal mood, but relapse may ensue if inappropriate lifestyle behaviours are continued after drug withdrawal. Patients were encouraged to modify their schedules, arrangements, etc, accordingly. The strategies used technically derived from lifestyle modification approaches that were effective in clinical cardiological studies. (3) Well-being therapy. In the last 2 or 3 sessions, a psychotherapeutic strategy for enhancing well-being was used. The technique is aimed at changing beliefs and attitudes detrimental to well-being, stimulating awareness of personal growth and recovery from affective illness, and reinforcing behaviour promoting well- being. It is based on Ryff and Singer's conceptual model of well-being as the result of self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth. Duration 20 weeks. Concurrent medication/care: 4 people in the CBT group had concomitant treatment with benzodiazepines. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=22) Intervention 2: Clinical management (CM) + taper. Both groups had ten 30-minute sessions once every other week. Antidepressant drug use was tapered at the rate of 25 mg of amitriptyline hydrochloride or its equivalent every other week and then the drugs were withdrawn completely (in the last 2 sessions, all patients were drug free). Discontinuation of antidepressant drug use was not feasible for 5 patients (3 in the

	CBT group and 2 in the CM group), and they were excluded from the study at that point. Clinical management consisted of monitoring medication tapering, reviewing the patient's clinical status, and providing the patient with support and advice if necessary. In CM, specific interventions such as exposure strategies, diary work, and cognitive restructuring were proscribed. The patient was encouraged to share the main events that took place in the previous 2 weeks. Duration 20 weeks. Concurrent medication/care: 4 people in the CM group were on concomitant benzodiazepines. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) + TAPER versus CLINICAL MANAGEMENT + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Antidepressants: tricyclics: Discontinuation of antidepressants (states the number of people in whom discontinuation was not feasible, and these people were excluded from further analysis) at Post-treatment (20 weeks); Group 1: 20/23, Group 2: 20/22; Comments: Calculated from the comment that discontinuation was not feasible in 3 people in the CBT group and in 2 people in the CM group. These people were excluded from further analysis, so only the 20 people in each group who discontinued treatment were analysed further.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Antidepressants: tricyclics: Relapse (occurrence of a Research Diagnostic Criteria-defined episode of major depression during follow up) at 2 years; Group 1: 5/20, Group 2: 16/20; Comments: Not including the people who were unable to discontinue during the taper stage, as does not specifically state that these people were unable to discontinue due to taper, and the study excluded these from further analysis.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Unable to discontinue during taper phase; Group 2 Number missing: 2, Reason: Unable to discontinue during taper phase

- Actual outcome for Antidepressants: tricyclics: Residual symptoms score (people in the study had residual symptoms after successful treatment with antidepressants (baseline) - this score was assessed again after CBT or CM + taper) at Post-treatment (20 weeks); Group 1: mean 24 (SD 3.8); n=20, Group 2: mean 28.1 (SD 4.1); n=20; total score on the modified version of the Paykel Clinical Interview for Depression unclear Top=High is poor

outcome; Comments: Notes that a residual symptom was scored as present when a rating of at least 3 of the 7-point scale was assigned, but does not report the range of values for the total score. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: Unable to discontinue during taper phase; Group 2 Number missing: 2, Reason: Unable to discontinue during taper phase	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study (subsidiary papers)	**Gallagher 2012[80]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=500 randomised for titration phase, n=384 randomised for taper stage).
Countries and setting	Not reported.
Line of therapy	1st line
Duration of study	Titration period 1 week and then 15-week treatment phase; and 2-week taper period followed by 8 weeks follow-up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: people completing a treatment phase with antidepressants were randomised to the discontinuation phase.
Stratum	Antidepressants: other antidepressants: all on desvenlafaxine
Subgroup analysis within study	Not applicable

Inclusion criteria	Healthy, postmenopausal women who experienced ≥ 50 moderate to severe hot flashes per week during each of the 2 weeks immediately preceding randomization. For inclusion in the taper phase: participants who completed the open-label phase or had received at least 5 weeks of open-label treatment at the time of discontinuation
Exclusion criteria	Excluded if had taken hormone-containing products or prohibited medications within 2 to 26 weeks before study initiation, had experienced major depressive disorder or generalized anxiety disorder requiring treatment within the previous 6 months or had a history of bipolar disorder or psychotic disorder.
Recruitment/selection of patients	Post-menopausal women with vasomotor symptoms.
Age, gender and ethnicity	Baseline demographic and clinical characteristics were reported as similar across the titration phase and taper phase. Mean (SD) age: Group 1: 54.52 (5.01), Group 2: 54.40 (6.37), Group 3: 53.98 (5.16), Group 4: 53.48 (5.27) Race, n (%): Asian: Group 1: 2 (1.6), Group 2: 1 (0.8), Group 3: 2 (1.6), Group 4: 1 (0.8) Black: Group 1: 12 (9.5), Group 2: 12 (9.9), Group 3: 8 (6.5), Group 4: 19 (15.6) White: Group 1: 109 (86.5), Group 2: 107 (88.4), Group 3: 112 (90.3), Group 4: 97 (79.5) Other: Group 1: 3 (2.4), Group 2: 1 (0.8), Group 3: 2 (1.6), Group 4: 5 (4.1)
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses: all on desvenlafaxine 100mg/day at randomisation to the taper phase

	Note: People were not on antidepressants at baseline, but were entered into a 15-week open label treatment with desvenlafaxine prior to the discontinuation. People who completed the open-label phase or had received at least 5 weeks of open-label treatment at the time of discontinuation were randomly assigned to the taper phase. The study also included a titration phase prior to the treatment phase. People were also randomised to a titration strategy, but there was a re-randomisation for the taper stage, so this was deemed acceptable. Adverse events during initial titration phase also reported.
Indirectness of population	No indirectness
Interventions	Titration phase (1 week): participants randomised to receive one of four desvenlafaxine regimens: desvenlafaxine 100mg/d for 7 days (no titration); desvenlafaxine 50 mg/d for 7 days; desvenlafaxine 25 mg/d (4 days) then 50 mg/d (3 days); desvenlafaxine 25 mg/d for 7 days Treatment (15 weeks): Participants received open label desvenlafaxine 100 mg/d Taper phase (2 weeks): Participants who had complete the open label phase or who had taken 5 weeks or more of treatment at the time of early discontinuation were randomised to one of the taper regimens below Follow-up (8 weeks): Follow up for discontinuation symptoms (n=94) Group 1: Desvenlafaxine succinate 50mg/d for 7 days followed by 25 mg/d for 7 days (n=101) Group 2: Desvenlafaxine succinate 50 mg/d every other day for 14 days (n=87) Group 3: Desvenlafaxine succinate 50 mg/d for 7 days followed by placebo for 7 days (n=102) Group 4: Placebo (no taper/abrupt)
Funding	Industry

RESULTS (NUMBER ANALYSED) AND RISK OF BIAS FOR COMPARISON: Desvenlafaxine 50mg/d followed by 25mg/d vs Desvenlafaxine 50 mg/d every other day vs desvenlafaxine 50 mg/d for 7 days then placebo vs placebo (no tapering)

Protocol outcome 1: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome: Discontinuation-Emergent Signs and Symptoms (DESS) checklist total score (higher scores indicate more symptoms experienced), mean (SD), at the post-intervention/post-taper timepoint (this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (group 1: week 3; group 2: week 3; group 3: week 2; group 4: week 1):

    - Group 1 (n=57, week 3): 4.11 (5.77), Group 2 (n=59, week 3): 3.22 (4.82), Group 3 (n=79, week 2): 4.46 (6.44), Group 4 (n=98, week 1): 7.07 (7.13)

Risk of bias: All domain –Very high (high for comparison Desvenlafaxine 50-placebo vs abrupt (placebo)), Selection - High, Blinding - Low, Incomplete outcome data - High (low for comparison Desvenlafaxine 50-placebo vs abrupt (placebo)), Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 37 (week 3); Group 2 Number missing: 42 (week 3), Group 3 Number missing: 8 (week 2), Group 4 Number missing: 4 (week 1). Reason*: Withdrew (22), unknown why others DESS not completed.

Note: Also reported taper week 1 and 2 combined and week 1, 2 and 3 combined.

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome: Incidences of specific discontinuation-emergent signs and symptoms at post-intervention/post-taper timepoint (this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine). Number of people having event (%) was provided in paper. Total number of people with DESS data at timepoint (for dichotomous data analysis) was as follows: group 1 n=57 (week 3), group 2 n=59 (week 3), group 3 n=79 (week 2), group 4 n=98 (week 1).

Dizziness light-headedness, sensation of spinning: Group 1: 17 (29.8), Group 2: 13 (22.0), Group 3: 21 (26.6), Group 4: 41 (41.8)

Headaches: Group 1: 11 (19.3), Group 2: 4 (6.8), Group 3: 8 (10.1), Group 4: 28 (28.6)

Increased dreaming/nightmare: Group 1: 10 (17.5), Group 2: 7 (11.9), Group 3: 10 (12.7), Group 4: 35 (35.7)

Irritability: Group 1: 9 (15.8), Group 2: 11 (18.6), Group 3: 18 (22.8), Group 4: 26 (26.5)

Nausea: Group 1: 5 (8.8), Group 2: 5 (8.5), Group 3: 15 (19.0), Group 4: 28 (28.6)

Sudden worsening of mood: Group 1: 4 (7.0), Group 2: 7 (11.9), Group 3: 18 (22.8), Group 4: 22 (22.5)

Sweating more than usual: Group 1: 19 (33.3), Group 2: 21 (35.6), Group 3: 23 (29.1), Group 4: 44 (44.9)

Trouble sleeping, insomnia: Group 1: 13 (22.8), Group 2: 12 (20.3), Group 3: 22 (27.9), Group 4: 37 (37.8)

Risk of bias: All domain –Very high (high for comparison Desvenlafaxine 50-placebo vs abrupt (placebo)), Selection - High, Blinding - Low, Incomplete outcome data - High (low for comparison Desvenlafaxine 50-placebo vs abrupt (placebo)), Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 37 (week 3); Group 2 Number missing: 42 (week 3), Group 3

Number missing: 8 (week 2), Group 4 Number missing: 4 (week 1). Reason*: Withdrew (22), unknown why others DESS not completed. Note: The study reported the incidence of 8 individual symptoms from the 43-item DESS checklist. These 8 symptoms appear to have been selected as they are the 8 'consensus panel symptoms'. Therefore, the outcome was not downgraded for selective outcome reporting.

Note: Study also reported taper week 1 and 2 combined and week 1, 2 and 3 combined.

Study also reports the incidence of spontaneous adverse events, some of which might be considered withdrawal symptoms. There is overlap between some of the individual symptoms reported as adverse events, and those in the DESS, but not all overlap (some adverse events such as hypertension not in DESS). The incidence of DESS symptoms were extracted under the protocol outcome of withdrawal symptoms, and not the spontaneous adverse events, as the DESS was assessed everyone rather than just spontaneously reported.

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome: incidence of taper emergent adverse events (post hoc analysis), adverse events that developed during the taper phase or were pre-existing adverse events that became worse during the taper. %s provided in paper – unclear total number in analysis in order to calculate the dichotomous data.

At end of taper period week 2 (% provided in paper): Group 1: 30.4%, Group 2: 30.9%, Group 3: 19.8%, Group 4: 15.6%

At end of week 4 (follow up week 2 after completion of taper in all groups): Group 1: 9.9%, Group 2: 14.1%, Group 3: 4.8%, Group 4: 7.4%

Risk of bias: All domain –Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement – High, Crossover - Low;

Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 4; Group 2 Number missing: 4, Group 3 Number missing; 7, Group 4 Number

missing; 7. Reason*: Withdrew (22).

Protocol outcome 4: patient satisfaction

- Actual outcome: tolerability satisfaction questionnaire, which asked study participants how satisfied they had been with tolerability of the study medication (i.e., lack of bothersome side effects). Study reports number of people in each category (possible responses were, very satisfied, satisfied, neutral, dissatisfied, very dissatisfied). Grouped very satisfied and satisfied for the purpose of analysis.

Summary of satisfaction assessment reported at week 3 (week 3 taken for all groups for this outcome, only timepoint reported in study for this outcome): Group 1 (n=52): 35; group 2 (n=53) 26; group 3 (n=40) 29; group 4 (n=54) 37.

Risk of bias: All domain –Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; At end of study - Group 1 Number missing: 42; Group 2 Number missing: 48, Group 3 Number missing; 47, Group 4 Number missing; 48. Reason*: Withdrew (22). Study comments that this outcome at week 3 disadvantaged the taper groups, as the subjects in the placebo group were adjusted to stopping therapy at this timepoint, 3 weeks after therapy cessation.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study (subsidiary papers)	**Khan 2014[124] (Ninan 2015[192])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=361 completed treatment phase and assigned to discontinuation (73 of these were assigned to the 'no discontinuation' arm and are not included in this review))
Countries and setting	Conducted in USA; Setting: Outpatients: 38 clinical research centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks (4-week intervention and 2-week follow-up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People a primary diagnosis of single or recurrent major depressive disorder (see inclusion criteria for assessment) put onto 24-week treatment with desvenlafaxine.

Stratum	Antidepressants: others: All on Desvenlafaxine
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult outpatients (≥ 18 years of age) with a primary diagnosis of single or recurrent MDD without psychotic features consistent with criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, using the modified Mini International Neuropsychiatric Interview. Patients were required to have depressive symptoms for ≥ 30 days prior to the screening visit and a 17-item Hamilton Depression Rating Scale total score ≥ 14 at baseline. Note: People were not on antidepressants at baseline, but were entered into a 24-week open label treatment with desvenlafaxine prior to the discontinuation trial. People who completed this 24-week treatment were randomly assigned.
Exclusion criteria	A current primary diagnosis of anxiety disorder, significant risk of suicide based on the Columbia Suicide Severity Rating Scale at screening or baseline, current psychoactive substance abuse or dependence, clinically important medical illness (unstable hepatic, renal, pulmonary or cardiovascular (including uncontrolled hypertension, unstable angina, recent myocardial infarction) opthalmologic or neurologic disorder; uncontrolled diabetes), clinically important abnormalities on physical or laboratory evaluation, or history of seizure disorder, gastrointestinal disease, neoplastic disorder, or narrow-angle glaucoma.
Recruitment/selection of patients	Adult outpatients meeting the criteria
Age, gender and ethnicity	Age - Mean (SD): Taper: 47.9 (11.2); abrupt discontinuation (placebo): 47.8 (13.7). Gender (M:F): 85/103. Ethnicity: Around 80% white; 17%; 1% American Indian/Alaskan Native; 2% other.
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses: all on desvenlafaxine 50mg/day at randomisation Study also had a third arm of 'no discontinuation' (continuing on 50mg/d desvenlafaxine). This arm was not included in the review.
Indirectness of population	No indirectness

Interventions	(n=148) Intervention 1: Abrupt discontinuation: switch straight to placebo for 4 weeks (this was following the 24-week open label treatment phase with 50mg/d desvenlafaxine). Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=140) Intervention 2: 1 week taper: received 25mg/d desvenlafaxine for 1 week, then placebo for 3 weeks (this was following the 24-week open label treatment phase with 50mg/d desvenlafaxine). Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABRUPT DISCONINUATION versus 1 WEEK TAPER

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality

- Actual outcome for Antidepressants: others: Deaths at 6 week; Group 1: 0/146, Group 2: 0/139; Comments: Number used for analysis as the number reported to have at least 1 post-randomisation record

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Antidepressants: others: Completing the double-blind phase (i.e. discontinuation intervention phase) at 4 weeks (end of double-blind phase); Group 1: 138/148, Group 2: 127/140; Comments: Reported in the study flowchart as the number of people completing the double-blind phase (therefore presumed to be the number of people successfully discontinuing antidepressants). 2 were lost to follow-up in each group - ITT assuming those lost to follow up did not have event (did not complete the double blind phase and discontinue antidepressants)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Antidepressants: others: Discontinuation Emergent Signs and Symptoms (DESS) scale total score at 2 weeks (during discontinuation); MD; 0.5 (95%CI -0.88 to 1.89) DESS total score (unclear if there is a range of values, suggests this is the number of DESS) Top=High is poor outcome, Comments: MD from ANCOVA. Control group adjusted final value (mean, SE) abrupt: 5.3 (0.52); taper: 4.8 (0.54). Note: investigator training on DESS was performed before the study to emphasise the definition of 'new' and 'old' symptoms. Discontinuation symptoms were defined as events that were reported by the patient on the DESS and judged to be related to discontinuation by the investigator completing the DSSI. Range of values for DESS not reported - checked original paper (Rosenbaum 1998) - it is a 43-item list based on signs and symptoms and the patient chooses from 1 of 4 responses (new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged or symptom not present) - total score seems to be the mean number of DESS.

Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Note: DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes.

- Actual outcome for Antidepressants: others: Proportion of people with discontinuation syndrome (increase in DESS score of more than or equal to 4 between baseline and mean score for the first 2 weeks of discontinuation) at 2 weeks (during discontinuation); Group 1: 31/146, Group 2: 30/139; Comments: Reported as the % of patients and calculated from the numbers analysed for other outcomes (taper n=139, abrupt n=146). Note: investigator training on DESS was performed before the study to emphasise the definition of 'new' and 'old' symptoms. Discontinuation symptoms were defined as events that were reported by the patient on the DESS and judged to be related to discontinuation by the investigator completing the DSSI.

Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported). Note: DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes.

- Actual outcome for Antidepressants: others note: study also reports the taper/posttherapy–emergent adverse events (TPAEs) - defined as any adverse event that started or increased in severity during the double-blind phase – this is in addition to the outcome of discontinuation symptoms according the DESS checklist. These were events like headache, nausea, dizziness – some overlap with other method of assessing discontinuation symptoms. At 4 weeks (during discontinuation phase); Group 1: 75/146, Group 2: 54/139

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Outcome is taper/posttherapy–emergent adverse events (TPAEs), unclear if

withdrawal/discontinuation symptoms; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

- Actual outcome for Antidepressants: others: Suicidal ideation reported on the Columbia Suicide Severity Rating Scale (C-SSRS) (reviewer judged as withdrawal symptom) at 6 week; Group 1: 1/146, Group 2: 1/139

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

Study also reports the breakdown of incidence of mild/moderate/severe for all 43 items on the DESS checklist.

Protocol outcome 4: Self-harm or harm to others

- Actual outcome for Antidepressants: others: Suicide attempt (intentional drug overdose of a non-study medication) at 6 week; Group 1: 1/146, Group 2: 0/139; Comments: Number used for analysis as the number reported with at least one post-randomisation record. Event occurred 2 days after completing double blind phase.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

Protocol outcome 5: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Antidepressants: others: Depressive symptoms (Quick Inventory of Depressive Symptomatology Self-Report, QIDS-SR16) at 4 weeks (end of discontinuation phase); Group 1: mean 6.5 (SD 4.7); n=146, Group 2: mean 6.2 (SD 4.5); n=139; Quick Inventory of Depressive Symptomatology Self-Report 0-27 Top=High is poor outcome; Comments: Range of the QIDS-SR16 not reported by the study. Online resources suggest this is a 16 item self-report measure of depression, with a total range of scores from 0-27 (0-5 no depression, 6-10 mild depression, 11-15 moderate depression, 16-20 severe depression, 21-27 very severe depression).

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: number without at least 1 post-randomisation record (reason not reported); Group 2 Number missing: 1, Reason: number without at least 1 post-randomisation record (reason not reported)

Protocol outcomes not reported by the study	Quality of life; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Scholten 2018[240]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=87)
Countries and setting	Conducted in Netherlands; Setting: Outpatient clinics
Line of therapy	1st line
Duration of study	Intervention + follow up: 16 months (4-month intervention & discontinuation period, 12 month follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People on antidepressants and at least a lifetime but no current anxiety panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and generalized anxiety disorder (Structured Clinical Interview for DSM IV axis I disorders (SCID-I). Assessments were done via face-to-face interviews.
Stratum	Antidepressants: Mixed antidepressants (n=69 on SSRIs, n=14 on SNRIs, n=2 on TCAs, n=2 on mirtazapine)
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients (> 18 years) (i) used antidepressants but were willing to discontinue, (ii) had no current anxiety or depressive disorder, and (iii) had a history of an anxiety disorder for which they took antidepressants (panic disorder with or without agoraphobia, agoraphobia, social phobia or generalized anxiety disorder).
Exclusion criteria	None reported
Recruitment/selection of patients	Patients were recruited from outpatient clinics through media advertisement

Age, gender and ethnicity	Age CBT: 42.7 (11.9); taper: 40.8 (13.4). Gender (M:F): 35/52. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline doses of antidepressants not reported n=51 had >1 anxiety or depressive disorder in their lifetime. Remission of anxiety disorder at baseline in months was 30.7 (34.2) in the intervention group and 43.3 (44.2) in the control group. Inclusion was stopped prematurely for ethical reasons and lack of effect (futility), though assessments of included participants continued until 16 months. Study also reported the following outcomes: re-/occurrence of any anxiety disorder; re-/occurrence of any anxiety disorder or major depressive disorder, these were judged not to match the protocol outcome as well as recurrence of the previous anxiety disorder, and reporting may result in 'double counting'.
Indirectness of population	No Indirectness
Interventions	(n=42) Intervention 1: Non-pharmacological interventions - Cognitive behavioural therapy (CBT) + taper. CBT group discontinuation consisted of 8 group sessions of relapse prevention, targeting vulnerability factors and discontinuation symptoms. The 8 sessions always contained: agenda setting, review of homework, agreement on a next step in discontinuation of antidepressants according to a fixed schedule, discussing discontinuation of symptoms, explanation of CBT techniques, practicing techniques and assignment of homework. The following aspects were included in the intervention: the presence of discontinuation symptoms assessed using the DESS and discontinuation symptoms discussed; cognitive therapy interventions were provided focusing on diminishing underlying dysfunctional attitudes (and not as in acute treatment on dysfunctional automatic thoughts), a focus on diminishing anxiety sensitivity (i.e. the tendency to interpret bodily sensations as catastrophic), exposure exercises were included to diminish residual avoidance behaviour, participants formulated a personal relapse prevention plan. Antidepressants were tapered every 2 weeks according to a fixed schedule (depending on the type and dosage of antidepressant), with full discontinuation completed well within 4 months. Duration 4 months (but states CBT was not only offered during tapering, but also after full discontinuation). Concurrent medication/care: 5 people did not receive the allocated intervention. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service

	(n=45) Intervention 2: Tapered withdrawal. Discontinuation without CBT was guided by psychiatrists in individual sessions. Antidepressants were tapered every 2 weeks according to a fixed schedule (depending on the type and dosage of antidepressant), with full discontinuation completed well within 4 months. Duration 4 months. Concurrent medication/care: 9 people did not receive the allocated intervention. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) + DISCONTINUATION versus DISCONTINUATION (TAPER) ALONE

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Antidepressants: others: Suicide at 16 months; Group 1: 1/42, Group 2: 0/45; Comments: Calculated as ITT, as available case analysis numbers unclear.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 13, Reason: 5 people did receive the allocated intervention (unclear if follow up available for these people); 8 people lost to follow-up after intervention (did no longer do assessments n=7; suicide n=1); Group 2 Number missing: 16, Reason: 9 people did receive the allocated intervention (unclear if follow up available for these people); 7 people lost to follow-up after intervention (did no longer do assessments n=4; discontinued intervention <4 sessions n=3: pregnancy, logistical reasons or afraid to discontinue antidepressants)

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Antidepressants: others: Discontinuing antidepressants at 16 months; Reported as the % of people with complete assessments who discontinued antidepressants: intervention group 41%; control group 32%. Unable to calculate numbers, as total number of people with complete assessments reported in the text (n=71) differs from the numbers of people lost to follow up in each group reported in the flowchart. Unable to calculate and analyse;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 13, Reason: 5 people did receive the allocated intervention (unclear if follow up available for these people); 8 people lost to follow-up after intervention (did no longer do assessments n=7; suicide n=1); Group 2 Number

missing: 16, Reason: 9 people did receive the allocated intervention (unclear if follow up available for these people); 7 people lost to follow-up after intervention (did no longer do assessments n=4; discontinued intervention <4 sessions n=3: pregnancy, logistical reasons or afraid to discontinue antidepressants) Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed - Actual outcome for Antidepressants: others: Recurrence of the previous anxiety disorder at 16 months; Group 1: n=42; Group 2: n=45; HR 1.042; Lower CI 0.526 to Upper CI 2.063; Follow up details: ITT. Study only provides HR summary statistic and % of people with the outcome. Numbers in each group calculated from these percentages (assumed all people analysed): CBT + taper 43% (18/42), taper 44% (20/45). Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 13, Reason: 5 people did receive the allocated intervention (unclear if follow up available for these people); 8 people lost to follow-up after intervention (did no longer do assessments n=7; suicide n=1); Group 2 Number missing: 16, Reason: 9 people did receive the allocated intervention (unclear if follow up available for these people); 7 people lost to follow-up after intervention (did no longer do assessments n=4; discontinued intervention <4 sessions n=3: pregnancy, logistical reasons or afraid to discontinue antidepressants)	
Protocol outcomes not reported by the study	Quality of life; Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Segal 2010[244]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160 entered open label phase (84 randomised for discontinuation phase, n=56 included in this analysis (2 relevant treatment arms)))
Countries and setting	Conducted in Canada; Setting: Outpatients
Line of therapy	1st line

Duration of study	Follow up (post intervention): 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients diagnosed with major depressive disorder. Diagnostic eligibility for the study was determined by means of the Structured Clinical Interview for DSM-IV diagnosis (Axis I and II) (SCID). People were not on antidepressants at the start of the study, but were entered into an open-label treatment phase of at least 7 months (minimum of 8 weeks to assess response, then those who met the criteria for remission were treated for an additional 5 months before randomisation for the discontinuation phase).
Stratum	Antidepressants: Mixed antidepressants: all started on SSRIs, but 14 of 84 (17%) required a second treatment step (although unclear what the proportion of people requiring step 2 treatment were in the 56 people randomised to one of the two relevant arms).
Subgroup analysis within study	Not applicable
Inclusion criteria	For inclusion in the open label phase: (1) diagnosis of MDD according to DSM-IV criteria, (2) a score of 16 or higher on the HRSD, (3) 2 or more previous episodes of MDD (to ensure that those randomized would have a minimum of 3 past episodes), (4) age between 18 and 65 years, and (5) English speaking and the ability to provide informed consent. For inclusion in the discontinuation phase: patients meeting criteria for treatment response (50% reduction in HRSD score) and clinical remission (HRSD score, <8 for 8 weeks) were treated for 5 additional months to ensure full remission. Among patients who achieved clinical remission, 14 of 84 (17%) required a second treatment step. Patients who did not respond to or tolerate the treatment options allowed in the protocol were withdrawn from the study.
Exclusion criteria	(1) a current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline or antisocial personality disorder; (2) a trial of electroconvulsive therapy within the past 6 months; (3) depression secondary to a concurrent medical disorder; (4) current or planned pregnancy within the 6 months of acute-phase treatment; and (5) current practice of meditation more than once per week or yoga more than twice per week.
Recruitment/selection of patients	Subjects were recruited through clinical referrals, physician outreach, and media announcements
Age, gender and ethnicity	Age - Mean (SD): MBCT: 44.8 (9.4); placebo: 41.9 (11.6). Gender (M:F): 23:33. Ethnicity: Of the n=56 randomised to the 2 treatment arms included in this analysis: 42 white (other details not reported)

Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient
Extra comments	Baseline details of doses of antidepressants not reported. 2 step antidepressant treatment schedule reported (below), and that 14 required step 2 treatment, but unclear what doses people reached. During the open label phase, all patients received 2-step antidepressant pharmacotherapy according to the Texas Medication Algorithm Project guidelines. Step 1: citalopram hydrobromide at a target dose of 20 mg that was increased in 10-mg steps if needed to a maximum of 60mg until either response was achieved or dose-limiting adverse effects emerged (if citalopram hydrobromide couldn't be tolerated, sertraline hydrochloride at 50 mg/d with 50-mg increments per week was initiated with a target dose of at least 100 mg and a maximum of 200 mg/d). Patients of failure during this phase of at least 8-week trial were switched to step 2 (either venlafaxine hydrochloride or mirtazapine). Venlafaxine hydrochloride was started at 37.5 mg per day for 1 week, increased to 75mg the next week and 150mg (the minimum target dose) the following week, and then increased in 75-mg increments until the patient showed a full response (HRSD score, <8) or was unable to tolerate adverse effects (maximum of 375mg). For patients who could not tolerate venlafaxine, mirtazapine was started at 15 mg per day for 1 week and increased in 15-mg increments per week to a minimum target dose of 30mg and a maximum of 45 mg on the basis of response and tolerability. Study also had a third arm of the trial (not included in the analysis for this review) - this arm of the trial was continuation on antidepressant treatment.
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Non-pharmacological interventions - Mindfulness based approaches + taper. Patients in MBCT condition had their medication tapered gradually, during a 4-week period, via reduced pill count (no placebo), at the recommended rate for their specific medication to minimize the risk of discontinuation syndrome. Once patients in the MCBT group had finished their taper, they no longer took any pills. MBCT intervention: Patients attended 8 weekly group meetings of 2 hours' duration and a retreat day held between sessions 6 and 7. In addition, an optional, monthly, 1-hour mindfulness meditation class was offered throughout the maintenance phase. Mindfulness-based cognitive therapy is based on empirical work showing that relapse is associated with the reinstatement of automatic modes of thinking and feeling

	that are characteristic of the depressed state (e.g., rumination and avoidance).By deliberately monitoring and observing their thinking patterns when they feel sad, patients develop skills in meta-cognition or decentring that serve to render this type of automatic processing more accessible to effortful reflection. This is accomplished through daily homework exercises featuring (1)guided (taped) awareness exercises directed at increasing moment-by-moment non-judgmental awareness of bodily sensations, thoughts, and feelings; (2)accepting difficulties with a stance of self-compassion; and (3) developing an “action plan” composed of strategies for responding to early warning signs of relapse/recurrence. A key theme stressed throughout the program is the transfer of these awareness skills into patients’ everyday lives. Duration 18 months (unclear), taper 4 weeks. Concurrent medication/care: Additional medication for sleep complaints or anxiety symptoms was also permitted during taper period (e.g., zopiclone and benzodiazepines). Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=30) Intervention 2: Placebo substitution taper. Patients in the placebo a condition had their medication tapered gradually, during a 4-week period, via placebo substitution at the recommended rate for their specific medication to minimize the risk of discontinuation syndrome. Duration placebo duration unclear, taper 4 weeks. Concurrent medication/care: Additional medication for sleep complaints or anxiety symptoms was also permitted during taper period (e.g., zopiclone and benzodiazepines). Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding (National Institute for Mental Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINDFULNESS-BASED COGNITIVE THERAPY + TAPER versus PLACEBO SUBSTITUTION + TAPER

Protocol outcome 1: Increase in symptoms for which the medication was originally prescribed
- Actual outcome for Antidepressants: SSRIs: Relapse/recurrence of DSM-IV major depressive episode, using the depression module of the SCID at 18 months; Group 1: 10/26, Group 2: 18/30; Comments: ITT analysis performed, and relapse rate given as % for each group. ANCOVA results provided, but adjusted risks only given for 'stable' and 'unstable' remitters, not overall for all people in the MBCT and placebo groups.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: dropped out (reason not reported).; Group 2 Number missing: 6, Reason: dropped out (reason not reported).	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Tint 2008[258]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in United Kingdom; Setting: Predominantly outpatients (2/28 inpatients)
Line of therapy	1st line
Duration of study	Intervention + follow up: 3- or 14-day taper, follow up at 5 to 7 days after drug-free washout
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of major depressive disorder, treated with an SSRI or venlafaxine for ≥6 weeks.
Stratum	Antidepressants: Mixed: 82% on SSRIs, 28% on venlafaxine
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical diagnosis of major depressive disorder, treated with an SSRI or venlafaxine for ≥6 weeks and in whom the treating clinician wanted to switch antidepressant.
Exclusion criteria	Not reported

Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 39 (12). Gender (M:F): 11/17. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable 3. Setting: Outpatient (26/28 outpatients).
Extra comments	Baseline antidepressant doses not reported Study also reports the Montgomery Asberg Depression Rating Scale (MADRS) and Discontinuation Emergent Signs and Symptoms checklist total score; however, results are only reported graphically.
Indirectness of population	Serious indirectness: Population differs from others included in this review, as the included population are discontinuing antidepressants in order to switch to another antidepressant, not because they no longer require to be on the antidepressant
Interventions	(n=13) Intervention 1: Longer taper (14 days): 14-day taper of their existing antidepressant with the taper individualised according to antidepressant, dose and tablet formulation Note: As the study was looking at people discontinuing antidepressants in order to switch to another antidepressant, all participants then commenced a new antidepressant (excluding monoamine oxidase inhibitors (MAOIs)) of the treating clinician's choice. They were reassessed after commencing the new antidepressant, but these results are not included in the current review. Duration 14 days. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=15) Intervention 2: Shorter taper (3 days): 3-day taper of their existing antidepressant with the taper individualised according to antidepressant, dose and tablet formulation Note: As the study was looking at people discontinuing antidepressants in order to switch to another antidepressant, all participants then commenced a new antidepressant (excluding monoamine oxidase inhibitors (MAOIs)) of the treating clinician's choice. They were reassessed after commencing the new antidepressant, but these results are not included in the current review. Duration 3 days. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service

Funding	No funding (The authors have received reimbursement for lecturing and consultancy, research grants and support to attend educational meetings from pharmaceutical companies that manufacture antidepressants. No external funding was involved in this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LONGER TAPER (14 DAYS) versus SHORTER TAPER (3 DAYS)

Protocol outcome 1: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome
- Actual outcome for Antidepressants: SSRIs: Occurrence of a discontinuation syndrome (≥3 new symptoms on the Discontinuation Emergent Signs and Symptoms checklist (DESS)) at 5-7 days after drug washout; Group 1: 6/13, Group 2: 7/15; Comments: The most common new or worsened DESS items at T2 were dizziness (42%), headache (42%), nervousness/anxiety (42%), panic/sudden anxiety (32%), agitation (32%), nausea (32%) and sudden worsening of mood (32%). With 13 people overall having a discontinuation syndrome.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Reduction/cessation of prescribed drug use; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

E.5 Mixed medicines

Study	Barros 2021[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Brazil; Setting: Outpatient
Line of therapy	1st line
Duration of study	Intervention + follow up: 8-week intervention + 6-month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Women taking hypnotics (states that 86.8% had a prescription). Self-report of hypnotic use for sleep induction (clinical criteria to define insomnia not inclusion criteria).
Stratum	Mixed (all drug classes): Hypnotics (benzodiazepines (61%) and non-benzodiazepines (Z-drugs; 39%)
Subgroup analysis within study	Stratified then randomised: Stratified before randomisation by low, medium or high dose and by short or long duration of use
Inclusion criteria	Women; over 18 years of age; literate in Portuguese; using hypnotic medication for sleep induction at least 4 times a week for a minimum of 90 days.
Exclusion criteria	Neurological conditions; cancer; anxiety refractory to other treatments; diagnosed psychiatric disorders; presence of secondary insomnia; other severe clinical conditions which might be worsened by cessation of the hypnotic treatment; dependence on or misuse of alcohol or other drugs, except tobacco; current acute treatment for psychological or psychiatric disorders; already undergoing hypnotic withdrawal; practiced yoga, meditation or other contemplative practices in the past 6 months; non-agreement of the participant's physician regarding the volunteer's participation in the research.

Recruitment/selection of patients	Recruited via traditional print and social media. Also presented to health professionals who were involved with the population to help recruit volunteers.
Age, gender and ethnicity	Age - Mean (SD): 53 (13) years. Gender (M:F): All female. Ethnicity: not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Indirectness of population	Serious indirectness: breakdown of benzodiazepines not reported, unclear if on guideline medicine list. >80% had a prescription so no downgrade for this reason.
Interventions	(n=36) Intervention 1: Mindfulness-based relapse prevention (MBRP) + initial psychoeducation group session (based on principles of motivational interviewing) + guidance on gradual voluntary withdrawal. MBRP began the week after the psychoeducation group session. MBRP was within group sessions. MBRP is a structured mindfulness intervention, with eight consecutive weekly sessions of 2 hours. Integrates formal meditation practices and exercises addressing elements of relapse prevention. Each session comprised 45 minutes of formal practices and 75 minutes of exercises, discussion and psychoeducation. Participants received a CD with guided meditations and were advised to engage in the formal practices for about 30 minutes a day at home. The mindfulness home practice was monitored at the end of each session. The intervention group received the initial psychoeducation group session (based on principles of motivational interviewing) and guidance on gradual voluntary withdrawal the same as in the control group (see control group for details). Duration 8 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service (n=34) Intervention 2: Initial psychoeducation group session (based on principles of motivational interviewing) + guidance on gradual voluntary withdrawal. Psychoeducation group session: 1.5-hour duration, based on the principles of motivational interviewing, consisting of brief intervention, that covered the chronic use of hypnotics according to the FRAMES model (a brief intervention designed to support behaviour change). FRAMES includes: feedback about the levels of consumption and possible related hazards; helping the participant taking responsibility for behaviour change; advice to the participant about what would be the most indicated action to take; menu of possibilities that the participant can take to change his or her behaviour; empathy towards the participant; and self-efficacy to help the participant realise they can do something about their situation. The possibility of gradual withdrawal was discussed in a psychiatric consultation and individualised guidance on

	gradual withdrawal was given. The psychiatrist informed participants the tapering would be voluntary and should only occur after the group psychoeducation session. Both groups monitored weekly (face-to-face after weekly MBRP sessions or by telephone for the control group). Duration 8 weeks (initial session and 8 weeks telephone monitoring). Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Addiction support services: No addiction support service
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MBRP + PSYCHOEDUCATION GROUP SESSION + GUIDANCE ON GRADUAL VOLUNTARY WITHDRAWAL versus PSYCHOEDUCATION GROUP SESSION + GUIDANCE ON GRADUAL VOLUNTARY WITHDRAWAL

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Mixed (all drug classes): Equivalent hypnotic dosage: defined daily dose/diazepam mg equivalent (DDD/DME) at Post-intervention (8 weeks); Group 1: mean 0.96 (SD 1.36); n=36, Group 2: mean 1.97 (SD 3.57); n=34; Comments: ITT analysis used (presumably with LOCF)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: Participants had a voluntary reduction schedule, therefore dose taken was subjective outcome; Group 1 Number missing: 10, Reason: did not receive intervention n=6; withdrew due to lack of time n=2; left due to a mental health issue n=2; Group 2 Number missing: 4, Reason: did not agree to be in control group n=3; withdrew for cancer treatment n=1

- Actual outcome for Mixed (all drug classes): Equivalent hypnotic dosage: defined daily dose/diazepam mg equivalent (DDD/DME) at 6-month follow-up; Group 1: mean 0.96 (SD 1.65); n=36, Group 2: mean 0.76 (SD 1.23); n=34; Comments: ITT analysis used (presumably with LOCF)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: Participants had a voluntary reduction schedule, therefore dose taken was subjective outcome; Group 1 Number missing: 12, Reason: did not receive intervention n=6; withdrew due to lack of time n=2; left due to a mental health issue n=2; due to lack of time n=1; due to lost interest n=1; Group 2 Number missing: 6, Reason: did not agree to be in control group n=3; withdrew for cancer treatment n=1; unable to get to site n=1; due to lost interest n=1

Protocol outcome 2: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Mixed (all drug classes): Insomnia Severity Index (ISI) at Post-intervention (8 weeks); Group 1: mean 14.15 (SD 5.24); n=36, Group 2: mean 15.43 (SD 6.11); n=34; Insomnia Severity Scale 0-28 Top=High is poor outcome; Comments: ITT analysis used (presumably with LOCF)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: Participants had a voluntary reduction schedule, therefore dose taken was subjective outcome; Group 1 Number missing: 10, Reason: did not receive intervention n=6; withdrew due to lack of time n=2; left due to a mental health issue n=2; Group 2 Number missing: 4, Reason: did not agree to be in control group n=3; withdrew for cancer treatment n=1 - Actual outcome for Mixed (all drug classes): Insomnia Severity Index (ISI) at 6 months follow-up; Group 1: mean 10.88 (SD 5.35); n=36, Group 2: mean 15.7 (SD 5.86); n=34; Insomnia Severity Scale 0-28 Top=High is poor outcome; Comments: ITT analysis used (presumably with LOCF) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Blinding details: Participants had a voluntary reduction schedule, therefore dose taken was subjective outcome; Group 1 Number missing: 12, Reason: did not receive intervention n=6; withdrew due to lack of time n=2; left due to a mental health issue n=2; due to lack of time n=1; due to lost interest n=1; Group 2 Number missing: 6, Reason: did not agree to be in control group n=3; withdrew for cancer treatment n=1; unable to get to site n=1; due to lost interest n=1	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Belleville 2007[21]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=53)
Countries and setting	Conducted in Canada; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 years or older; use of a medication to promote sleep (Benzodiazepines, zopiclone or zaleplon) >3 nights/week for at least 3 months; difficulty with initiating or maintaining sleep; significant distress or daytime impairment related to sleep disturbances.
Exclusion criteria	the presence of a medical or psychological disorder related to the sleep problems; another sleep disorder; use of a psychotropic medication for a condition other than insomnia; current involvement in psychotherapy; use of another medication interfering with sleep.
Recruitment/selection of patients	Recruited through media advertisement
Age, gender and ethnicity	Age - Mean (SD): 55.3 (11.4). Gender (M:F): 34F/ 19M. Ethnicity: Caucasian
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: 17 participants used non-benzodiazepine hypnotic (zopiclone or zaleplon), 32 used short or intermediate acting benzodiazepine (oxazepam, lorazepam), 12 used long-acting benzodiazepine (flurazepam)). 3. Setting: Outpatient
Extra comments	17 participants used non-benzodiazepine hypnotic (zopiclone or zaleplon), 32 used short or intermediate acting benzodiazepine (oxazepam, lorazepam), 12 used long-acting benzodiazepine (flurazepam)
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Non-pharmacological interventions - Cognitive behavioural therapy (CBT) + taper. Participants were given self-help materials in the form of five booklets for treatment for insomnia, each of which covered a specific component of the CBT of insomnia. Participants were sent the booklets throughout the 8-week intervention period and asked to follow the guidelines as closely as possible. The booklets covered: self-management, stimulus control, cognitive therapy for changing dysfunctional beliefs and attitudes, education, and evaluation. Participants were also asked by therapists regarding their adherence to the CBT guidance during

	weekly telephone calls. Duration 8 weeks. Concurrent medication/care: All patients were given a step-by-step withdrawal programme. Dose was reduced by 25% every two weeks with the aim to achieve complete drug withdrawal by the end of week 8. Participants met with a physician to provide an individualized withdrawal schedule, and offer support and encouragement, and to adjust the withdrawal schedule if necessary. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=25) Intervention 2: Tapered withdrawal. Participants received taper programme only. No additional services were received. Duration 8 weeks. Concurrent medication/care: All patients were given a step-by-step withdrawal programme. Dose was reduced by 25% every two weeks with the aim to achieve complete drug withdrawal by the end of week 8. Participants met with a physician to provide an individualized withdrawal schedule, and offer support and encouragement, and to adjust the withdrawal schedule if necessary. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE BEHAVIOURAL THERAPY (CBT) + TAPER versus TAPERED WITHDRAWAL STRATEGIES ALONE

Protocol outcome 1: Quality of life

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): SF-36 - Physical component at Post-treatment (8 weeks); Group 1: mean 69 (SD 18.7); n=23, Group 2: mean 79.42 (SD 18.31); n=25; SF-36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): SF-36 - Physical component at 6 months follow-up; Group 1: mean 69.85 (SD 19.56); n=20, Group 2: mean 78.17 (SD 17.65); n=23; sf-36 0-100 Top=High is good outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): SF-36 - Mental component at Post-treatment (8 weeks); Group 1: mean 65.95 (SD 18.5); n=23, Group 2: mean 69.67 (SD 13.34); n=25; sf36 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): SF-36 - Mental component at 6 months; Group 1: mean 73 (SD 17.55); n=20, Group 2: mean 74.09 (SD 14.57); n=23; sf36 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Drug-free participants at Post-treatment (8 weeks); Group 1: 16/22, Group 2: 6/25

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 6, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Drug-free participants at 6 months; Group 1: 9/19, Group 2: 13/24

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: lost to follow up; Group 2 Number missing: 1, Reason: lost to follow up

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Daily hypnotic dose (lorazepam equivalent, mg) at Post-treatment (8 weeks); Group 1: mean 0.17 (SD 0.4); n=23, Group 2: mean 0.09 (SD 0.2); n=25

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Daily hypnotic dose (lorazepam equivalent, mg) at 6 months; Group 1: mean 0.33 (SD 0.8); n=20, Group 2: mean 0.37 (SD 0.6); n=23

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Depression (BDI) at Post-intervention (8 weeks); Group 1: mean 7.32 (SD 6.31); n=23, Group 2: mean 4.21 (SD 3.67); n=25; BDI 0-36 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Depression (BDI) at 6 months; Group 1: mean 4.35 (SD 3.86); n=20, Group 2: mean 4.78 (SD 4.11); n=23; BDI 0-36 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Anxiety (STAI-state) at Post-intervention (8 weeks); Group 1: mean 36.18 (SD 13.43); n=23, Group 2: mean 37.04 (SD 8.62); n=25; STAI-state 20-80 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Anxiety (STAI-state) at 6 months; Group 1: mean 31.35 (SD 7.44); n=20, Group 2: mean 35.48 (SD 10.9); n=23; STAI-state 20-80 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Clinical institute withdrawal assessment - Benzodiazepine (CIWA-B) at Post-intervention (8 weeks); Group 1: mean 24.71 (SD 13.5); n=23, Group 2: mean 23.53 (SD 16.66); n=25; CIWA-B 0-100 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Clinical institute withdrawal assessment - Benzodiazepine (CIWA-B) at 6 months; Group 1: mean 18.95 (SD 10.8); n=20, Group 2: mean 17.33 (SD 13.05); n=23; CIWA-B 0-100 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

Protocol outcome 4: Increase in symptoms for which the medication was originally prescribed - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Insomnia severity index (ISI) at Post-intervention (8 weeks); Group 1: mean 11.73 (SD 5.14); n=23, Group 2: mean 14.25 (SD 6.05); n=25; Insomnia Severity Scale 0-28 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Procedure too difficult to follow; Group 2 Number missing: 0 - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Insomnia severity index (ISI) at 6 months; Group 1: mean 10.7 (SD 5.91); n=20, Group 2: mean 11.48 (SD 7.54); n=23; Insomnia Severity Scale 0-28 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up	
Protocol outcomes not reported by the study	Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Giblin 1983[90]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 20 weeks

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were currently using hypnotics nightly and had been doing so for six months or more.
Exclusion criteria	Patients who were taking any other psychotropic medication; had a diagnosis of psychosis; had a known terminal illness.
Recruitment/selection of patients	All subjects were initially approached by letter from the general practitioner and were interviewed by him. They were told about the study and were asked if they wished to participate.
Age, gender and ethnicity	Age - Mean (range): 71.3 (56-83). Gender (M:F): 4/16. Ethnicity:
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Indirectness of population	Serious indirectness: Specific benzodiazepines were not reported
Interventions	(n=10) Intervention 1: Non-pharmacological interventions - Patient advice/education and support. Psychological treatment: Relaxation technique - This was a form of the autogenic relaxation procedure. The technique was taught in the first session and practised at the start of all the other sessions. Information - Information was given in simple written form and discussed in the treatment sessions. The information was concerned with sleep, insomnia, hypnotics and their effects on sleep, and sleep-preventing behaviour. General advice - Subjects were encouraged to view their problems in a systematic and logical way, to adopt a positive optimistic attitude to their difficulties, and to use the techniques every night. They were told that there might be a number of effects as a result of drug-withdrawal, but that these would soon end. A lot of reinforcement, in other words, approval, from the therapist was given when anyone reported any success. Duration 4 weeks. Concurrent medication/care: All subjects were then asked to stop taking hypnotics, and to refrain from using them for as long as they could. Indirectness: No indirectness

	Further details: 1. Addiction support services: Not applicable (n=10) Intervention 2: Usual care. No psychological intervention was available. Duration 4 weeks. Concurrent medication/care: All subjects were then asked to stop taking hypnotics, and to refrain from using them for as long as they could. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PATIENT ADVICE/EDUCATION AND SUPPORT versus USUAL CARE (TO DEFINE)

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Benzodiazepines: No hypnotic use during previous 4-week period at 12 weeks; Group 1: 6/10, Group 2: 1/10

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing:

- Actual outcome for Benzodiazepines: No hypnotic use during previous 4-week period at Post intervention (4 weeks); Group 1: 7/10, Group 2: 1/10

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing:

Protocol outcome 2: Relapse into medication use

- Actual outcome for Benzodiazepines: Resumption on nightly hypnotic use at 12 weeks; Group 1: 2/10, Group 2: 8/10

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing:

- Actual outcome for Benzodiazepines: Resumption on nightly hypnotic use at Post intervention (4 weeks); Group 1: 1/10, Group 2: 7/10

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing:; Group 2 Number missing:

Protocol outcome 3: Increase in symptoms for which the medication was originally prescribed- Actual outcome for Benzodiazepines: Sleep latency (per night) at 12 weeks; Group 1: mean 30 minutes (SD 27); n=10, Group 2: mean 32 minutes (SD 24); n=10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: Group 2 Number missing: - Actual outcome for Benzodiazepines: Sleep latency (per night) at Post intervention; Group 1: mean 70 minutes (SD 40); n=10, Group 2: mean 27 minutes (SD 11); n=10 Risk of bias: All domain -; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

2

Study	**Gorenstein 2005[96]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=42)
Countries and setting	Conducted in USA; Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention time: 13 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Mixed (all drug classes): 26 benzodiazepine, 7 antidepressant, 2 opiate, 1 valerian, 1 diphenhydramine, 5 meprobamate
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients were eligible if they had a sufficient number of anxiety symptoms, as rated on the SCID sections pertaining to GAD or panic disorder, to meet criteria for one or both disorders, and/or aTRait Anxiety Inventory T score of 60 (one SD above the normative mean) or higher. Patients had to have confirmed use of antianxiety medication for at least the past 8 weeks. Any medication with legitimate anxiety-reducing properties that had been prescribed for that purpose was allowed.
Exclusion criteria	Current diagnosis of major depression, a history of psychosis or bipolar illness, significant substance use disorder, suicidality in the past 6 months, a medical condition incompatible with study participation, or a Dementia Rating Scale score of 131 or lower.
Recruitment/selection of patients	Participants were recruited through professional referrals and advertisements seeking anxious elderly individuals who were getting unsatisfactory results from anxiolytic medications.
Age, gender and ethnicity	Age - Mean (SD): CBT-MM: 67.8 (7.1) years, MM: 68.7 (6.6) years. Gender (M:F): CBT-MM: 11F/12M, MM: 10F/9M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Outpatient
Extra comments	Medication use was frequent (mean: 5.8 days/ week; SD 2.0) but doses were low. In benzodiazepine users, the mean daily dose was the equivalent of 7.6mg (SD 6.5) of diazepam.
Indirectness of population	Serious indirectness: No breakdown of benzodiazepines used- some may not have been on the guideline medicine list. 7/42 (17%) were on a drug outside protocol (valerian, diphenhydramine, meprobamate)
Interventions	(n=23) Intervention 1: Non-pharmacological interventions - CBT plus medical management taper (CBT-MM) involved medical management as per MM group plus 13 concurrent weekly CBT sessions (50 minutes each) with a study psychologist experienced in CBT. Medical management and CBT sessions were conducted on the same day, with the CBT session usually scheduled first. CBT was conducted according to a manual and involved established methods for treating anxiety and panic. The principal methods involved progressive muscle relaxation,

	diaphragmatic breathing, cognitive restructuring, worry-behaviour prevention, problem-solving, interoceptive exposure (controlled exposure to sensations of autonomic arousal), cognitive-behavioural strategies for coping with medication withdrawal, daily activity structuring, in vivo exposure and sleep hygiene. The manual offered a session-by-session protocol, but the clinician had the flexibility to emphasise certain techniques over others or to delay the application of a given technique in order to accommodate patient differences. The tapering guidelines involved an approximately 20% reduction each week for benzodiazepines. However, the patient was allowed to proceed at a faster or slower rate, depending on clinical status. For non-benzodiazepines such as SSRIs the clinician followed standard clinical practice. Patients who could not tolerate taper or whose benefits from medication exceeded drawbacks stayed on medication. If medication was eliminated before the final sessions, discussion centred on clinical state and residual side effects, if any. Duration 13weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=19) Intervention 2: Medical management taper (MM) involved 13 weekly sessions with a psychiatrist, lasting about 10-15 minutes each, conducted according to a pharmacotherapy manual. At the first session, after a review of symptoms and medication history, a tapering schedule was devised and discussed. Subsequent sessions dealt with the patient's clinical state, medication efficacy, side effects, the next medication step and prescription of medication. The tapering guidelines involved an approximately 20% reduction each week for benzodiazepines. However, the patient was allowed to proceed at a faster or slower rate, depending on clinical status. For non-benzodiazepines such as SSRIs the clinician followed standard clinical practice. Patients who could not tolerate taper or whose benefits from medication exceeded drawbacks stayed on medication. If medication was eliminated before the final sessions, discussion centred on clinical state and residual side effects, if any. Duration 13 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (Work was supported, in part, by NIMH grants RO1MH53582 and K02 MH001397)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT-MM + TAPER versus MM + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Mixed (all drug classes): Medication elimination at 13 weeks; Group 1: 7/14, Group 2: 4/14; Comments: calculated from % reported

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: 3 had 'clinical difficulties' such as worsening of condition, 1 disliked the treatment, 5 for reasons unrelated to treatment such physical illness or travel, 1 dropped out before starting treatment (this totals 10 patients); Group 2 Number missing: 5, Reason: 1 had 'clinical difficulties' such as worsening of condition, 1 for reasons unrelated to treatment such physical illness or travel, 2 dropped out before starting treatment, 1 unknown

- Actual outcome for Mixed (all drug classes): Medication reduction- taking less medication at the end of treatment than at the beginning. at 13 weeks; Group 1: 13/14, Group 2: 10/14; Comments: Calculated from % reported by study

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: 3 had 'clinical difficulties' such as worsening of condition, 1 disliked the treatment, 5 for reasons unrelated to treatment such physical illness or travel, 1 dropped out before starting treatment (this totals 10 patients); Group 2 Number missing: 5, Reason: 1 had 'clinical difficulties' such as worsening of condition, 1 for reasons unrelated to treatment such physical illness or travel, 2 dropped out before starting treatment, 1 unknown

- Actual outcome for Mixed (all drug classes): Average proportion of medication taken post-treatment relative to pre-treatment at 13 weeks; Group 1: 0.465 (SD 0.82), Group 2: 0.583 (SD 0.81)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: 3 had 'clinical difficulties' such as worsening of condition, 1 disliked the treatment, 5 for reasons unrelated to treatment such physical illness or travel, 1 dropped out before starting treatment (this totals 10 patients); Group 2 Number missing: 5, Reason: 1 had 'clinical difficulties' such as worsening of condition, 1 for reasons unrelated to treatment such physical illness or travel, 2 dropped out before starting treatment, 1 unknown

Protocol outcome 2: Increase in symptoms for which the medication was originally prescribed

- Actual outcome for Mixed (all drug classes): 'Responder' Clinical Global Impression Scale; 'much improved' or 'very much improved' at 13 weeks; Group 1: 9/14, Group 2: 5/14; Comments: Scale 1-7; higher value is worse.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: 3 had 'clinical difficulties' such as worsening of condition, 1 disliked the treatment, 5 for reasons unrelated to treatment such physical illness or travel, 1 dropped out before starting treatment (this totals 10 patients); Group 2 Number missing: 5, Reason: 1 had 'clinical difficulties' such as worsening of condition, 1 for reasons unrelated to treatment such physical illness or travel, 2 dropped out before starting treatment, 1 unknown

Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study (subsidiary papers)	**Lahteenmaki 2014[139] (Puustinen 2018[219])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=92)
Countries and setting	Conducted in Finland; Setting: Primary healthcare outpatient clinic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 55 years or older who were long term users of benzodiazepines as hypnotics, defined as 1 month or longer regular night-time use.
Exclusion criteria	The key exclusion criteria consisted of concurrent use of antipsychotic or anti-epileptic medications, use of a benzodiazepine other than temazepam, zopiclone or zolpidem; a history of, or active alcohol or drug abuse, severe anxiety disorder or other severe psychiatric disorder, severe neurological disease, smoking more than 10

	cigarettes a day, autoimmune disease or galactosaemia or use of medication that potentially interacts with melatonin.
Recruitment/selection of patients	Personnel working in local health centres informed patients about the study and recruited volunteers. Two advertisements were also placed in local newspapers.
Age, gender and ethnicity	Age - Median (IQR): 65.7 (10.5). Gender (M:F): 33/61. Ethnicity: Not reported
Further population details	1. Gabapentinoids: Not applicable 2. Half-life of benzodiazepines: Not applicable (Mixed population: temazepam (14), zopiclone (52) or zolpidem (26)). 3. Setting: Outpatient
Extra comments	The three most common benzodiazepines used as hypnotics in Finland, temazepam, zopiclone or zolpidem, were the focus, but they must have been prescribed according to DSM-IV criteria for primary insomnia. temazepam (14), zopiclone (52) or zolpidem (26)
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Pharmacological interventions. Melatonin + taper (CRM) (Circadin® 2mg depot tablet, RAD NeurimPharmaceuticals EEC Limited, UK) in benzodiazepine withdrawal during a 1-month period. One tablet daily. Duration 1 month. Concurrent medication/care: At baseline, a physician provided psychosocial support and sleep hygiene counselling, including discussions about regular sleep rhythm and the influence of the following on sleep: normal changes in sleep patterns related to ageing, conditions of the bedroom and bed, exercise, eating and alcohol use, coffee and stimulants prior to sleeping, deep and calm breathing, and psychic and physical relaxation in bed and, if anxieties arise, to write them on paper. The physician performed a clinical examination of each participant and determined an individual withdrawal schedule. Most often the recommended reduction from the initial benzodiazepine daily dose was 50% per week. The psychosocial support was further continued by a nurse who provided supportive visits once a week during the withdrawal period and was available for advice by phone. Indirectness: No indirectness Further details: 1. Addiction support services: Not applicable (n=46) Intervention 2: Placebo once daily + taper. Duration 1 month. Concurrent medication/care: At baseline, a physician provided psychosocial support and sleep hygiene counselling, including discussions about regular sleep rhythm and the influence of the following on sleep: normal changes in sleep patterns related to ageing, conditions of the bedroom and bed, exercise, eating and alcohol use, coffee and stimulants prior to sleeping, deep and calm

	breathing, and psychic and physical relaxation in bed and, if anxieties arise, to write them on paper. The physician performed a clinical examination of each participant and determined an individual withdrawal schedule. Most often the recommended reduction from the initial benzodiazepine daily dose was 50% per week. The psychosocial support was further continued by a nurse who provided supportive visits once a week during the withdrawal period and was available for advice by phone. Indirectness: No indirectness Further details: 1. Addiction support services:
Funding	Study funded by industry (Financial support for the study was provided by Nycomed. Finnish Cultural Foundation and Satakunta Hospital District Grant EVO, Southwest Finland Hospital District Grant EVO and Härkätie Grant EVO have financially supported this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MELATONIN + PSYCHOLOGICAL SUPPORT + TAPER versus PSYCHOLOGICAL SUPPORT + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Complete withdrawal of benzodiazepine at Post-intervention (1 month); Group 1: 36/45, Group 2: 41/45

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: drop out; Group 2 Number missing: 1, Reason: drop out

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Complete withdrawal of benzodiazepine at 6 months; Group 1: 14/44, Group 2: 20/45

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: drop out; Group 2 Number missing: 1, Reason: drop out

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine usage (any daily use) at 6 months; OR; 2.5 (95%CI 1.1 to 5.5, Comments: CRM vs placebo. CRM: n=44, placebo n=45.);

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: drop out; Group 2 Number missing: 1, Reason: drop out

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Complete withdrawal of benzodiazepine at 3 years; Group 1: 12/42, Group 2: 14/41

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4, Reason: lost to follow up; Group 2 Number missing: 5, Reason: lost to follow

up. Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): BWSQ at Post-intervention (1 month); Group 1: mean 3.2 Sum of symptoms (SD 2.9); n=43, Group 2: mean 3.2 Sum of symptoms (SD 3.8); n=42; Comments: Values are median (IQR) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: drop out; Group 2 Number missing: 1, Reason: drop out - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): BWSQ at 6 months; Group 1: mean 3.6 Sum of symptoms (SD 3); n=44, Group 2: mean 3.1 Sum of symptoms (SD 2.8); n=43; Comments: Values are median (IQR) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: drop out; Group 2 Number missing: 1, Reason: drop out	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Van de Steeg-van Gompel 2009[263]**
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	(n=19398 in 90 pharmacies)
Countries and setting	Conducted in Netherlands; Setting: Primary care.
Line of therapy	1st line

Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs): Z-drugs: Intensive support programme: 12.4% Written manual: 12.7%
Subgroup analysis within study	Not applicable
Inclusion criteria	Pharmacies treating long-term users of benzodiazepines, defined as the dispensing of at least four prescriptions for benzodiazepines for at least 91 dosage units (tablets or capsules) in total in the relevant 12-month period, including prescription for at least 60 dosage units in the last 3 months of the 12-month period.
Exclusion criteria	Medical reasons (currently being treated by a specialist for mental illness, drug or alcohol dependence, psychotic episodes in medical history, epilepsy, terminal illness or severe co-morbidity.) Psychosocial reasons (insufficient mastery of the Dutch language or old age/ severe disability). Administrative reason (moved/ changed practices).
Recruitment/selection of patients	All pharmacies in the region were contacted and invited to participate. Participation was voluntary but encouraged by one of the two major health insurance companies in that part of the Netherlands as participating pharmacies were exempted from having to submit their annual plans and reports of patient care activities.
Age, gender and ethnicity	Age - Mean (SD): Intensive support programme: 64.7 (15.3), Written manual: 65.1 (15.3). Gender (M:F): intensive support programme: 69.6%F/30.4%M Written manual: 70.1%F/29.9%M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed 3. Setting: Outpatient (General practice and pharmacies).
Extra comments	Cluster randomised
Indirectness of population	Serious indirectness: 20.9% and 19.8% in each group were taking unspecified benzodiazepines which may not be on the protocol.

Interventions	(n=14244) Intervention 1: Non-pharmacological interventions - Prescriber education. The programme included an educational manual; an interactive educational meeting which was held at the start of the study and tailored to the individual needs of the pharmacists; and one or more telephone calls by a coach to remind the pharmacist to get started on the intervention and ask if they needed more help. The educational manual consisted of information about the project, step by step instructions for managing the project, schedules for the reduction of benzodiazepine use, an electronic example of the discontinuation letter encouraging patients to discontinue their benzodiazepine use, background information regarding long term benzodiazepine use and publications on the effectiveness of sending such a letter to long term benzodiazepine users. The first phone call was made about 4 weeks after the pharmacists had planned to initiate the intervention. If desired after the first call, the pharmacist could schedule a second. The interactive educational meeting with a duration of 6 hours was specially designed to address the co-operation with GPs. The pharmacists listed and discussed perceived barriers to and facilitators of co-operation with GPs; were informed about some essential aspects of communication with GPs; analysed their individual strengths and weaknesses, which were then discussed with the entire group; practiced points for improvement; and made a plan for communication regarding the present intervention with the GPs. Duration 6 months. Concurrent medication/care: In both groups pharmacists were expected to: identify long term benzodiazepine users and present the resulting list to co-operating GPs for exclusion of those who should not be sent a letter for one reason or another. The discontinuation letter was signed by both the GP and the pharmacist and was supposed to be sent to the relevant patients by each of the pharmacies in both groups. Patients who wanted to stop but thought they would not be able to do this on their own were also instructed in the letter to contact their pharmacist or GP. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear Comments: 47 pharmacies were randomised to this intervention (n=11429) Intervention 2: Non-pharmacological interventions - Prescriber education. Pharmacies only received the written educational manual, and no further implementation support was given. Duration 6 months. Concurrent medication/care: In both groups pharmacists were expected to: identify long term benzodiazepine users and present the resulting list to co-operating GP for exclusion of those who should not be sent a letter for one reason or another. The discontinuation letter was signed by both the GP and the pharmacist and was supposed to be sent

	to the relevant patients by each of the pharmacies in both groups. Patients who wanted to stop but thought they would not be able to do this on their own were also instructed in the letter to contact their pharmacist or GP. Indirectness: No indirectness Further details: 1. Addiction support services: Comments: 43 pharmacies were randomised to this intervention.
Funding	Other (Health insurance company CZ Actief in Gezondheid and the Scientific Institute of Dutch Pharmacists.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTENSIVE SUPPORT PROGRAMME versus WRITTEN EDUCATIONAL MANUAL

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Patients who completely discontinued benzodiazepine use at 0-3 months after sending of discontinuation letter; Group 1: 998/11423, Group 2: 659/7975

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomised: adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias); Indirectness of outcome: No indirectness; Baseline details: Taking >1 benzodiazepine: Intensive support: 23.1%, written manual 18.5%; Group 1 Number missing: 2821, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.; Group 2 Number missing: 3454, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Patients who completely discontinued benzodiazepine use at 4-6 months after sending of discontinuation letter; Group 1: 1129/11423, Group 2: 810/7975

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomised: adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias); Indirectness of outcome: No indirectness; Baseline details: Taking >1 benzodiazepine: Intensive support: 23.1%, written manual 18.5%; Group 1 Number missing: 2821, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.; Group 2 Number missing: 3454, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Patients who reduced use by at least 50% at 0-3 months after sending of discontinuation letter; Group 1: 1793/11423, Group 2: 1179/7975

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomised: adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias); Indirectness of outcome: No indirectness; Baseline details: Taking >1 benzodiazepine: Intensive support: 23.1%, written manual 18.5%; Group 1 Number missing: 2821, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.; Group 2 Number missing: 3454, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent. - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Patients who reduced use by at least 50% at 4-6 months after sending of discontinuation letter; Group 1: 1820/11423, Group 2: 1331/7975 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomised: adjusted analysis not provided, accounting for cluster randomisation (downgraded for other risk of bias); Indirectness of outcome: No indirectness; Baseline details: Taking >1 benzodiazepine: Intensive support: 23.1%, written manual 18.5%; Group 1 Number missing: 2821, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.; Group 2 Number missing: 3454, Reason: No process information; Patient selection not handed over to any GP; patient selections not retrieved; letters not sent.	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study (subsidiary papers)	**Vicens 2014[265] (Vicens 2011[269]; Vicens 2016[268])**
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	(n=532)
Countries and setting	Conducted in Spain; Setting: 21 primary care centres.

Line of therapy	1st line
Duration of study	Follow up (post intervention): 12months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs). Note: baseline information shows that at least 13.9% were on Z-drugs.
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-80 years and taking benzodiazepines or related drugs (zopiclone, zolpidem, or zaleplon) daily for at least 6 months
Exclusion criteria	Psychotic or personality disorder; current treatment by a psychiatrist; severe anxiety; depressive disorder; severe mental illness including dementia and epilepsy as clinically assessed by the GP, or in cases where they considered that stopping the benzodiazepine might be harmful; alcohol or illicit drug misuse; patients in residential care or terminally ill; inability to read and speak Spanish or unwillingness to provide informed consent.
Recruitment/selection of patients	Randomly chosen by co-ordinating centre
Age, gender and ethnicity	Age - Other: Median 64 years, IQR 55-72. Gender (M:F): 72%F/ 28%M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed 3. Setting: Outpatient (Primary care centres.).
Extra comments	Cluster randomised. The most frequently prescribed drugs were lorazepam (32.3%), alprazolam (17.7%), lormetazepam (15.2%) and zolpidem (13.9%).
Indirectness of population	Serious indirectness: No breakdown of benzodiazepines used- may have included those not on protocol

Interventions	(n=191) Intervention 1: Non-pharmacological interventions - Patient advice/education and support. Structured intervention with follow-up visits (SIF). This intervention was based on a structured educational interview and GP-tailored stepped benzodiazepine dose reduction. The content of the educational interview was structured and included 4 key points: 1) information on benzodiazepine dependence, abstinence and withdrawal symptoms 2) the risks of long-term use, memory and cognitive impairment, accidents and falls 3) reassurance about reducing medication 4) a self-help leaflet to improve sleep quality if patients were taking benzodiazepines for insomnia. After the first intervention visit patients attended follow-up appointments with their GP every 2-3 weeks until the end of the dose reduction. The GPs reinforced education, reassured patients regarding withdrawal symptoms and obtained patient agreement for the next step in dose reduction. The tailored gradual taper consisted of a 10-25% reduction in the daily dose of the benzodiazepine every 2-3 weeks. Practitioners assigned to this group attended a supplementary 3-hour workshop on structured interviews, individualised patient information and training in managing benzodiazepine discontinuation and optimal gradual dose reduction. In addition, they attended a 30-minute workshop to standardise the dose-reduction follow-up visits. Duration 6 months. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=168) Intervention 2: Non-pharmacological interventions - Brief intervention and advice. Structured intervention with written instructions (SIW). This intervention was based on a structured educational interview and GP-tailored stepped benzodiazepine dose reduction. The content of the educational interview was structured and included 4 key points: 1) information on benzodiazepine dependence, abstinence and withdrawal symptoms 2) the risks of long-term use, memory and cognitive impairment, accidents and falls 3) reassurance about reducing medication 4) a self-help leaflet to improve sleep quality if patients were taking benzodiazepines for insomnia. Patients received written instructions reinforcing educational information at their first and only contact with their GP, along with a tailored gradual dose reduction until benzodiazepine cessation. No follow- up visit was scheduled, although patients could request an appointment with their GP when needed. The tailored gradual taper consisted of a 10-25% reduction in the daily dose of the benzodiazepine every 2-3 weeks. Practitioners assigned to this group attended a supplementary 3-hour workshop on structured interviews, individualised patient information and training in managing benzodiazepine discontinuation and optimal

	gradual dose reduction. Duration 6 months. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear (n=173) Intervention 3: Usual care. Patients received routine care; their GPs could provide brief advice but did not receive any specific recommendation about the management of long-term benzodiazepine use from the study trainers. Duration 6 months. Concurrent medication/care: NR. Indirectness: Serious indirectness; Indirectness comment: Unclear if usual care involves deprescribing benzodiazepines. Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (Carlos III Health Institute of the Ministry of Economy and Competitiveness (contract PS09/00947).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED INTERVENTION + FOLLOW-UP + TAPER versus STRUCTURED INTERVENTION + WRITTEN INSTRUCTIONS + TAPER

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Death at 36 months; Group 1: 1/159, Group 2: 4/145

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 32, Reason: no longer contactable (27), major morbid event (4), withdrew consent (1); Group 2 Number missing: 23, Reason: protocol exclusion (2), no longer contactable (19), major morbid event (1), withdrew consent (1)

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 6 months; Group 1: 71/191, Group 2: 72/168

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments - results not adjusted for cluster randomisation; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 6, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 36 months; Group 1: 79/191, Group 2: 66/168

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Comments - Results not adjusted for cluster randomisation; Indirectness of outcome: No indirectness; Group 1 Number missing: 33, Reason: no longer contactable (27), major morbid event (4), withdrew consent (1), death (1); Group 2 Number missing: 27, Reason: death (4), protocol exclusion (2), no longer contactable (19), major morbid event (1), withdrew consent (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 12 months; RR; 1.00 (95%CI 0.78 to 1.28, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), major morbid event (4), withdrew consent (1); Group 2 Number missing: 11, Reason: death (1), protocol exclusion (2), no longer contactable (6), major morbid event (1), withdrew consent (1)

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 6 months; Group 1: 30/186, Group 2: 18/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 6 months; Group 1: 42/186, Group 2: 42/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 6 months; Group 1: 87/186, Group 2: 83/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 6 months; Group 1: 72/186, Group 2: 64/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 6 months; Group 1: 3/186, Group 2: 1/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 12 months; Group 1: 13/184, Group 2: 11/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 12 months; Group 1: 26/184, Group 2: 23/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 12 months; Group 1: 66/184, Group 2: 53/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 12 months; Group 1: 48/184, Group 2: 47/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 12 months; Group 1: 0/184, Group 2: 0/159

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)

Protocol outcome 4: self-harm or harm to others

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Attempted suicide at 12 months; Group 1: 0/180, Group 2: 1/157

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), major morbid event (4), withdrew consent 1); Group 2 Number missing: 11, Reason: death (1), protocol exclusion (2), no longer contactable (6), major morbid event (1), withdrew consent (1)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED INTERVENTION + FOLLOW-UP + TAPER versus USUAL CARE

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Death at 36 months; Group 1: 1/159, Group 2: 2/149

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 32, Reason: no longer contactable (27), major morbid event (4), withdrew consent (1); Group 2 Number missing: 24, Reason: protocol exclusion (2), no longer contactable (19), major morbid event (2), withdrew consent (1)

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 12 months; RR; 3 (95%CI 2.04 to 4.4, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), major morbid event (4), withdrew consent (1); Group 2 Number missing: 13, Reason: no longer contactable (8), protocol exclusion (2), major morbid event (2), withdrew consent (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 36 months; RR; 1.59 (95%CI 1.15 to 2.19, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 33, Reason: no longer contactable (27), death (1), major morbid event (4), withdrew consent (1); Group 2 Number missing: 26, Reason: death (3), protocol exclusion (2), no longer contactable (19), major morbid event (1), withdrew consent (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 6 months; RR; 2.58 (95%CI 1.77 to 3.75, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 2, Reason: no longer contactable

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 6 months; Group 1: 30/186, Group 2: 9/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 3, Reason: no longer contactable

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms: insomnia (mild/moderate/severe) at 12 months; Group 1: 66/184, Group 2: 47/164

Risk of bias: All domain -; Indirectness of outcome: No indirectness

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 6 months; Group 1: 42/186, Group 2: 15/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 3, Reason: no longer contactable

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 6 months; Group 1: 87/186, Group 2: 30/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 3, Reason: no longer contactable

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 6 months; Group 1: 72/186, Group 2: 21/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 3, Reason: no longer contactable

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 6 months; Group 1: 3/186, Group 2: 1/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: no longer contactable; Group 2 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3)
- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 12 months; Group 1: 13/184, Group 2: 11/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent; Group 2 Number missing: 9, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 12 months; Group 1: 26/184, Group 2: 20/164Risk of bias: All domain -; Indirectness of outcome: No indirectness

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 12 months; Group 1: 66/184, Group 2: 47/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent; Group 2 Number missing: 9, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 12 months; Group 1: 48/184, Group 2: 33/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent; Group 2 Number missing: 9, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 12 months; Group 1: 0/184, Group 2: 0/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7, Reason: no longer contactable, major morbid event, withdrew consent; Group 2 Number missing: 9, Reason: no longer contactable, major morbid event, withdrew consent, protocol exclusion

Protocol outcome 4: self-harm or harm to others

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Attempted suicide at 12 months; Group 1: 0/180, Group 2: 0/160

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), major morbid event (4), withdrew consent (1); Group 2 Number missing: 13, Reason: protocol exclusion (2), no longer contactable (8), major morbid event (2), withdrew consent (1)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED INTERVENTION + WRITTEN INSTRUCTIONS + TAPER versus USUAL CARE

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Death at 36 months; Group 1: 4/145, Group 2: 2/149
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover

- Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 23, Reason: protocol exclusion (2), no longer contactable (19), major morbid event (1), withdrew consent (1); Group 2 Number missing: 24, Reason: protocol exclusion (2), no longer contactable (19), major morbid event (2), withdrew consent (1)

Protocol outcome 2: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 12 months; RR; 3.01 (95%CI 2.03 to 4.46, Comments: Adjusted for cluster randomisation);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results not adjusted for cluster randomisation.; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), death (1), protocol exclusion (2), major morbid event (1), withdrew consent (1); Group 2 Number missing: 13, Reason: protocol exclusion (2), no longer contactable (8), major morbid event (2), withdrew consent (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 36 months; RR; 1.51 (95%CI 1.1 to 2.05, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 27, Reason: no longer contactable (19), death (4), protocol exclusion (2), major morbid event (1), withdrew consent (1); Group 2 Number missing: 26, Reason: death (2), protocol exclusion (2), no longer contactable (19), withdrew consent (1), major morbid event (2)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): benzodiazepine discontinuation at 6 months; RR; 2.97 (95%CI 2.07 to 4.26, Comments: Adjusted for cluster randomisation.);

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 6, Reason: no longer contactable (2), death (1), protocol exclusion (2), major morbid event (1); Group 2 Number missing: 2, Reason: no longer contactable

Protocol outcome 3: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 6 months; Group 1: 18/159, Group 2: 9/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3); Group 2 Number missing: 3, Reason: no longer contactable (2), unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 6 months; Group 1: 42/159, Group 2: 15/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3); Group 2 Number missing: 3, Reason: no longer contactable (2), unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 6 months; Group 1: 83/159, Group 2: 30/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3); Group 2 Number missing: 3, Reason: no longer contactable (2), unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 6 months; Group 1: 64/159, Group 2: 21/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3); Group 2 Number missing: 3, Reason: no longer contactable (2), unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 6 months; Group 1: 1/159, Group 2: 1/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), unclear (3); Group 2 Number missing: 3, Reason: no longer contactable (2), unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : tremor (mild/moderate/severe) at 12 months; Group 1: 11/159, Group 2: 11/170

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), withdrew consent (1), unclear (2); Group 2 Number missing: 9, Reason: no longer contactable (3), major morbid event (2), withdrew consent,(1) protocol exclusion (2) unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : insomnia (mild/moderate/severe) at 12 months; Group 1: 53/159, Group 2: 47/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), withdrew consent (1), unclear (2); Group 2 Number missing: 9, Reason: no longer contactable (3), major morbid event (2), withdrew consent,(1) protocol exclusion (2) unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : anxiety (mild/moderate/severe) at 12 months; Group 1: 47/159, Group 2: 33/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), withdrew consent (1), unclear (2); Group 2 Number missing: 9, Reason: no longer contactable (3), major morbid event (2), withdrew consent,(1) protocol exclusion (2) unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : convulsions (mild/moderate/severe) at 12 months; Group 1: 0/159, Group 2: 0/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), withdrew consent (1), unclear (2); Group 2 Number missing: 9, Reason: no longer contactable (3), major morbid event (2), withdrew consent,(1) protocol exclusion (2) unclear (1)

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Withdrawal symptoms : irritability (mild/moderate/severe) at 12 months; Group 1: 23/159, Group 2: 20/164

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: death (1), protocol exclusion (2), no longer contactable (2), major morbid event (1), withdrew consent (1), unclear (2); Group 2 Number missing: 9, Reason: no longer contactable (3), major morbid event (2), withdrew consent,(1) protocol exclusion (2) unclear (1)

Protocol outcome 4: self-harm or harm to others

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Attempted suicide at 12 months; Group 1: 1/157, Group 2: 0/160

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11, Reason: no longer contactable (6), death

(1), protocol exclusion (2), major morbid event (1), withdrew consent (1); Group 2 Number missing: 13, Reason: protocol exclusion (2), no longer contactable (8), major morbid event (2), withdrew consent (1)	
Protocol outcomes not reported by the study	Quality of life; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Reduced tolerance; Patient Satisfaction; Non-fatal overdose; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study (subsidiary papers)	**Yeung 2019[294] (Yeung 2017[293])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=144)
Countries and setting	Conducted in Hong Kong (China); Setting: Psychiatric outpatient clinics of three regional hospitals in Hong Kong and an integrative health clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Hypnotics (benzodiazepines and Z-drugs)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 or over including elderly patients, having at least one of the following psychiatric diagnoses : depressive episodes/ disorders, panic disorder, generalised anxiety disorder, mixed anxiety and depressive disorder, adjustment disorders and nonorganic insomnia, were taking benzodiazepines coded as N05BA (benzodiazepine derivatives, anxiolytics), N05CD (benzodiazepine derivatives, hypnotics and sedatives, N05CF (benzodiazepine related drugs, hypnotics and sedatives and M03BX07 (benzodiazepine derivatives,

	muscle relaxants), according to the WHO Collaborating Centre for Drug Statistics Methodology, on more than 50% of days for at least 3 months and during a prospective 2 week period prior to baseline, and willing to taper benzodiazepine as per protocol.
Exclusion criteria	Any increase by ≥50% in the dosage of antidepressants or anxiolytics in the previous year, ≥8 score in either HADS anxiety or HADS depression, any concurrent psychiatric disorders or medical conditions, such as: bipolar affective disorder, OCD, PTSD, schizophrenia, other schizotypal and delusional disorders, abuse of non-dependence producing substances, abuse of other psychoactive substances. Other conditions such as serious physical conditions considered as unsuitable for participation, valvular heart defects or bleeding disorders, taking anticoagulant drugs, or had been fitted with any implanted electrical device, received acupuncture treatment within 6 months, being pregnant or breastfeeding or had childbearing potential without adequate contraception, had infection or abscess close to the selected acupoints rendered unsafe, significant suicide risks rate by the Hamilton Depression Rating Scale (item on suicide scored ≥3)
Recruitment/selection of patients	Doctor referral and advertisements at the hospitals and clinic.
Age, gender and ethnicity	Age - Mean (SD): 57.5 (10.6). Gender (M:F): 139M/105F. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Systematic review: mixed 3. Setting: Outpatient
Indirectness of population	Serious indirectness: No breakdown of drugs provided.
Interventions	(n=72) Intervention 1: Non-pharmacological interventions - Acupuncture. Electroacupuncture combined with gradual tapering. Electroacupuncture twice per week for 4 consecutive weeks. Participants were needled by sterile, disposable acupuncture needles at preselected acupoints until an indicator of 'effective needling' in Traditional Chinese medicine theory was obtained. The inserted needles were retained for 30 minutes, and 4 pairs of needles were connected to an electric stimulator to deliver continuous and constant electrical stimulation at 4Hz. Taper: 25% reduction of daily benzodiazepine consumption in the first and second weeks, followed by 25% reduction for the remaining 50% of benzodiazepine every 3-4 days. Duration 4 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear

	(n=72) Intervention 2: Sham acupuncture+ taper. Sham acupuncture used placebo needles, a non-invasive sham device, after the same sterilisation procedure as the electroacupuncture group. The placebo needles ensured the appearance of skin penetration without creating real skin penetration when the needles were pressed. Needles were placed 1 inch away from the acupoints and connected with an electric stimulator without any supply of electrical stimulation. Taper: 25% reduction of daily benzodiazepine consumption in the first and second weeks, followed by 25% reduction for the remaining 50% of benzodiazepine every 3-4 days. Duration 4 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (Health and Medical Research Fund of Food and Health Bureau, Hong Kong SAR (HMRF No. 12133661), the Hong Kong Special Administrative Region Government.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPUNCTURE+ TAPER versus SHAM ACUPUNCTURE + TAPER

Protocol outcome 1: Reduction/cessation of prescribed drug use

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Cessation rate, % at 6 weeks; OR; 1.03 (95%CI 0.26 to 4.08) (SE 0.7 ln 0.029), Comments: Adjusted OR (logistic regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, unstable mood: 1, reluctant to complete follow-up: 3, protocol violation: 2.; Group 2 Number missing: 13, Reason: withdrawal due to AEs: 3, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Cessation rate, % at 16 weeks; OR; 0.87 (95%CI 0.29 to 2.64) (SE: 0.56 ln: -0.14), Comments: Adjusted OR (logistic regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2 withdrawal due to AEs: 5,

incompatible schedule: 1, lack of efficacy: 2, unstable mood: 1, reluctant to complete follow-up: 3, protocol violation: 2.; Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Equivalent dose of usage in diazepam, mg/d at 6 weeks; Mean; -0.06 (95%CI -0.38 to 0.27) (SE: -0.16
SD: -1.00), Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Equivalent dose of usage in diazepam, mg/d at 16 weeks; Mean; -0.10 (95%CI -0.43 to 0.22) (SE: -0.15), Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

Protocol outcome 2: Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): BWSQ at 6 weeks; Mean; 0.21 (95%CI -0.12 to 0.54) (SE: 0.1594) Benzodiazepine Withdrawal Symptom Questionnaire 0-40 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion

of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): BWSQ at 16 weeks; Mean; 0.11 (95%CI -0.22 to 0.43) (SE: 0.166) Benzodiazepine Withdrawal Symptom Questionnaire 0-40 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Insomnia Severity Scale at 6 weeks; Mean; 0.04 (95%CI -0.29 to 0.36) (SE: -0.12074) Insomnia Severity Index 0-28 Top=, Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

; Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Insomnia Severity Scale at 16 weeks; Mean; -0.06 (95%CI -0.39 to 0.26) (SE: -0.12074) 0-28 Insomnia Severity Index Top=, Comments: Adjusted MD (linear regression analysis)
Multiple imputation used to handle missing values adjusted with covariates.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion

of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Chinese version of HADS-anxiety at 6 weeks; Mean; -0.03 (95%CI -0.35 to 0.3) (SE: -0.21652) Hospital Anxiety and Depression Scale- anxiety subset 0-21 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis) Multiple imputation used to handle missing values adjusted with covariates.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Chinese version of HADS-anxiety at 16 weeks; Mean; 0.09 (95%CI -0.23 to 0.42) (SE: 0.186243) Hospital Anxiety and Depression Scale- anxiety subset 0-21 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis) Multiple imputation used to handle missing values adjusted with covariates.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2

Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5

- Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Chinese version of HADS-depression at 6 weeks; Mean; 0.06 (95%CI -0.27 to 0.39) (SE: 0.145168) Hospital Anxiety and Depression scale- depression subset 0-21 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis) Multiple imputation used to handle missing values adjusted with covariates.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion

of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2 Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5 - Actual outcome for Hypnotics (benzodiazepines and Z-drugs): Chinese version of HADS-depression at 16 weeks; Mean; 0.14 (95%CI -0.19 to 0.47) (SE: 0.162365) Hospital Anxiety and Depression Scale- depression subset 0-21 Top=High is poor outcome, Comments: Adjusted MD (linear regression analysis) Multiple imputation used to handle missing values adjusted with covariates. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: differences in severity of dependence scale, proportion of patients on ADs and proportion of patients taking two or more benzodiazepines; Group 1 Number missing: 14, Reason: withdrawal due to AEs: 5, incompatible schedule: 1, lack of efficacy: 2, reluctant to complete follow-up: 3, unstable mood: 1, protocol violation: 2 Group 2 Number missing: 13, Reason: withdrawal due to AEs: 2, incompatible schedule: 3, lack of efficacy: 1, perceived as placebo: 1, reluctant to complete follow-up: 5	
Protocol outcomes not reported by the study	Quality of life; Mortality (all-cause mortality and breakdown of overdose or suicide related mortality); Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Study	**Zahradnik 2009[295]**
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	(n=126)

Countries and setting	Conducted in Germany; Setting: Internal, surgical and gynaecological wards of either a general hospital or a university hospital in Lubeck.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-69 years. Either consumption of prescription drugs with addiction potential for >60 days in the last 3 months or fulfilment of criteria for prescription drug dependence or abuse according to DSM-IV. The study included drug groups according to the Anatomical Therapeutic Classification of opioids, anxiolytics, hypnotics and sedatives and caffeine.
Exclusion criteria	Use of opioid analgesic due to any cancer disease; terminal disease; dependence on or misuse of illegal drugs; current treatment of associated substance abuse problems; not having a telephone.
Recruitment/selection of patients	All patients.
Age, gender and ethnicity	Age - Mean (SD): 55.13 years (11.59) range 30-69. Gender (M:F): Motivational interviewing group: 36F/20M Taper only group: 42F/28M. Ethnicity: NR
Further population details	1. Gabapentinoids: Not stated/Unclear 2. Half-life of benzodiazepines: Not stated/Unclear 3. Setting: Inpatient (Internal, surgical and gynaecological wards of a general and university hospital in Lubeck.).
Extra comments	84.2% consumed medication of only one substance group: 71 took opioids (55.6%) or caffeine (0.8%), 14 hypnotics (11.1%) and 21 sedatives (16.7%). 20 people were taking medication from >1 substance group (15.8%). Cluster randomised by ward-not taken into account in analysis. Study also reports results from logistic regression analysis for the effect of the intervention for different drug

	classes, but this was only reported for hypnotics and sedatives combined and opioids separately. Overall data have been used.
Indirectness of population	Serious indirectness: Breakdown of drugs not provided- may have included those not on protocol.
Interventions	(n=56) Intervention 1: Non-pharmacological interventions - Motivational interviewing. The first intervention took place in the hospital and was targeted to last 30-45 minutes; the second intervention, 4 weeks later, was conducted by telephone. Core constructs of the Transtheoretical Model of behaviour change was assessed and an individualised feedback letter was developed. This was sent to study participants 8 weeks after the first intervention. When appropriate, strategies for improving self-efficacy and maintaining changes were included in the feedback letter. In each step of the intervention, it was pointed out that it was necessary to discontinue or reduce the medication only with help from professionals, e.g., the GP or medical specialist. Duration 2 sessions. Concurrent medication/care: NR. Indirectness: Serious indirectness; Indirectness comment: Possibly indirect- no specific aim to withdraw medication. Further details: 1. Addiction support services: Not stated/Unclear (n=70) Intervention 2: Non-pharmacological interventions - Brief intervention and advice. Participants received an information booklet about prescription drugs generally. Duration information booklet. Concurrent medication/care: NR. Indirectness: Serious indirectness; Indirectness comment: Possibly indirect- no specific aim to withdraw medication. Further details: 1. Addiction support services: Not stated/Unclear
Funding	Academic or government funding (The study was part of the German research network EARLINT (Early substance use Intervention) and was funded by the German Federal Ministry of Health.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MOTIVATIONAL INTERVIEWING versus INFORMATION BOOKLET

Protocol outcome 1: Mortality (all-cause mortality and breakdown of overdose or suicide related mortality)

- Actual outcome for Mixed (all drug classes): Mortality at 3 months; Group 1: 0/55, Group 2: 1/62

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomisation used- not taken into account in analysis; Indirectness of outcome: No indirectness; Baseline details: difference for dependence on prescription drugs, assessed by SCID-I which was higher in the motivational interviewing group.; Group 1 Number missing: 1, Reason: patient was unable to be contacted; Group 2 Number missing: 8, Reason: 1 died; 3 were too ill; 4 were unable to be

contacted. Protocol outcome 2: Reduction/cessation of prescribed drug use - Actual outcome for Mixed (all drug classes): Reduction >25% at 3 months; Group 1: 29/55, Group 2: 21/62 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomisation used- not taken into account in analysis; Indirectness of outcome: No indirectness; Baseline details: difference for dependence on prescription drugs, assessed by SCID-I which was higher in the motivational interviewing group.; Group 1 Number missing: 1, Reason: patient was unable to be contacted; Group 2 Number missing: 8, Reason: 1 died; 3 were too ill; 4 were unable to be contacted. - Actual outcome for Mixed (all drug classes): Discontinuation of prescription drug at 3 months; Group 1: 10/55, Group 2: 6/62; Comments: Paper reports number stopping in motivational interviewing group as 10 in table, 16 in text. The percentage given (17.9%) matches with 10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomisation used- not taken into account in analysis; Indirectness of outcome: No indirectness; Baseline details: difference for dependence on prescription drugs, assessed by SCID-I which was higher in the motivational interviewing group.; Group 1 Number missing: 1, Reason: patient was unable to be contacted; Group 2 Number missing: 8, Reason: 1 died; 3 were too ill; 4 were unable to be contacted. - Actual outcome for Mixed (all drug classes): Mean defined daily dosage difference at 3 months; Group 1: mean 0.42 (SD 2.7); n=55, Group 2: mean 0.12 (SD 1.4); n=62; Comments: Follow-up minus baseline, on the basis of 114 completed 3-month follow-up data Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Cluster randomisation used- not taken into account in analysis; Indirectness of outcome: No indirectness; Baseline details: difference for dependence on prescription drugs, assessed by SCID-I which was higher in the motivational interviewing group.; Group 1 Number missing: 1, Reason: patient was unable to be contacted; Group 2 Number missing: 8, Reason: 1 died; 3 were too ill; 4 were unable to be contacted.	
Protocol outcomes not reported by the study	Quality of life; Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome; Relapse into medication use; Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs; Non-fatal overdose; Reduced tolerance; Patient Satisfaction; Self-harm or harm to others; Increase in symptoms for which the medication was originally prescribed; Improvements in adverse effects commonly associated with long-term prescribed medication use; Distress

1

Appendix F Forest plots:

F.1 Opioids

F.1.1 Varenicline + taper vs Placebo + taper for opioid withdrawal

Figure 4: Number of people who discontinued (at dismissal- 3 weeks)

Study or Subgroup	Varenicline+taper Events	Total	Placebo+taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hooten 2015	7	7	11	11	100.0%	1.00 [0.81, 1.24]
Total (95% CI)		**7**		**11**	**100.0%**	**1.00 [0.81, 1.24]**
Total events	7		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

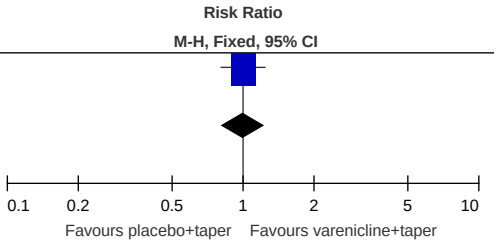
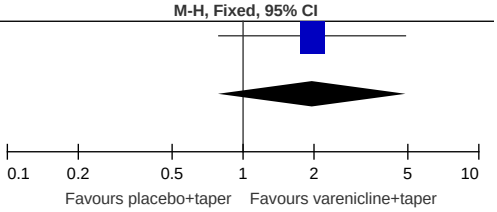


Figure 5: Decrease in severity of withdrawal symptoms (at dismissal-3 weeks)

Study or Subgroup	Varenicline+taper Events	Total	Placebo+taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hooten 2015	5	7	4	11	100.0%	1.96 [0.79, 4.89]
Total (95% CI)		**7**		**11**	**100.0%**	**1.96 [0.79, 4.89]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)



F.1.2 Acupuncture + standard medication management with opioid weaning vs standard outpatient medication management with opioid weaning

Figure 6: Morphine equivalent dose at post-intervention

Study or Subgroup	Acupuncture + taper Mean	SD	Total	Taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jackson 2021	78	44	9	125	124	6	100.0%	-47.00 [-150.30, 56.30]
Total (95% CI)			**9**			**6**	**100.0%**	**-47.00 [-150.30, 56.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

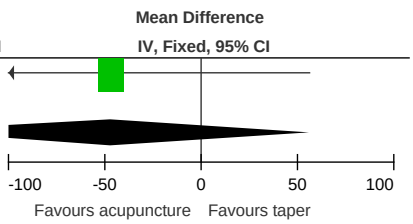
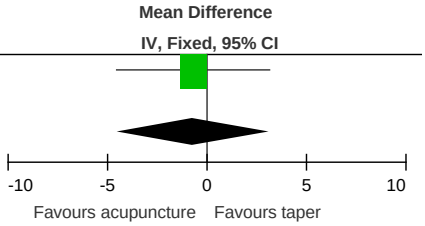


Figure 7: Subjective withdrawal symptoms (CINA) at post-intervention

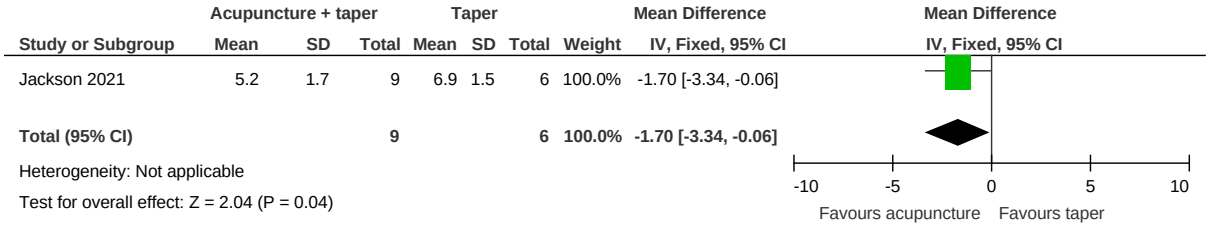
Study or Subgroup	Acupuncture + taper Mean	SD	Total	Taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jackson 2021	6.4	3.6	9	7.1	3.8	6	100.0%	-0.70 [-4.54, 3.14]
Total (95% CI)			**9**			**6**	**100.0%**	**-0.70 [-4.54, 3.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



CINA range unclear

Figure 8: Pain at post-intervention



Numerical rating scale (range unclear)

F.1.3 Multicomponent taper support + taper for opioid withdrawal vs usual prescribing

Figure 9: Patient global impression of change (at 22 weeks)

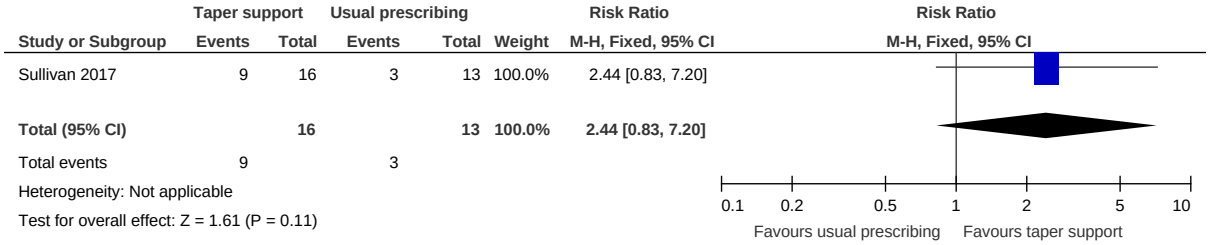


Figure 10: Patient global impression of change (at 34 weeks)

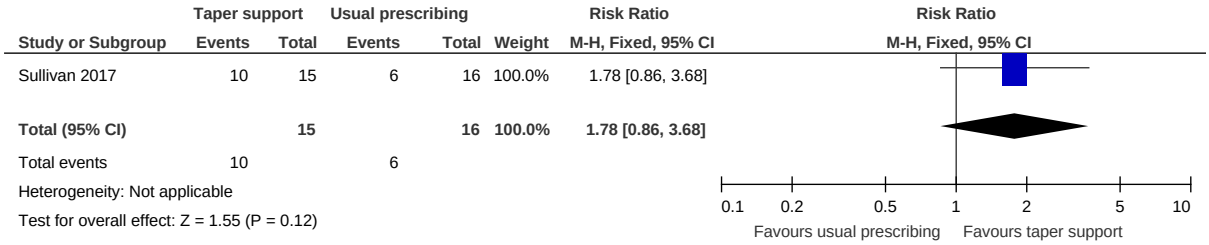


Figure 11: Opioid discontinuation (at 22 weeks)

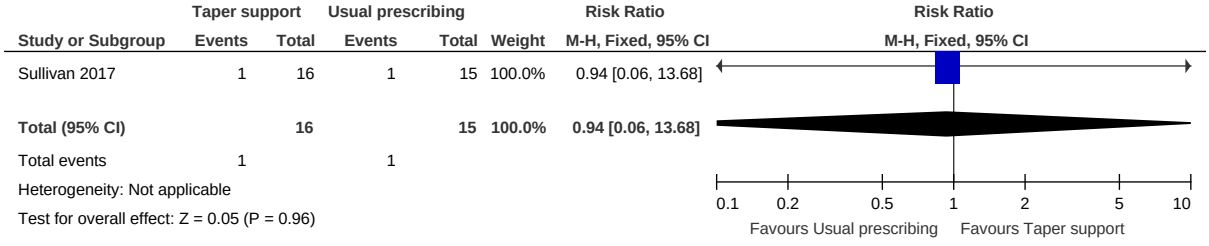
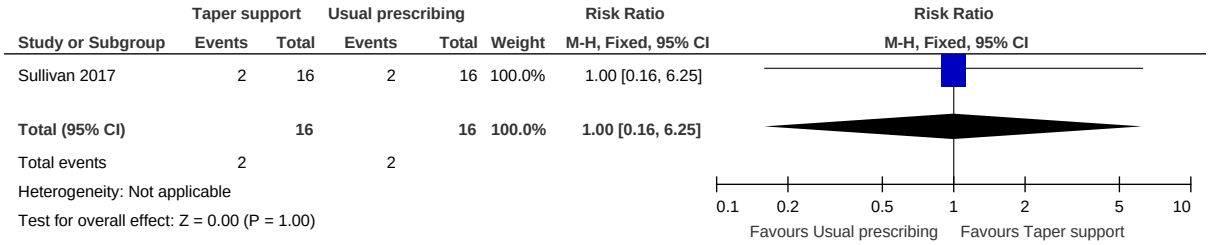
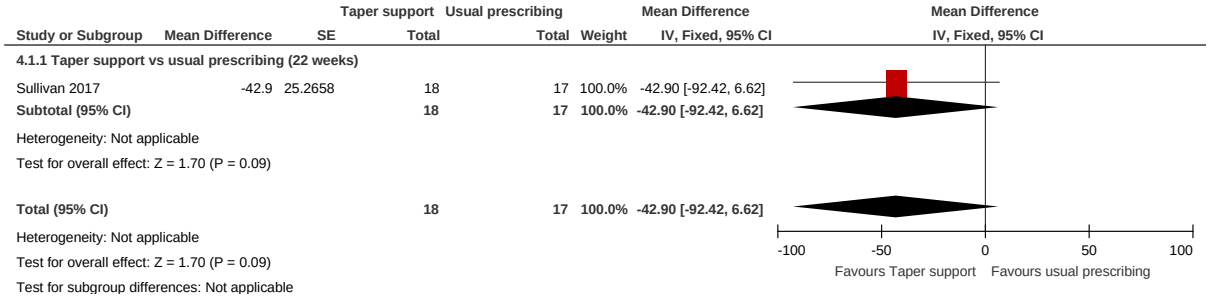


Figure 12: Opioid discontinuation (at 34 weeks)



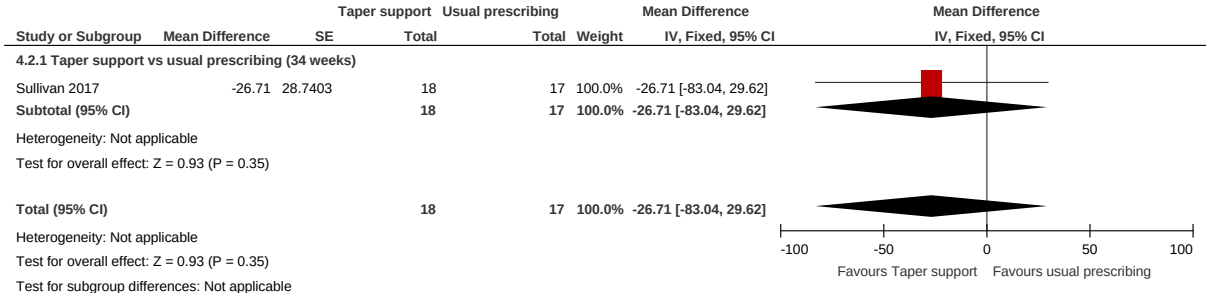
1

Figure 13: Mean daily opioid dose in the past week (at 22 weeks)



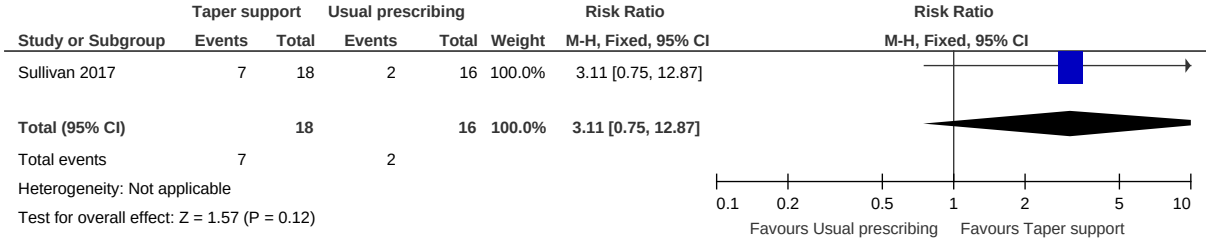
2

Figure 14: Mean daily opioid dose in the past week (at 34 weeks)



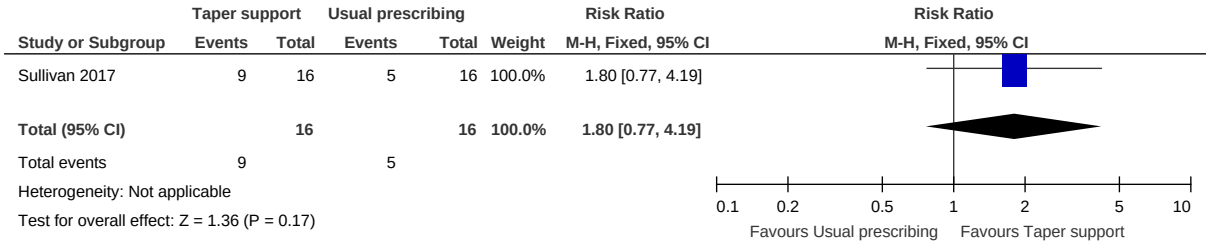
3

Figure 15: Opioid dose reduction of 50% or more (at 22 weeks)



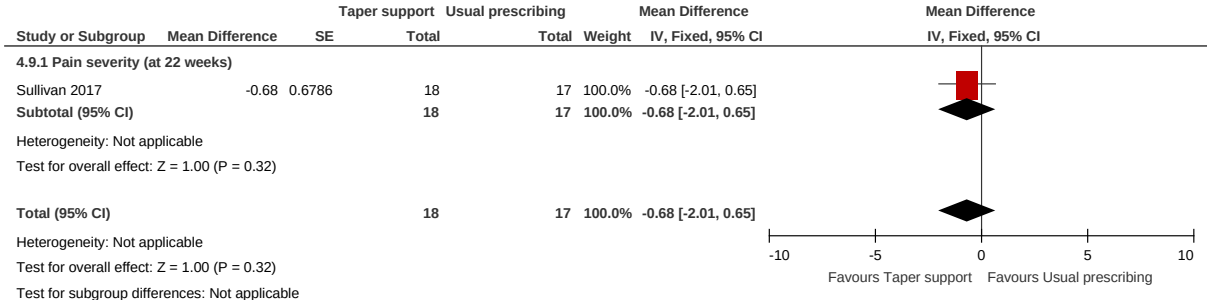
4

Figure 16: Opioid dose reduction of 50% or more (at 34 weeks)



1

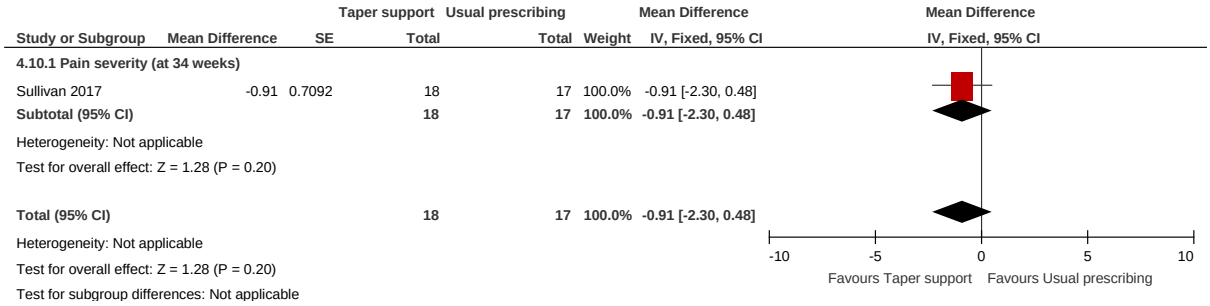
Figure 17: Pain severity (BPI; at 22 weeks)



2

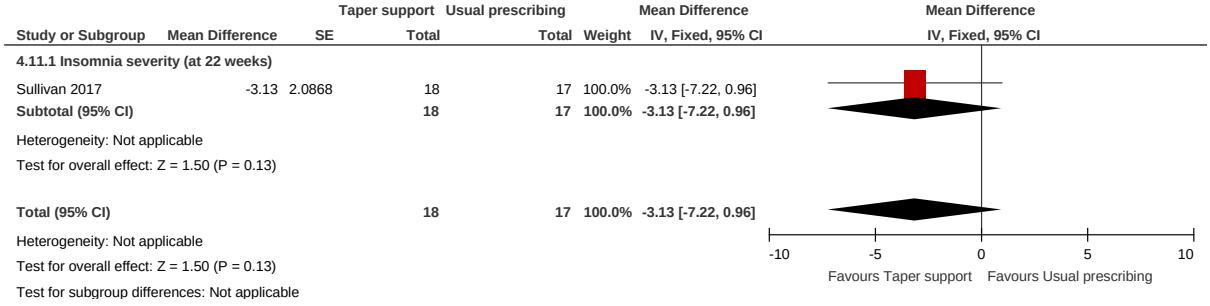
3

Figure 18: Pain severity (BPI; at 34 weeks)



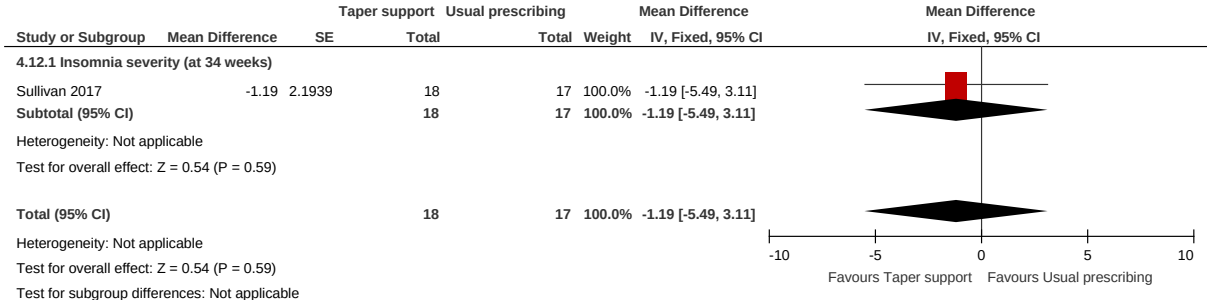
4

Figure 19: Insomnia severity (ISI; at 22 weeks)



5

Figure 20: Insomnia severity (ISI; at 34 weeks)



F.1.4 Electroacupuncture + taper (taper schedule or taper as part of PMM) vs sham electroacupuncture + taper (taper schedule or taper as part of PMM)

Figure 21: QoL (SF-36 0-100, at end of treatment: average of weeks 11-14)

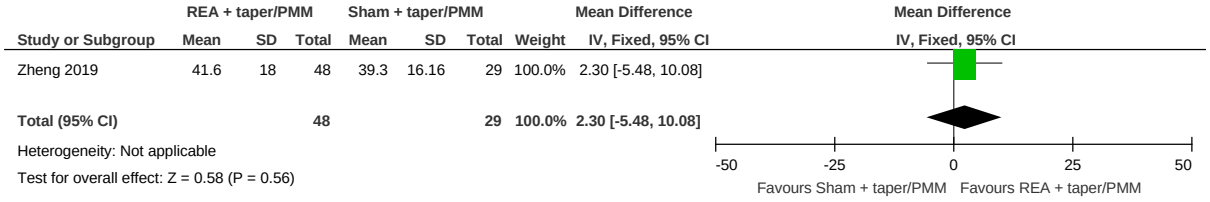


Figure 22: QoL (SF-36 Physical health 0-100, at end of treatment: average of weeks 11-14)

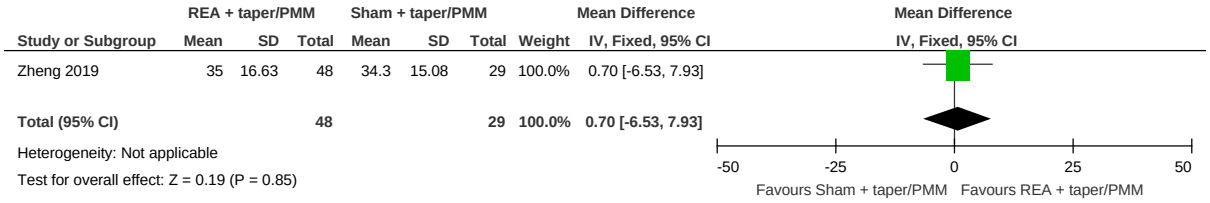


Figure 23: QoL (SF-36 Mental health 0-100, at end of treatment: average of weeks 11-14)

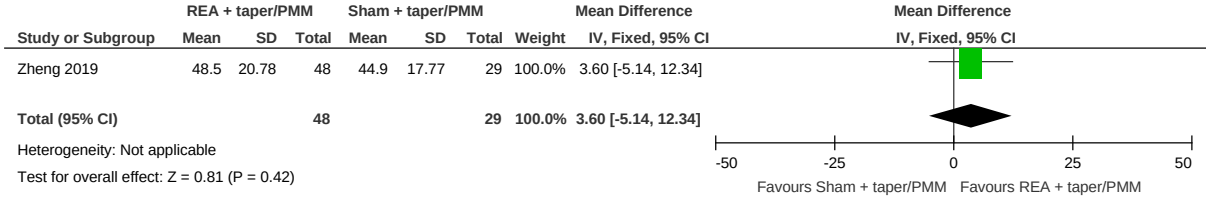
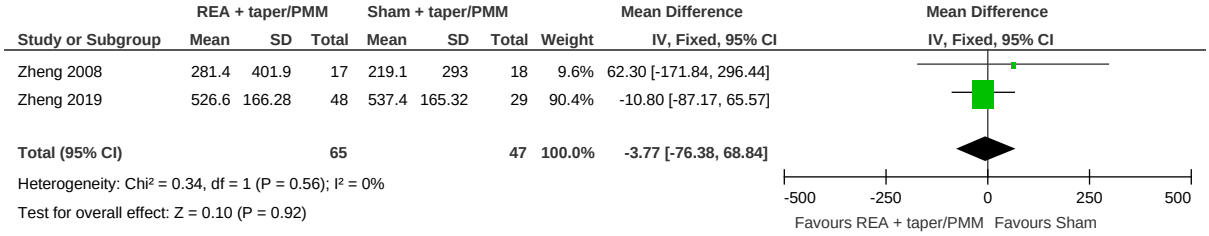
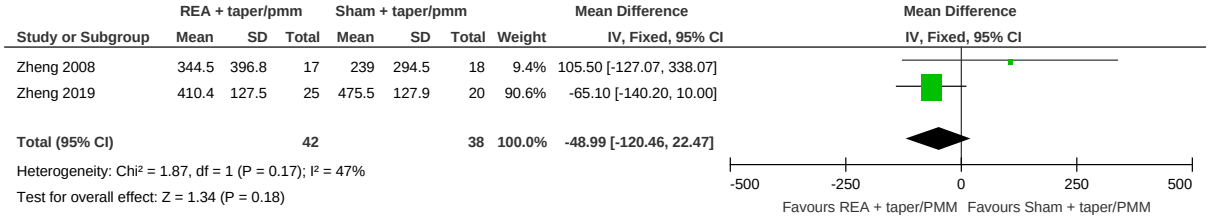


Figure 24: Opioid consumption (mg/week; post-intervention/ average of weeks 11-14)



1

Figure 25: Opioid consumption (mg/week; at 12-week to 3-month follow-up)



2

Figure 26: 50% OM reduction (at end of treatment: average of weeks 11-14)

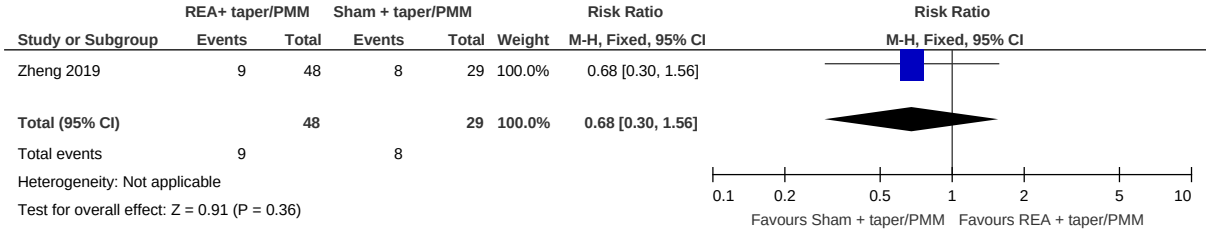
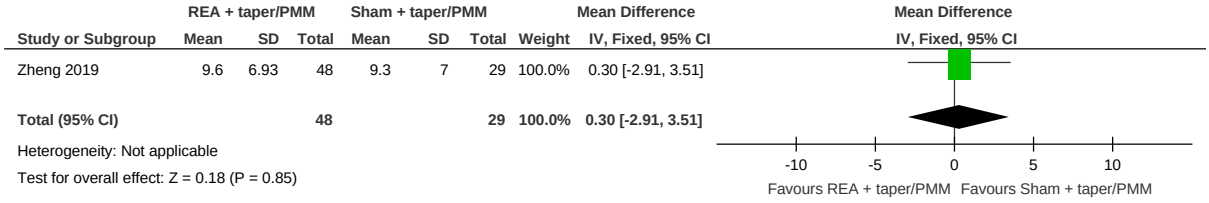
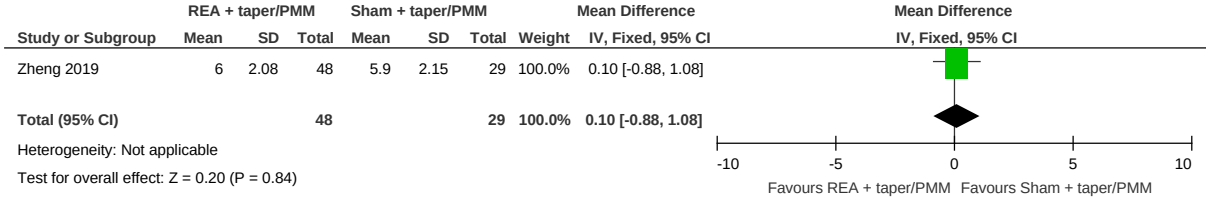


Figure 27: Non-OM dosage (Medication quantification scale III, at end of treatment: average of weeks 11-14)



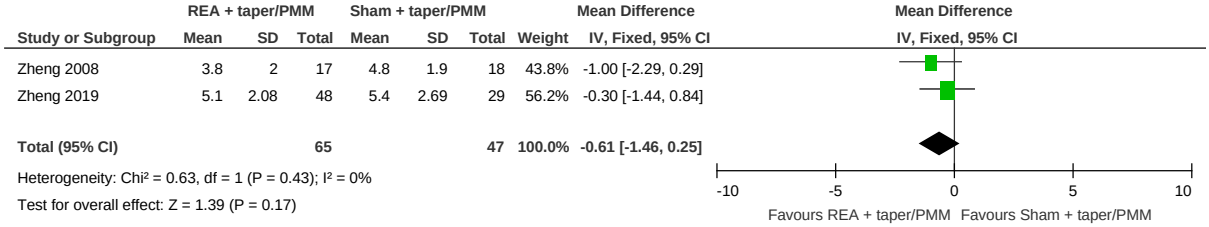
3

Figure 28: Intensity of the highest pain (VAS, 0-10, at end of treatment: average of weeks 11-14)



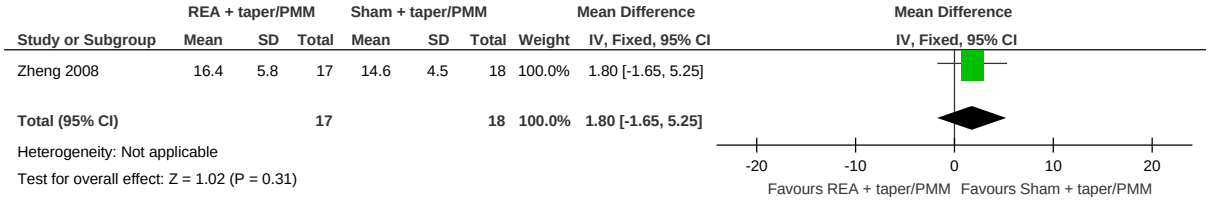
4

Figure 29: Average pain (VAS 0-10, at end of treatment: week 8/average of weeks 11-14)



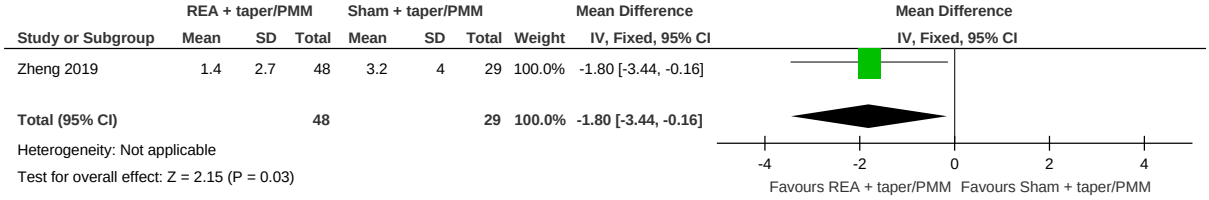
1

Figure 30: Duration of pain (hr/day, post intervention: week 8)



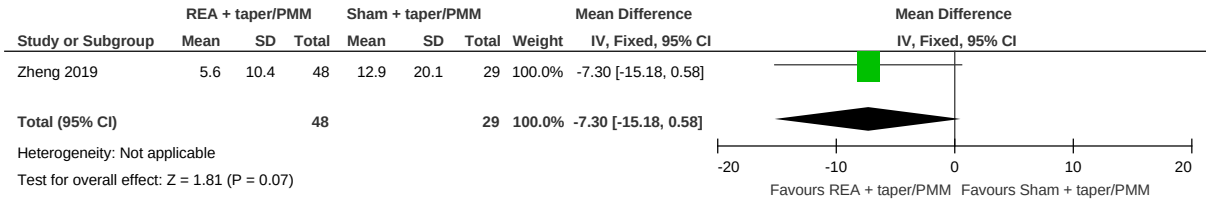
2

Figure 31: Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14)



3

Figure 32: Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)



4

F.1.5 Electroacupuncture + PMM vs PMM alone

Figure 33: QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)

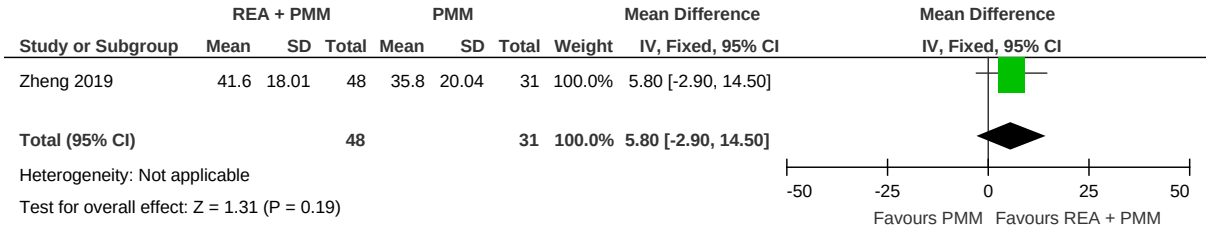


Figure 34: QoL (SF-36 Physical health; 0-100; at end of treatment: average of weeks 11-14)

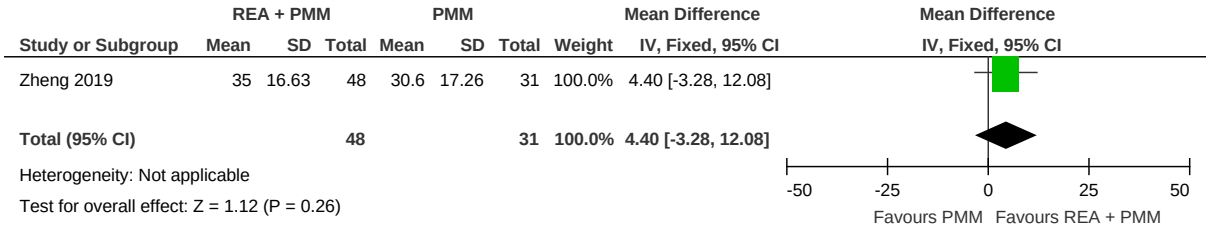


Figure 35: QoL (SF-36 Mental health; 0-100; at end of treatment: average of weeks 11-14)

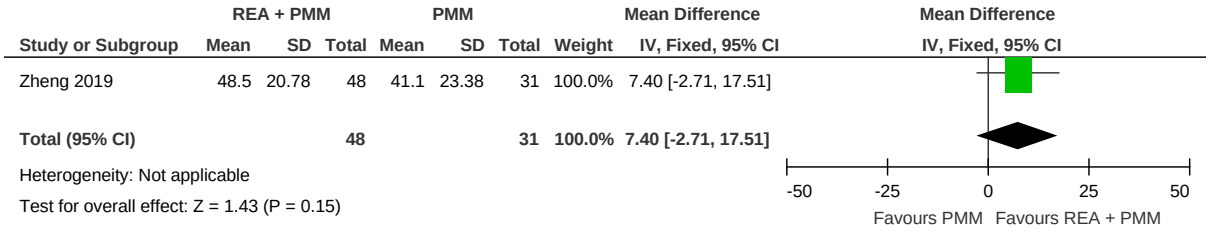


Figure 36: Opioid dosage (mg; end of treatment: average of weeks 11-14)

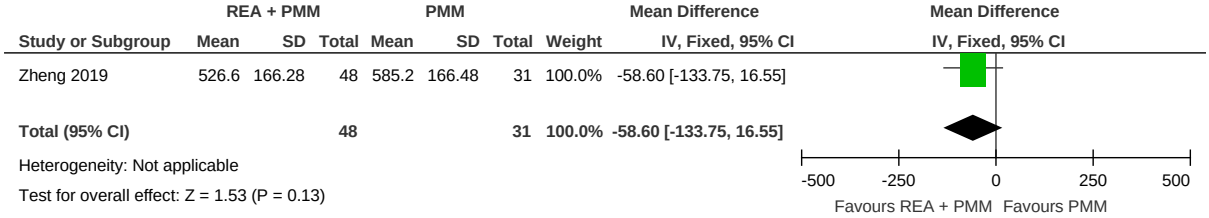
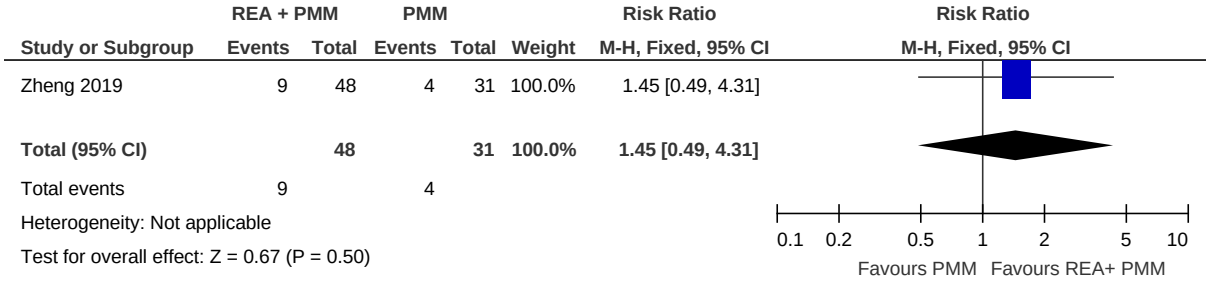
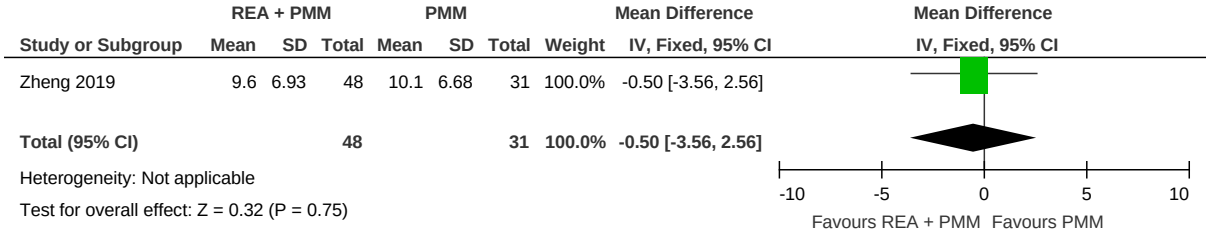


Figure 37: 50% OM reduction (at end of treatment: average of weeks 11-14)



1

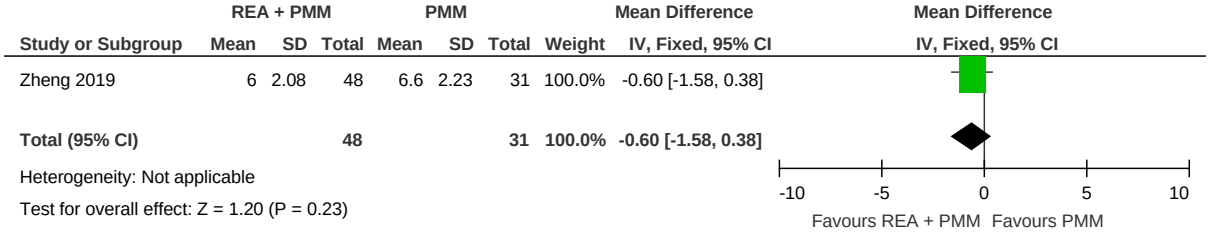
Figure 38: Non-OM dosage (Medication quantification scale III, at end of treatment: average of weeks 11-14)



2

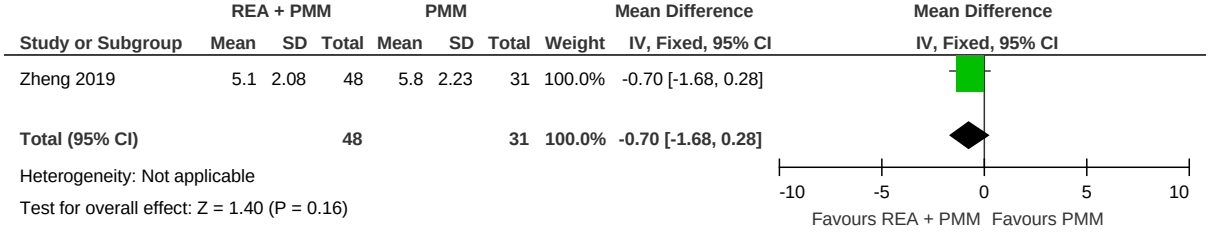
3

Figure 39: Intensity of the highest pain (VAS 0-10, at end of treatment: average of weeks 11-14)



4

Figure 40: Intensity of the average pain (VAS 0-10, at end of treatment: average of weeks 11-14)



5

Figure 41: Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14)

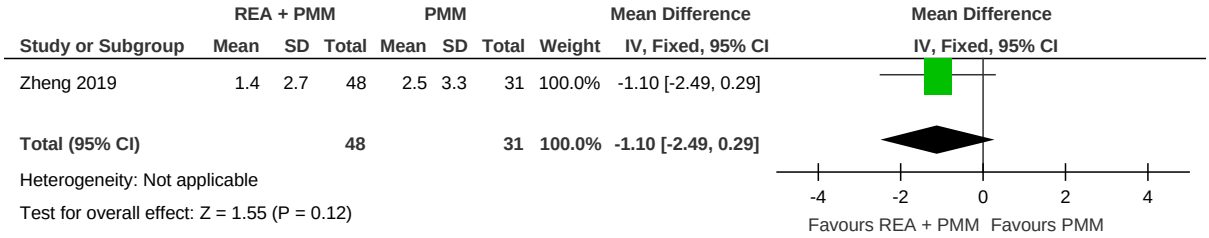
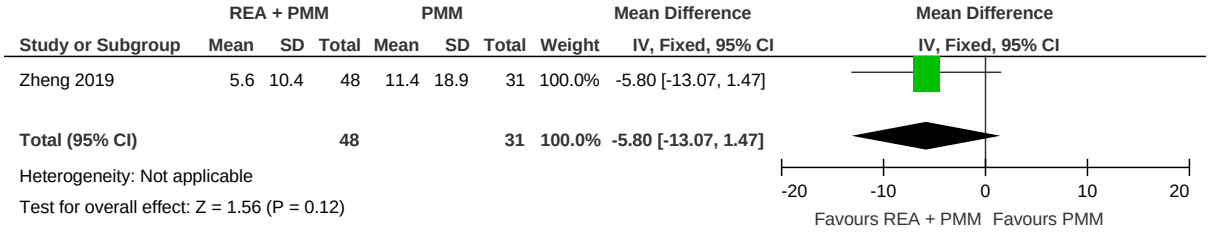


Figure 42: Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)



F.1.6 Sham electroacupuncture + PMM vs PMM alone

Figure 43: QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)

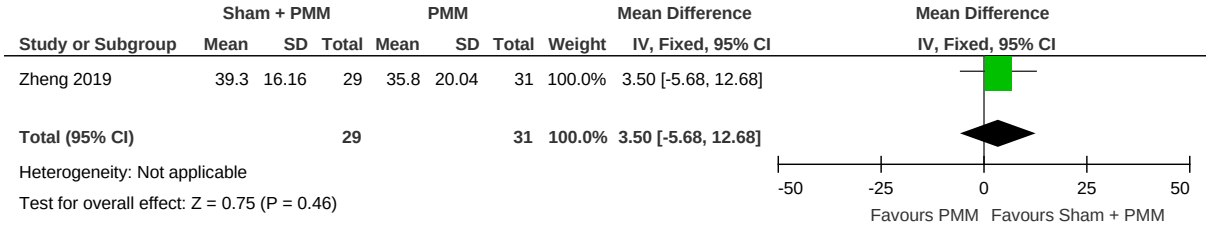


Figure 44: QoL (SF-36 Physical health; 0-100; at end of treatment: average of weeks 11-14)

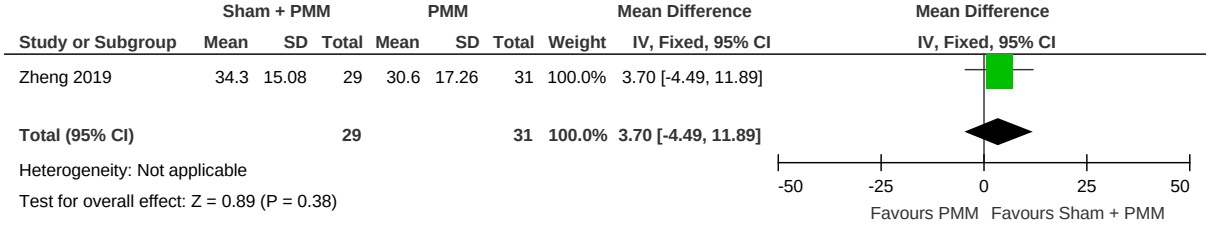


Figure 45: QoL (SF-36 Mental health; 0-100; at end of treatment: average of weeks 11-14)

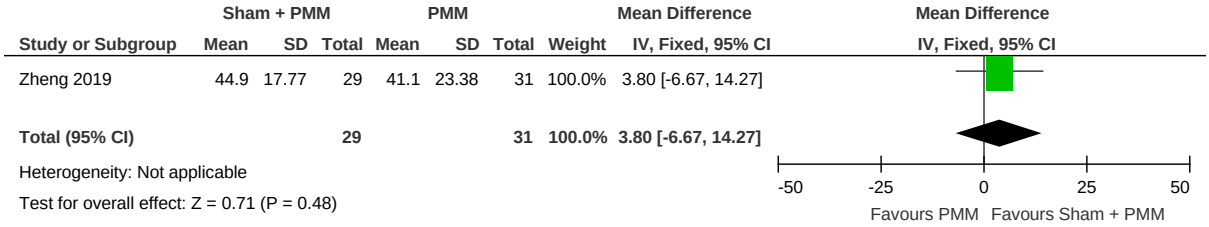


Figure 46: Opioid dosage (mg; at end of treatment: average of weeks 11-14)

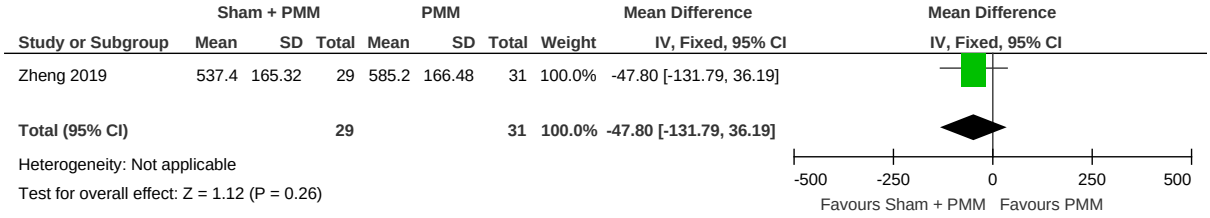
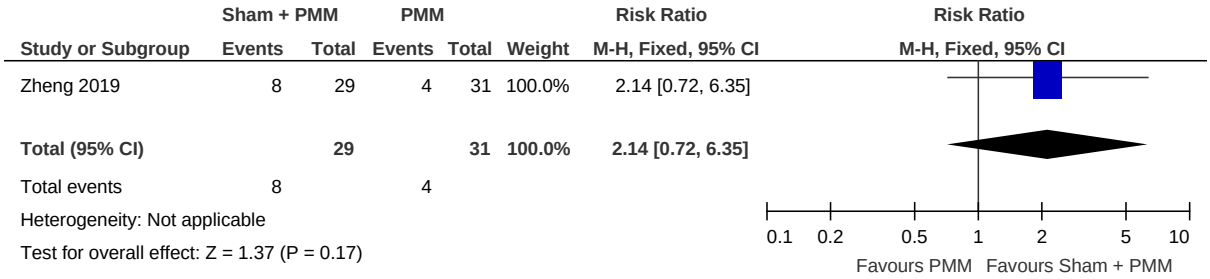
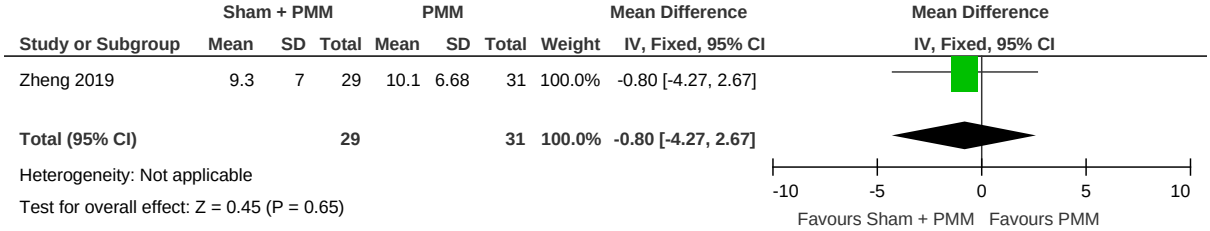


Figure 47: 50% OM-reduction (at end of treatment: average of weeks 11-14)



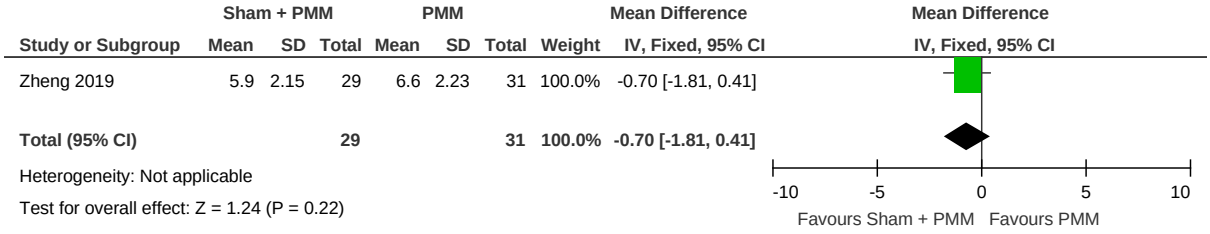
Source: <Insert Source text here>

Figure 48: Non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14)



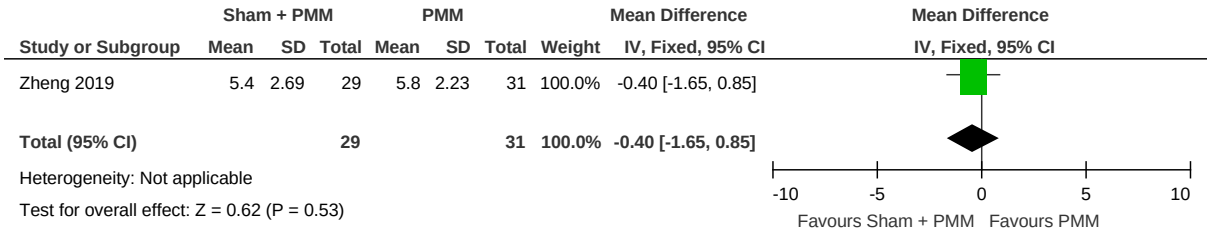
Source: <Insert Source text here>

Figure 49: Intensity of the highest pain (VAS 0-10; at end of treatment: average of weeks 11-14)



1

Figure 50: Intensity of the average pain (VAS 0-10; at end of treatment: average of weeks 11-14)



2

Figure 51: Weekly OM-related adverse events per person (at end of treatment: average of weeks 11-14)

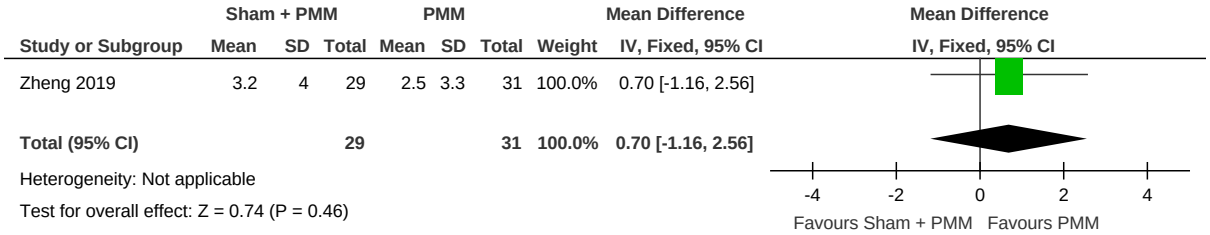


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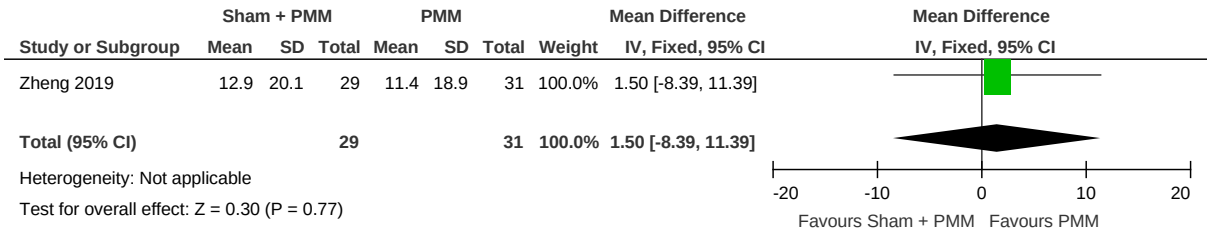
Figure 52: Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)



4

F.2 Benzodiazepines

F.2.1 CBT + tapered withdrawal vs CBT + abrupt withdrawal:

Figure 53: Cessation of benzodiazepine (post-intervention)

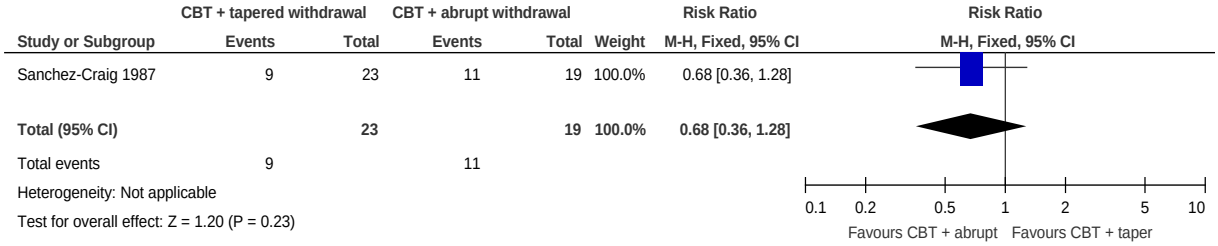


Figure 54: Cessation of benzodiazepine (12-month follow-up)

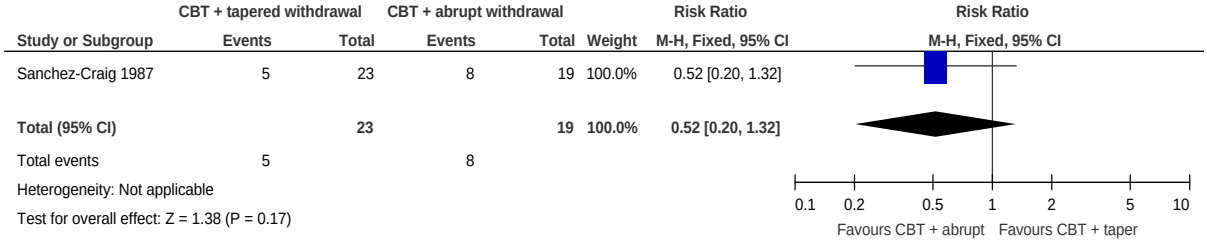


Figure 55: Reduced benzodiazepine use - 50% reduction in benzodiazepine plasma level (post-intervention)

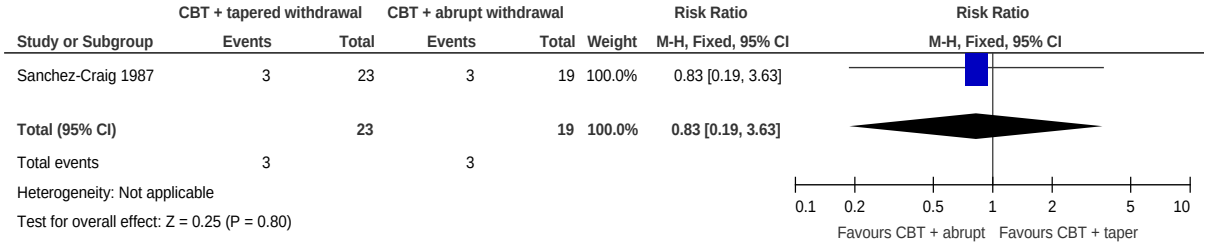


Figure 56: Reduced benzodiazepine use - 50% reduction in benzodiazepine plasma level (12-month follow-up)

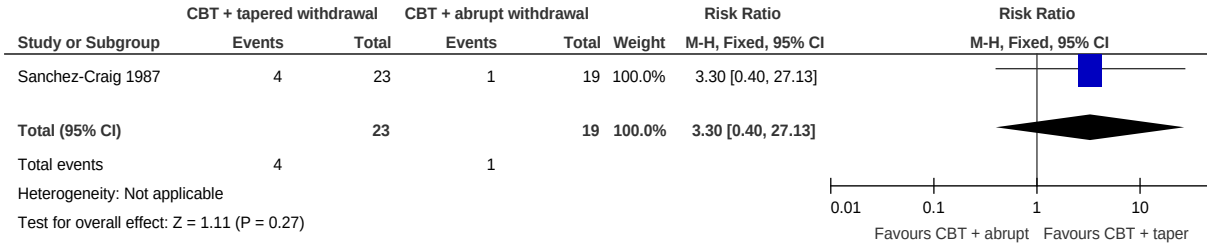


Figure 57: Withdrawal symptoms per patient (post-intervention)

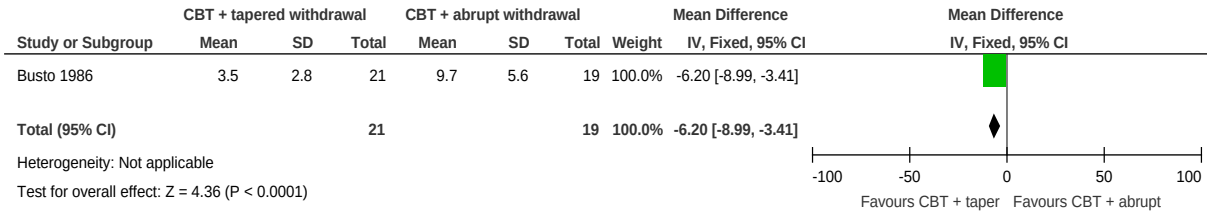


Figure 58: Withdrawal symptom severity score (range 0-10, high poor outcome)(post-intervention)

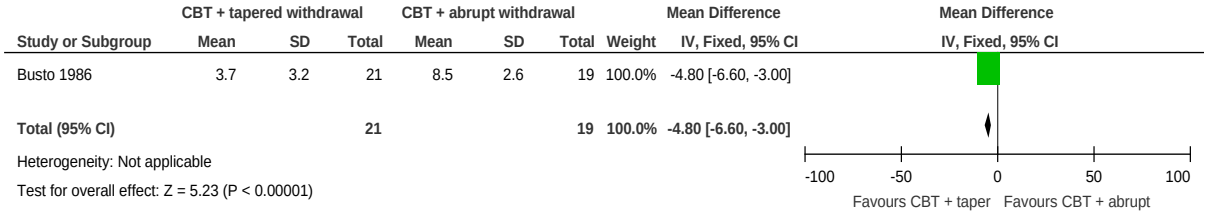
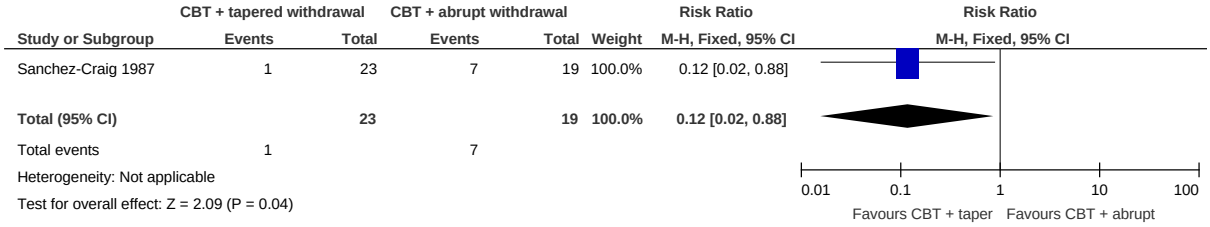


Figure 59: Relapse - additional use of own benzodiazepine supply (post-intervention)



F.2.2 CBT + tapered withdrawal vs Tapered withdrawal only

Figure 60: Quality of life - SF36: Physical function (18-month follow-up)

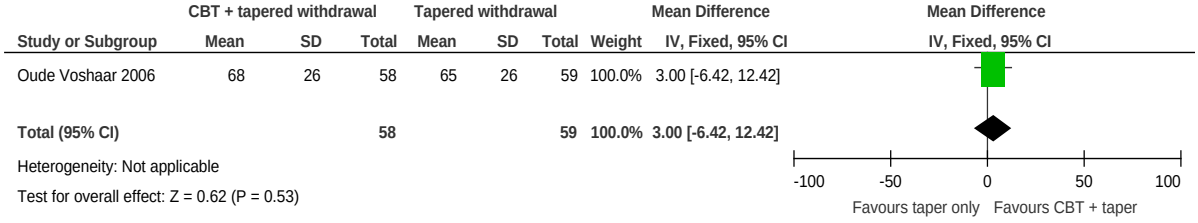


Figure 61: Quality of life - SF36: Social function (18-month follow-up)

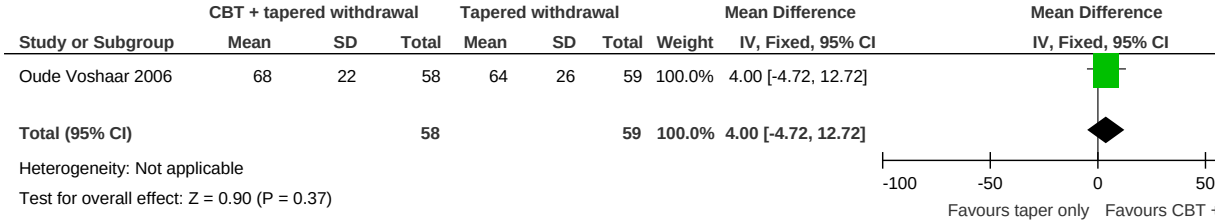


Figure 62: Quality of life - SF36: Role limitation (physical) (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	57	44	58	54	42	59	100.0%	3.00 [-12.59, 18.59]
Total (95% CI)			**58**			**59**	**100.0%**	**3.00 [-12.59, 18.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)

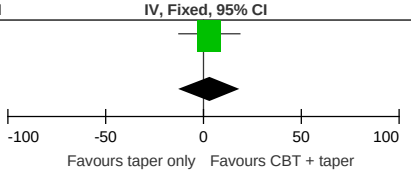


Figure 63: Quality of life - SF36: Role limitation (emotional) (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	67	41	58	76	39	59	100.0%	-9.00 [-23.50, 5.50]
Total (95% CI)			**58**			**59**	**100.0%**	**-9.00 [-23.50, 5.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

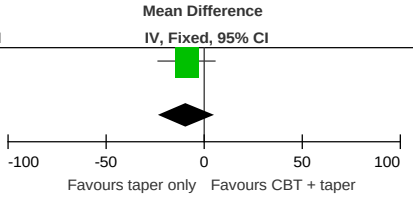


Figure 64: Quality of life - SF36: Mental health (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	71	17	58	76	39	59	100.0%	-5.00 [-15.87, 5.87]
Total (95% CI)			**58**			**59**	**100.0%**	**-5.00 [-15.87, 5.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)

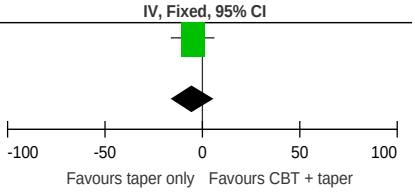


Figure 65: Quality of life - SF36: Vitality (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	63	20	58	61	20	59	100.0%	2.00 [-5.25, 9.25]
Total (95% CI)			**58**			**59**	**100.0%**	**2.00 [-5.25, 9.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

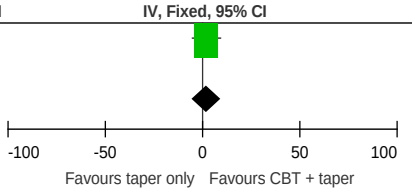


Figure 66: Quality of life - SF36: Pain (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	67	26	58	61	27	59	100.0%	6.00 [-3.60, 15.60]
Total (95% CI)			**58**			**59**	**100.0%**	**6.00 [-3.60, 15.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)

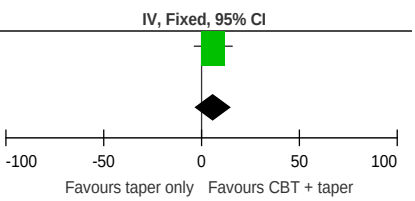
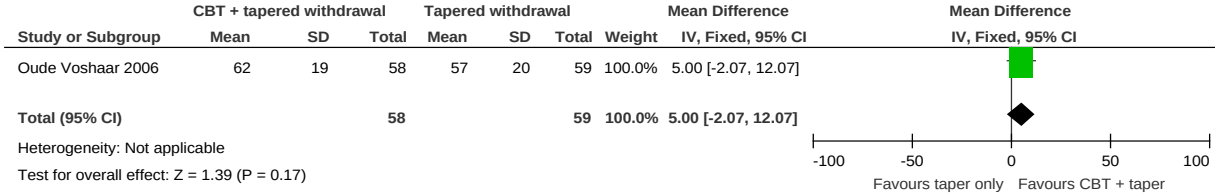


Figure 67: Quality of life - SF36: General health (18-month follow-up)



1

Figure 68: Cessation of benzodiazepine (post-intervention)

2

Figure 69: Cessation of benzodiazepine (3-month follow-up)

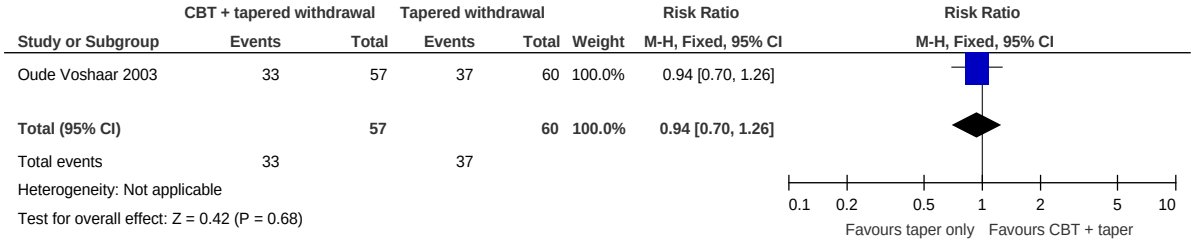
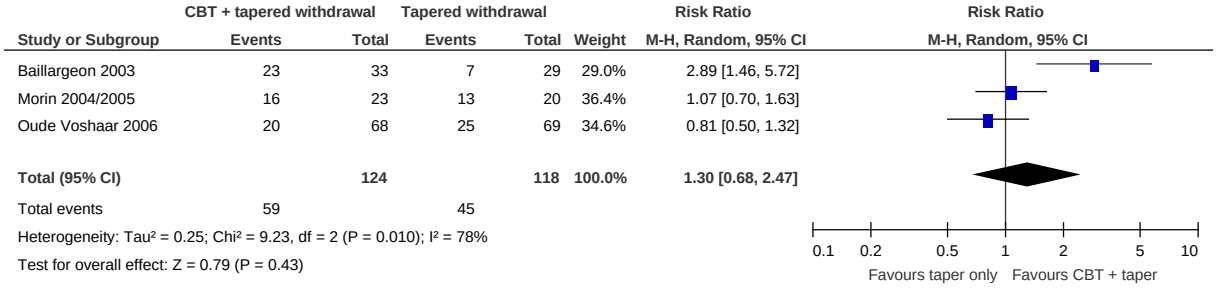
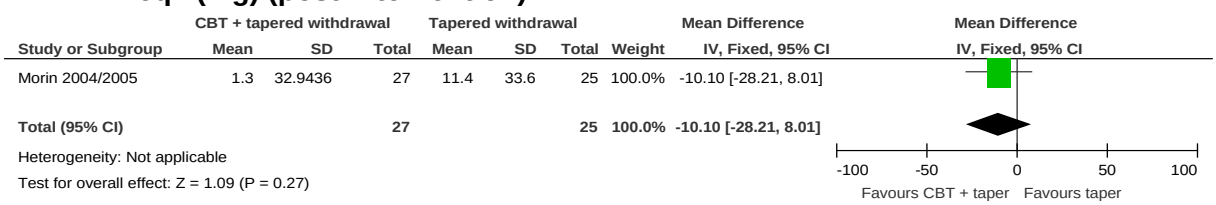


Figure 70: Cessation of benzodiazepine (12–15-month follow-up)



3

Figure 71: Reduction of benzodiazepine: weekly benzodiazepine use - diazepam eqv (mg) (post-intervention)



4

Figure 72: Reduction of benzodiazepine: weekly benzodiazepine use - diazepam eqv (mg) (12 months follow-up)

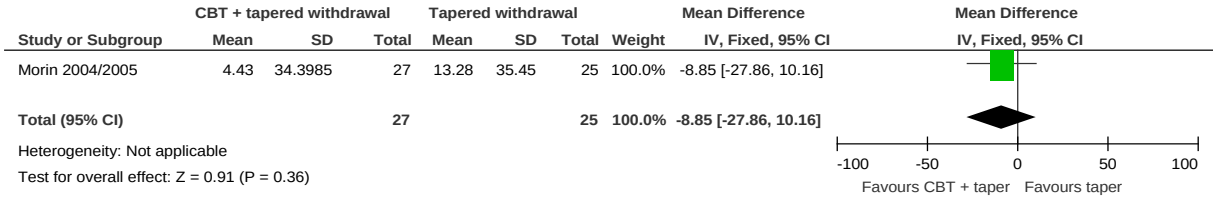


Figure 73: Reduction of benzodiazepine - >50% dose reduction (post-intervention)

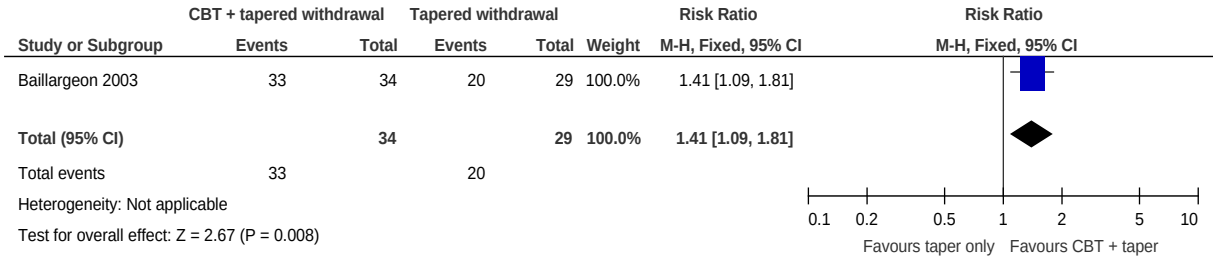


Figure 74: Reduction of benzodiazepine - >50% dose reduction (12 months follow-up)

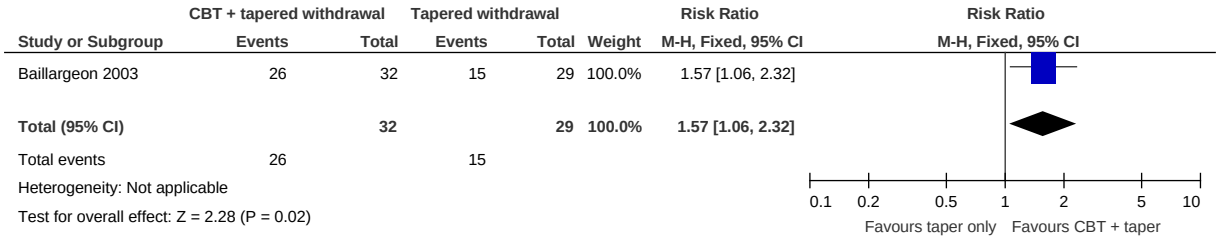


Figure 75: Relapse into drug use (12 months follow-up)

Figure 76: Withdrawal symptoms score - BWSQ (3 months follow-up)

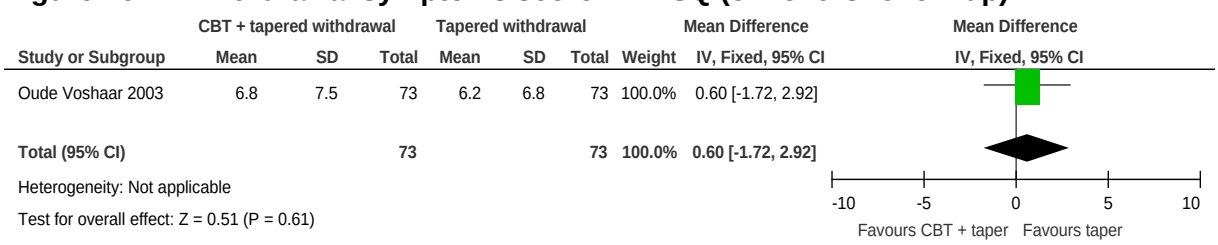


Figure 77: Insomnia severity index (post-intervention)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Morin 2004/2005	11.18	5.5079	27	12.72	5.6	25	100.0%	-1.54 [-4.56, 1.48]
Total (95% CI)			**27**			**25**	**100.0%**	**-1.54 [-4.56, 1.48]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.00 (P = 0.32)

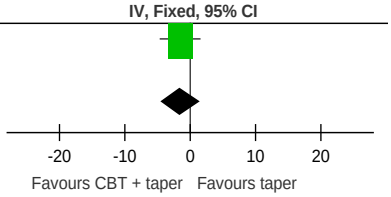


Figure 78: Insomnia severity index (12-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Tapered withdrawal Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Morin 2004/2005	11.06	5.7677	27	9.97	5.9	25	100.0%	1.09 [-2.09, 4.27]
Total (95% CI)			**27**			**25**	**100.0%**	**1.09 [-2.09, 4.27]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.67 (P = 0.50)

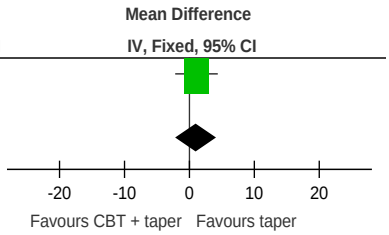
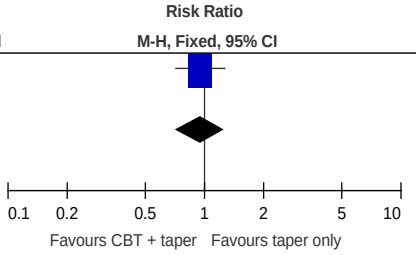


Figure 79: Patients using alcohol

Study or Subgroup	CBT + tapered withdrawal Events	Total	Tapered withdrawal Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2003	40	73	42	73	100.0%	0.95 [0.71, 1.27]
Total (95% CI)		**73**		**73**	**100.0%**	**0.95 [0.71, 1.27]**
Total events	40		42			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.33 (P = 0.74)



F.2.3 CBT + tapered withdrawal vs Group work + tapered withdrawal

Figure 80: Quality of life - systemic QoL inventory (3-month follow-up)

Study or Subgroup	CBT + tapered Mean	SD	Total	Group work + taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Connor 2008	8.4	1.88	11	8.35	0.72	10	100.0%	0.05 [-1.15, 1.25]
Total (95% CI)			**11**			**10**	**100.0%**	**0.05 [-1.15, 1.25]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.08 (P = 0.93)

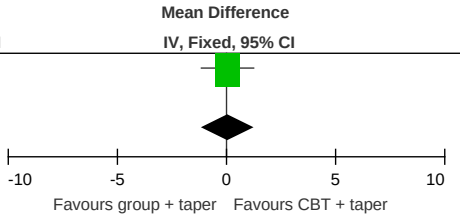


Figure 81: Cessation of benzodiazepine (post-intervention)

Study or Subgroup	CBT + tapered withdrawal Events	Total	Group work + taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Connor 2008	15	23	11	22	100.0%	1.30 [0.78, 2.18]
Total (95% CI)		**23**		**22**	**100.0%**	**1.30 [0.78, 2.18]**
Total events	15		11			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

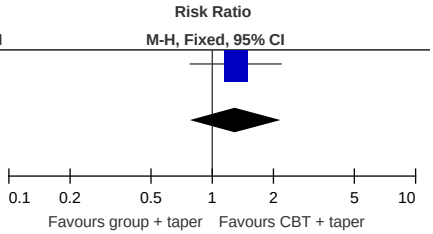


Figure 82: Withdrawal symptoms score - BWSQ (post-intervention)

Study or Subgroup	CBT + taper Mean	SD	Total	Group work + taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Connor 2008	7.57	4.48	14	8.64	4.12	12	100.0%	-1.07 [-4.38, 2.24]
Total (95% CI)			**14**			**12**	**100.0%**	**-1.07 [-4.38, 2.24]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

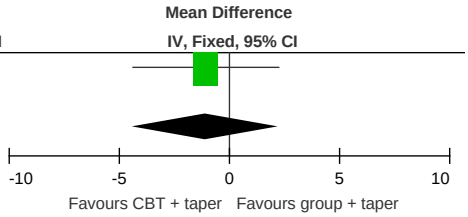


Figure 83: Withdrawal symptoms score - BWSQ (3 months follow-up)

Study or Subgroup	CBT + taper Mean	SD	Total	Group work + taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Connor 2008	7.67	5.32	11	7.22	3.15	10	100.0%	0.45 [-3.25, 4.15]
Total (95% CI)			**11**			**10**	**100.0%**	**0.45 [-3.25, 4.15]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.24 (P = 0.81)

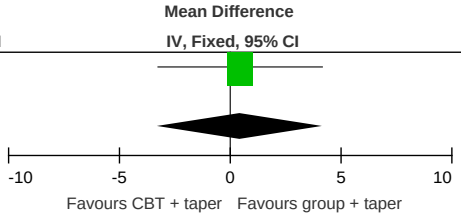


Figure 84: Relapse into drug use (11-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Events	Total	Tapered withdrawal Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
O'Connor 2008	1	10	1	10	100.0%	1.00 [0.07, 13.87]
Total (95% CI)		**10**		**10**	**100.0%**	**1.00 [0.07, 13.87]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

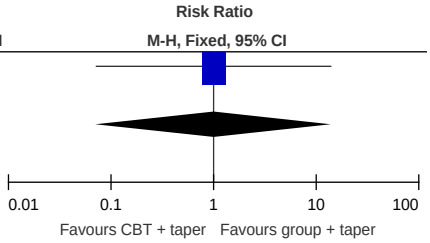


Figure 85: Anxiety - Spielberger state (post-intervention)

Study or Subgroup	CBT + taper Mean	SD	Total	Group work + taper Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Connor 2008	43.29	12.15	14	43.18	9.66	12	100.0%	0.11 [-8.28, 8.50]
Total (95% CI)			**14**			**12**	**100.0%**	**0.11 [-8.28, 8.50]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.03 (P = 0.98)

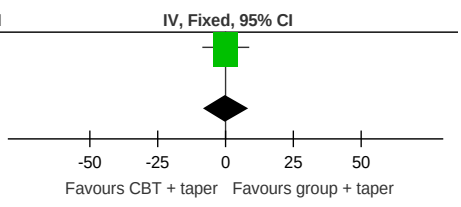
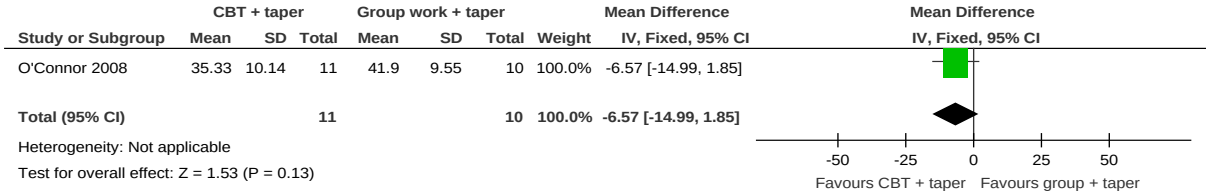
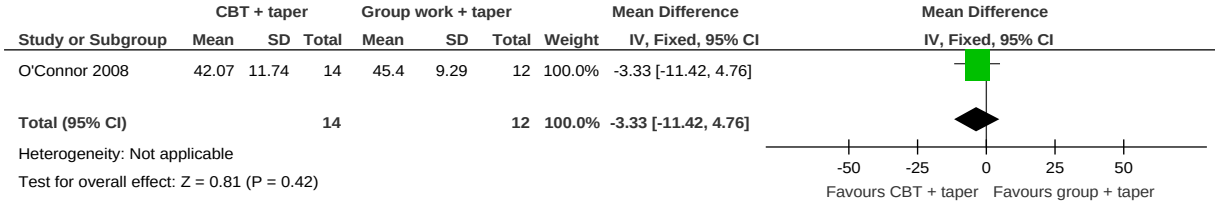


Figure 86: Anxiety - Spielberger state (3-month follow-up)



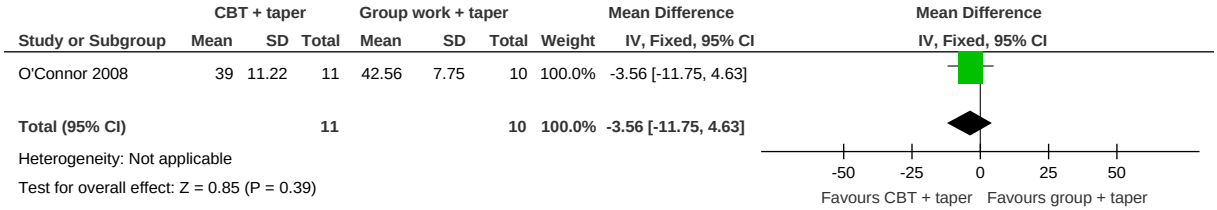
1

Figure 87: Anxiety - Spielberger trait (post-intervention)



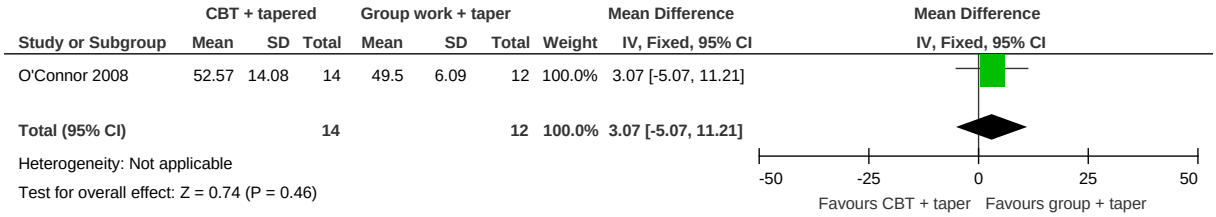
2

Figure 88: Anxiety - Spielberger trait (3-month follow-up)



3

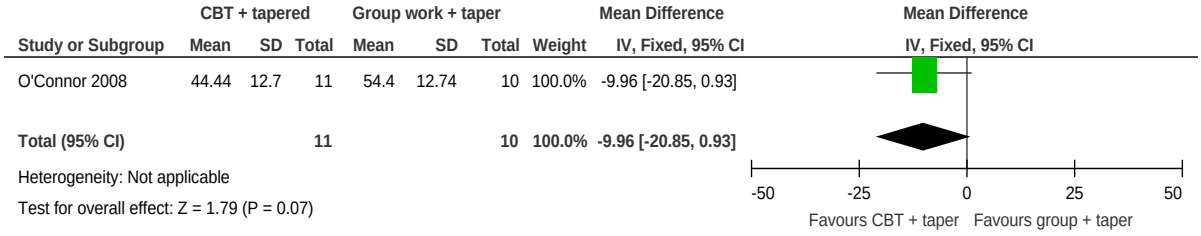
Figure 89: Psychological Distress Inventory (post-intervention)



4

5

Figure 90: Psychological Distress Inventory (3 months follow-up)



6

F.2.4 CBT + tapered withdrawal vs Usual care

Figure 91: Quality of life - SF36: Physical function (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	68	26	58	72	26	26	100.0%	-4.00 [-16.03, 8.03]
Total (95% CI)			**58**			**26**	**100.0%**	**-4.00 [-16.03, 8.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

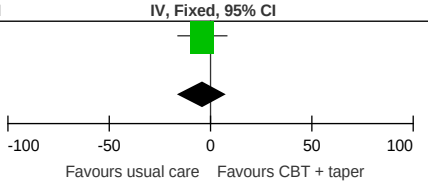


Figure 92: Quality of life - SF36: Social function (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	68	22	58	69	19	26	100.0%	-1.00 [-10.24, 8.24]
Total (95% CI)			**58**			**26**	**100.0%**	**-1.00 [-10.24, 8.24]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)

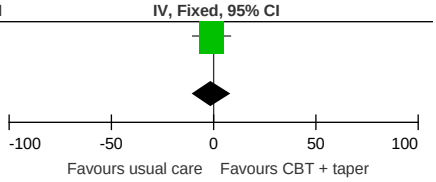


Figure 93: Quality of life - SF36: Role limitation (physical) (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	57	44	58	76	36	26	100.0%	-19.00 [-36.88, -1.12]
Total (95% CI)			**58**			**26**	**100.0%**	**-19.00 [-36.88, -1.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)

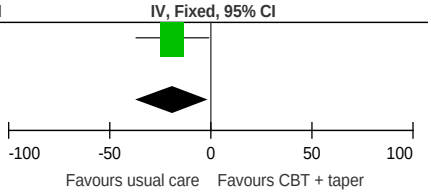


Figure 94: Quality of life - SF36: Role limitation (emotional) (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	67	41	58	81	29	26	100.0%	-14.00 [-29.35, 1.35]
Total (95% CI)			**58**			**26**	**100.0%**	**-14.00 [-29.35, 1.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)

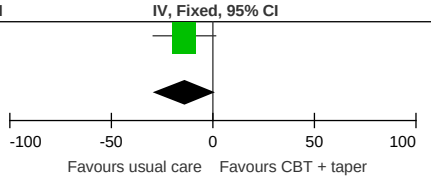


Figure 95: Quality of life - SF36: Mental health (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	71	17	58	81	29	26	100.0%	-10.00 [-21.97, 1.97]
Total (95% CI)			**58**			**26**	**100.0%**	**-10.00 [-21.97, 1.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)

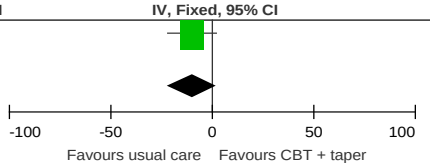
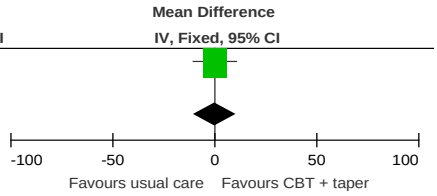


Figure 96: Quality of life - SF36: Vitality (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	63	20	58	63	24	26	100.0%	0.00 [-10.56, 10.56]
Total (95% CI)			**58**			**26**	**100.0%**	**0.00 [-10.56, 10.56]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

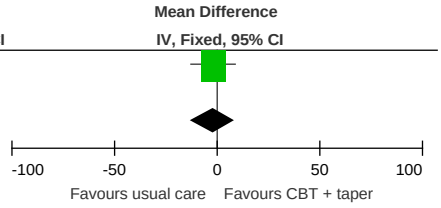


1

Figure 97: Quality of life - SF36: Pain (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	67	26	58	69	22	26	100.0%	-2.00 [-12.78, 8.78]
Total (95% CI)			**58**			**26**	**100.0%**	**-2.00 [-12.78, 8.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

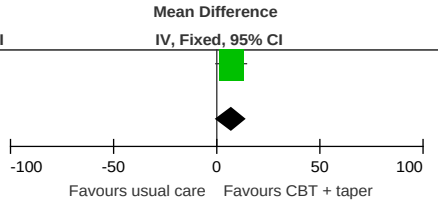


2

Figure 98: Quality of life - SF36: General health (18-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	62	19	58	55	22	59	100.0%	7.00 [-0.44, 14.44]
Total (95% CI)			**58**			**59**	**100.0%**	**7.00 [-0.44, 14.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.84 (P = 0.07)

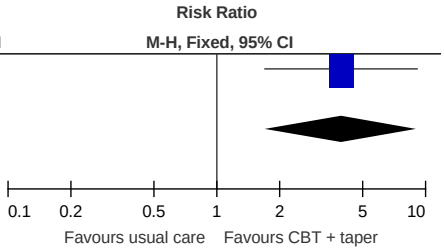


3

Figure 99: Cessation of benzodiazepine (3-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2003	33	57	5	34	100.0%	3.94 [1.70, 9.11]
Total (95% CI)		**57**		**34**	**100.0%**	**3.94 [1.70, 9.11]**
Total events	33		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.20 (P = 0.001)



4

Figure 100: Cessation of benzodiazepine (15-month follow-up)

Study or Subgroup	CBT + tapered withdrawal Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2006	20	68	5	33	100.0%	1.94 [0.80, 4.71]
Total (95% CI)		**68**		**33**	**100.0%**	**1.94 [0.80, 4.71]**
Total events	20		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)

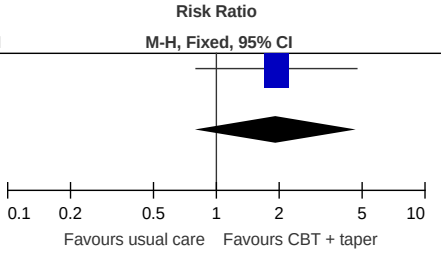


Figure 101: Withdrawal symptoms score - BWSQ (3-months follow-up)

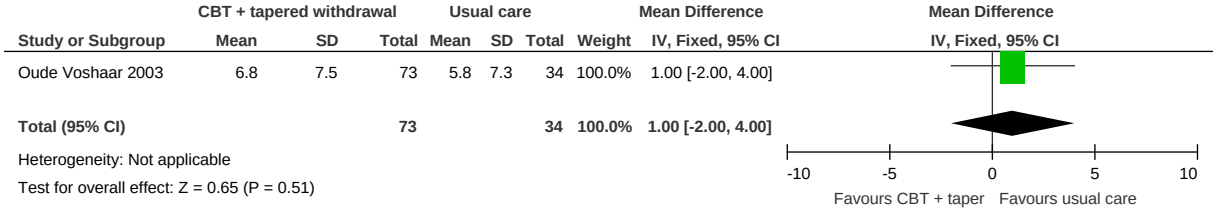
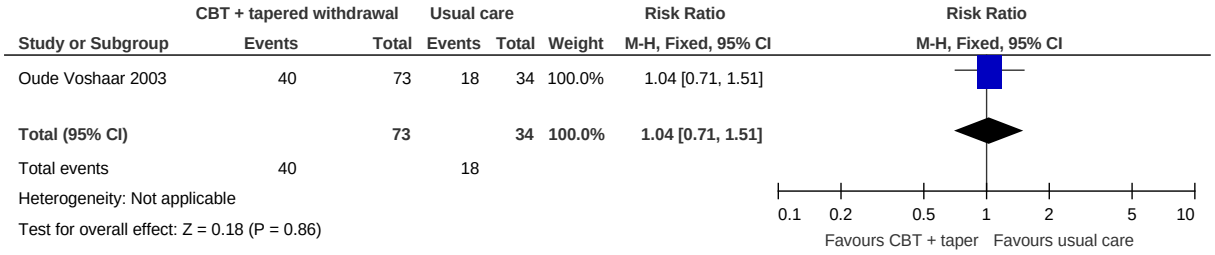


Figure 102: Patients using alcohol



F.2.5 Tapered withdrawal vs Usual care

Figure 103: Quality of life - SF36: Physical function (18-month follow-up)

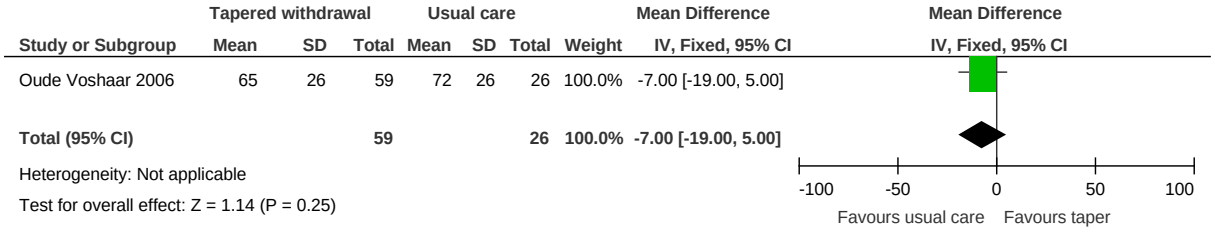


Figure 104: Quality of life - SF36: Social function (18-month follow-up)

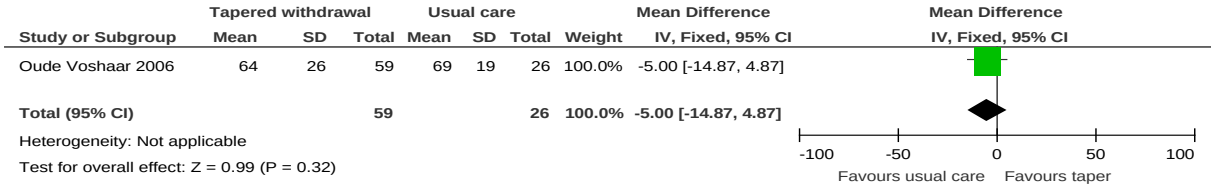


Figure 105: Quality of life - SF36: Role limitation (physical) (18-month follow-up)

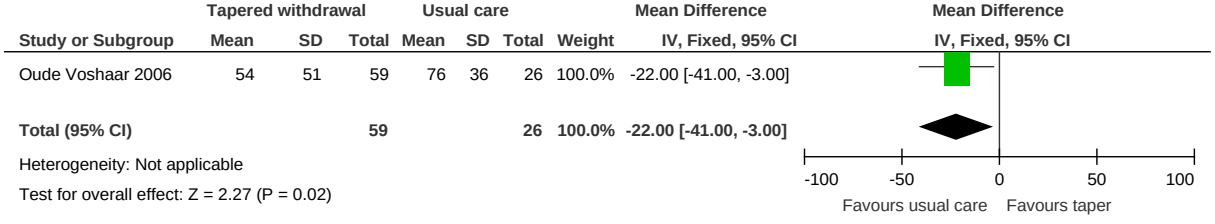


Figure 106: Quality of life - SF36: Role limitation (emotional) (18-month follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	76	39	59	81	29	26	100.0%	-5.00 [-19.94, 9.94]
Total (95% CI)			**59**			**26**	**100.0%**	**-5.00 [-19.94, 9.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

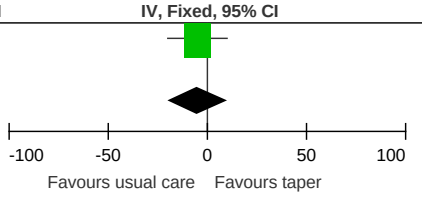


Figure 107: Quality of life - SF36: Mental health (18-month follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	76	39	59	81	29	26	100.0%	-5.00 [-19.94, 9.94]
Total (95% CI)			**59**			**26**	**100.0%**	**-5.00 [-19.94, 9.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)

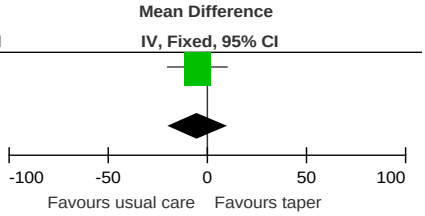


Figure 108: Quality of life - SF36: Vitality (18-month follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	61	20	59	63	24	26	100.0%	-2.00 [-12.54, 8.54]
Total (95% CI)			**59**			**26**	**100.0%**	**-2.00 [-12.54, 8.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

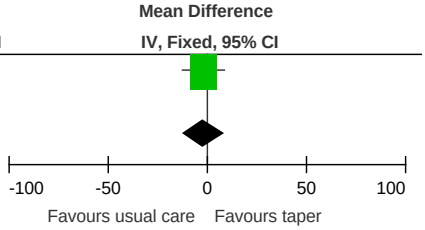


Figure 109: Quality of life - SF36: Pain (18-month follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	61	27	59	69	22	26	100.0%	-8.00 [-18.91, 2.91]
Total (95% CI)			**59**			**26**	**100.0%**	**-8.00 [-18.91, 2.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)

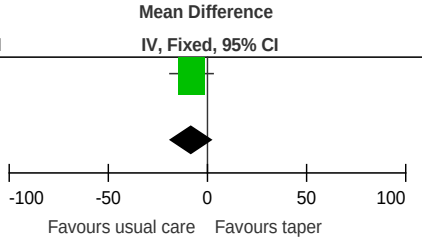


Figure 110: Quality of life - SF36: General health (18-month follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2006	57	20	59	55	22	59	100.0%	2.00 [-5.59, 9.59]
Total (95% CI)			**59**			**59**	**100.0%**	**2.00 [-5.59, 9.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.61)

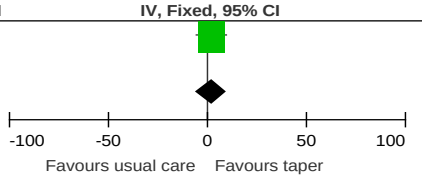


Figure 111: Cessation of benzodiazepine (3-month follow-up)

Study or Subgroup	Tapered withdrawal Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2003	37	60	5	34	100.0%	4.19 [1.82, 9.65]
Total (95% CI)		**60**		**34**	**100.0%**	**4.19 [1.82, 9.65]**
Total events	37		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.37 (P = 0.0008)

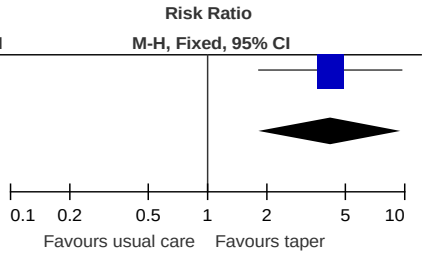


Figure 112: Cessation of benzodiazepine (15-month follow-up)

Study or Subgroup	Tapered withdrawal Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2006	25	69	5	33	100.0%	2.39 [1.01, 5.68]
Total (95% CI)		**69**		**33**	**100.0%**	**2.39 [1.01, 5.68]**
Total events	25		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)

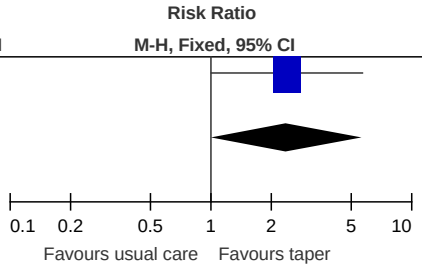


Figure 113: Withdrawal symptoms score - BWSQ (3-months follow-up)

Study or Subgroup	Tapered withdrawal Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Oude Voshaar 2003	6.2	6.8	73	5.8	7.3	34	100.0%	0.40 [-2.51, 3.31]
Total (95% CI)			**73**			**34**	**100.0%**	**0.40 [-2.51, 3.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

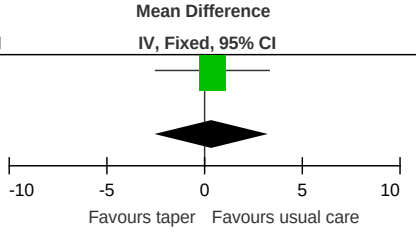
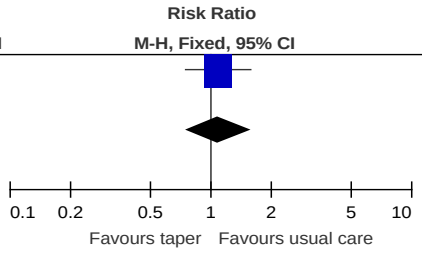


Figure 114: Patients using alcohol

Study or Subgroup	Tapered withdrawal Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Oude Voshaar 2003	42	73	18	34	100.0%	1.09 [0.75, 1.58]
Total (95% CI)		**73**		**34**	**100.0%**	**1.09 [0.75, 1.58]**
Total events	42		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)



F.2.6 Lorazepam substitution + tapered withdrawal vs Diazepam substitution + tapered withdrawal

Figure 115: Mortality - suicide (14 weeks follow-up)

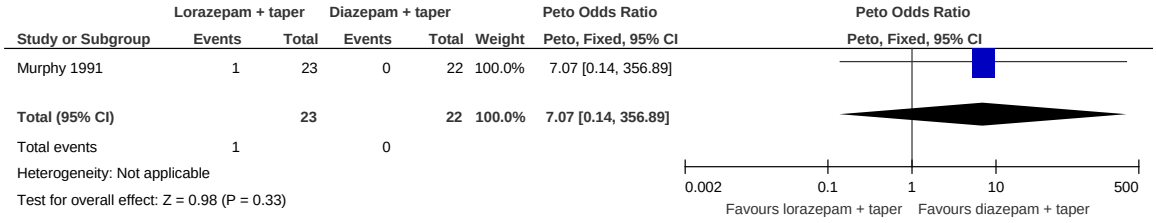
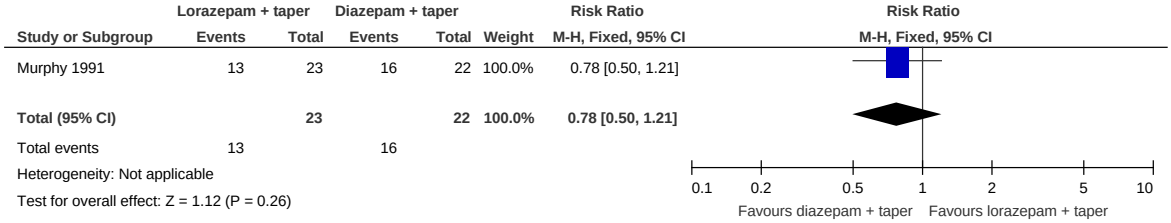
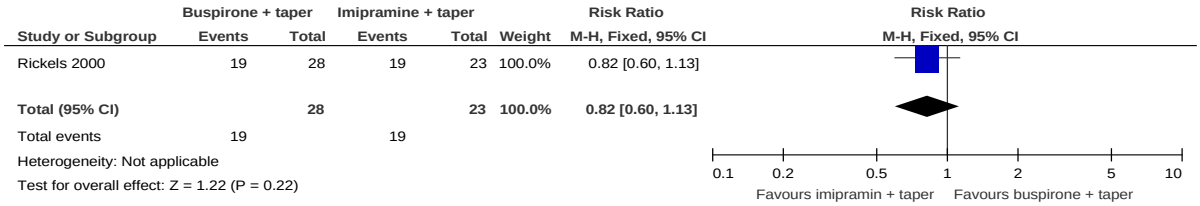


Figure 116: Cessation of benzodiazepine (14-weeks follow-up)



F.2.7 Buspirone substitution + tapered withdrawal vs Imipramine substitution + tapered withdrawal

Figure 117: Cessation of benzodiazepine (3-months follow-up)



F.2.8 Buspirone substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal

Figure 118: Cessation of benzodiazepine (post-intervention)

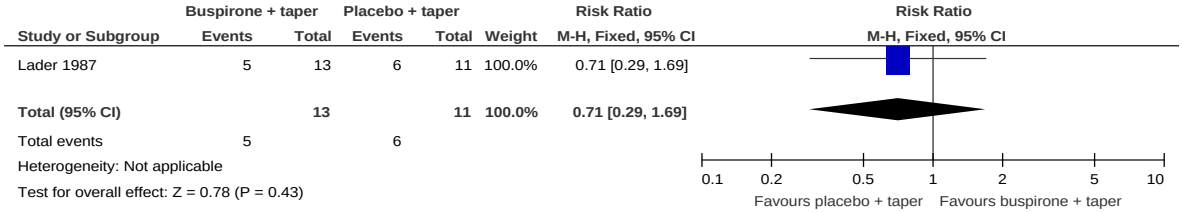
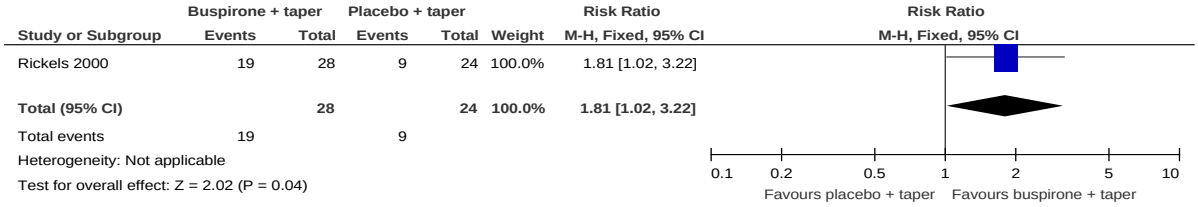
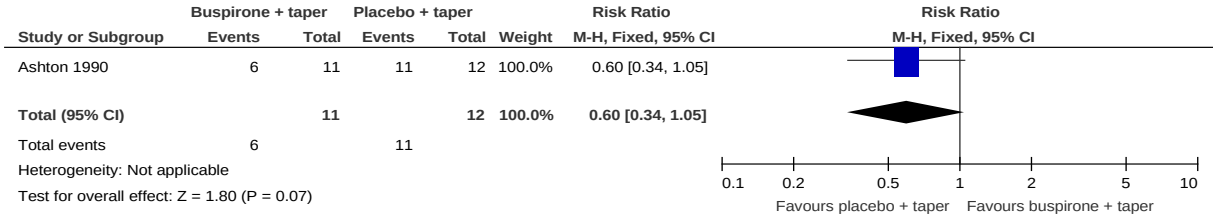


Figure 119: Cessation of benzodiazepine (3-months follow-up)



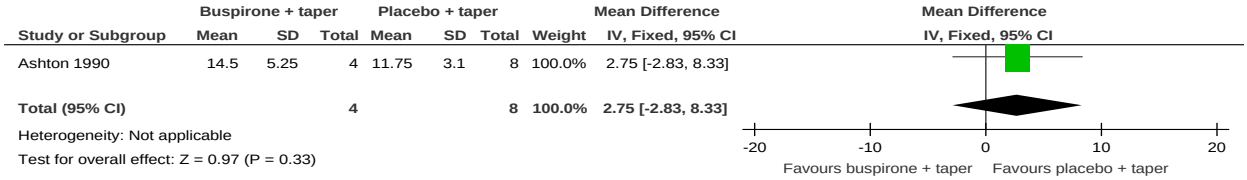
1

Figure 120: Cessation of benzodiazepine (12-months follow-up)



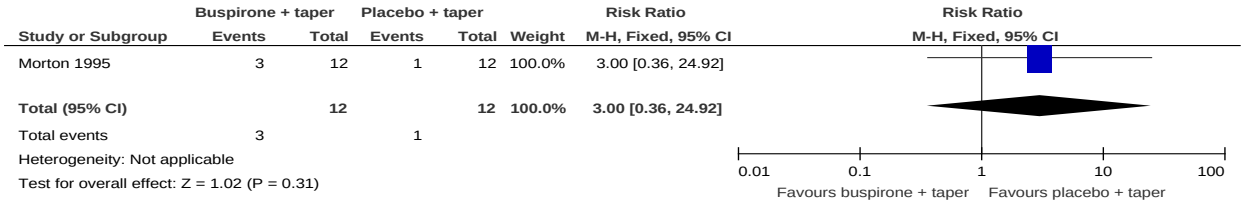
2

Figure 121: HADS - anxiety (16-weeks)



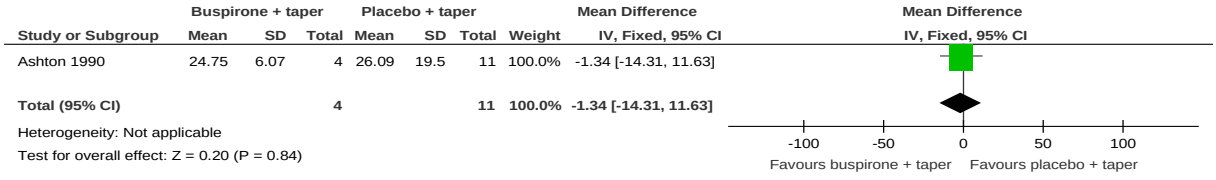
3

Figure 122: Withdrawal symptoms – patients with insomnia (post-intervention)



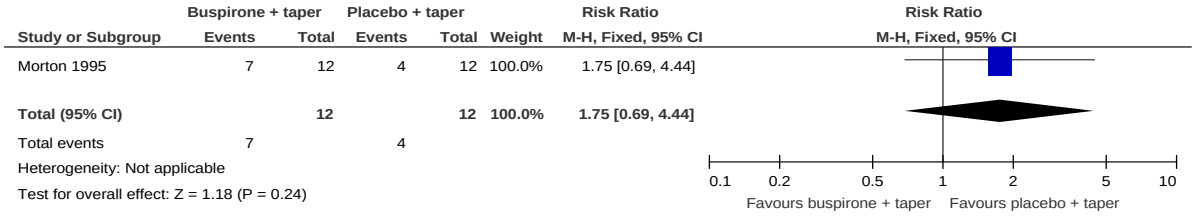
4

Figure 123: Withdrawal symptom score (tool unclear, range 0-147, high poor outcome)(16 wee



5

Figure 124: Adverse events: giddiness (20-weeks follow-up)



1

Figure 125: Adverse events: GI symptoms (20-weeks follow-up)

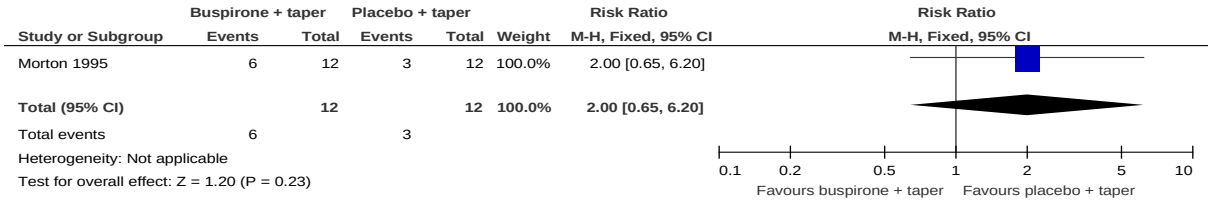
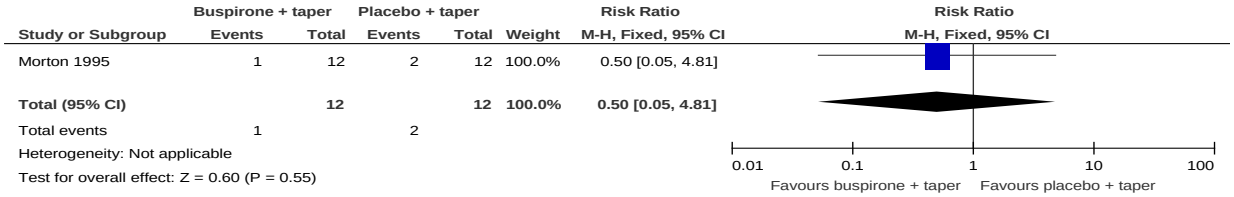


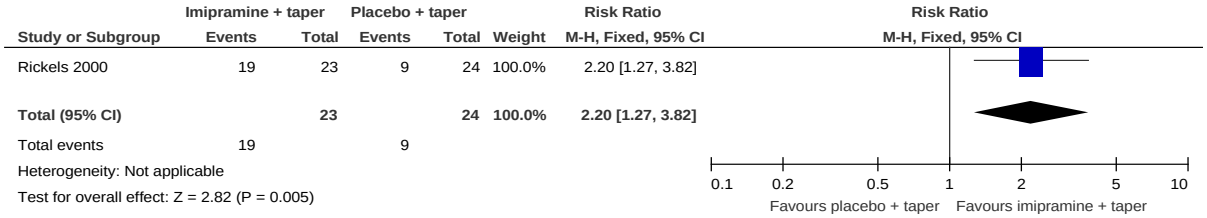
Figure 126: Adverse events: headache (20-weeks follow-up)



2

F.2.9 Imipramine substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal

Figure 127: Cessation of benzodiazepine (3 months follow-up)



5

F.2.10 Melatonin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal

8

Figure 128: Cessation of benzodiazepine (post-intervention)

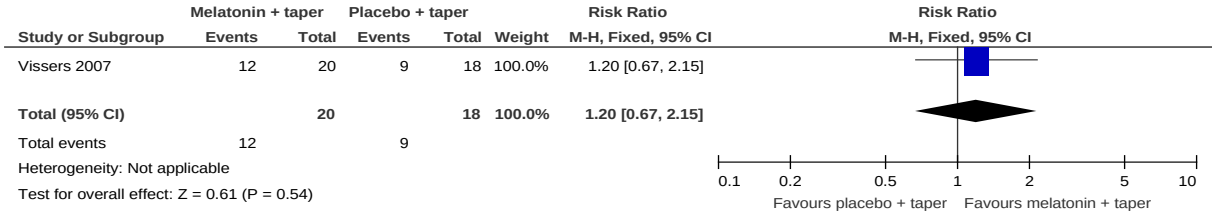
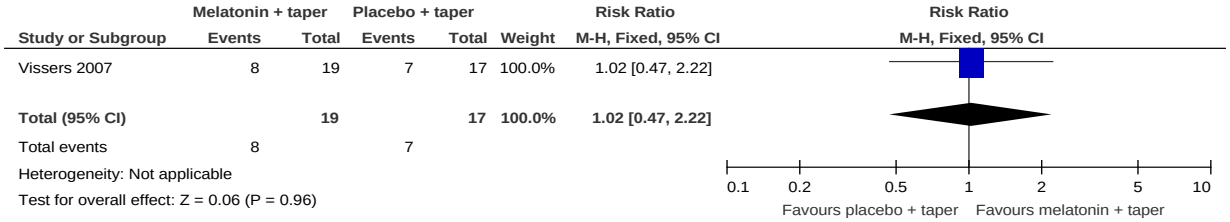


Figure 129: Cessation of benzodiazepine (12-month follow-up)



F.2.11 Dothiepin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal

Figure 130: Cessation of benzodiazepine (14-week follow-up)

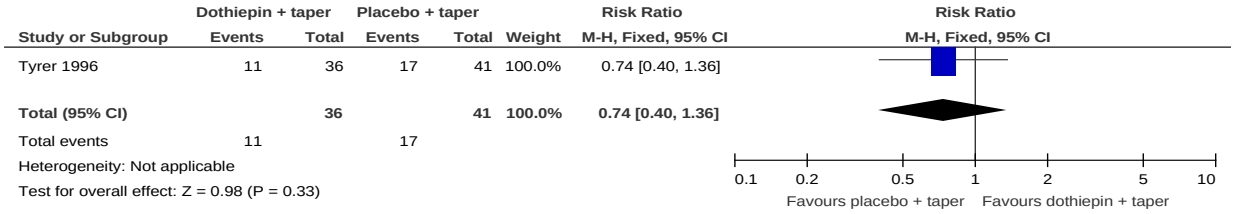
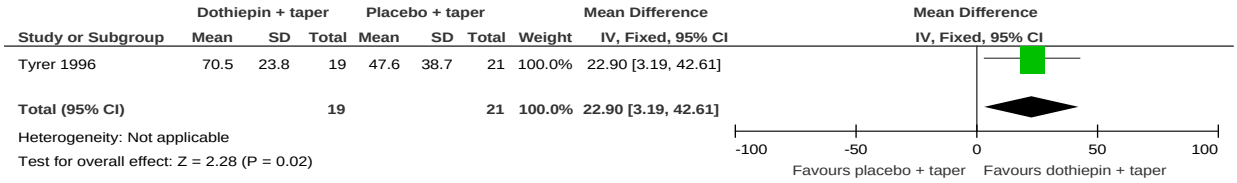


Figure 131: Satisfaction analogue scale (14-week follow-up)



F.2.12 Valproate substitution + tapered withdrawal vs Tapered withdrawal alone

Figure 132: Withdrawal symptoms - CIWA-B (post-intervention)

Study or Subgroup	Valproate + taper Mean	SD	Total	Taper alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Vorma 2011	5.2	3.7	14	6.3	3.9	15	100.0%	-1.10 [-3.87, 1.67]
Total (95% CI)			**14**			**15**	**100.0%**	**-1.10 [-3.87, 1.67]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)

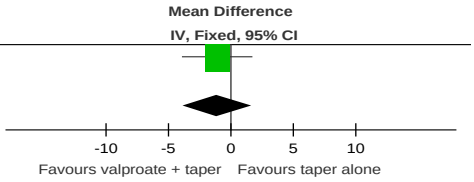
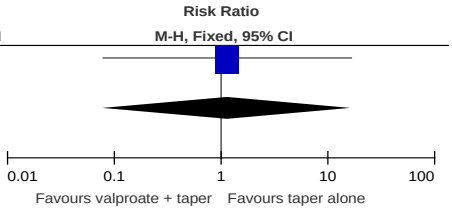


Figure 133: Use of illicit drugs (post-intervention)

Study or Subgroup	Valproate + taper Events	Total	Tapered withdrawal alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vorma 2011	1	14	1	16	100.0%	1.14 [0.08, 16.63]
Total (95% CI)		**14**		**16**	**100.0%**	**1.14 [0.08, 16.63]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)



F.2.13 Propranolol substitution + abrupt withdrawal vs Tapered withdrawal alone

Figure 134: Cessation of benzodiazepine (6-months follow-up)

Study or Subgroup	Propranolol + abrupt stop Events	Total	Tapered withdrawal alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cantopher 1990	4	15	11	16	100.0%	0.39 [0.16, 0.96]
Total (95% CI)		**15**		**16**	**100.0%**	**0.39 [0.16, 0.96]**
Total events	4		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)

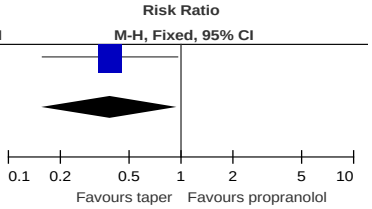
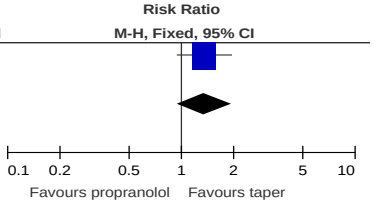


Figure 135: Withdrawal symptoms (6-months follow-up)

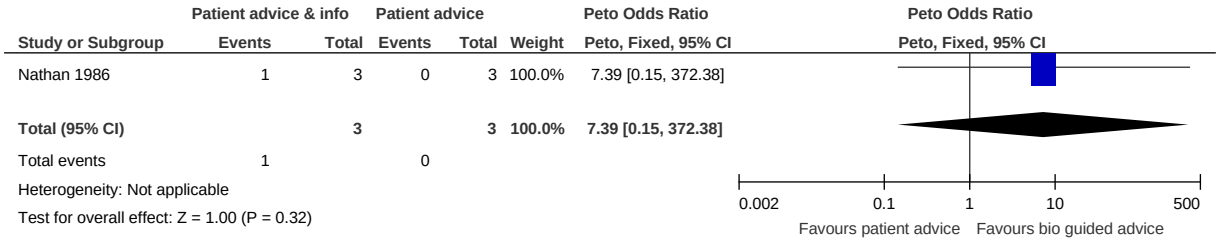
Study or Subgroup	Propranolol + abrupt stop Events	Total	Tapered withdrawal alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cantopher 1990	14	15	11	16	100.0%	1.36 [0.95, 1.94]
Total (95% CI)		**15**		**16**	**100.0%**	**1.36 [0.95, 1.94]**
Total events	14		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



F.2.14 Patient advice & biofeedback guided information + tapered withdrawal vs Patient advice + tapered withdrawal

Figure 136: Cessation of benzodiazepine (post-intervention)



F.2.15 Psychological intervention, education and training + tapered withdrawal vs Psychological intervention, education and advice + tapered withdrawal

Figure 137: Reduction of benzodiazepine (mg) (6-months follow-up)

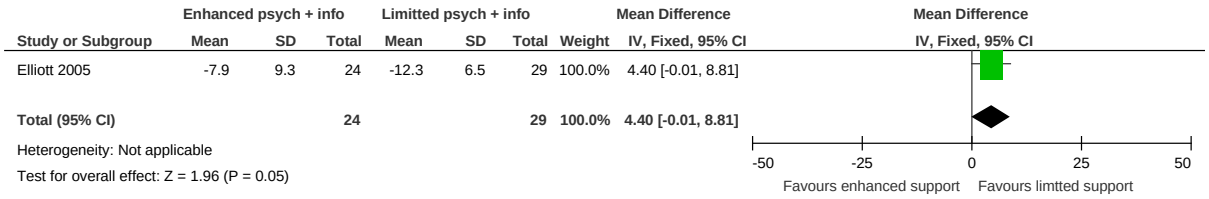


Figure 138: Relapse - weeks of taper suspension (6-months follow-up)

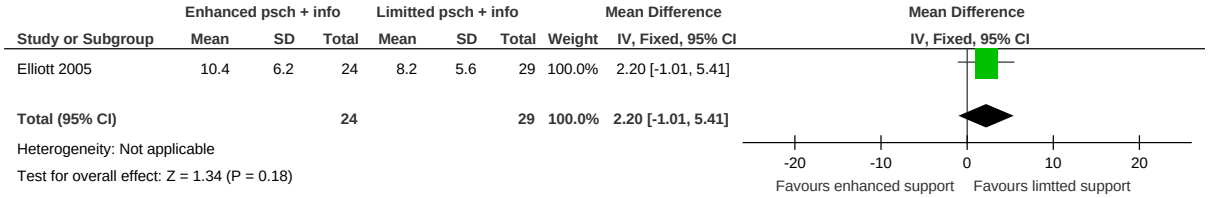


Figure 139: Illicit use of benzodiazepine (6-months follow-up)

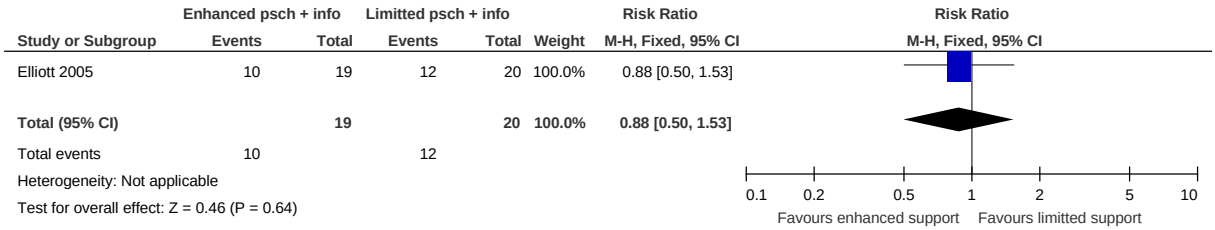
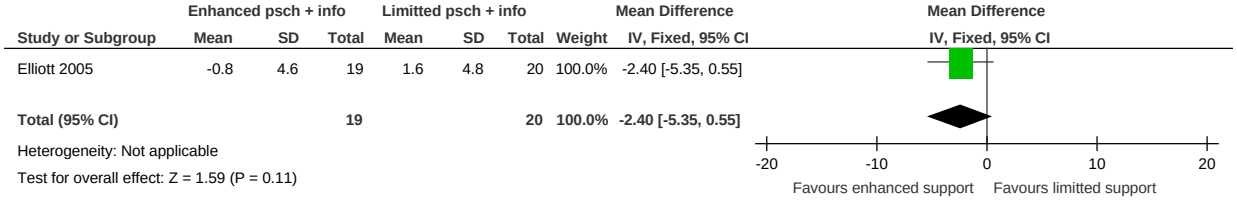
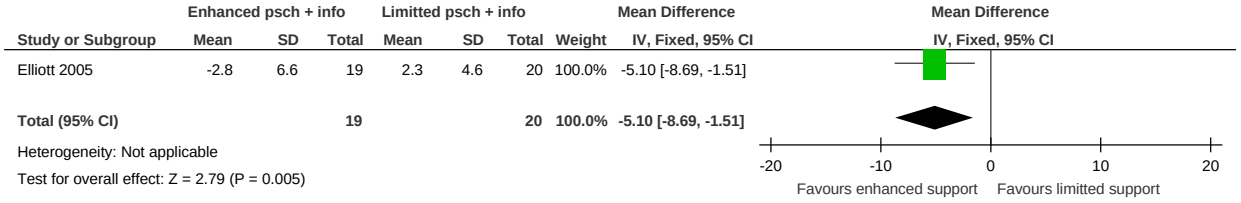


Figure 140: HADS - anxiety (6-months follow-up)



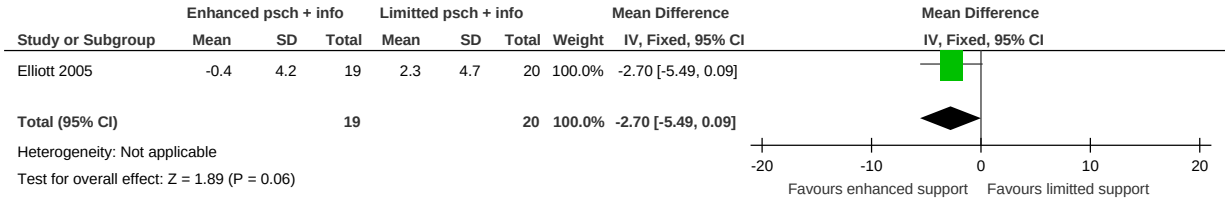
1

Figure 141: HADS - depression (6-months follow-up)



2

Figure 142: Sleep quality – PSQI: high score represents low sleep quality (6-months follow-up



3

F.2.16 Patient advice, education & support + gradual withdrawal vs Patient advice, education & support + abrupt withdrawal

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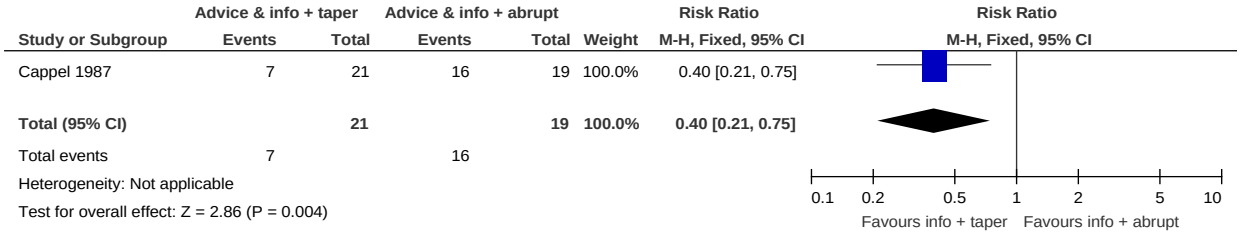
6

Figure 143: Relapse - unauthorised use of benzodiazepine (post-intervention)



7

F.2.17 Patient advice & information vs Patient advice

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Figure 144: Cessation of benzodiazepine (6-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Patient advice Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cormack 1994	10	75	15	65	63.2%	0.58 [0.28, 1.20]
Heather 2004	10	95	9	88	36.8%	1.03 [0.44, 2.41]
Total (95% CI)		**170**		**153**	**100.0%**	**0.74 [0.43, 1.29]**
Total events	20		24			

Heterogeneity: Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 1.06 (P = 0.29)

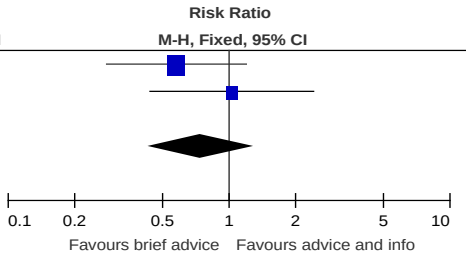


Figure 145: Reduction of benzodiazepine (6-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Patient advice Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cormack 1994	37	75	24	65	100.0%	1.34 [0.90, 1.98]
Total (95% CI)		**75**		**65**	**100.0%**	**1.34 [0.90, 1.98]**
Total events	37		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

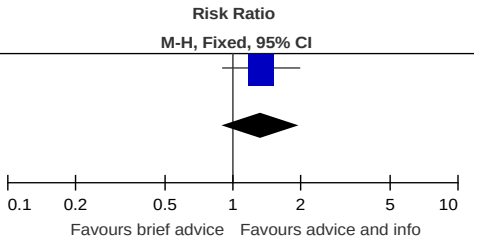
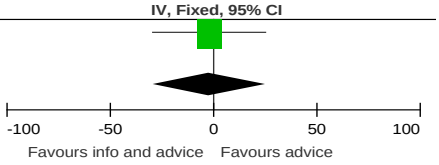


Figure 146: Reduction of benzodiazepine (mg) (6-months follow-up)

Study or Subgroup	Patient advice & info Mean	SD	Total	Patient advice Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Heather 2004	121.01	88.5	95	123.17	98.96	88	100.0%	-2.16 [-29.44, 25.12]
Total (95% CI)			**95**			**88**	**100.0%**	**-2.16 [-29.44, 25.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)



F.2.18 Patient advice & information vs Usual care

Figure 147: Cessation of benzodiazepine (6-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cormack 1994	10	75	4	69	40.2%	2.30 [0.76, 7.00]
Heather 2004	10	95	6	89	59.8%	1.56 [0.59, 4.12]
Total (95% CI)		**170**		**158**	**100.0%**	**1.86 [0.90, 3.85]**
Total events	20		10			

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.10)

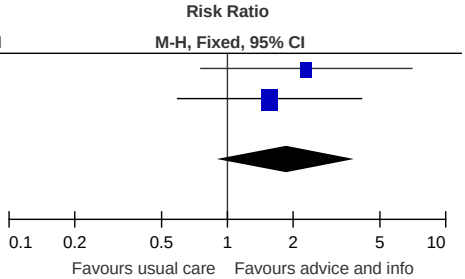


Figure 148: Cessation of benzodiazepine - ≤1 use in previous 15 days (12-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2006	33	71	6	64	100.0%	4.96 [2.22, 11.05]
Total (95% CI)		**71**		**64**	**100.0%**	**4.96 [2.22, 11.05]**
Total events	33		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.91 (P < 0.0001)

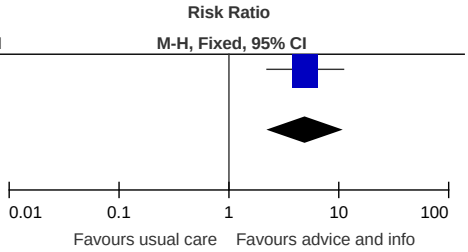


Figure 149: Reduction of benzodiazepine (6-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cormack 1994	37	75	11	69	100.0%	3.09 [1.72, 5.57]
Total (95% CI)		**75**		**69**	**100.0%**	**3.09 [1.72, 5.57]**
Total events	37		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.76 (P = 0.0002)

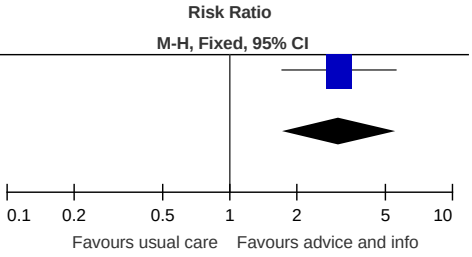


Figure 150: Reduction of benzodiazepine (mg) (6-months follow-up)

Study or Subgroup	Patient advice & info Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Heather 2004	121.01	88.5	95	126.76	111.31	89	100.0%	-5.75 [-34.93, 23.43]
Total (95% CI)			**95**			**89**	**100.0%**	**-5.75 [-34.93, 23.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

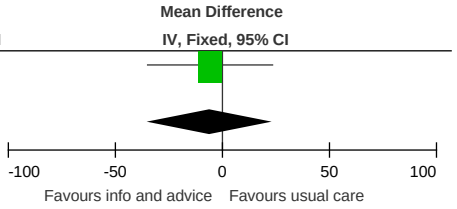
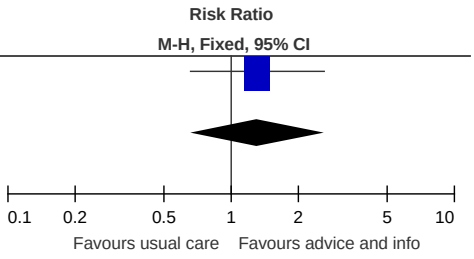


Figure 151: Reduction of benzodiazepine - ≥50% reduction (12-months follow-up)

Study or Subgroup	Patient advice & info Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2006	16	71	11	64	100.0%	1.31 [0.66, 2.61]
Total (95% CI)		**71**		**64**	**100.0%**	**1.31 [0.66, 2.61]**
Total events	16		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)



F.2.19 Brief advice, education & support vs Usual care

Figure 152: Cessation of benzodiazepine (1-month follow-up)

Study or Subgroup	Brief information/advice Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gnjidic 2019	6	11	7	11	100.0%	0.86 [0.43, 1.73]
Total (95% CI)		**11**		**11**	**100.0%**	**0.86 [0.43, 1.73]**
Total events	6		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.43 (P = 0.67)

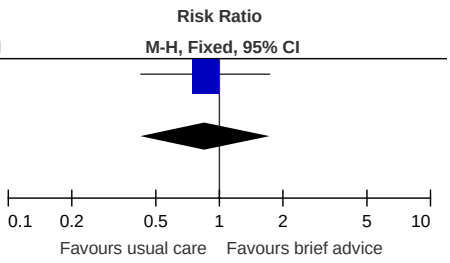


Figure 153: Cessation of benzodiazepine (6-month follow-up)

Study or Subgroup	Brief information/advice Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cormack 1994	15	65	4	69	39.4%	3.98 [1.39, 11.37]
Heather 2004	9	88	6	89	60.6%	1.52 [0.56, 4.08]
Total (95% CI)		**153**		**158**	**100.0%**	**2.49 [1.23, 5.02]**
Total events	24		10			

Heterogeneity: Chi² = 1.73, df = 1 (P = 0.19); I² = 42%

Test for overall effect: Z = 2.54 (P = 0.01)

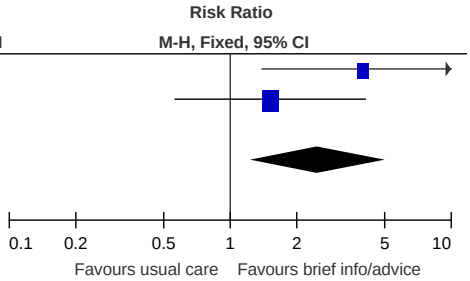


Figure 154: Reduced benzodiazepine use (6-month follow-up)

Study or Subgroup	Brief information/advice Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bashir 1994	20	46	11	44	51.3%	1.74 [0.95, 3.20]
Cormack 1994	24	65	11	69	48.7%	2.32 [1.24, 4.34]
Total (95% CI)		**111**		**113**	**100.0%**	**2.02 [1.30, 3.13]**
Total events	44		22			

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%

Test for overall effect: Z = 3.15 (P = 0.002)

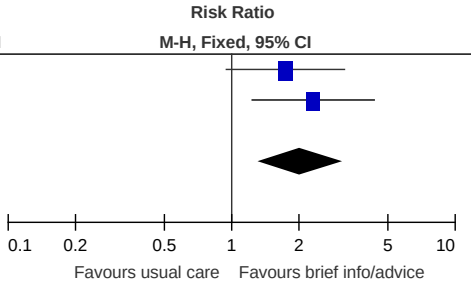


Figure 155: Reduction of benzodiazepine (mg) (6-months follow-up)

Study or Subgroup	Patient advice & info Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Heather 2004	123.17	98.96	88	126.76	111.31	89	100.0%	-3.59 [-34.61, 27.43]
Total (95% CI)			**88**			**89**	**100.0%**	**-3.59 [-34.61, 27.43]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.23 (P = 0.82)

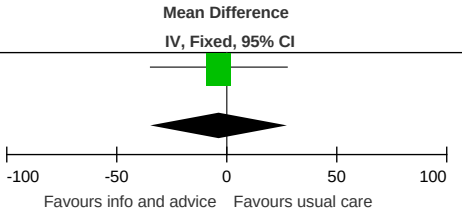


Figure 156: Presence of psychiatric morbidity

Study or Subgroup	Brief information/advice Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bashir 1994	24	46	19	47	100.0%	1.29 [0.83, 2.01]
Total (95% CI)		**46**		**47**	**100.0%**	**1.29 [0.83, 2.01]**
Total events	24		19			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

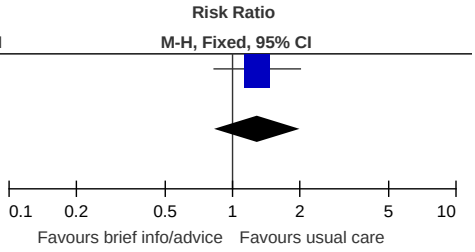
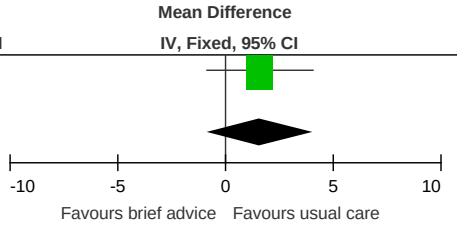


Figure 157: Withdrawal symptoms (6-months follow-up)

Study or Subgroup	Brief advice & support Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bashir 1994	7.3	6.2	46	5.7	5.9	47	100.0%	1.60 [-0.86, 4.06]
Total (95% CI)			**46**			**47**	**100.0%**	**1.60 [-0.86, 4.06]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.27 (P = 0.20)



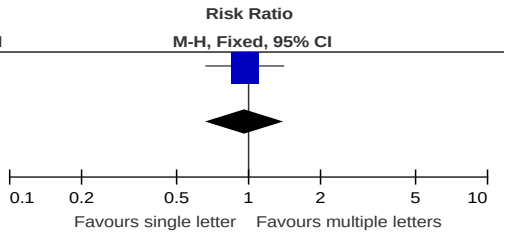
F.2.20 Brief advice, education & support (multiple letters) vs Brief advice, education & support (single letter)

Figure 158: Cessation of benzodiazepine (12-month follow-up)

Study or Subgroup	Multiple letters Events	Total	Single letter Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ten wolde 2008	44	186	40	163	100.0%	0.96 [0.66, 1.40]
Total (95% CI)		**186**		**163**	**100.0%**	**0.96 [0.66, 1.40]**
Total events	44		40			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.19 (P = 0.85)



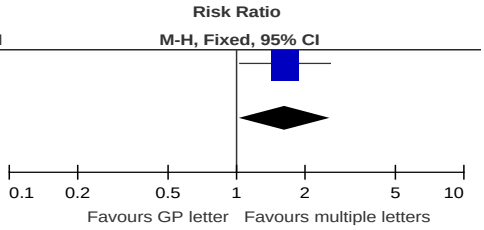
F.2.21 Brief advice, education & support (multiple letters) vs Brief advice, education & support (GP letter)

Figure 159: Cessation of benzodiazepine (12-month follow-up)

Study or Subgroup	Multiple letters Events	Total	GP letter Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ten wolde 2008	44	186	23	159	100.0%	1.64 [1.03, 2.58]
Total (95% CI)		**186**		**159**	**100.0%**	**1.64 [1.03, 2.58]**
Total events	44		23			

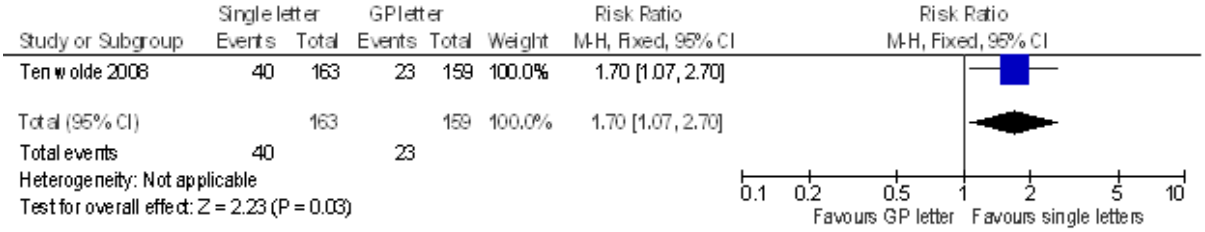
Heterogeneity: Not applicable

Test for overall effect: Z = 2.11 (P = 0.04)



F.2.22 Brief advice, education & support (single letter) vs Brief advice, education & support (GP letter)

Figure 160: Cessation of benzodiazepine (12-month follow-up)



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F.3 Z-drugs

F.3.1 Acupuncture vs. CBT

Figure 161: Cessation of drug post intervention (4-6 weeks)

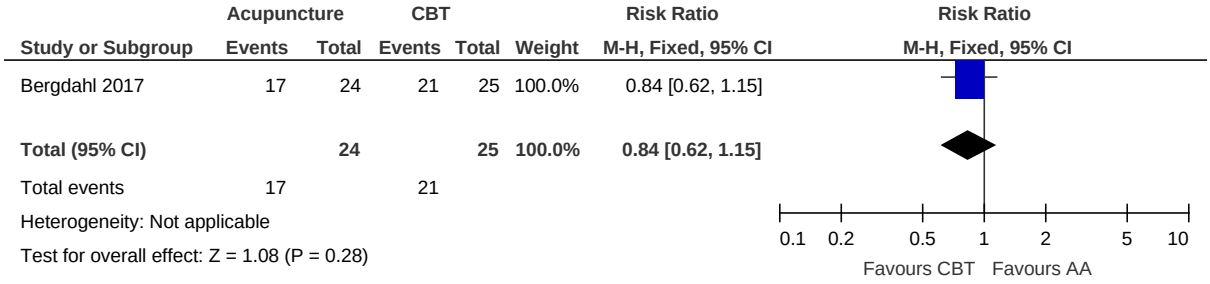
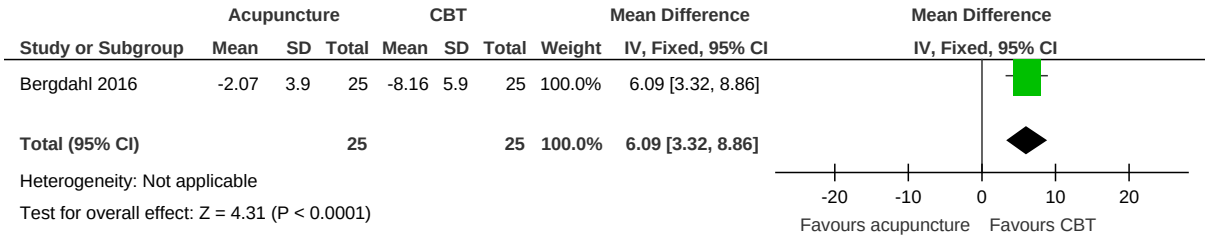


Figure 162: Insomnia severity (ISI) post intervention (4-6 weeks)



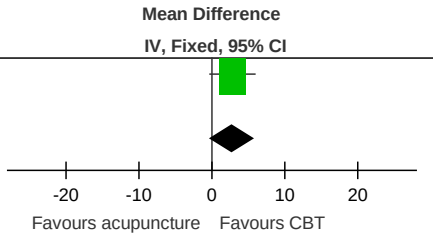
Insomnia severity index scale: 0-28, higher value is worse

Figure 163: Insomnia severity (ISI) at 6 months

Study or Subgroup	Acupuncture Mean	SD	Total	CBT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bergdahl 2016	-3.27	3.9	22	-6.09	6.37	23	100.0%	2.82 [-0.25, 5.89]
Total (95% CI)			**22**			**23**	**100.0%**	**2.82 [-0.25, 5.89]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.80 (P = 0.07)



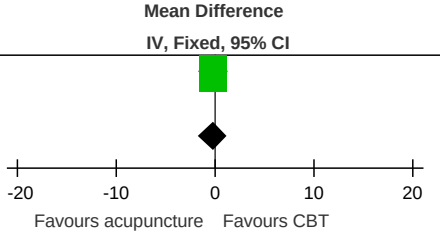
Insomnia severity index scale: 0-28, higher value is worse

Figure 164: HADS anxiety post intervention (4-6 weeks)

Study or Subgroup	Acupuncture Mean	SD	Total	CBT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bergdahl 2016	-0.9	2.3	25	-0.68	2.7	25	100.0%	-0.22 [-1.61, 1.17]
Total (95% CI)			**25**			**25**	**100.0%**	**-0.22 [-1.61, 1.17]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.31 (P = 0.76)



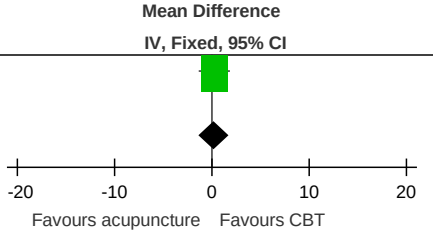
HADS anxiety scale 0-21, higher value is worse

Figure 165: HADS anxiety at 6 months

Study or Subgroup	Acupuncture Mean	SD	Total	CBT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bergdahl 2016	-0.36	2.53	22	-0.61	2.69	23	100.0%	0.25 [-1.28, 1.78]
Total (95% CI)			**22**			**23**	**100.0%**	**0.25 [-1.28, 1.78]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.32 (P = 0.75)



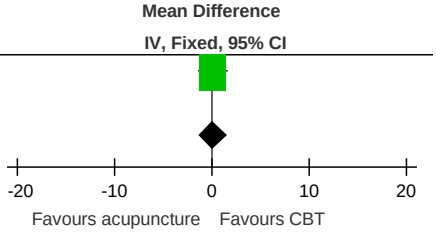
HADS anxiety scale 0-21, higher value is worse

Figure 166: HADS depression post intervention (4-6 weeks)

Study or Subgroup	Acupuncture Mean	SD	Total	CBT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bergdahl 2016	-0.39	2	25	-0.49	3.15	25	100.0%	0.10 [-1.36, 1.56]
Total (95% CI)			**25**			**25**	**100.0%**	**0.10 [-1.36, 1.56]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.13 (P = 0.89)



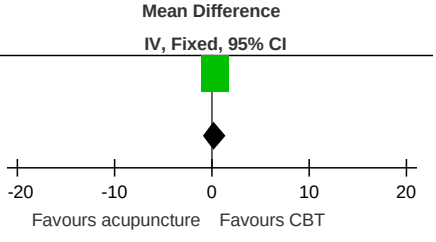
HADS depression scale 0-21, higher value is worse

Figure 167: HADS depression at 6 months

Study or Subgroup	Acupuncture Mean	SD	Total	CBT Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bergdahl 2016	-0.7	1.74	22	-0.99	2.35	23	100.0%	0.29 [-0.91, 1.49]
Total (95% CI)			**22**			**23**	**100.0%**	**0.29 [-0.91, 1.49]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.47 (P = 0.64)



HADS depression scale 0-21, higher value is worse

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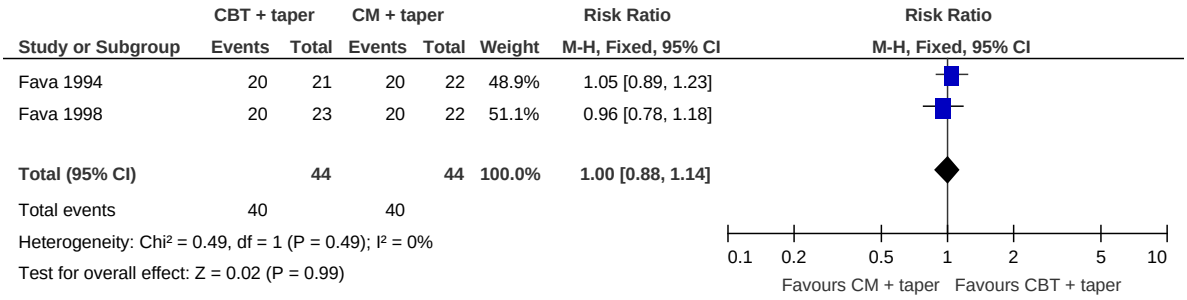
F.4 Antidepressants

F.4.1 TCAs:

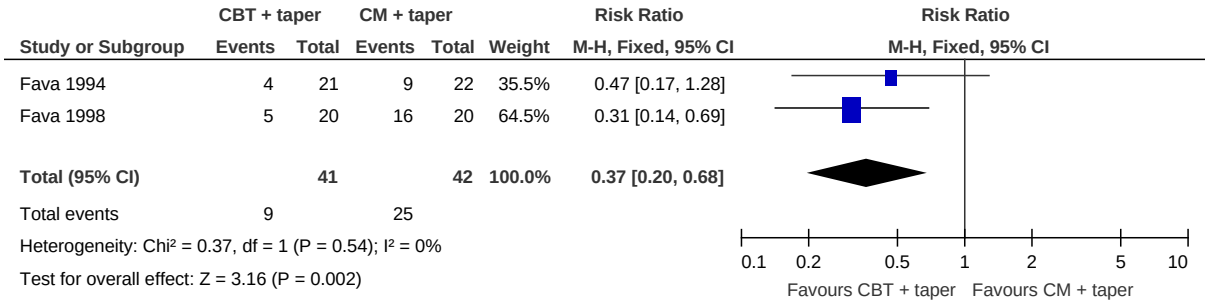
F.4.1.1 CBT + taper vs clinical management + taper

Figure 168: Discontinuation of antidepressants at 20 weeks



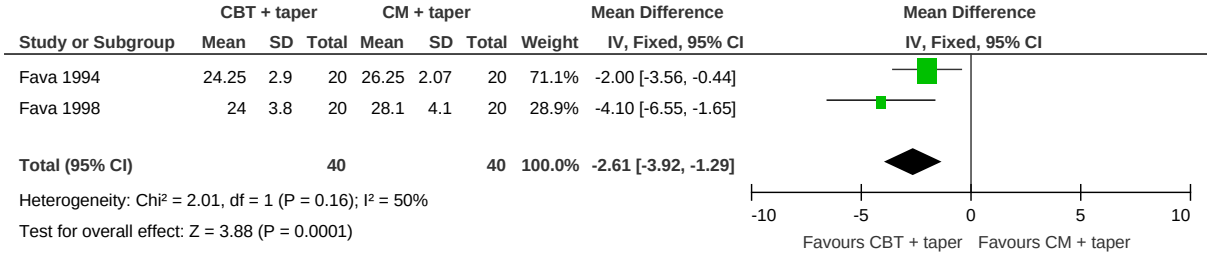
Note: calculated from the information on the number of people in whom discontinuation was not feasible

Figure 169: Relapse (episode of major depression): 2 years



Note: For Fava 1994 this is including the people who were unable to discontinue during the taper stage, as it specifically states that these people were withdrawn because of relapse during the medication tapering phase. For Fava 1998, this does not include the people who were unable to discontinue during the taper stage, as does not specifically state that these people were unable to discontinue due to taper, and the study excluded these from further analysis.

Figure 170: Residual symptoms score at 20 weeks



Note: people in the study had residual symptoms after successful treatment with antidepressants (baseline) - this score was assessed again after CBT or CM + taper. Total score on the modified version of the Paykel Clinical Interview for Depression – range of values not reported, assumed to be 0-133 (based on 19 symptom areas and a 1–7-point scale) Top=High is poor outcome

F.4.2 Other antidepressants (desvenlafaxine):

F.4.2.1 Abrupt discontinuation vs 1 week taper

Figure 171: Mortality at 6 weeks

Study or Subgroup	Abrupt discontinuation Events	Total	1 week taper Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Khan 2014	0	146	0	139	100.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**146**		**139**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

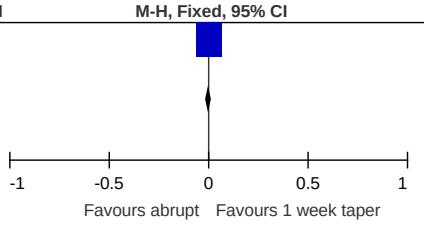


Figure 172: Completing the double-blind phase (i.e., antidepressant discontinuation) at 4 weeks

Study or Subgroup	Abrupt discontinuation Events	Total	1 week taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2014	138	148	127	140	100.0%	1.03 [0.96, 1.10]
Total (95% CI)		**148**		**140**	**100.0%**	**1.03 [0.96, 1.10]**
Total events	138		127			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

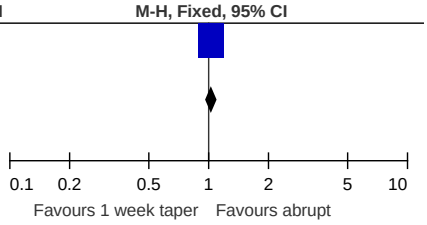
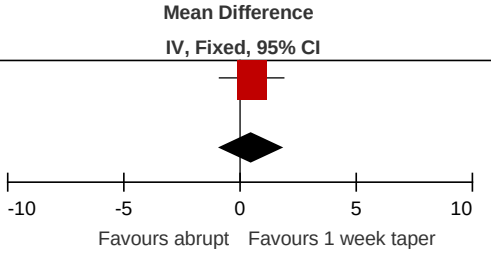


Figure 173: Discontinuation Emergent Signs and Symptoms score at 2 weeks

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Khan 2014	0.5	0.7041	100.0%	0.50 [-0.88, 1.88]
Total (95% CI)			**100.0%**	**0.50 [-0.88, 1.88]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

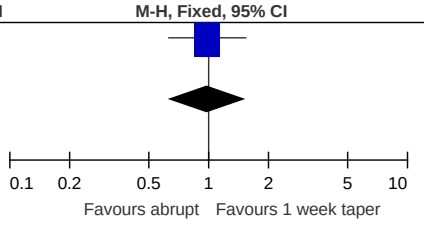


Note: DESS total score (unclear if there is a range of values, suggests this is the number of signs and symptoms) Top=High is poor outcome, Comments: MD from ANCOVA. Control group adjusted final value (mean, SD) abrupt: 5.3 (0.52); taper: 4.8 (0.54).

Figure 174: Discontinuation syndrome (increase in DESS score of ≥4) at 2 weeks

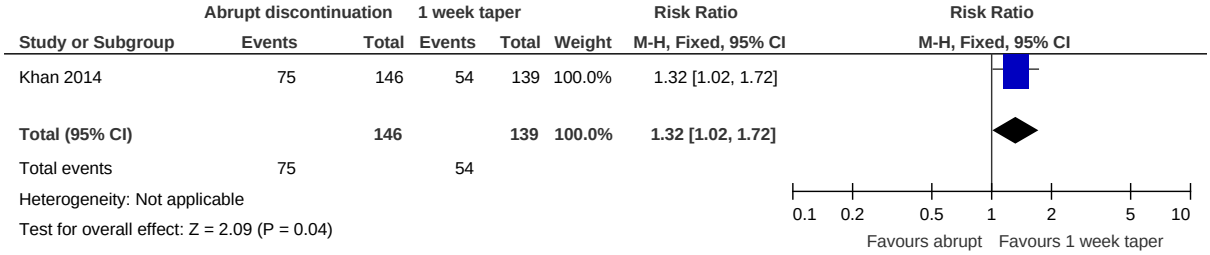
Study or Subgroup	Abrupt discontinuation Events	Total	1 week taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Khan 2014	31	146	30	139	100.0%	0.98 [0.63, 1.54]
Total (95% CI)		**146**		**139**	**100.0%**	**0.98 [0.63, 1.54]**
Total events	31		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)



Note: Proportion of people with discontinuation syndrome (increase in DESS score of more than or equal to 4 between baseline and mean score for the first 2 weeks of discontinuation).DESS total score (unclear if there is a range of values, suggests this is the number of signs and symptoms).

Figure 175: Taper/post-therapy–emergent adverse events (TPAEs) at 4 weeks



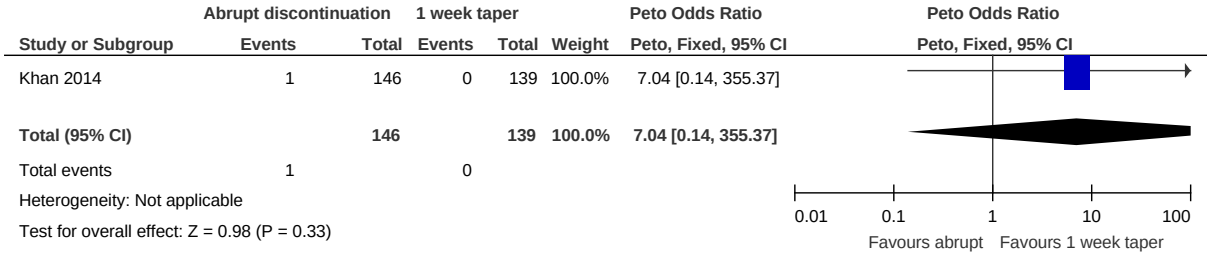
1

Figure 176: Suicidal ideation reported on the C-SSRS at 6 weeks

2

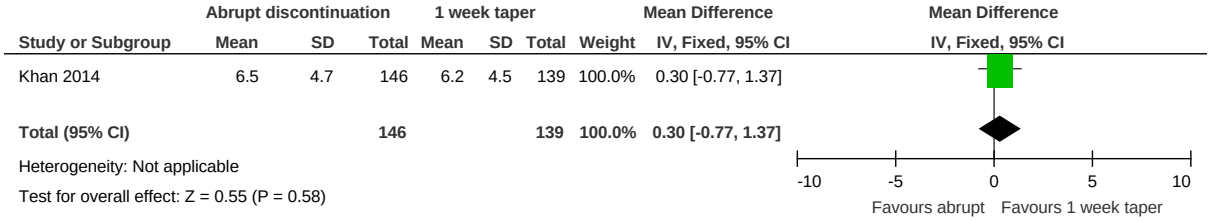
3

Figure 177: Suicide attempt (intentional drug overdose of a non-study medication) at 6 weeks



4

Figure 178: Depressive symptoms (QIDS-SR16) at 4 weeks



Note: Quick Inventory of Depressive Symptomatology Self-Report 0-27 Top=High is poor outcome; Comments: Range of the QIDS-SR16 not reported by the study. Online resources suggest this is a 16 item self-report measure of depression, with a total range of scores from 0-27 (0-5 no depression, 6-10 mild depression, 11-15 moderate depression, 16-20 severe depression, 21-27 very severe depression).

F.4.2.2 Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs abrupt (placebo)

Figure 179: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

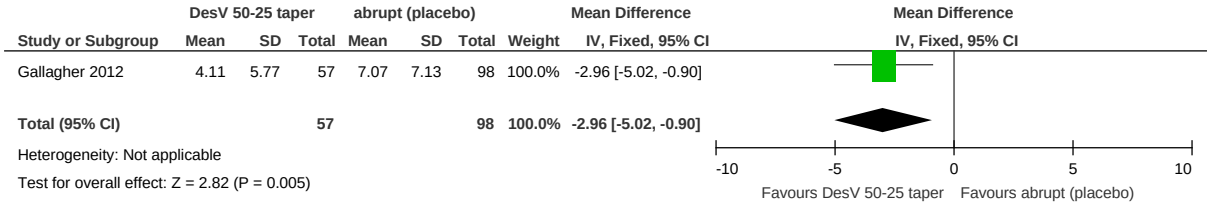


Figure 180: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

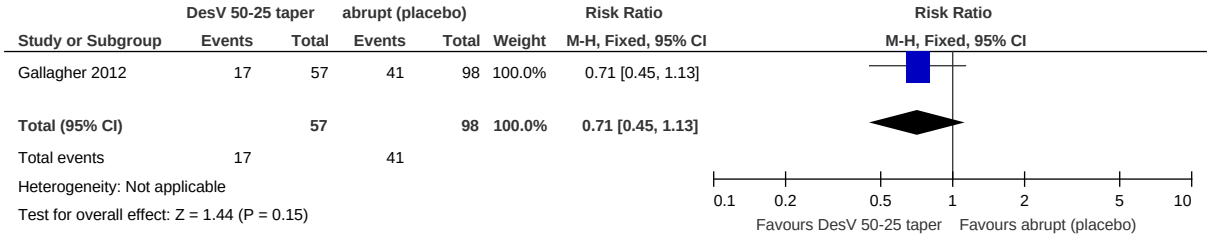


Figure 181: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

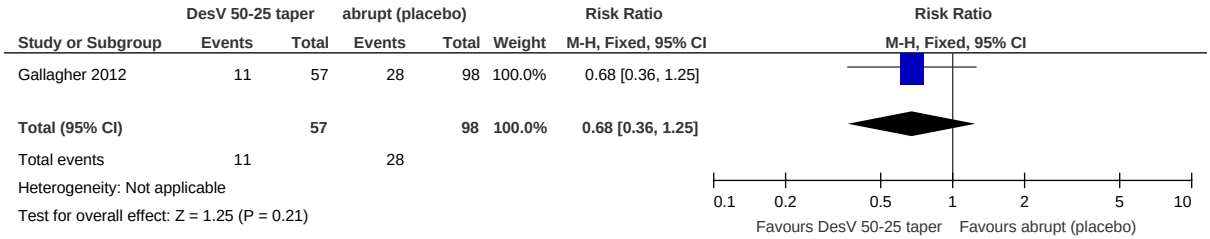


Figure 182: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

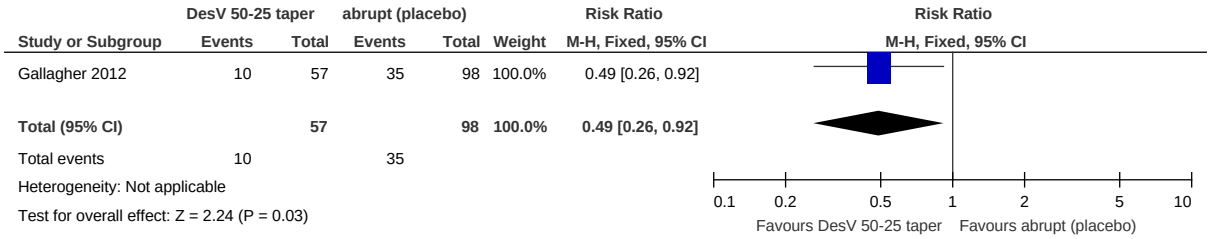


Figure 183: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

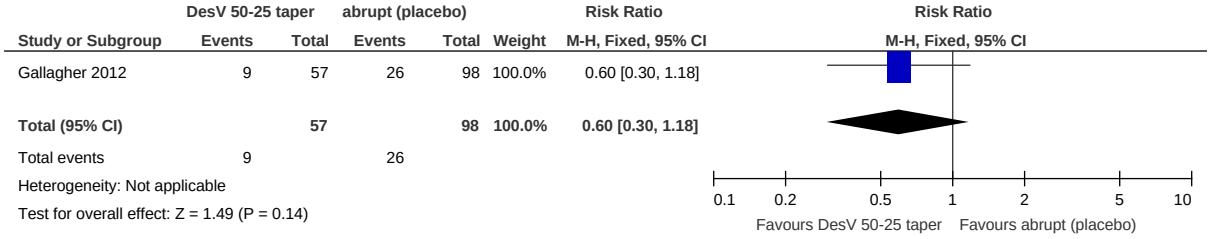


Figure 184: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

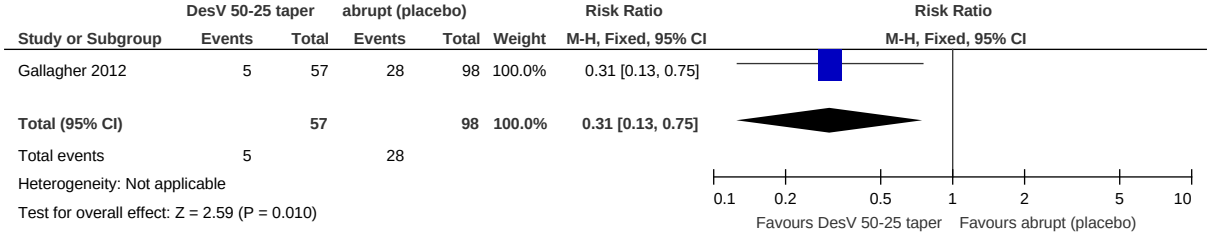


Figure 185: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

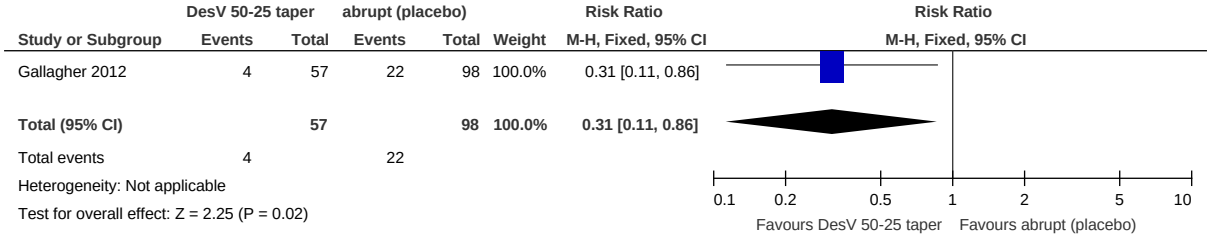


Figure 186: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

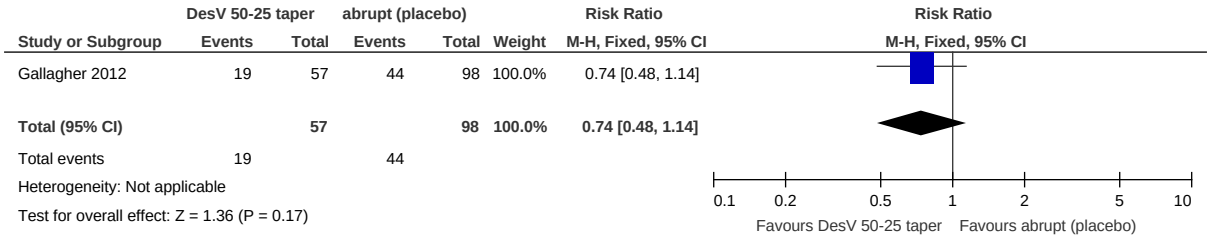


Figure 187: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

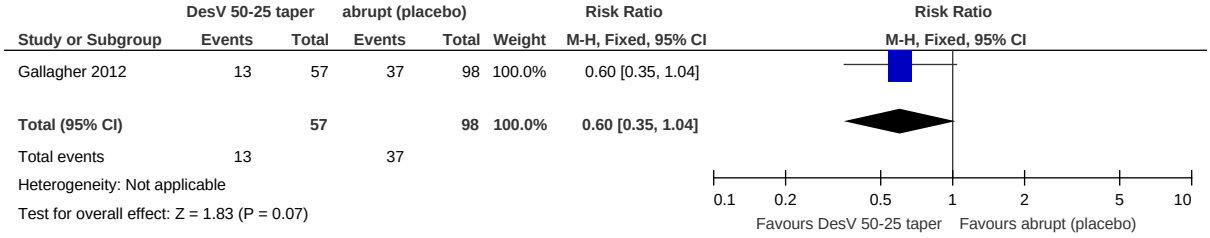


Figure 188: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)

F.4.2.3 Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper) vs abrupt (placebo)

Figure 189: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

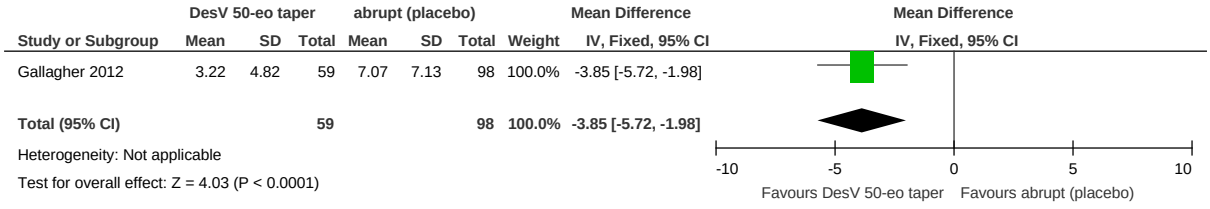


Figure 190: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

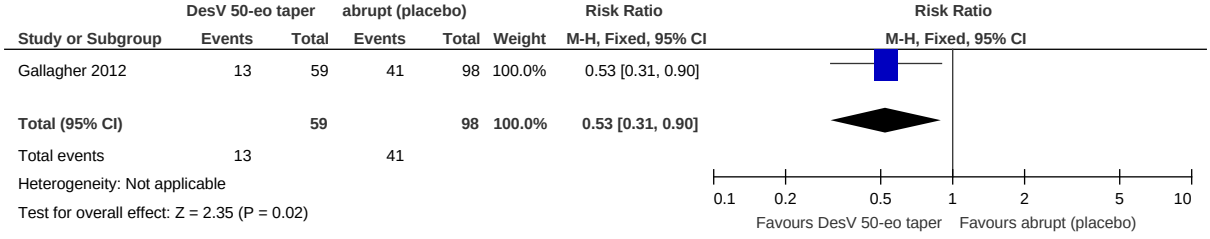


Figure 191: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

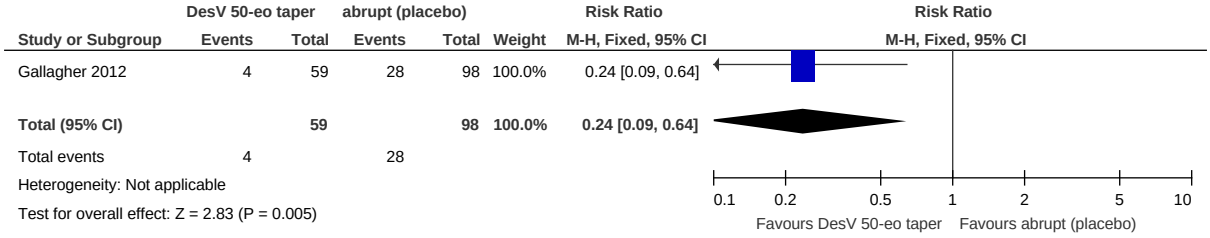


Figure 192: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

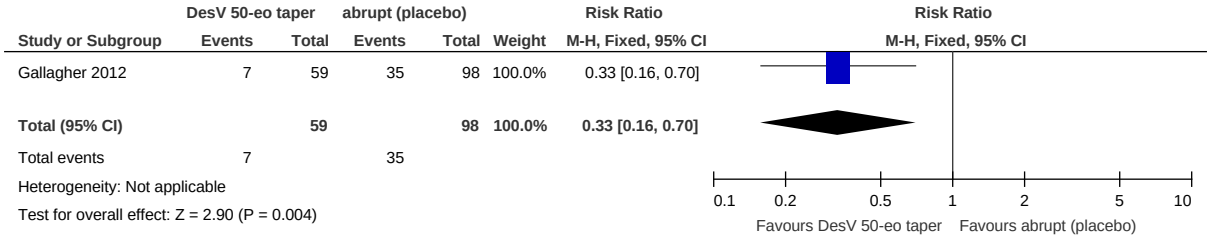


Figure 193: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

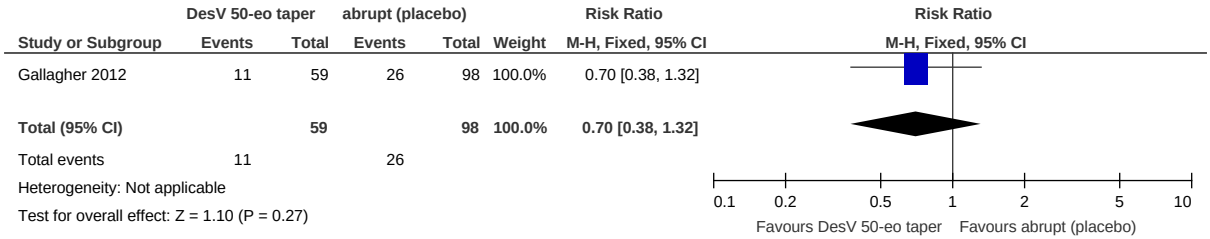


Figure 194: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

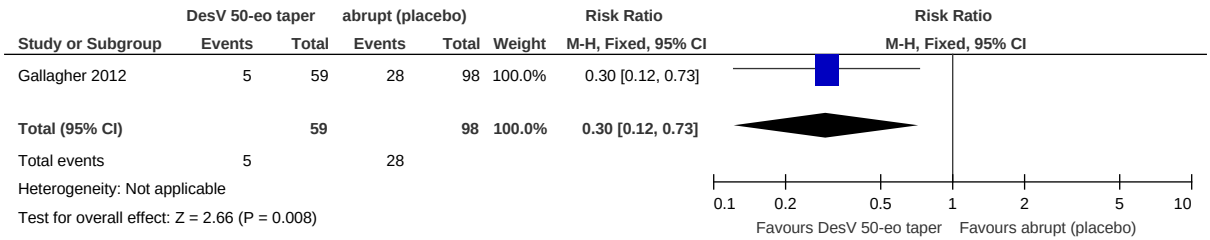
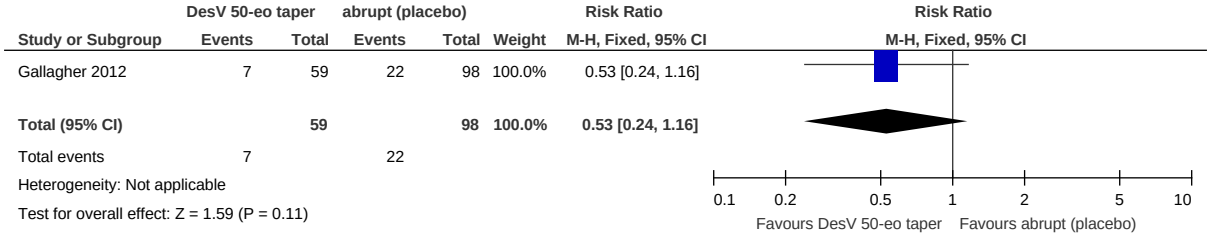
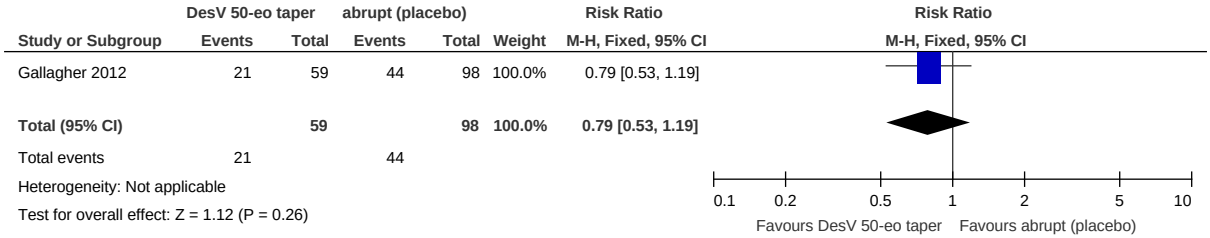


Figure 195: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



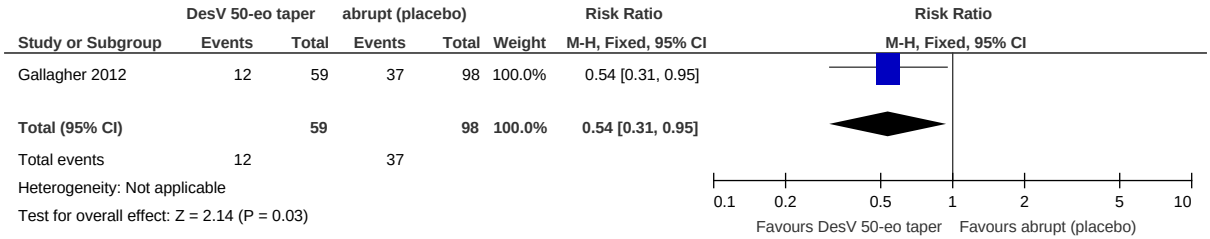
1

Figure 196: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



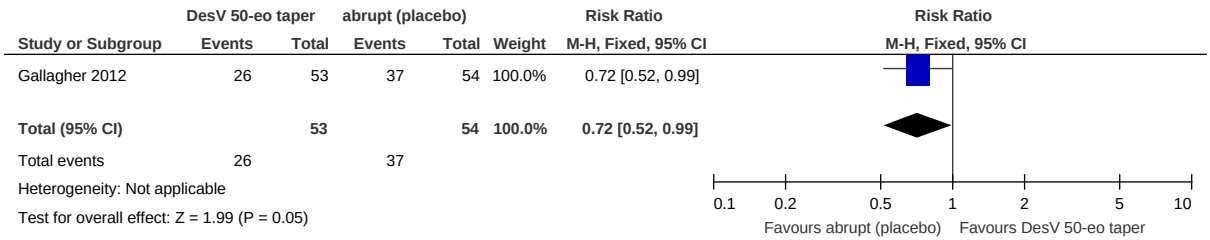
2

Figure 197: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



3

Figure 198: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)



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F.4.2.4 Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper) vs abrupt (placebo)

Figure 199: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

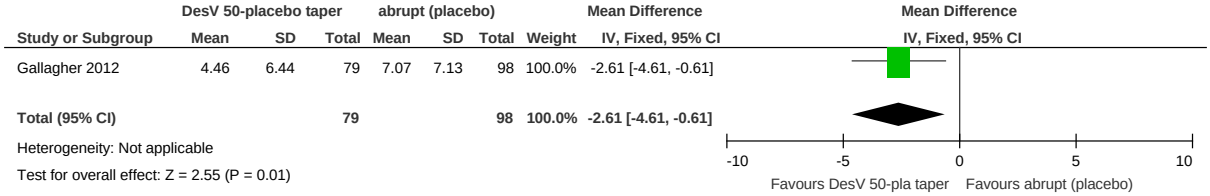


Figure 200: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

Figure 201: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

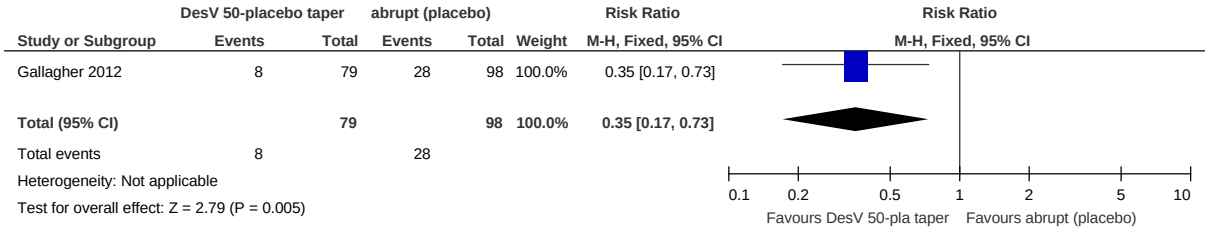


Figure 202: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

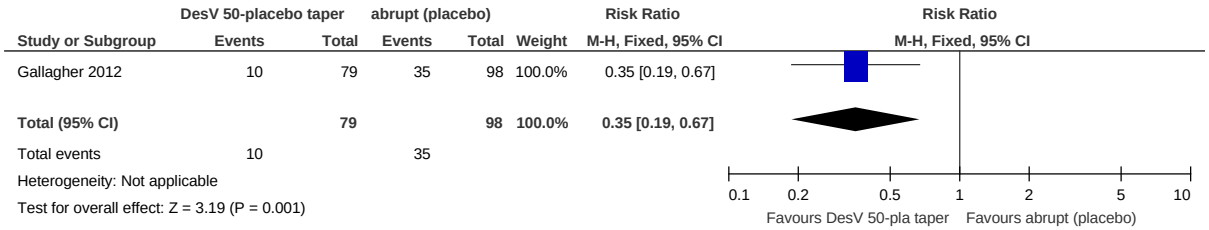


Figure 203: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

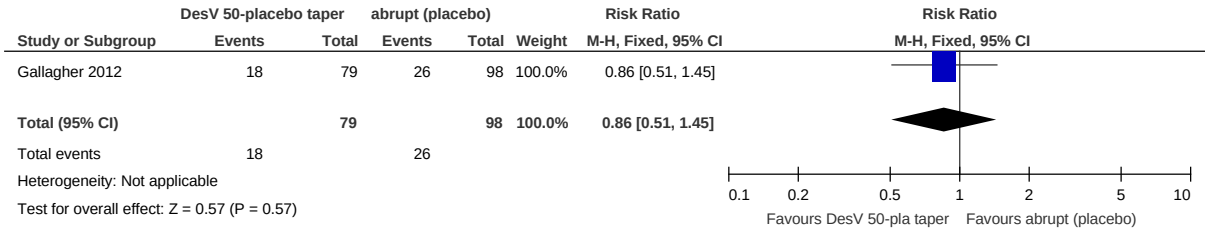


Figure 204: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

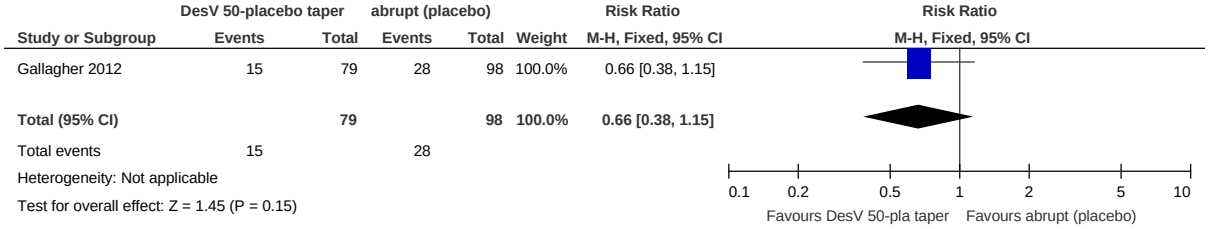


Figure 205: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

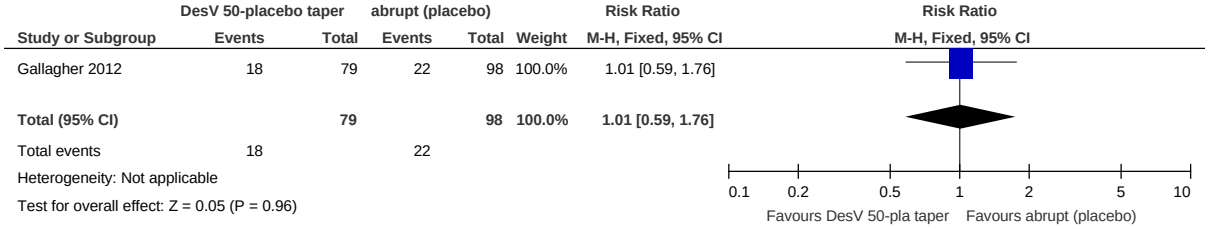


Figure 206: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

Figure 207: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

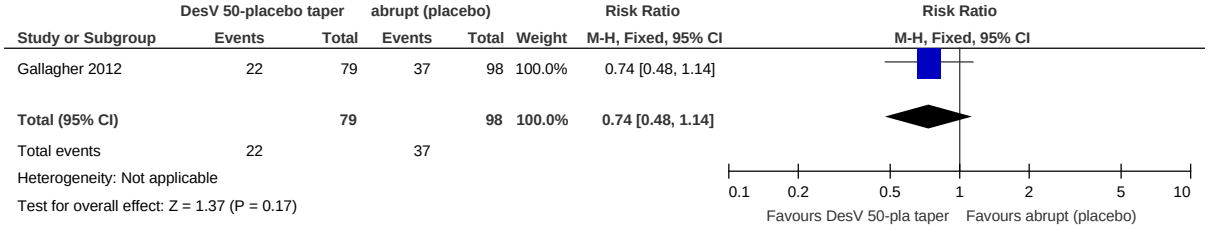
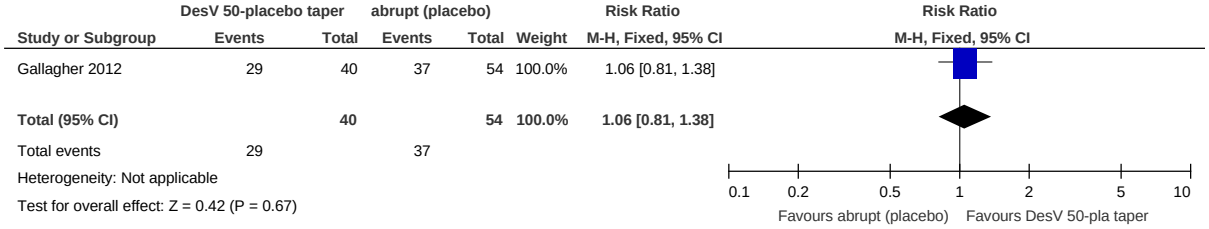


Figure 208: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)



F.4.2.5 Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper)

Figure 209: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

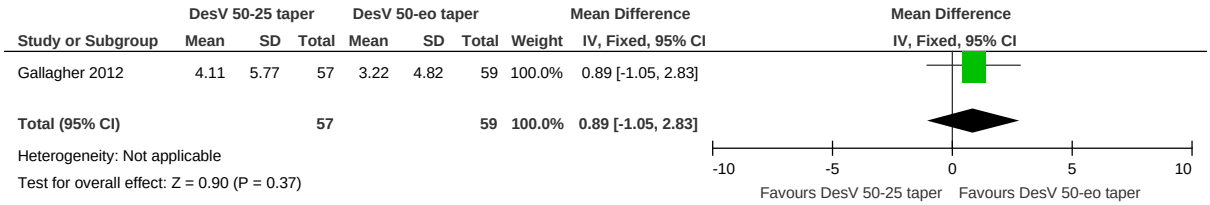


Figure 210: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

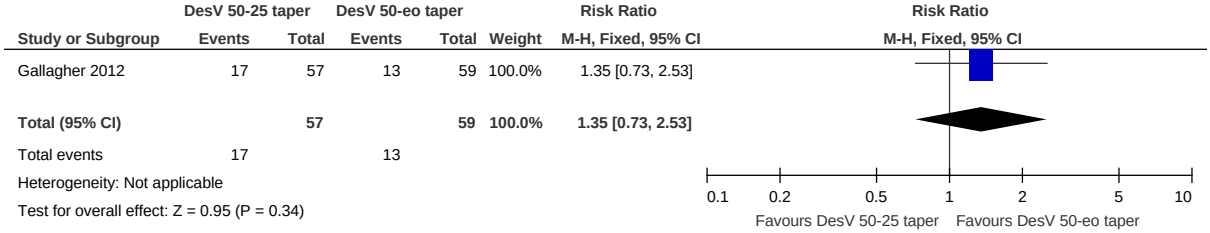
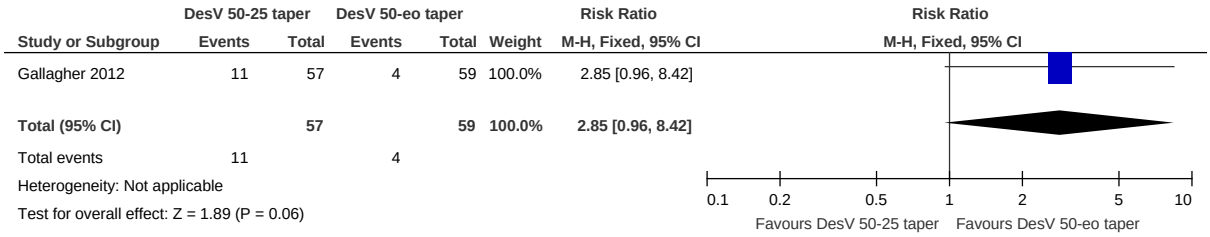
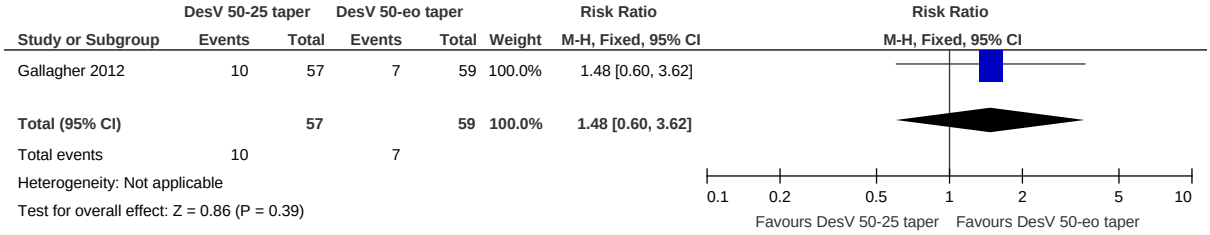


Figure 211: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)



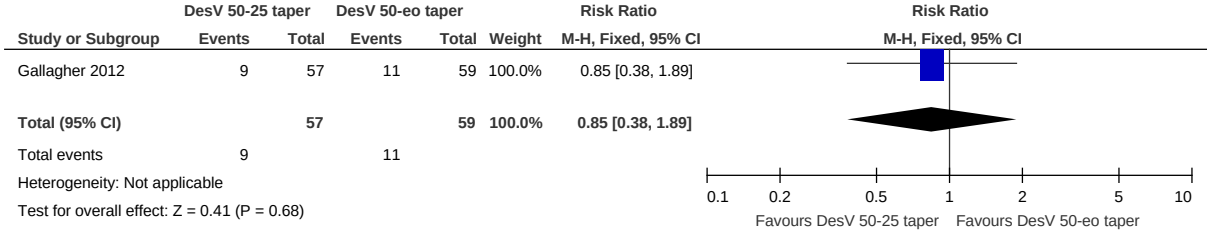
1

Figure 212: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



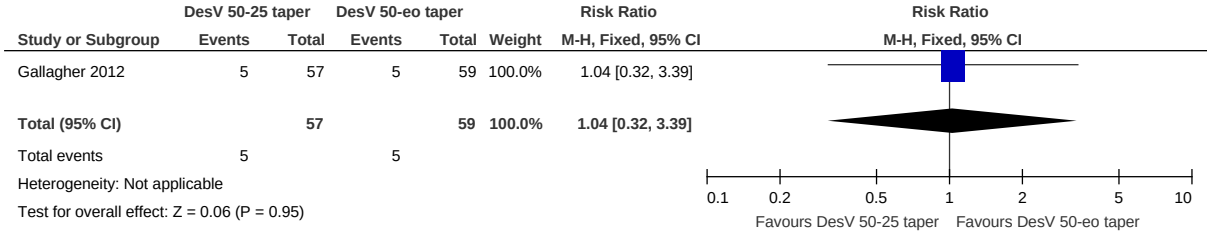
2

Figure 213: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



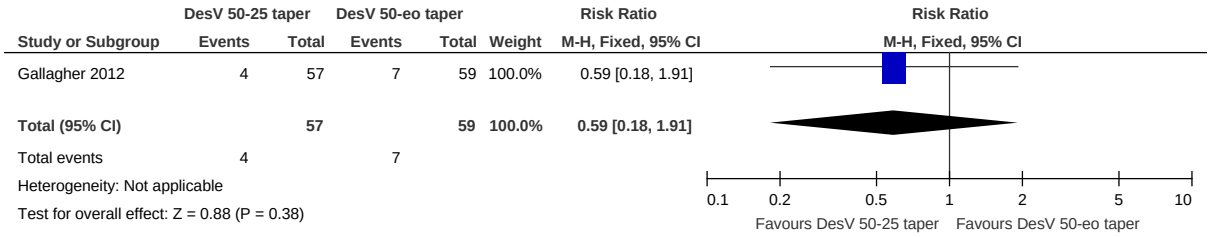
3

Figure 214: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



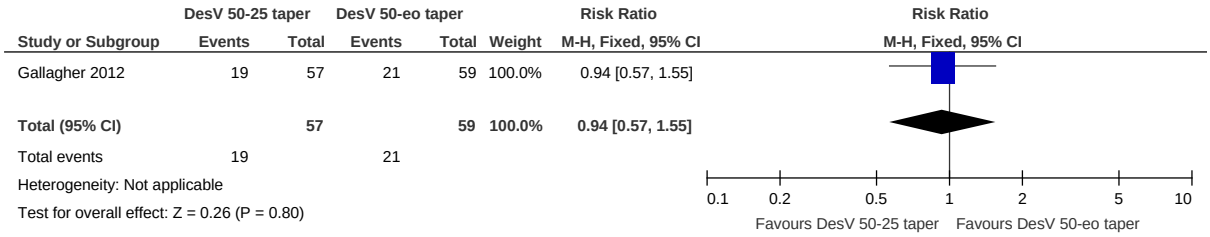
4

Figure 215: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



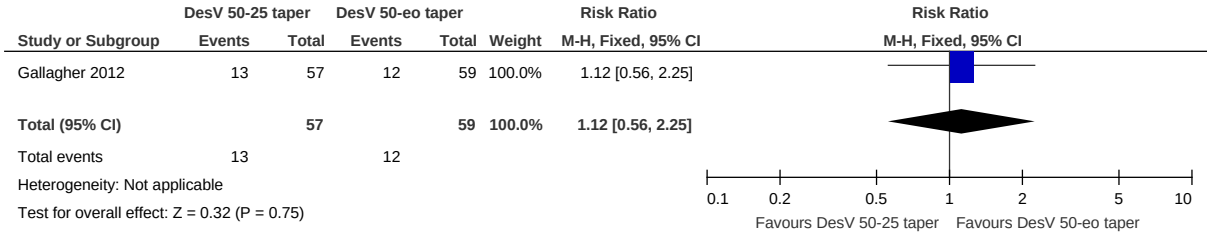
1

Figure 216: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



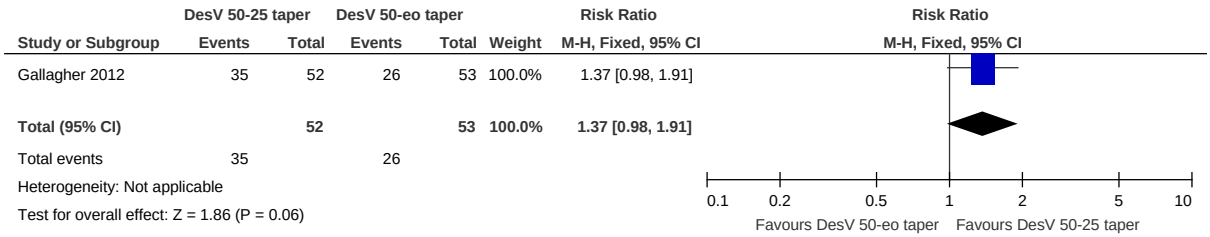
2

Figure 217: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



3

Figure 218: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)



4

F.4.2.6 Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Figure 219: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

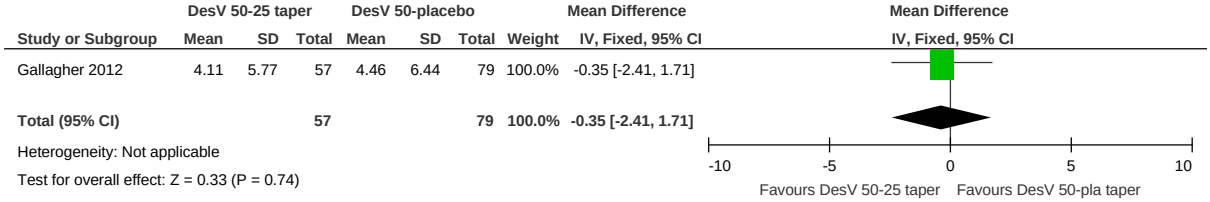


Figure 220: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

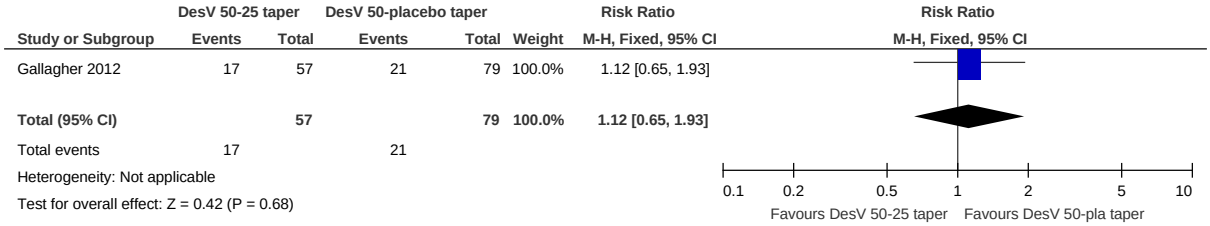


Figure 221: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

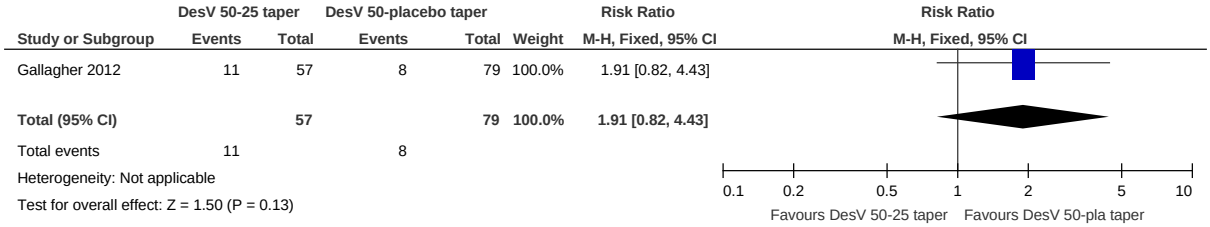


Figure 222: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

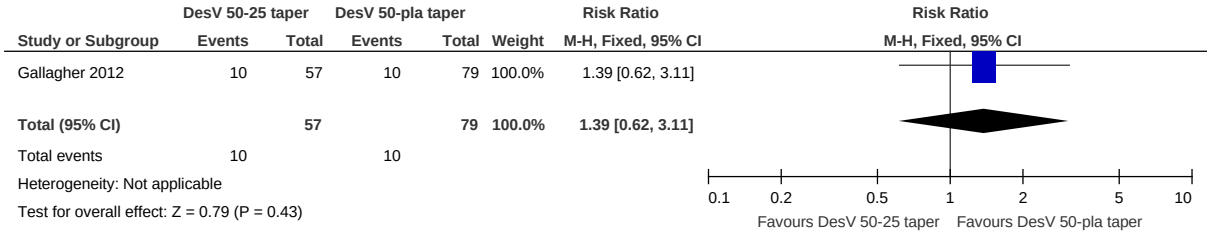
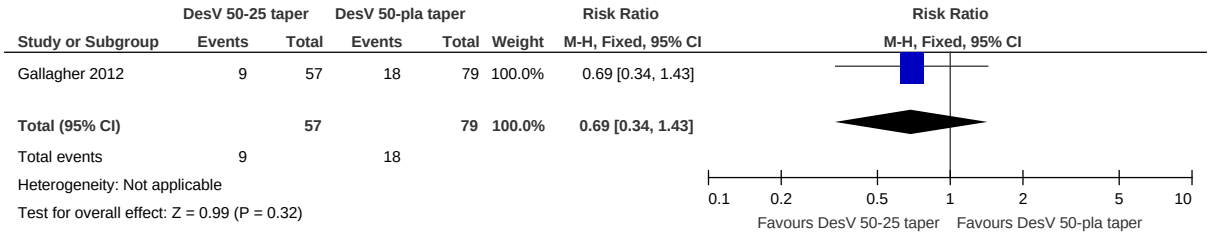
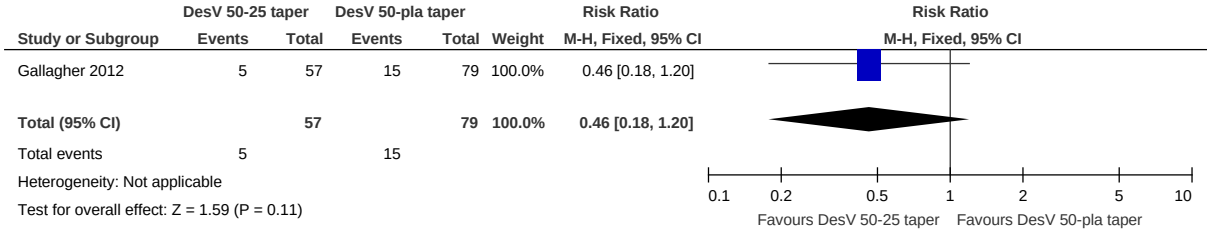


Figure 223: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



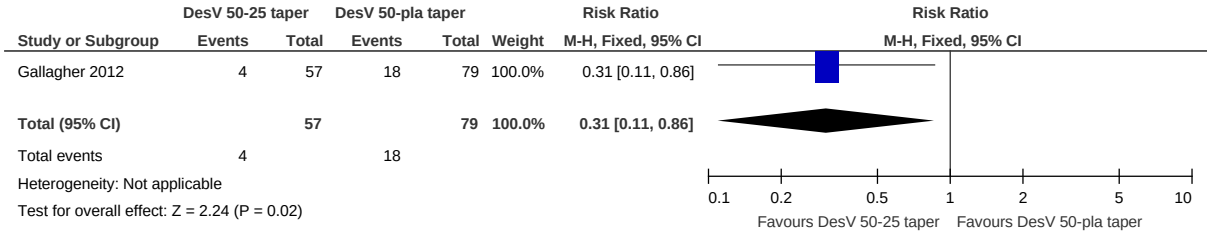
1

Figure 224: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



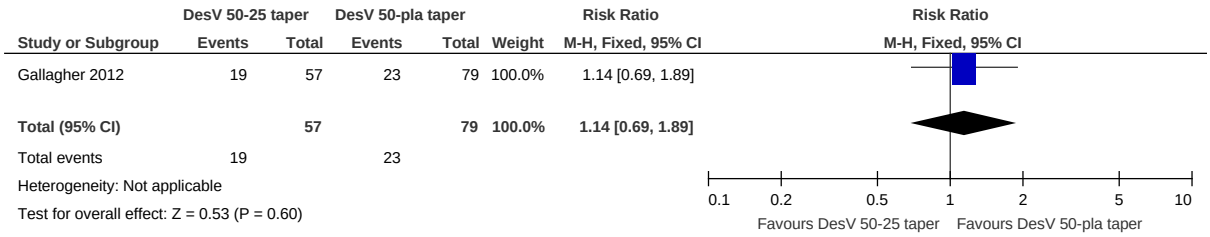
2

Figure 225: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



3

Figure 226: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



4

Figure 227: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

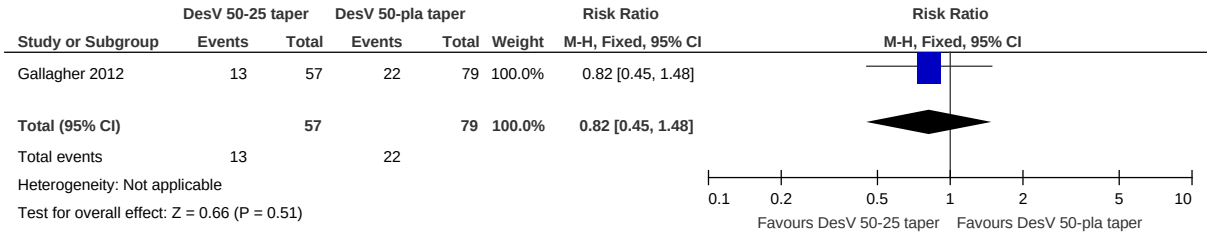
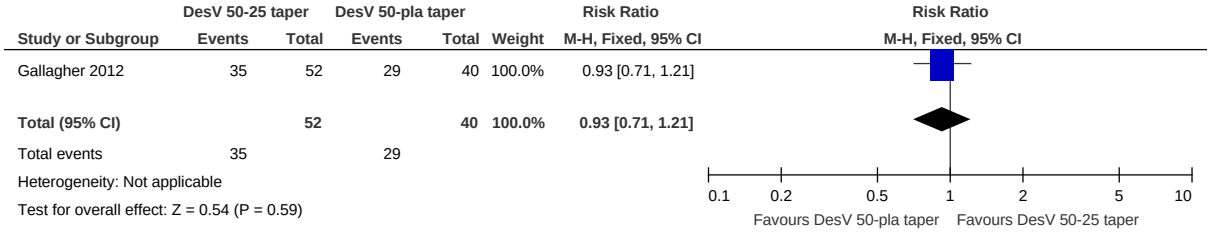


Figure 228: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)



F.4.2.7 Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Figure 229: Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper, 1 week after last dose in the taper)

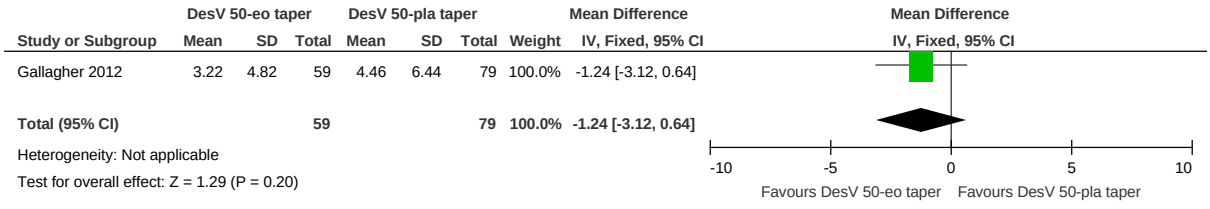


Figure 230: Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)

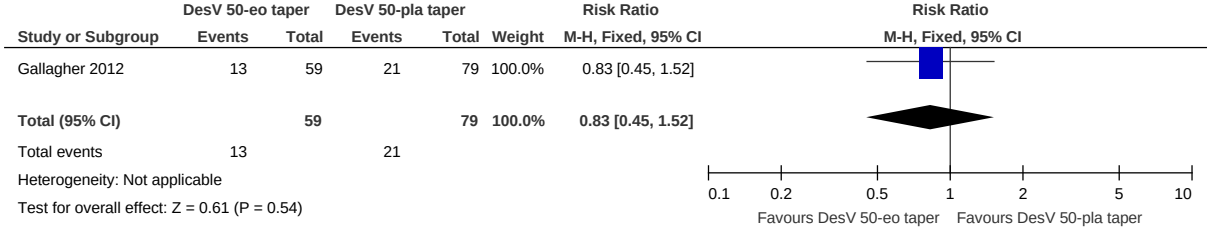
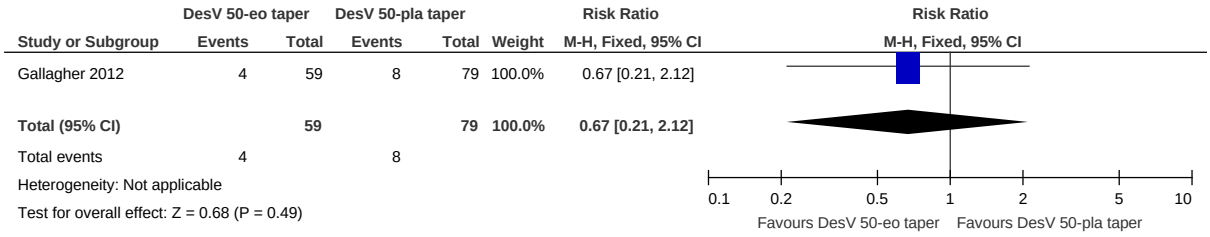
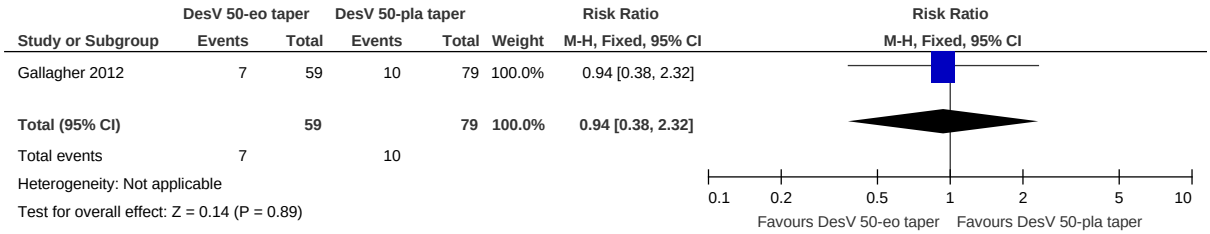


Figure 231: Headaches (incidence of symptom on the DESS, post-taper, 1 week after last dose in the taper)



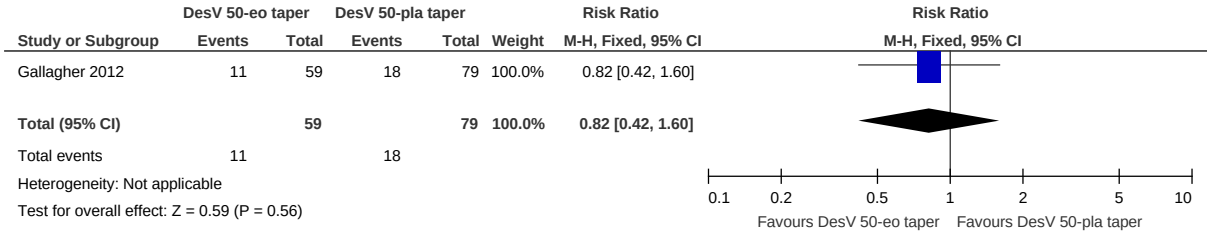
1

Figure 232: Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



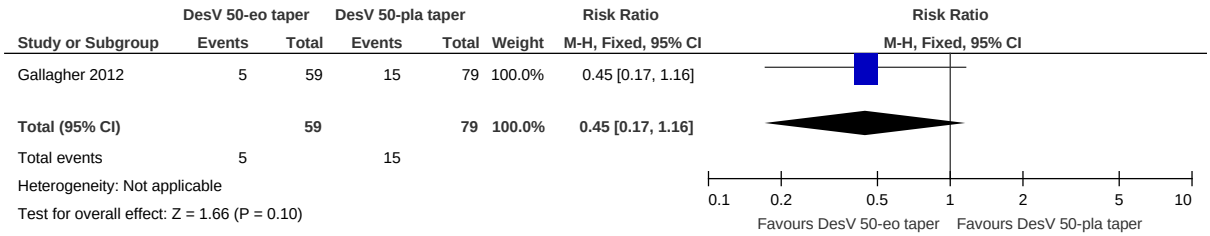
2

Figure 233: Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



3

Figure 234: Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)



4

Figure 235: Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

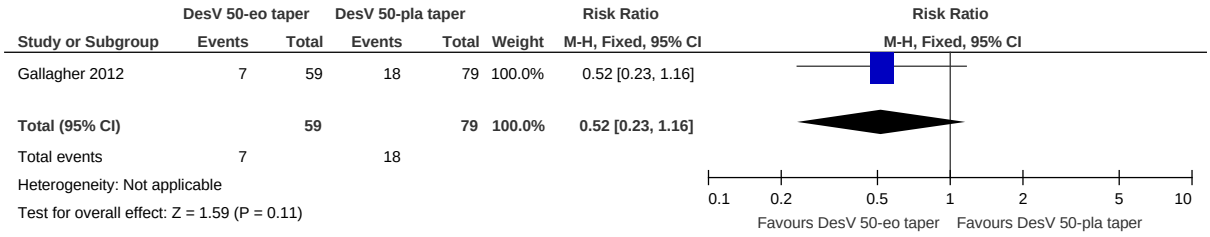


Figure 236: Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

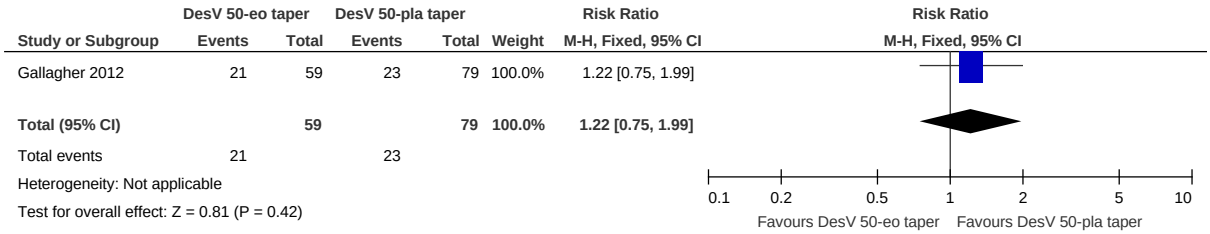


Figure 237: Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper)

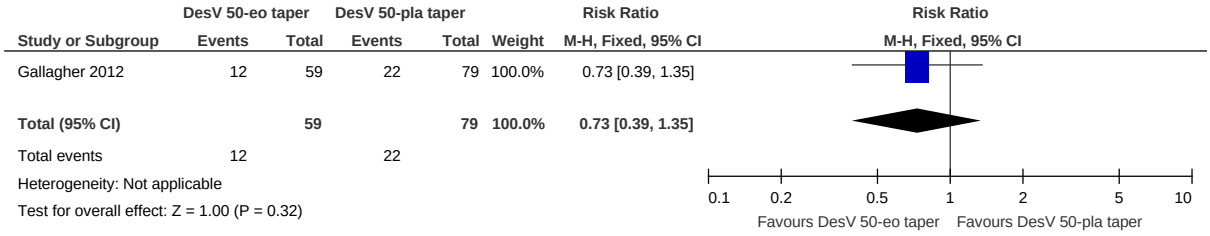
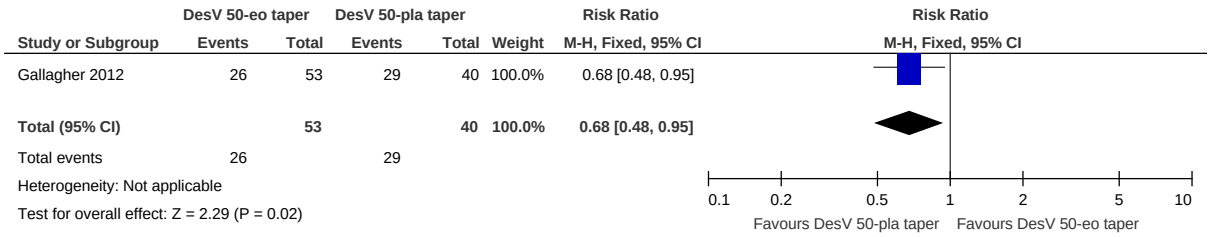


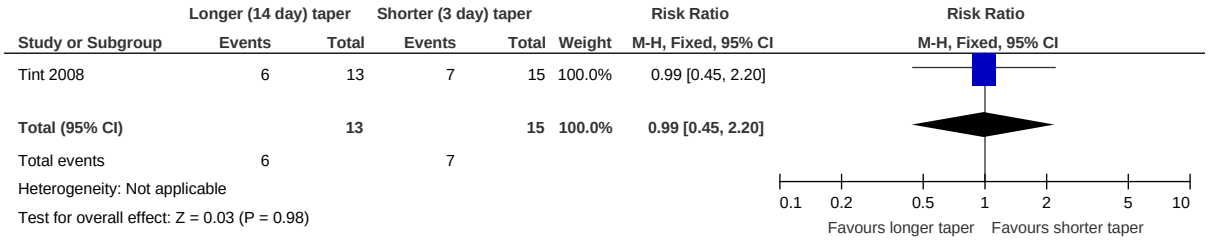
Figure 238: Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)



F.4.3 Mixed antidepressants:

F.4.3.1 Longer (14 day) taper vs shorter (3 day) taper

Figure 239: Discontinuation syndrome (≥3 new symptoms on the DESS checklist) at 5-7 days post-taper



F.4.3.2 CBT + taper vs taper

Figure 240: Suicide at 16 months

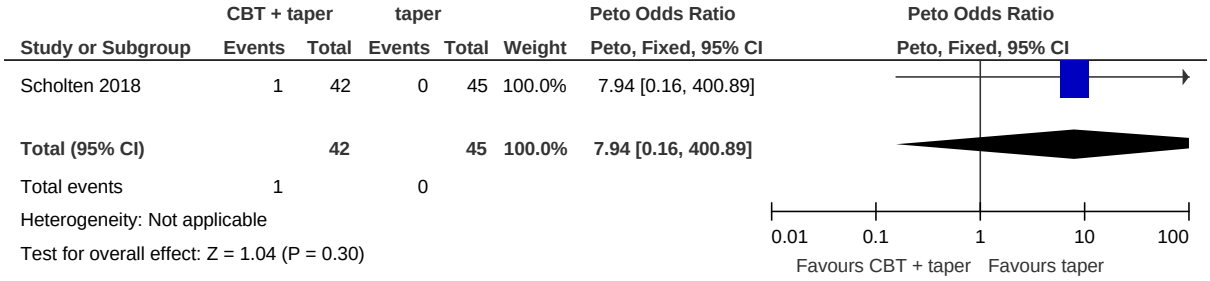
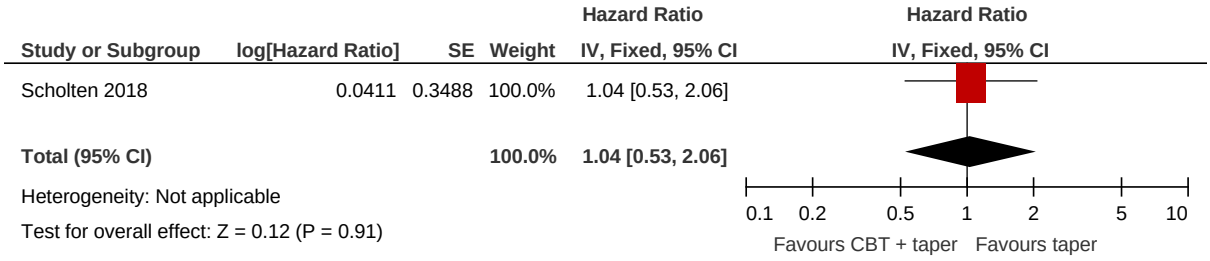
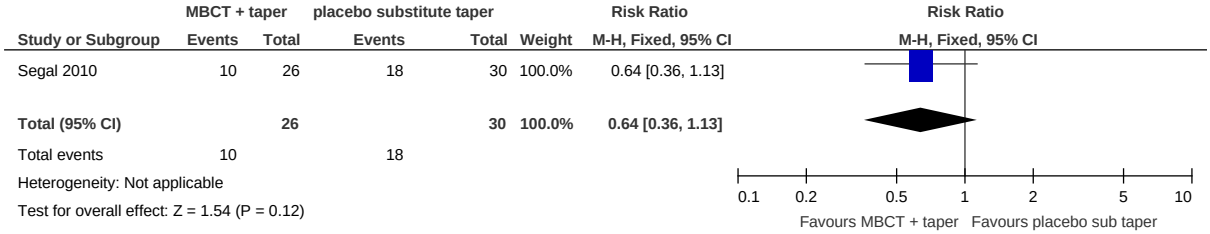


Figure 241: Recurrence of the previous anxiety disorder at 16 months



F.4.3.3 Mindfulness-based cognitive therapy (MBCT) + taper vs placebo substitution taper

Figure 242: Relapse (recurrence of major depressive episode) at 18 months



F.4.3.4 Advice to GP to discontinue the patient's antidepressants vs usual care

Figure 243: Antidepressant discontinuation

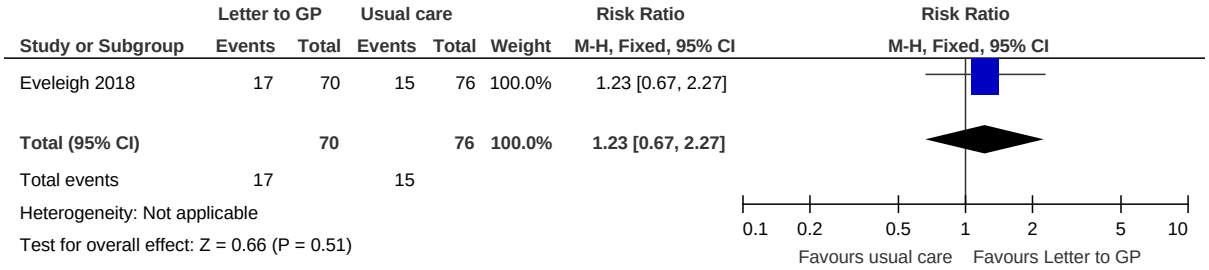


Figure 244: Antidepressant restart at 1 year

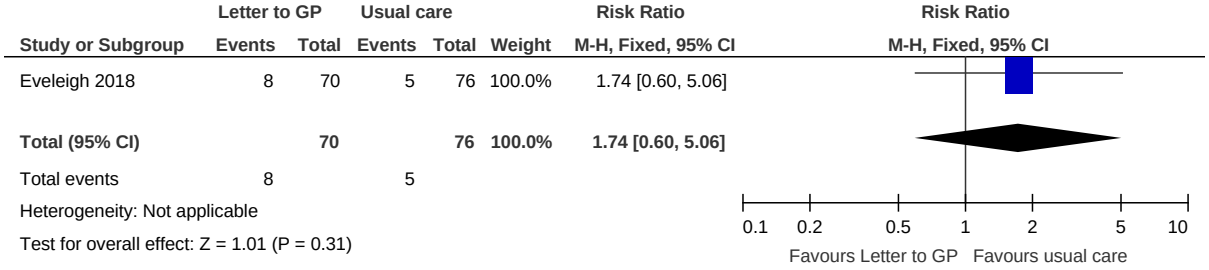
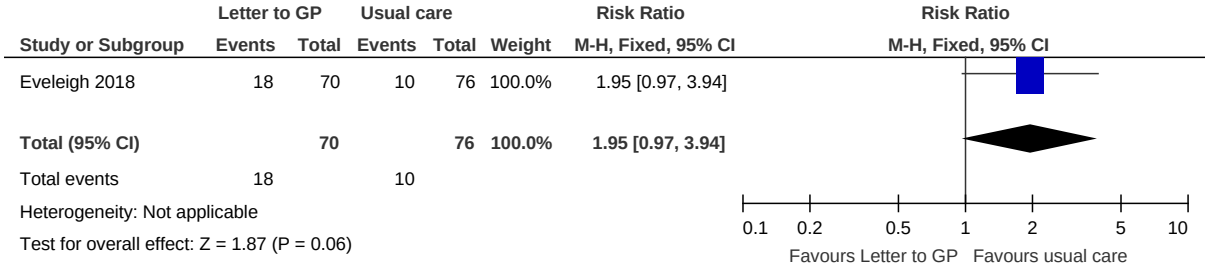


Figure 245: Relapse (depressive or anxiety disorder during the 1-year follow-up)



F.5 Mixed medicines

F.5.1 MBRP + initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal vs initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal

Figure 246: Equivalent hypnotic dosage: defined daily dose/diazepam mg equivalent (DDD/DME) at post-intervention (8 weeks)

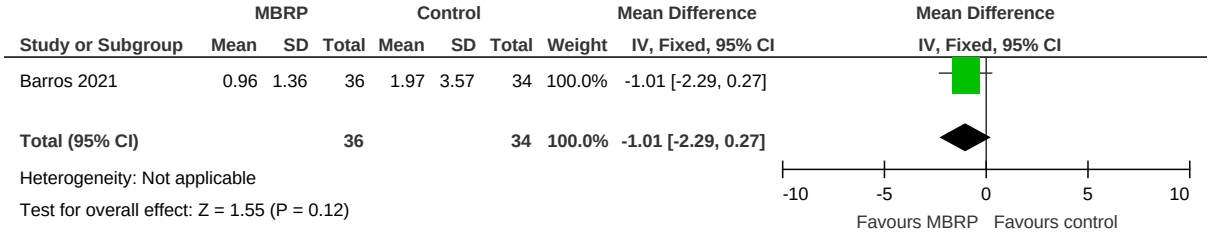


Figure 247: Equivalent hypnotic dosage: defined daily dose/diazepam mg equivalent (DDD/DME) at 6 months follow-up

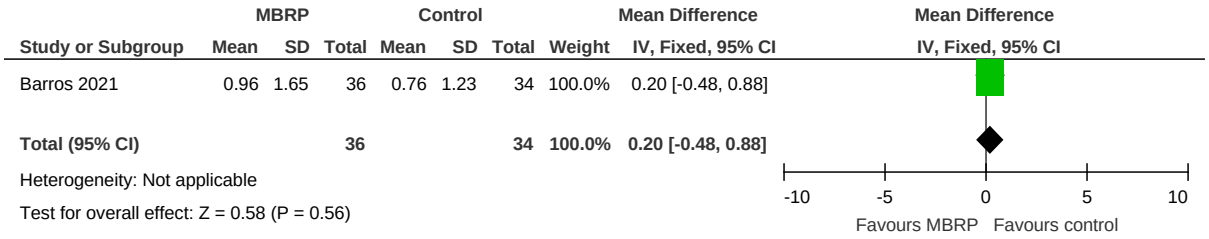
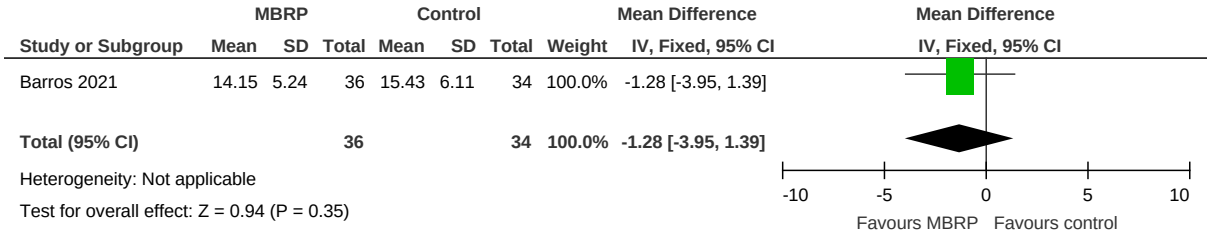
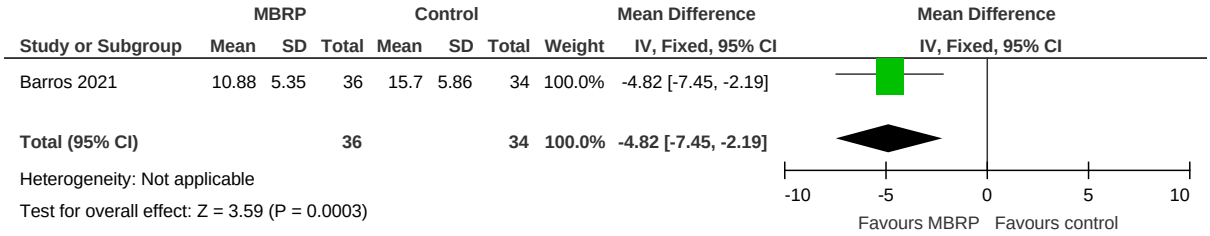


Figure 248: Insomnia severity rating (ISI) at post-intervention (8 weeks)



Insomnia Severity Scale 0-28, higher value is worse

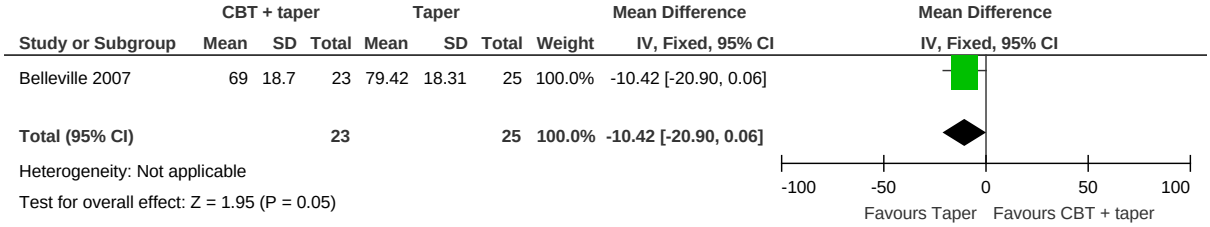
Figure 249: Insomnia severity rating (ISI) at 6 months follow-up



Insomnia Severity Scale 0-28, higher value is worse

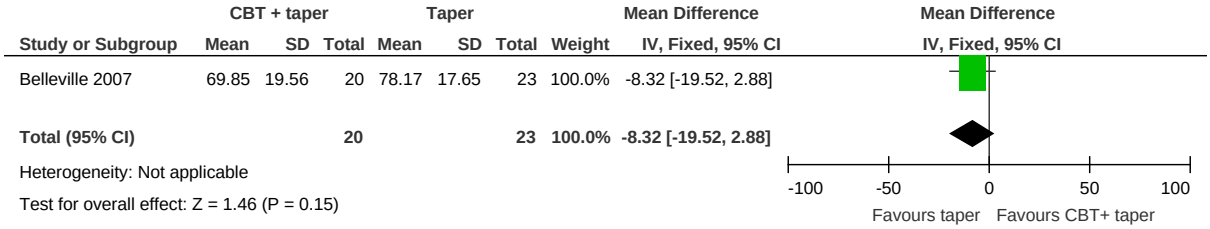
F.5.2 CBT plus taper vs taper

Figure 250: SF-36 physical health component post intervention (8 weeks)



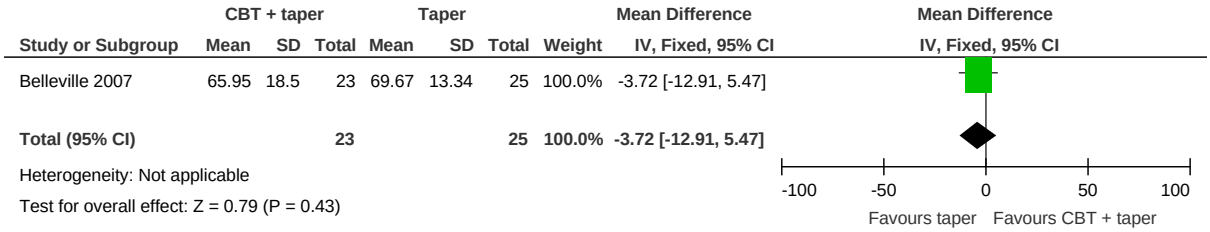
SF-36 physical component scale 0-100, higher value is better

Figure 251: SF-36 physical health component at 6 months



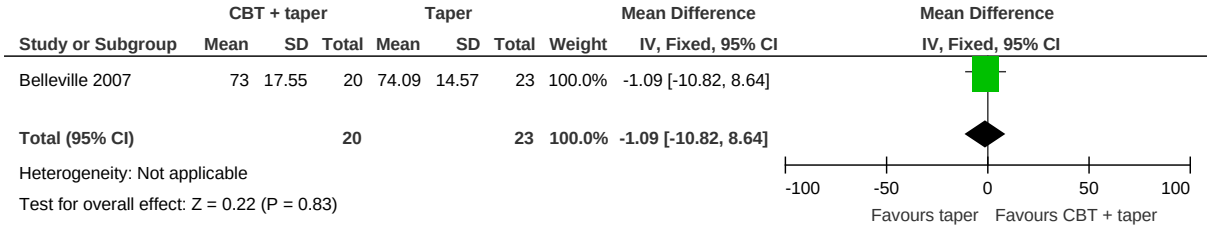
Source: SF-36 physical component scale 0-100, higher value is better

Figure 252: SF-36 mental health component post intervention (8 weeks)



SF-36 mental health component scale 0-100, higher value is better

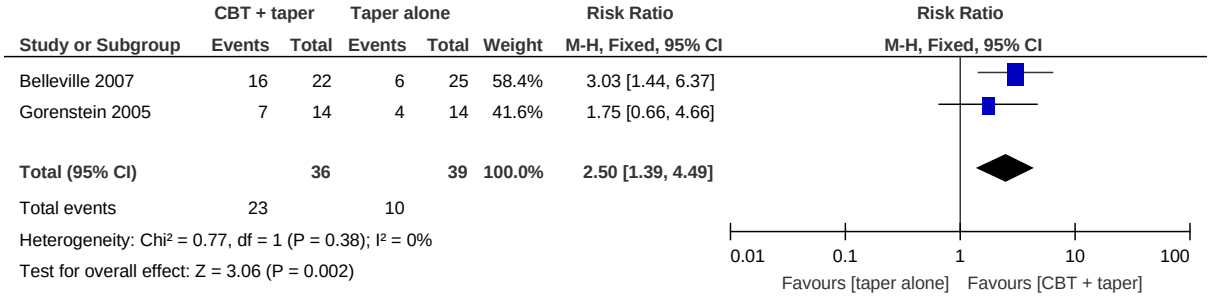
Figure 253: SF-36 mental health component at 6 months



SF-36 mental health component scale 0-100, higher value is better

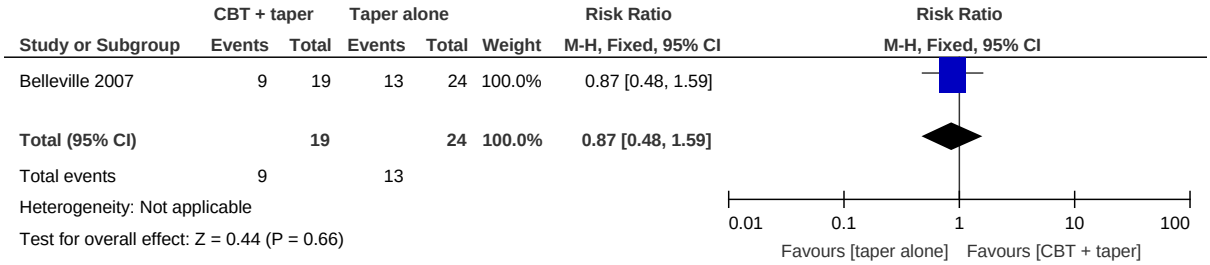
1

Figure 254: Cessation of drugs post intervention (8 and 13 weeks)



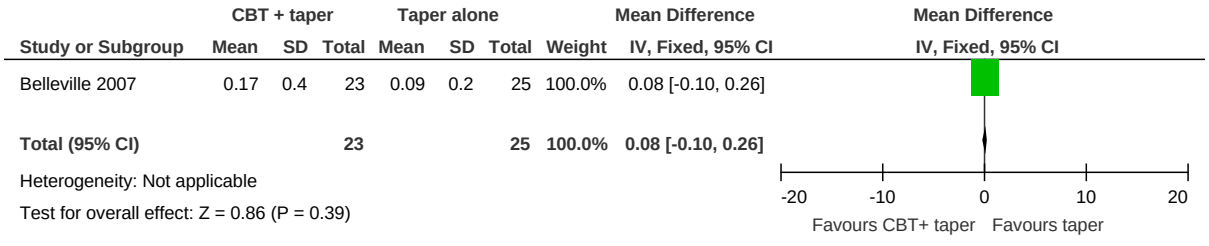
2

Figure 255: Cessation of drugs at 6 months



3

Figure 256: Benzodiazepine usage (Daily hypnotic dose) post intervention (8 weeks)



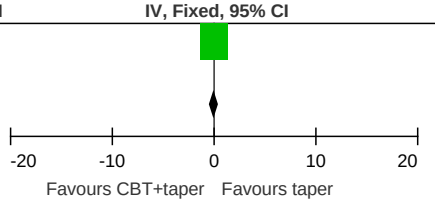
4

Figure 257: Benzodiazepine usage (Daily hypnotic dose) at 6 months

Study or Subgroup	CBT + taper Mean	SD	Total	Taper alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Belleville 2007	0.33	0.8	20	0.37	0.6	23	100.0%	-0.04 [-0.47, 0.39]
Total (95% CI)			**20**			**23**	**100.0%**	**-0.04 [-0.47, 0.39]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.18 (P = 0.85)



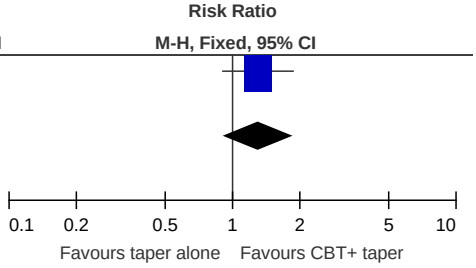
1

Figure 258: Decrease in prescribed drug use at 13 weeks

Study or Subgroup	CBT+ taper Events	Total	taper alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gorenstein 2005	13	14	10	14	100.0%	1.30 [0.91, 1.87]
Total (95% CI)		**14**		**14**	**100.0%**	**1.30 [0.91, 1.87]**
Total events	13		10			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.42 (P = 0.16)



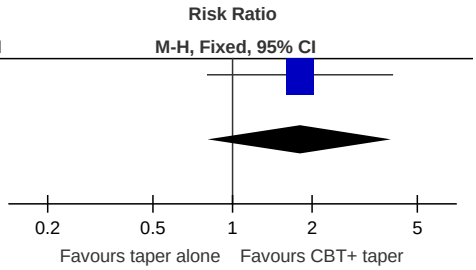
2

Figure 259: Responder' at 13 weeks

Study or Subgroup	CBT+ taper Events	Total	taper alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gorenstein 2005	9	14	5	14	100.0%	1.80 [0.81, 4.02]
Total (95% CI)		**14**		**14**	**100.0%**	**1.80 [0.81, 4.02]**
Total events	9		5			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.43 (P = 0.15)



Clinical Global Impressions Scale 'much improved' or 'very much improved'

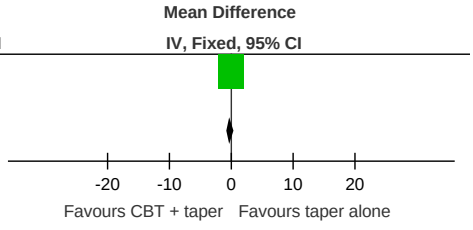
3

Figure 260: Average proportion of medication taken at post-treatment relative to pre-treatment

Study or Subgroup	CBT + taper Mean	SD	Total	Taper alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gorenstein 2005	0.465	0.82	14	0.583	0.81	14	100.0%	-0.12 [-0.72, 0.49]
Total (95% CI)			**14**			**14**	**100.0%**	**-0.12 [-0.72, 0.49]**

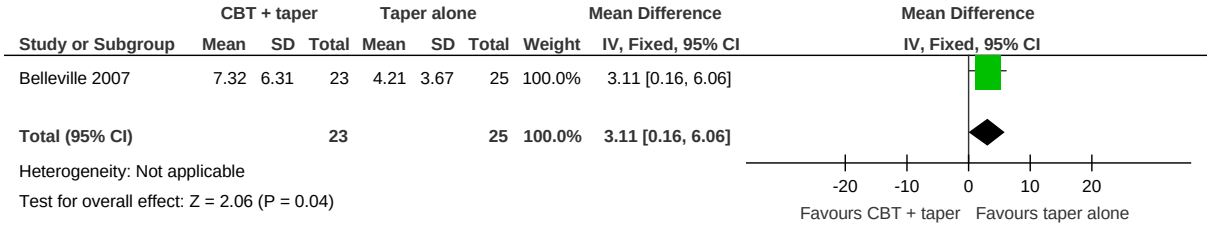
Heterogeneity: Not applicable

Test for overall effect: Z = 0.38 (P = 0.70)



4

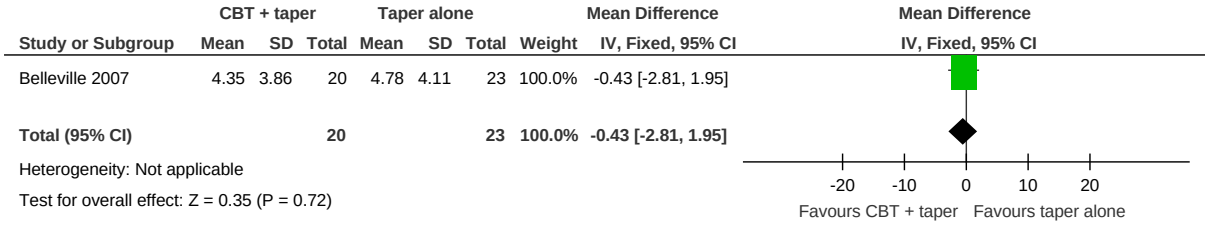
Figure 261: BDI post intervention (8 weeks)



Beck depression inventory scale 0-63, higher value is worse

1

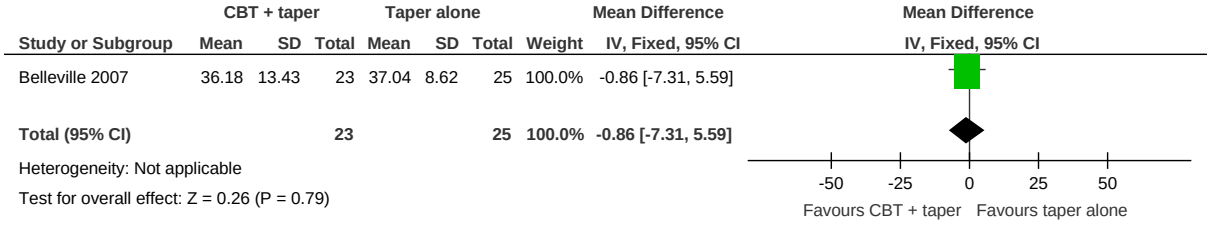
Figure 262: BDI at 6 months



Beck Depression Inventory 0-63, higher value is worse

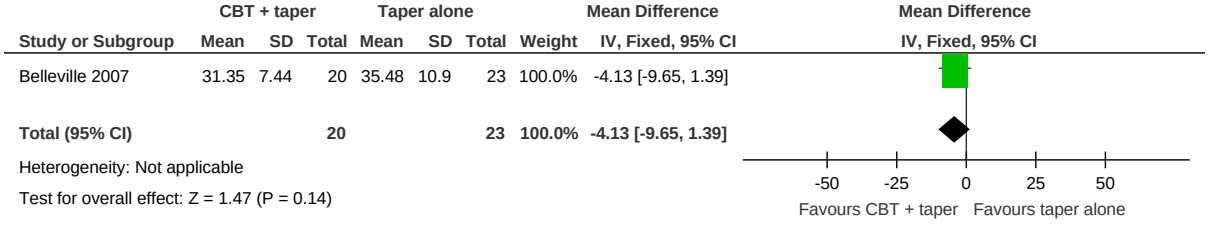
2
3

Figure 263: Anxiety- STAI post intervention (8 weeks)



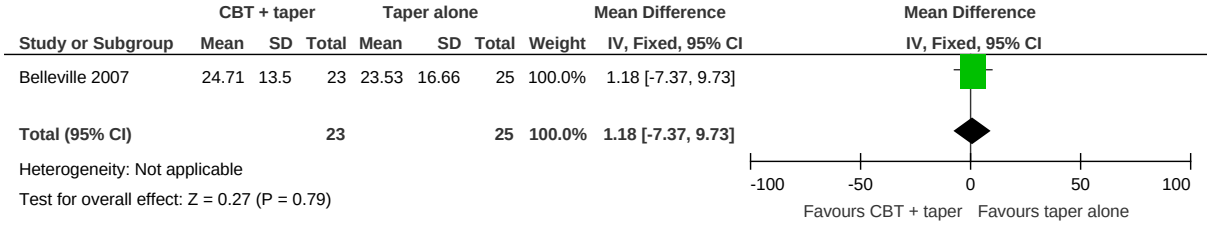
STAI score 20-80, higher value is worse

Figure 264: Anxiety- STAI at 6 months



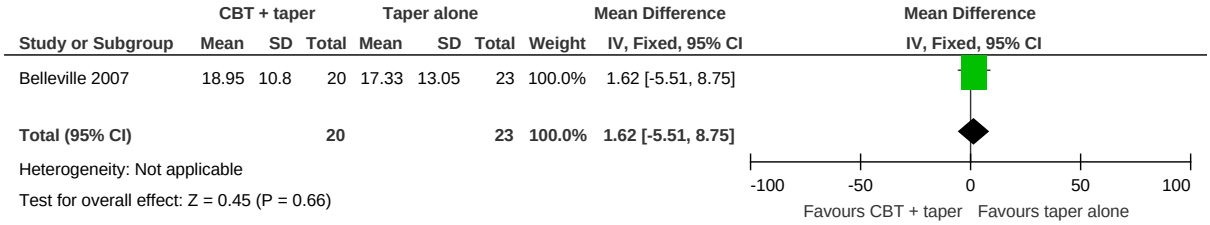
STAI score 20-80, higher value is worse

Figure 265: Withdrawal symptoms post intervention- CIWA-B (8 weeks)



Source: CIWA-B score 1-80, higher value is worse

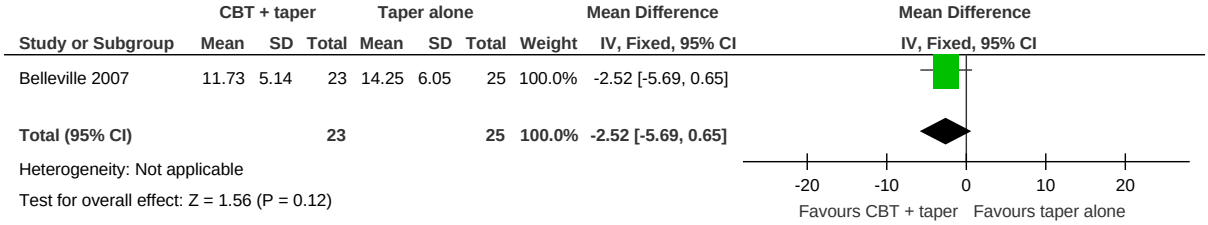
Figure 266: Withdrawal symptoms at 6 months- CIWA-B



CIWA-B score 1-80, higher value is worse

1

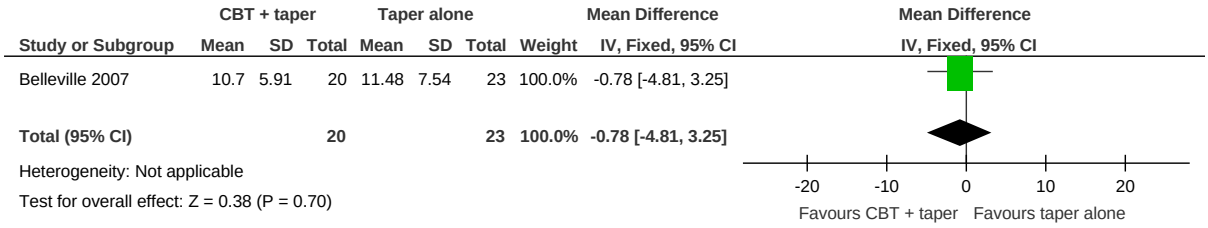
Figure 267: Insomnia- Insomnia Severity Scale post intervention (8 weeks)



Insomnia severity index scale 0-28, higher value is worse

2

Figure 268: Insomnia- Insomnia Severity Scale at 6 months

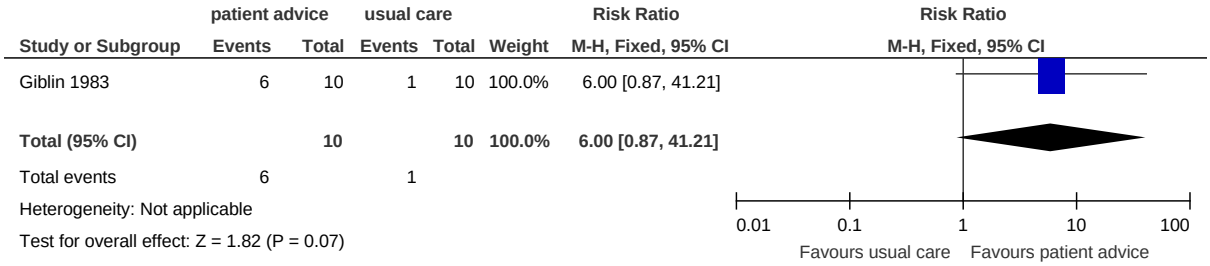


Insomnia severity index scale 0-28, higher value is worse

3

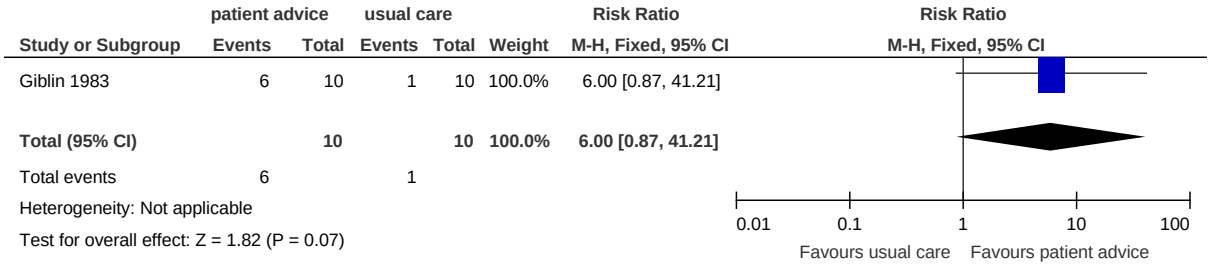
F.5.3 Patient advice + relaxation vs usual care

Figure 269: No hypnotic use during previous 4-week period post intervention (4 weeks)



4

Figure 270: No hypnotic use during previous 4-week period at 12 weeks



5
6

Figure 271: Resumption of nightly hypnotic use post intervention (4 weeks)

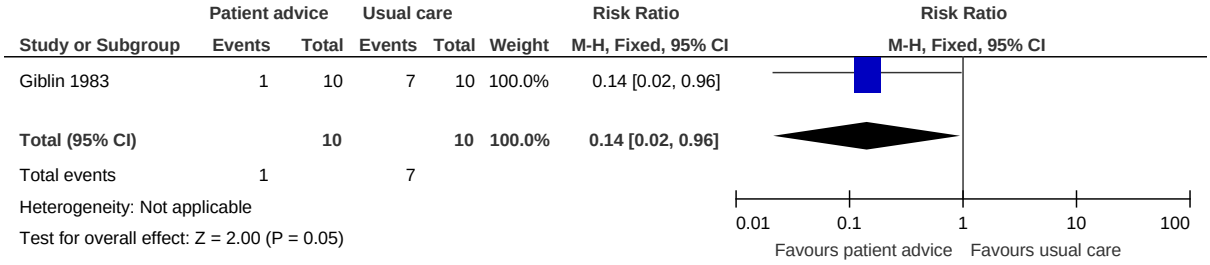


Figure 272: Resumption of nightly hypnotic use at 12 weeks

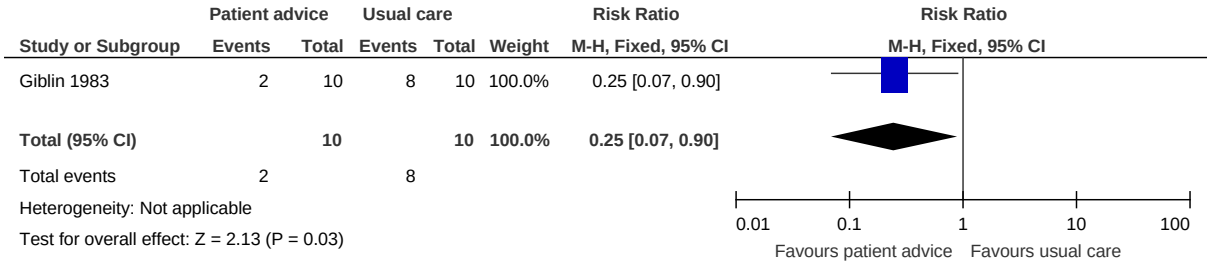


Figure 273: Sleep latency per night post intervention (4 weeks)

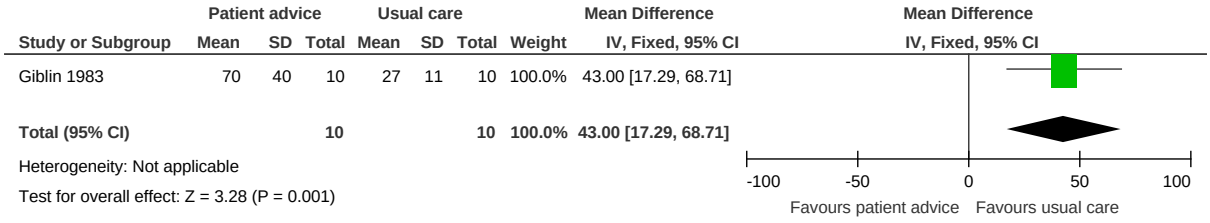
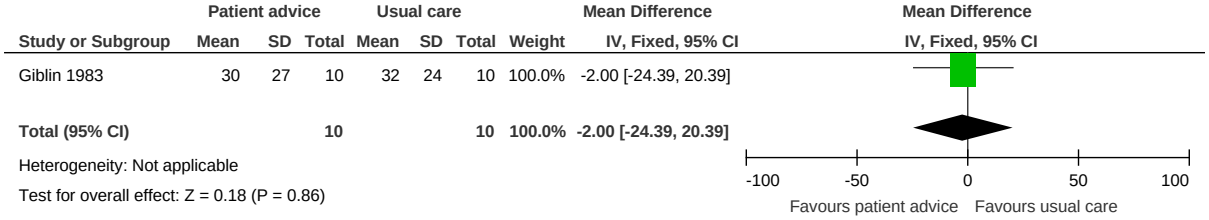


Figure 274: Sleep latency per night at 12 weeks



F.5.4 Melatonin + support + taper vs Placebo + support + taper

Figure 275: Cessation of drug post intervention (1 month)

Study or Subgroup	Melatonin+support+taper Events	Total	Support+taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lahteenmaki 2014	36	45	41	45	100.0%	0.88 [0.74, 1.04]
Total (95% CI)		**45**		**45**	**100.0%**	**0.88 [0.74, 1.04]**
Total events	36		41			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

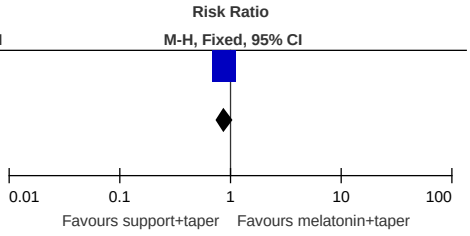


Figure 276: Cessation of drug at 6 months

Study or Subgroup	Melatonin+support+taper Events	Total	Support+taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lahteenmaki 2014	14	44	20	45	100.0%	0.72 [0.42, 1.23]
Total (95% CI)		**44**		**45**	**100.0%**	**0.72 [0.42, 1.23]**
Total events	14		20			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.21 (P = 0.23)

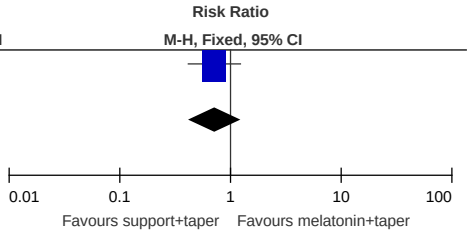


Figure 277: Cessation of drug at 3 years

Study or Subgroup	Melatonin+support+taper Events	Total	Support+taper Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lahteenmaki 2014	14	44	20	45	100.0%	0.72 [0.42, 1.23]
Total (95% CI)		**44**		**45**	**100.0%**	**0.72 [0.42, 1.23]**
Total events	14		20			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.21 (P = 0.23)

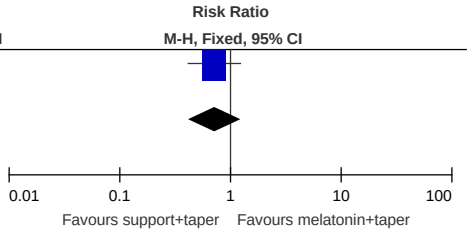
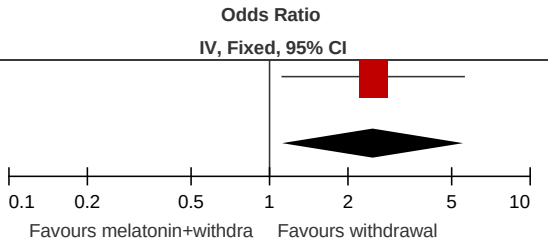


Figure 278: Benzodiazepine usage at 6 months

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Lahteenmaki 2014	0.9162907	0.41	100.0%	2.50 [1.12, 5.58]
Total (95% CI)			**100.0%**	**2.50 [1.12, 5.58]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.23 (P = 0.03)



F.5.5 Prescriber education vs written manual for prescribers

Figure 279: Cessation of drug at 0-3 months

Study or Subgroup	Intensive support Events	Total	Written manual Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van de Steeg van Gompel 2009	998	11423	659	7975	100.0%	1.06 [0.96, 1.16]
Total (95% CI)		**11423**		**7975**	**100.0%**	**1.06 [0.96, 1.16]**
Total events	998		659			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)

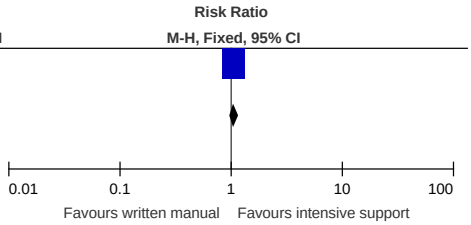


Figure 280: Cessation of drug at 4-6 months

Study or Subgroup	Intensive support Events	Total	Written manual Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van de Steeg van Gompel 2009	1129	11423	810	7975	100.0%	0.97 [0.89, 1.06]
Total (95% CI)		**11423**		**7975**	**100.0%**	**0.97 [0.89, 1.06]**
Total events	1129		810			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.53)

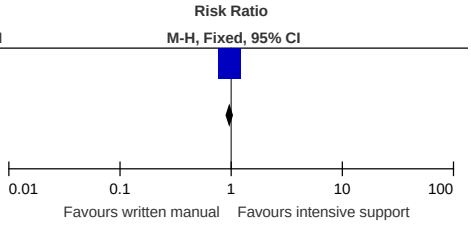


Figure 281: 50% reduction in drug use at 0-3 months

Study or Subgroup	Intensive support Events	Total	Written manual Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van de Steeg van Gompel 2009	1793	11423	1179	7975	100.0%	1.06 [0.99, 1.14]
Total (95% CI)		**11423**		**7975**	**100.0%**	**1.06 [0.99, 1.14]**
Total events	1793		1179			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)

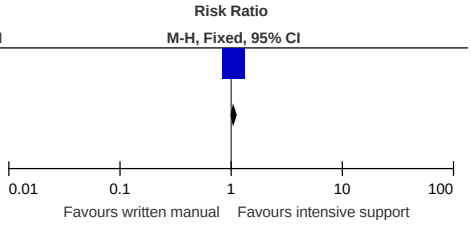
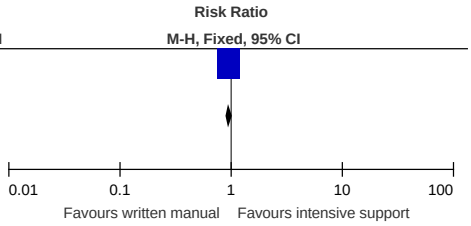


Figure 282: 50% reduction in benzodiazepine use at 4-6 months

Study or Subgroup	Intensive support Events	Total	Written manual Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van de Steeg van Gompel 2009	1820	11423	1331	7975	100.0%	0.95 [0.89, 1.02]
Total (95% CI)		**11423**		**7975**	**100.0%**	**0.95 [0.89, 1.02]**
Total events	1820		1331			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)



F.5.6 Structured intervention + follow-up vs usual care

Figure 283: Cessation of drug at 6 months

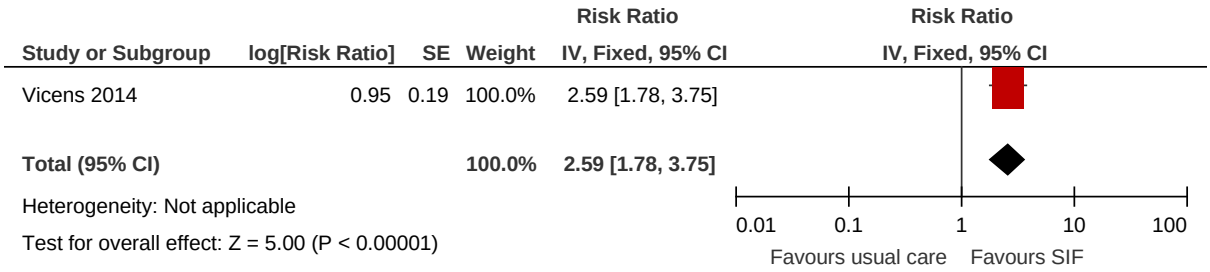


Figure 284: Cessation of drug at 12 months

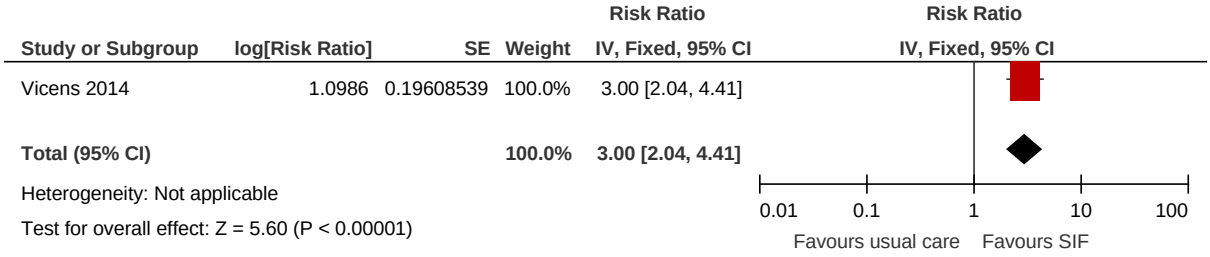


Figure 285: Cessation of drug at 36 months

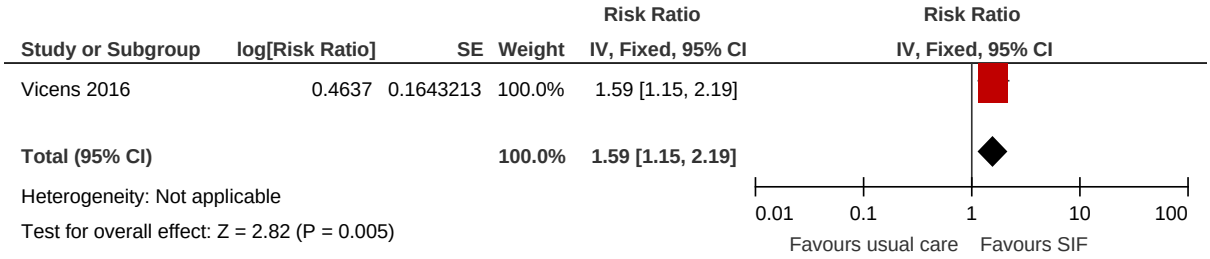


Figure 286: Mortality at 36 months

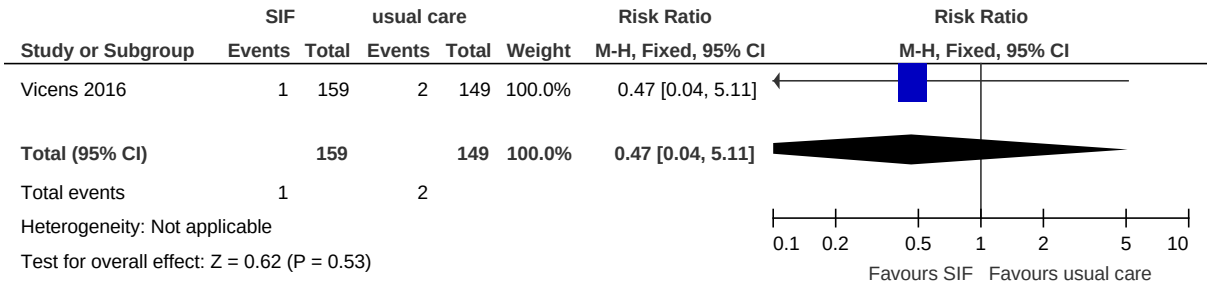
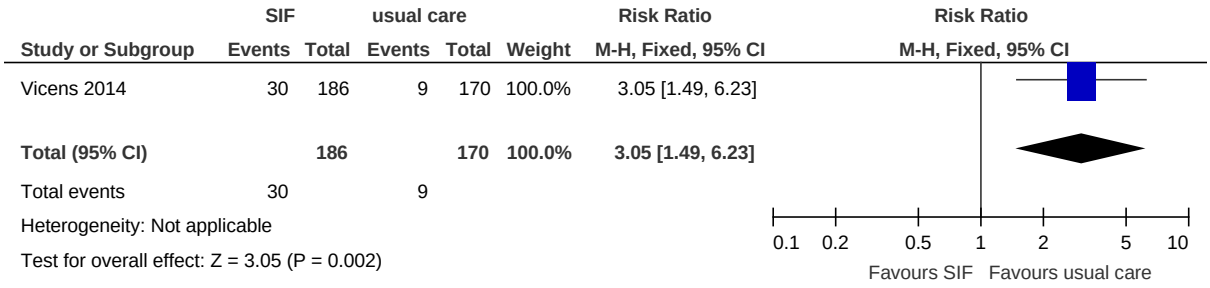
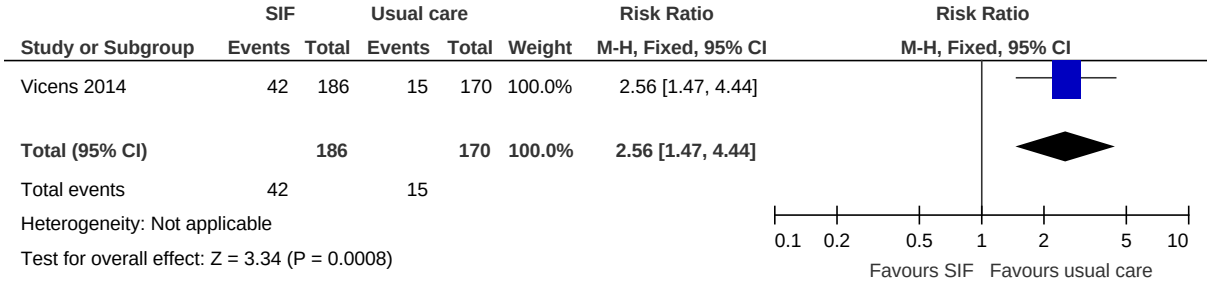


Figure 287: Tremor at 6 months



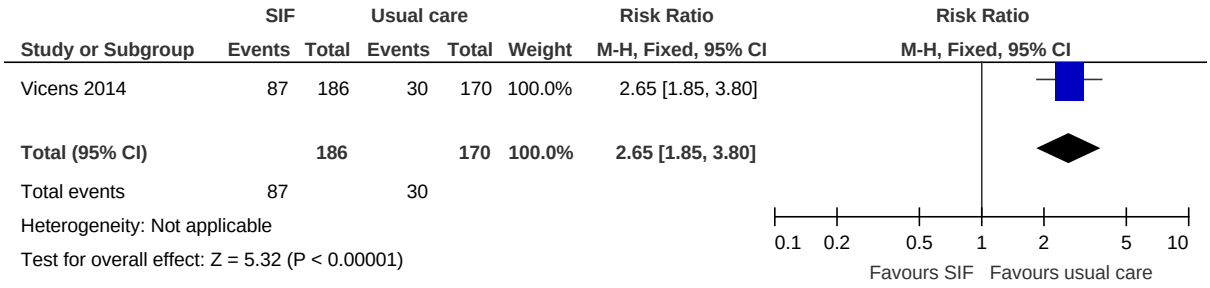
Self-reported- mild/moderate/severe

Figure 288: Irritability at 6 months



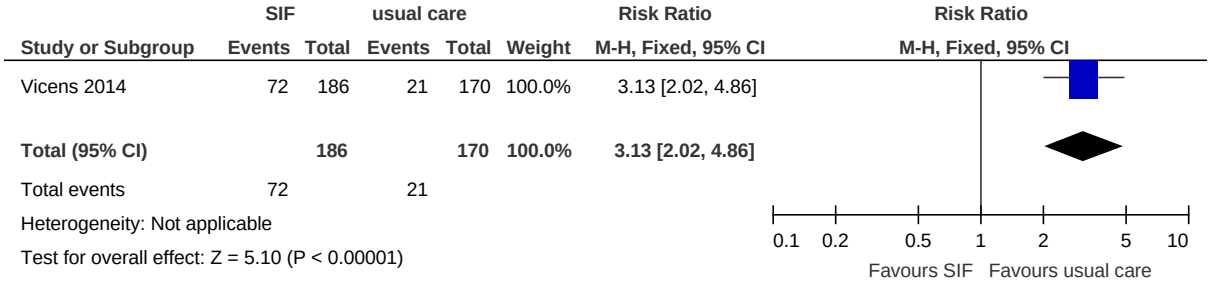
Self-reported- mild/moderate/severe

Figure 289: Insomnia at 6 months



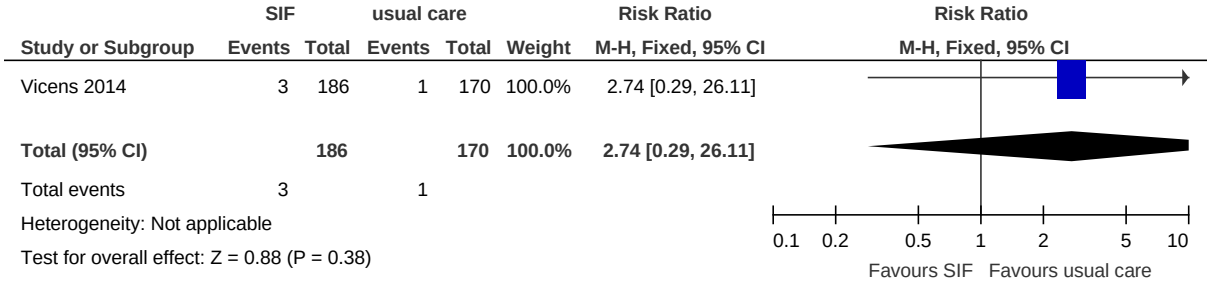
Self-reported- mild/moderate/severe

Figure 290: Anxiety at 6 months



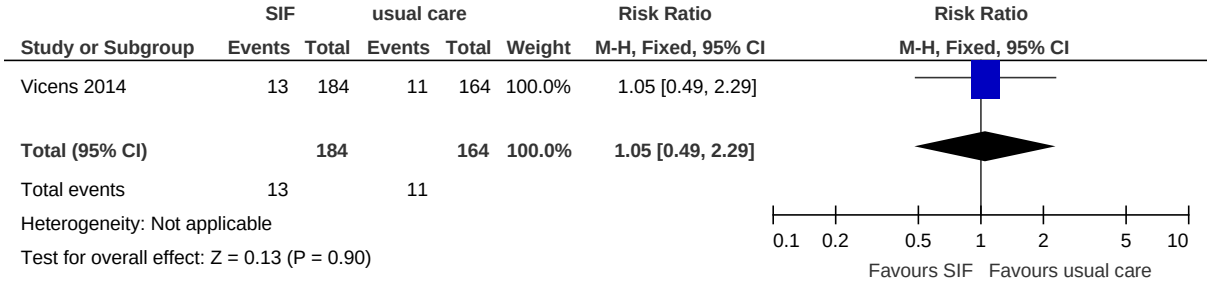
Self-reported- mild/moderate/severe

Figure 291: Convulsions at 6 months



Self-reported- mild/moderate/severe

Figure 292: Tremor at 12 months

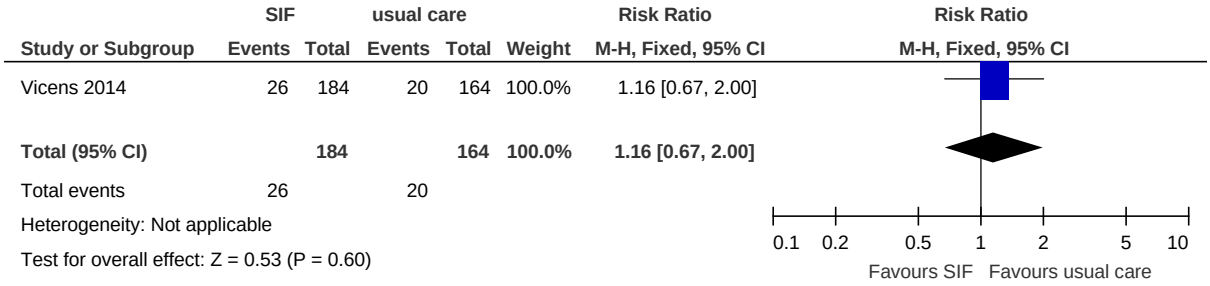


Self-reported- mild/moderate/severe

1

2

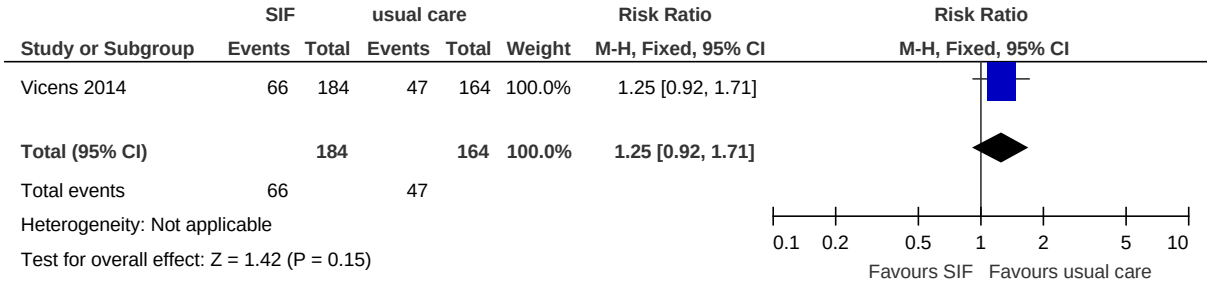
Figure 293: Irritability at 12 months



Self-reported- mild/moderate/severe

3

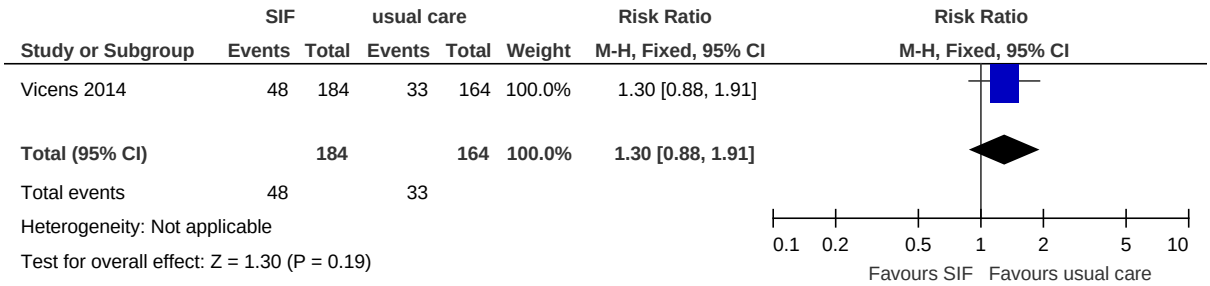
Figure 294: Insomnia at 12 months



Self-reported- mild/moderate/severe

4

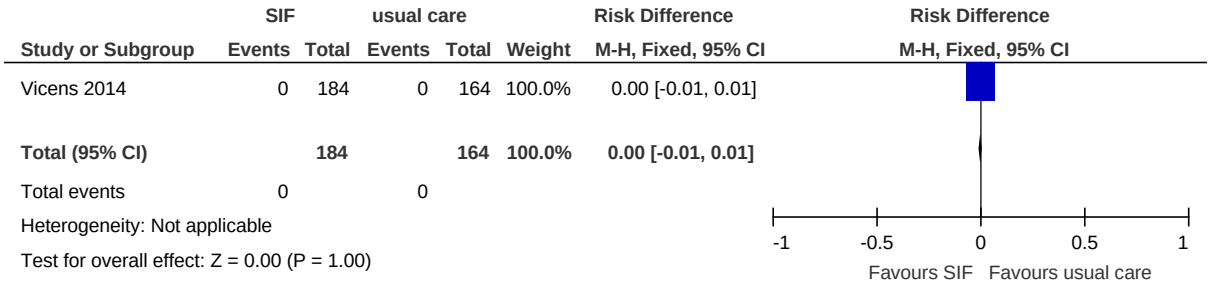
Figure 295: Anxiety at 12 months



Self-reported- mild/moderate/severe

5

Figure 296: Convulsions at 12 months



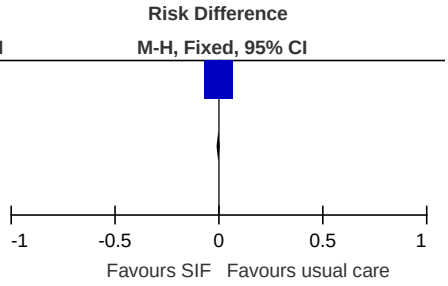
Self-reported- mild/moderate/severe

Figure 297: Self-harm or harm to others

Study or Subgroup	SIF Events	SIF Total	usual care Events	usual care Total	Weight	Risk Difference M-H, Fixed, 95% CI
Vicens 2014	0	191	0	173	100.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**191**		**173**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)



F.5.7 Structured Intervention with written instructions vs usual care

Figure 298: Cessation of drug at 6 months

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Vicens 2014	1.09	0.18	100.0%	2.97 [2.09, 4.23]
Total (95% CI)			**100.0%**	**2.97 [2.09, 4.23]**

Heterogeneity: Not applicable

Test for overall effect: Z = 6.06 (P < 0.00001)

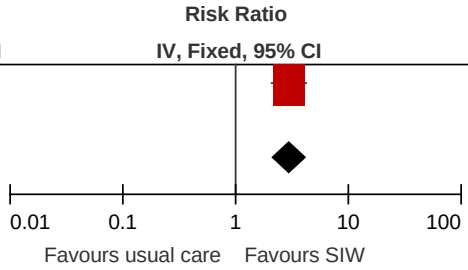


Figure 299: Cessation of drug at 12 months

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Vicens 2014	1.1019	0.2	100.0%	3.01 [2.03, 4.45]
Total (95% CI)			**100.0%**	**3.01 [2.03, 4.45]**

Heterogeneity: Not applicable

Test for overall effect: Z = 5.51 (P < 0.00001)

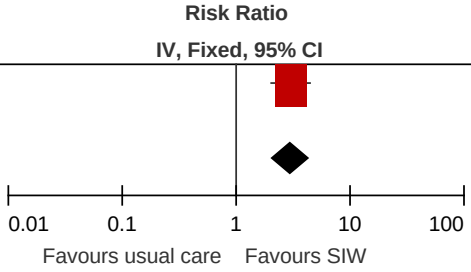


Figure 300: Cessation of drug at 36 months

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Vicens 2016	0.4121097	0.1588086	100.0%	1.51 [1.11, 2.06]
Total (95% CI)			**100.0%**	**1.51 [1.11, 2.06]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.60 (P = 0.009)

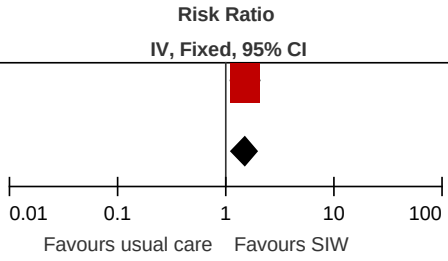
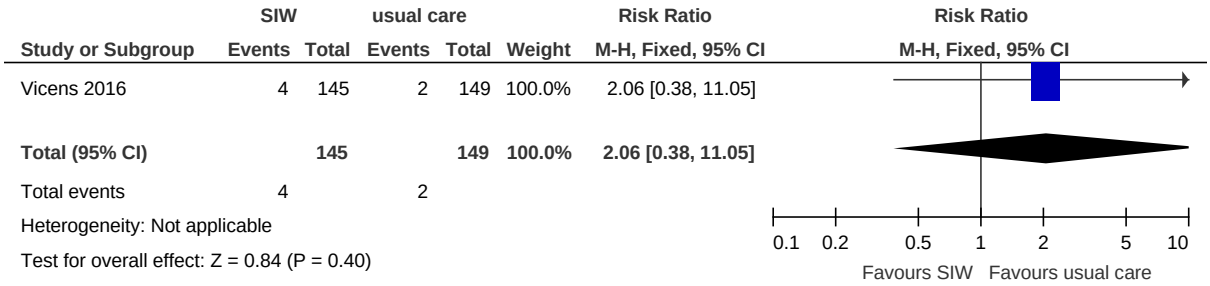
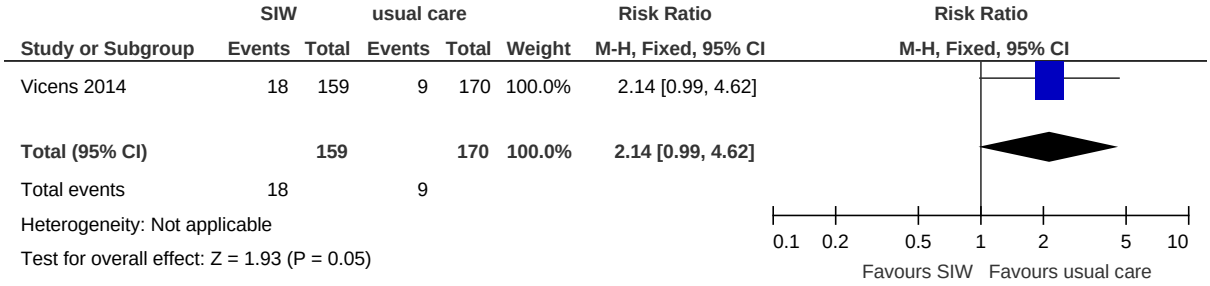


Figure 301: Mortality at 36 months



1

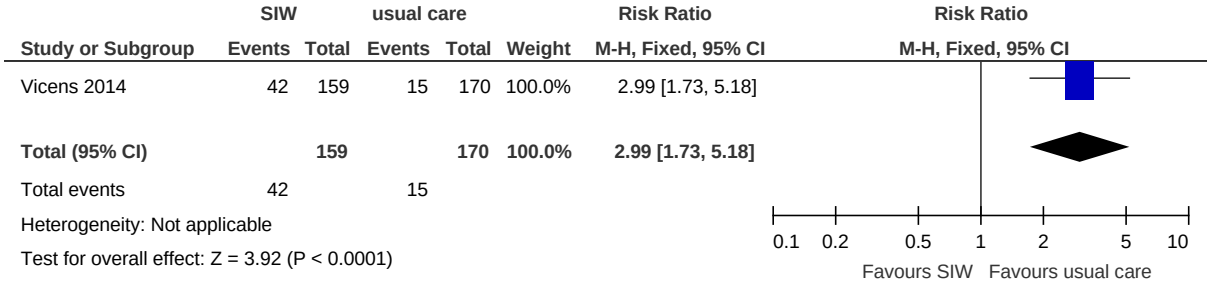
Figure 302: Tremor at 6 months



Self-reported- mild/moderate/severe

2

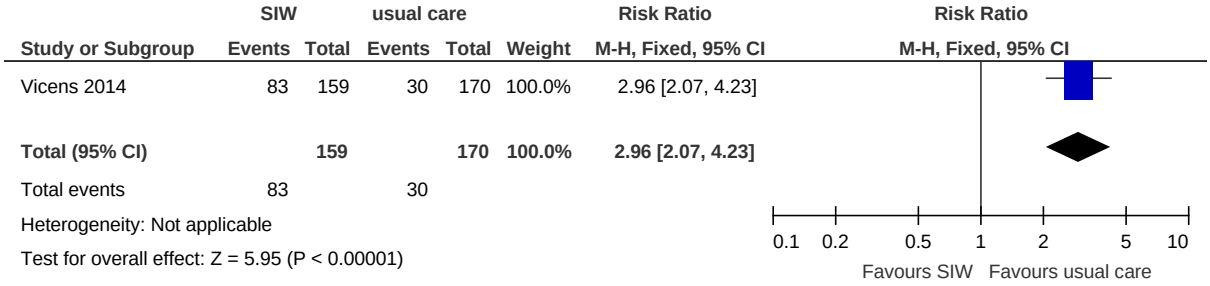
Figure 303: Irritability at 6 months



Self-reported- mild/moderate/severe

3

Figure 304: Insomnia at 6 months



Self-reported- mild/moderate/severe

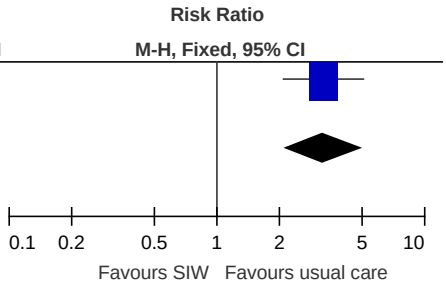
1

Figure 305: Anxiety at 6 months

Study or Subgroup	SIW Events	SIW Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	64	159	21	170	100.0%	3.26 [2.09, 5.07]
Total (95% CI)		**159**		**170**	**100.0%**	**3.26 [2.09, 5.07]**
Total events	64		21			

Heterogeneity: Not applicable

Test for overall effect: Z = 5.23 (P < 0.00001)



Self-reported- mild/moderate/severe

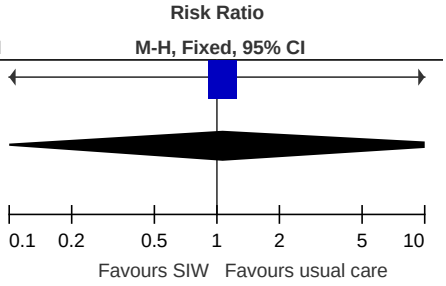
2

Figure 306: Convulsions at 6 months

Study or Subgroup	SIW Events	SIW Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	1	159	1	170	100.0%	1.07 [0.07, 16.95]
Total (95% CI)		**159**		**170**	**100.0%**	**1.07 [0.07, 16.95]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.05 (P = 0.96)



Self-reported- mild/moderate/severe

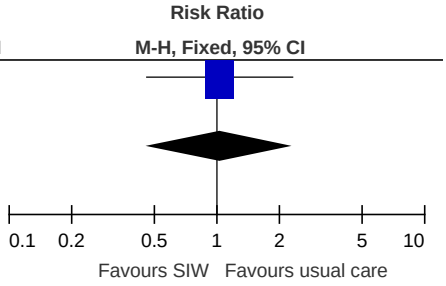
3

Figure 307: Tremor at 12 months

Study or Subgroup	SIW Events	SIW Total	usual care Events	usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	11	159	11	164	100.0%	1.03 [0.46, 2.31]
Total (95% CI)		**159**		**164**	**100.0%**	**1.03 [0.46, 2.31]**
Total events	11		11			

Heterogeneity: Not applicable

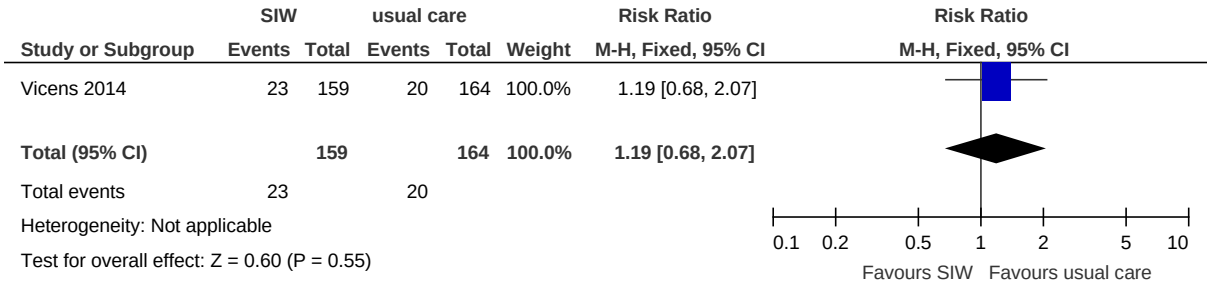
Test for overall effect: Z = 0.08 (P = 0.94)



Self-reported- mild/moderate/severe

4

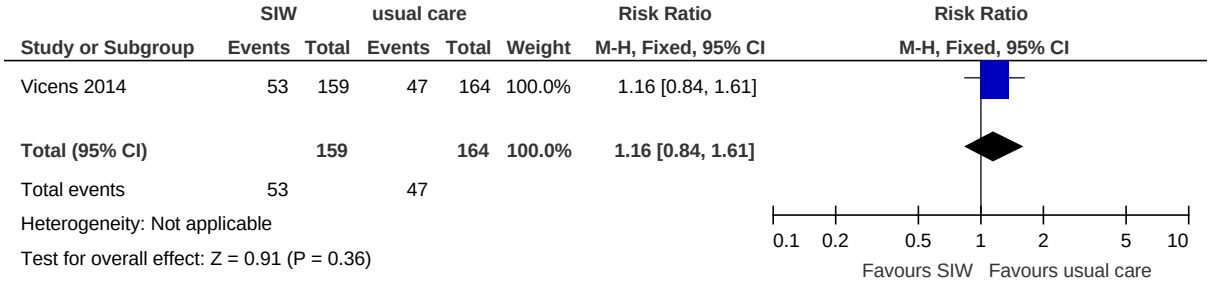
Figure 308: Irritability at 12 months



Self-reported- mild/moderate/severe

1

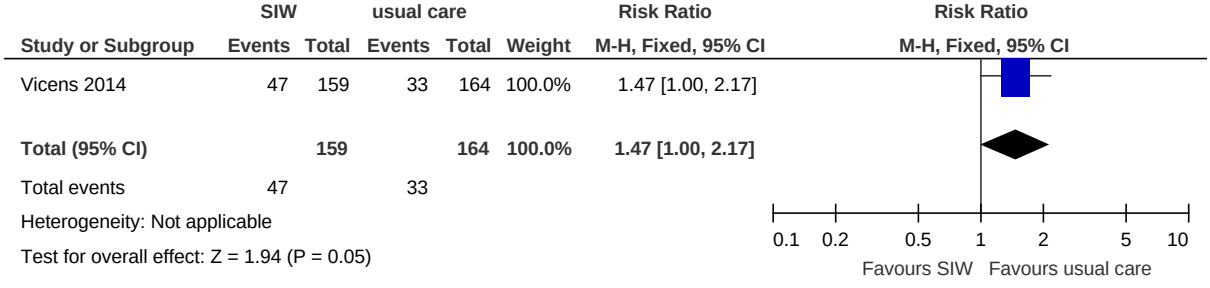
Figure 309: Insomnia at 12 months



Self-reported- mild/moderate/severe

2

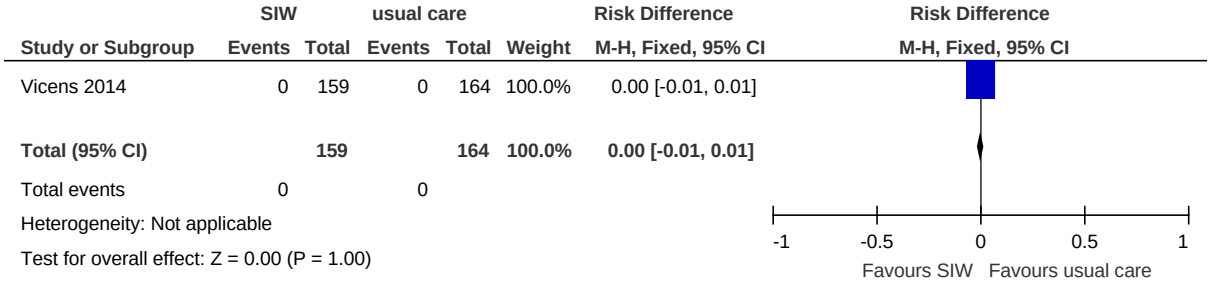
Figure 310: Anxiety at 12 months



Self-reported- mild/moderate/severe

3

Figure 311: Convulsions at 12 months



Self-reported- mild/moderate/severe

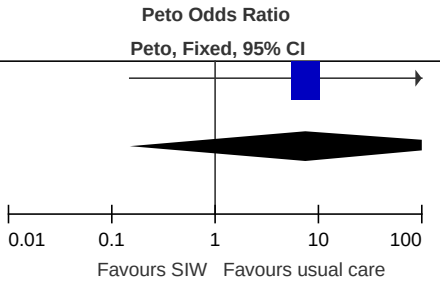
1

Figure 312: Self-harm or harm to others

Study or Subgroup	SIW Events	SIW Total	usual care Events	usual care Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Vicens 2014	1	157	0	160	100.0%	7.53 [0.15, 379.64]
Total (95% CI)		**157**		**160**	**100.0%**	**7.53 [0.15, 379.64]**
Total events	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.01 (P = 0.31)



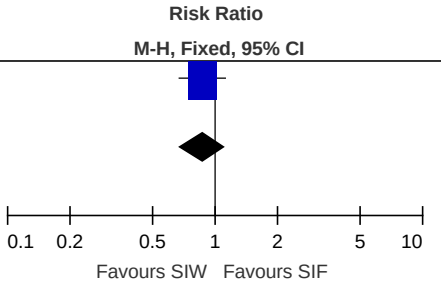
2 **F.5.8 Structured intervention with follow-up vs structured intervention with written**
3 **instructions**

Figure 313: Cessation of drug at 6 months

Study or Subgroup	SIF Events	SIF Total	SIW Events	SIW Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	71	191	72	168	100.0%	0.87 [0.67, 1.12]
Total (95% CI)		**191**		**168**	**100.0%**	**0.87 [0.67, 1.12]**
Total events	71		72			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.10 (P = 0.27)



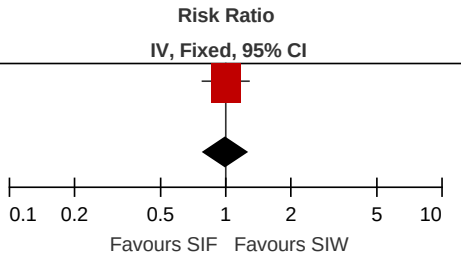
4

Figure 314: Cessation of drug at 12 months

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Vicens 2014	0	0.1263575	100.0%	1.00 [0.78, 1.28]
Total (95% CI)			**100.0%**	**1.00 [0.78, 1.28]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)



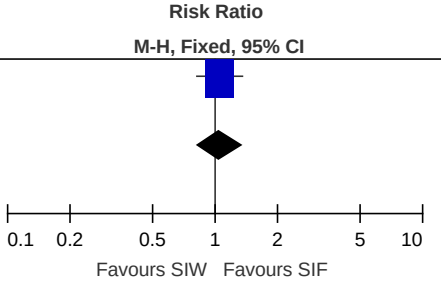
5

Figure 315: Cessation of drug at 36 months

Study or Subgroup	SIF Events	SIF Total	SIW Events	SIW Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2016	79	191	66	168	100.0%	1.05 [0.82, 1.36]
Total (95% CI)		**191**		**168**	**100.0%**	**1.05 [0.82, 1.36]**
Total events	79		66			

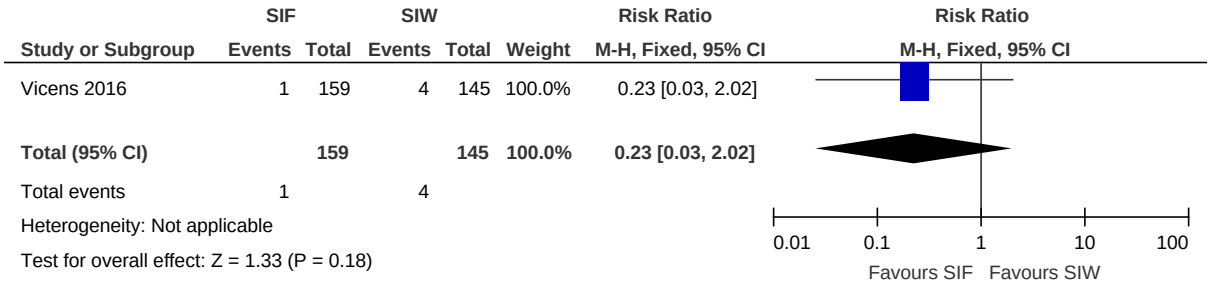
Heterogeneity: Not applicable

Test for overall effect: Z = 0.40 (P = 0.69)



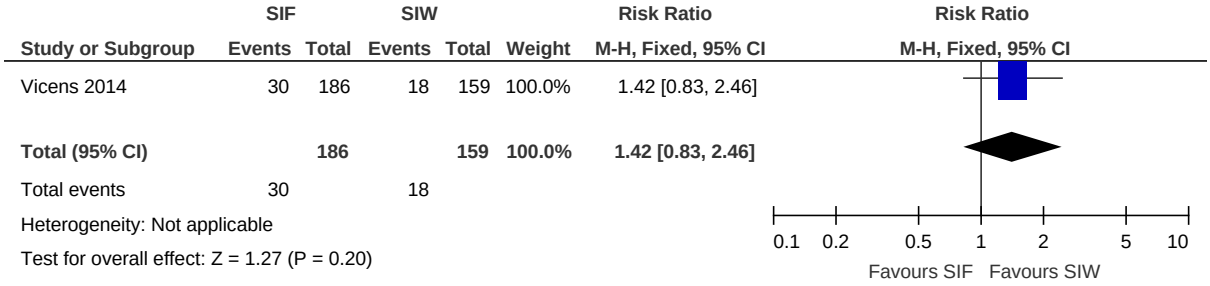
6

Figure 316: Mortality at 36 months



1

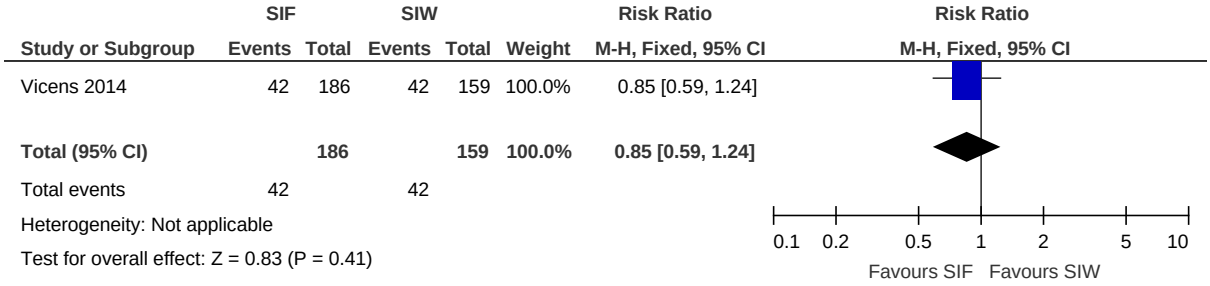
Figure 317: Tremor at 6 months



Self-reported- mild/moderate/severe

2

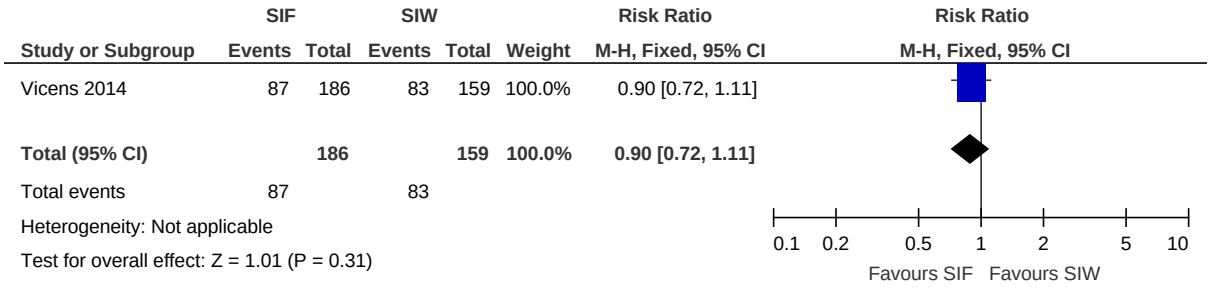
Figure 318: Irritability at 6 months



Self-reported- mild/moderate/severe

3

Figure 319: Insomnia at 6 months



Self-reported- mild/moderate/severe

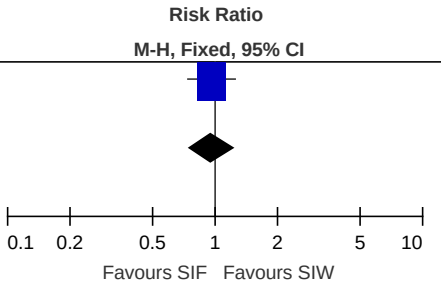
1

Figure 320: Anxiety at 6 months

Study or Subgroup	SIF Events	SIF Total	SIW Events	SIW Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	72	186	64	159	100.0%	0.96 [0.74, 1.25]
Total (95% CI)		**186**		**159**	**100.0%**	**0.96 [0.74, 1.25]**
Total events	72		64			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.29 (P = 0.77)



Self-reported- mild/moderate/severe

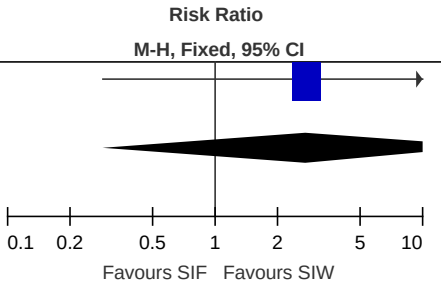
2

Figure 321: Convulsions at 6 months

Study or Subgroup	SIF Events	SIF Total	SIW Events	SIW Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	3	186	1	170	100.0%	2.74 [0.29, 26.11]
Total (95% CI)		**186**		**170**	**100.0%**	**2.74 [0.29, 26.11]**
Total events	3		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.88 (P = 0.38)



Self-reported- mild/moderate/severe

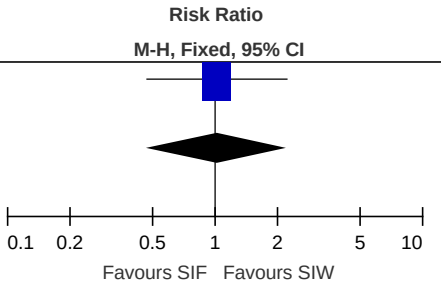
3

Figure 322: Tremor at 12 months

Study or Subgroup	SIF Events	SIF Total	SIW Events	SIW Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vicens 2014	13	184	11	159	100.0%	1.02 [0.47, 2.22]
Total (95% CI)		**184**		**159**	**100.0%**	**1.02 [0.47, 2.22]**
Total events	13		11			

Heterogeneity: Not applicable

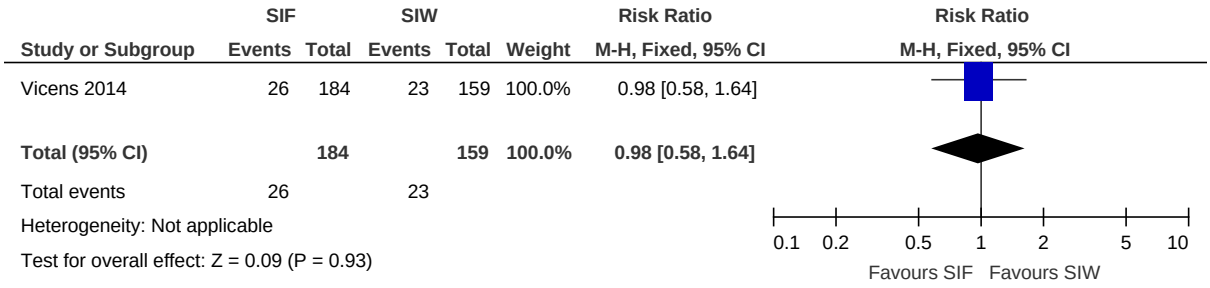
Test for overall effect: Z = 0.05 (P = 0.96)



Self-reported- mild/moderate/severe

4

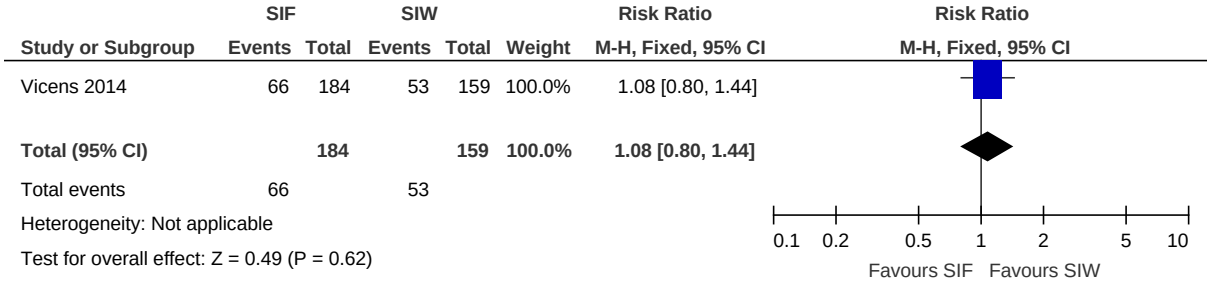
Figure 323: Irritability at 12 months



Self-reported- mild/moderate/severe

1

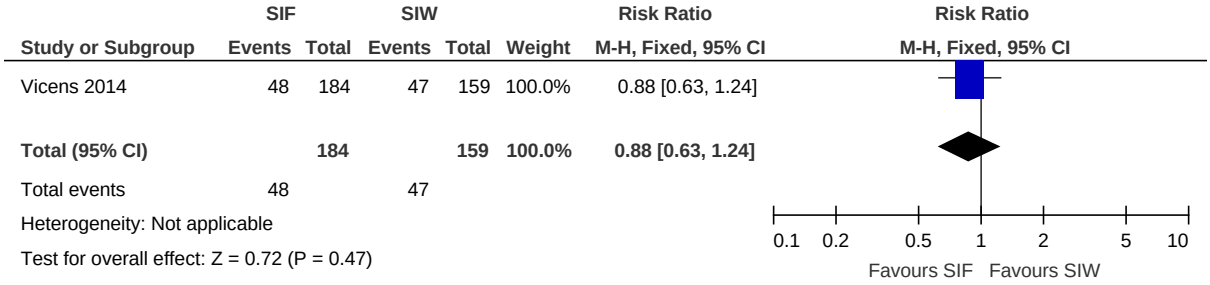
Figure 324: Insomnia at 12 months



Self-reported- mild/moderate/severe

2

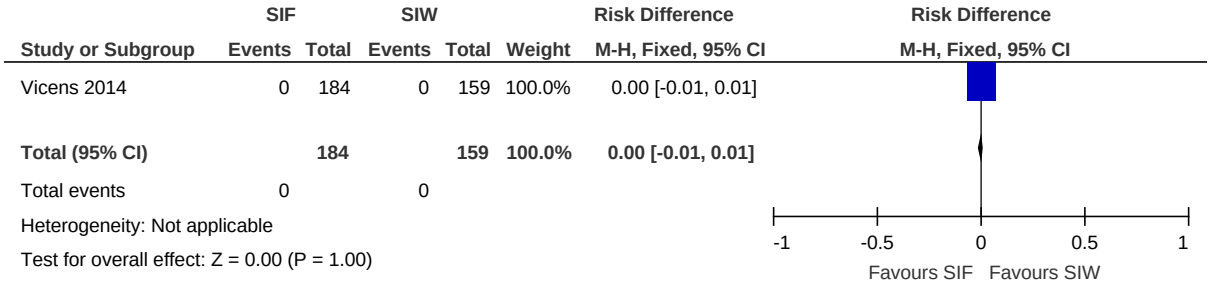
Figure 325: Anxiety at 12 months



Self-reported- mild/moderate/severe

3

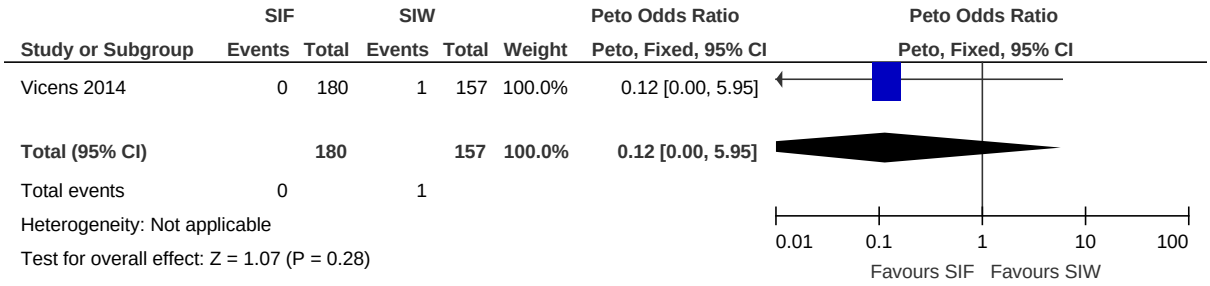
Figure 326: Convulsions at 12 months



Self-reported- mild/moderate/severe

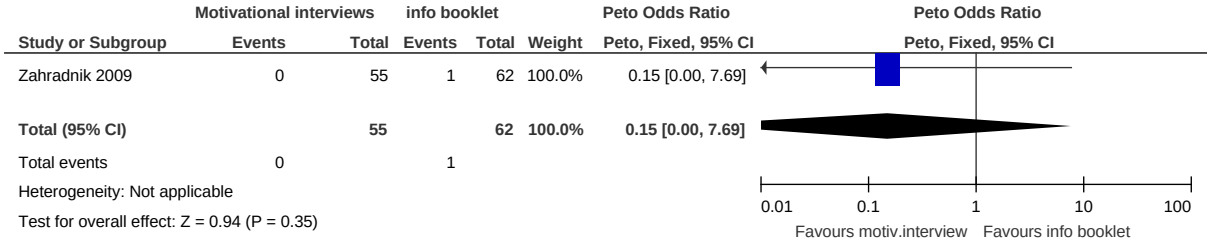
4

Figure 327: Self-harm or harm to others



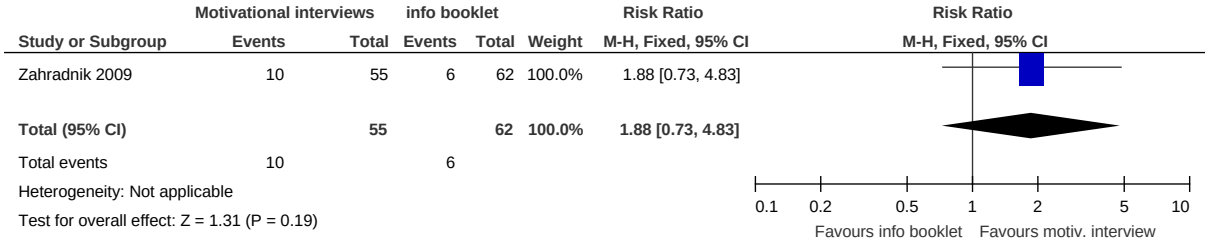
1 **F.5.9 Motivational interviewing vs Brief advice (information booklet)**

Figure 328: Mortality at 3 months



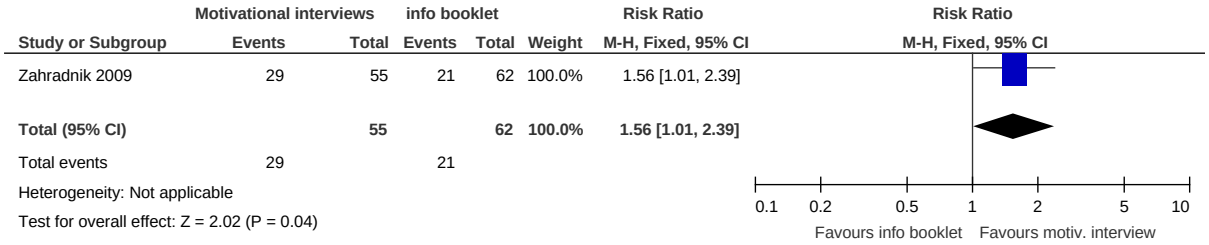
2

Figure 329: Cessation of drug at 3 months



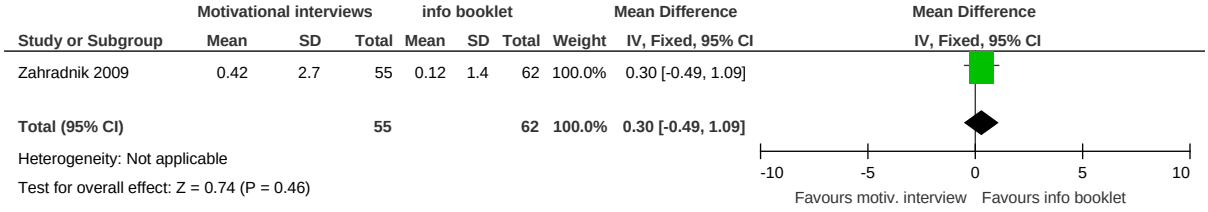
3

Figure 330: Reduction by 25% at 3 months



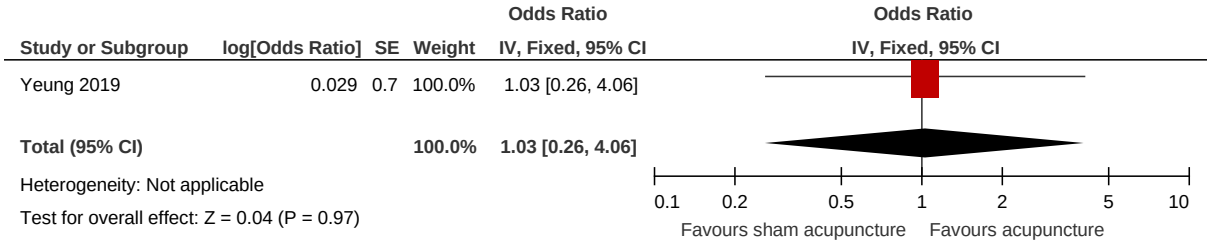
4

Figure 331: Mean Defined Daily Dosage difference at 3 months



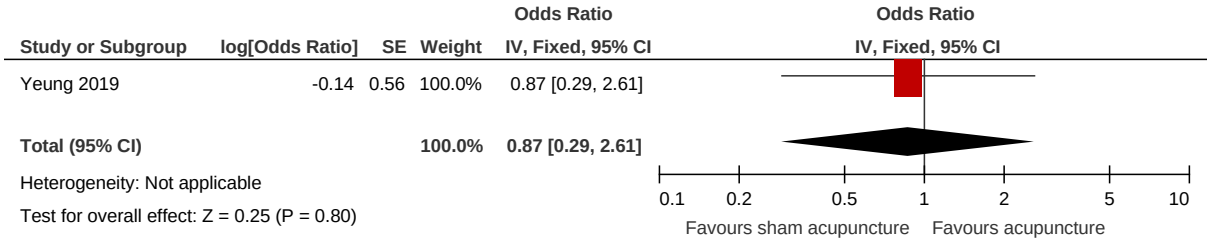
1 **F.5.10 Electroacupuncture + taper vs Sham acupuncture + taper**

Figure 332: Cessation rate at week 6



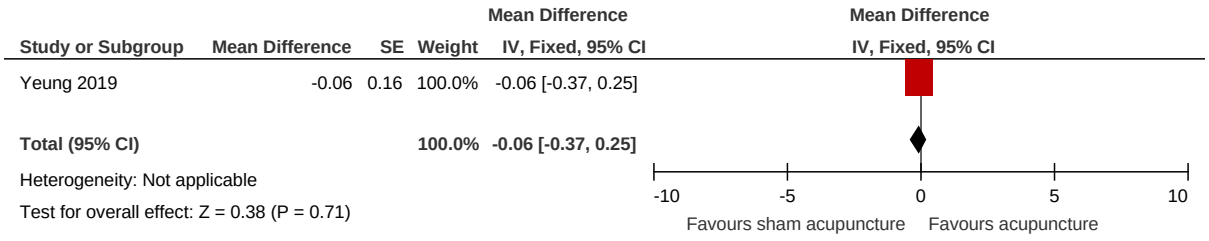
2

Figure 333: Cessation rate at week 16



3

Figure 334: Equivalent dose of usage of diazepam, mg/d at week 6



4

Figure 335: Equivalent dose of usage of diazepam, mg/d at week 16

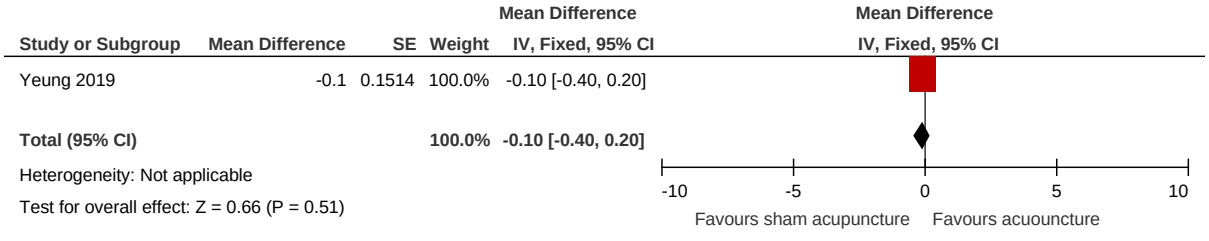
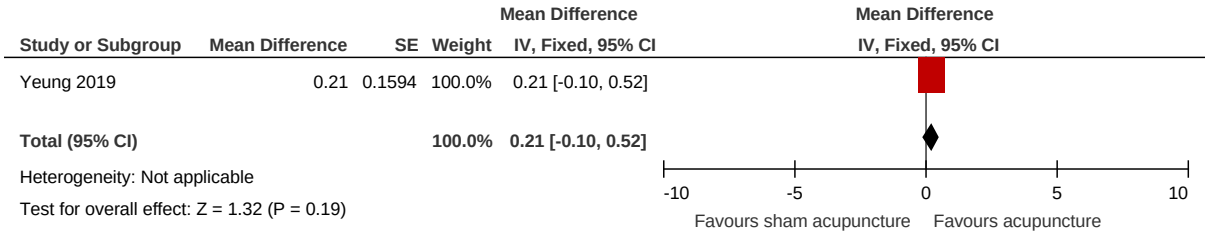
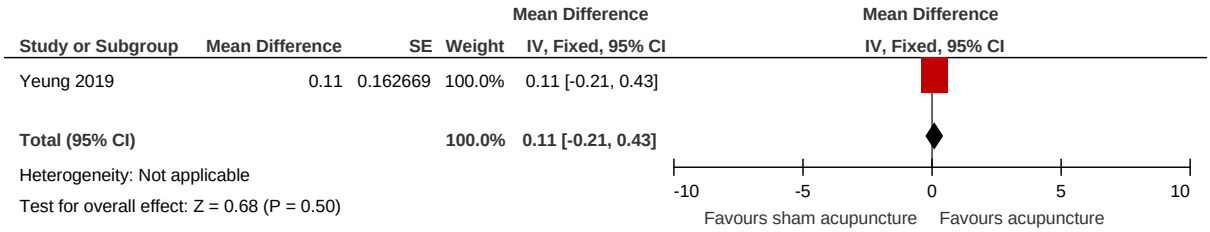


Figure 336: Withdrawal symptoms (BWSQ) at week 6



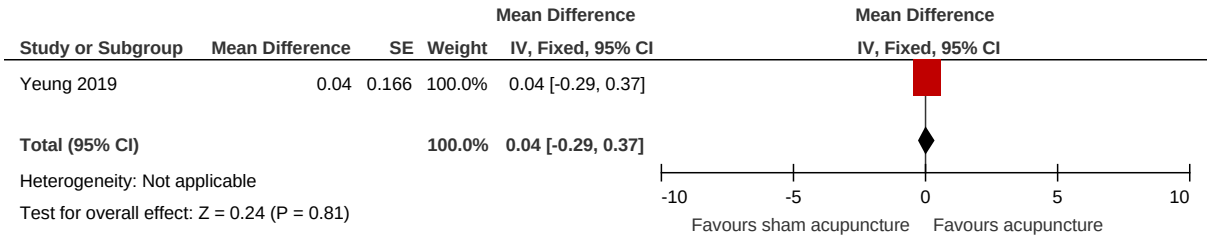
Benzodiazepine Withdrawal Symptom Questionnaire scale 0-40, higher value is worse

Figure 337: Withdrawal symptoms (BWSQ) at week 16



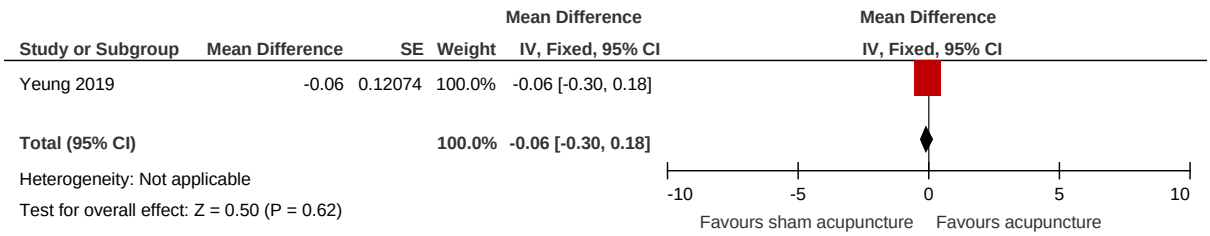
Benzodiazepine Withdrawal Symptom Questionnaire scale 0-40, higher value is worse

Figure 338: Insomnia (ISI) at week 6



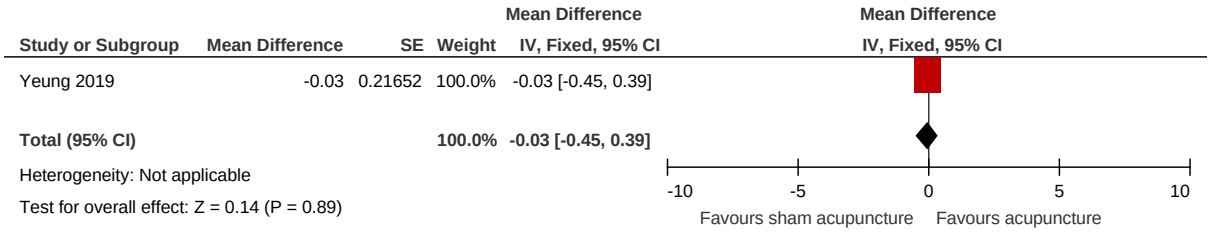
Insomnia Severity Scale 0-28, higher value is worse

Figure 339: Insomnia (ISI) at week 16



Insomnia Severity Scale 0-28, higher value is worse

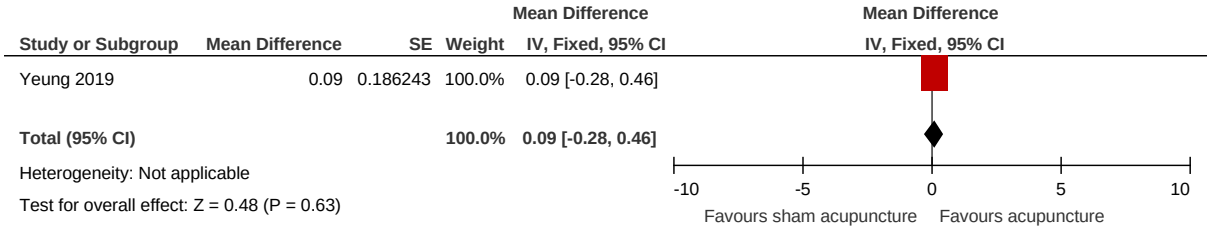
Figure 340: Anxiety (HADS anxiety) at week 6



Hospital Anxiety and Depression Scale, anxiety subset 0-21, higher value is worse

1

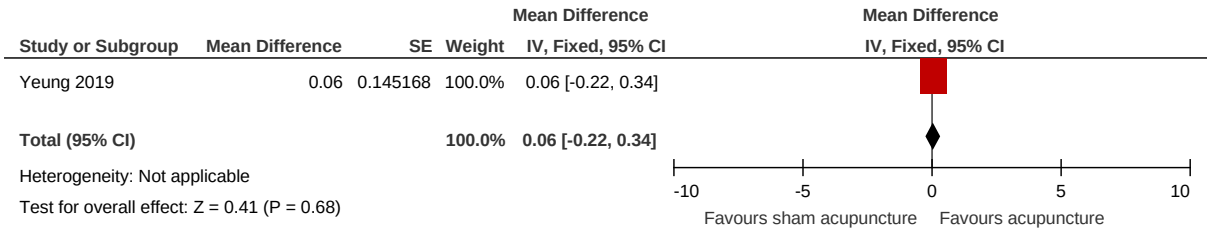
Figure 341: Anxiety (HADS anxiety) at week 16



Hospital Anxiety and Depression Scale, anxiety subset 0-21, higher value is worse

2

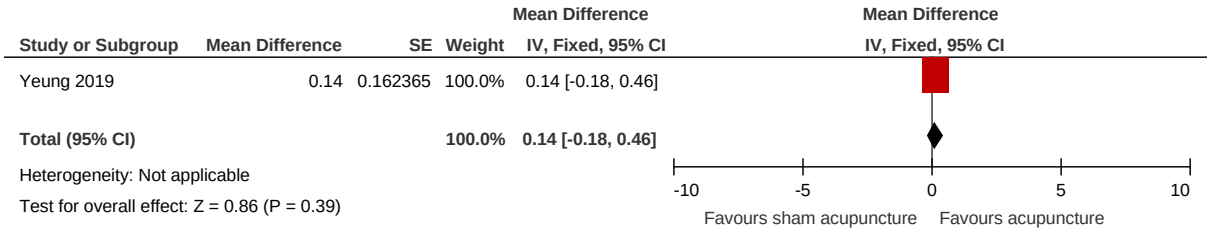
Figure 342: Depression (HADS depression) at week 6



Hospital Anxiety and Depression Scale, depression subset 0-21, higher value is worse

3

Figure 343: Depression (HADS depression) at week 16



Hospital Anxiety and Depression Scale, depression subset 0-21, higher value is worse

4

5

Appendix G GRADE tables

G.1 Opioids

Table 70: Clinical evidence profile: Varenicline + taper vs Placebo + taper for opioid withdrawal

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline + taper program	placebo + taper program	Relative (95% CI)	Absolute (95% CI)		
Number of people who discontinued (at dismissal- 3 weeks)												
1	randomised trials	very serious a	not serious	not serious	not serious	none	7/7 (100.0%)	11/11 (100.0%)	**RR 1.00** (0.81 to 1.24)	0 fewer per 1,000 (from 190 fewer to 240 more)	⨁⨁◯◯ LOW	CRITICAL
Decrease in severity of withdrawal symptoms (at dismissal-3 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	5/7 (71.4%)	4/11 (36.4%)	**RR 1.96** (0.79 to 4.89)	**349 more per 1,000** (from 76 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 2 increments as the evidence was at very high risk of bias
b. Downgraded by 2 increments as the confidence interval crossed both MIDs (0.8 and 1.25)

Table 71: Clinical evidence profile: Acupuncture + standard medication management with opioid weaning vs standard outpatient medication management with opioid weaning

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture + taper	taper (opioids)	Relative (95% CI)	Absolute (95% CI)		
Morphine equivalent dose (MED; protocol outcome: reduction in prescribed medication use) at post-intervention												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture + taper	taper (opioids)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	9	6	-	MD **47 lower** (150.3 lower to 56.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Subjective withdrawal symptoms (clinical institute narcotic assessment; CINA; range of values unclear) at post-intervention												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9	6	-	MD **0.7 lower** (4.54 lower to 3.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (numerical rating scale; NRS; range of values unclear; protocol outcome: symptoms for which the medication was originally prescribed) at post-intervention												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	9	6	-	MD **1.7 lower** (3.34 lower to 0.06 lower)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of intervention and control groups for continuous outcomes). Calculated MIDs for continuous outcomes were as follows: MED: 48; CINA: 2.9; NRS: 2.83*

Table 72: Clinical evidence profile: Multicomponent taper support for opioid withdrawal + taper vs usual prescribing

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent taper support + taper	usual prescribing	Relative (95% CI)	Absolute (95% CI)		
QoL-Patient global impression of change (22 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent taper support + taper	usual prescribing	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	9/16 (56.3%)	3/13 (23.1%)	**RR 2.44** (0.83 to 7.20)	**332 more per 1,000** (from 39 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

QoL-Patient global impression of change (34 weeks)

1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	10/15 (66.7%)	6/16 (37.5%)	**RR 1.78** (0.86 to 3.68)	**293 more per 1,000** (from 53 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Discontinuation (at 22 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	1/16 (6.3%)	1/15 (6.7%)	**RR 0.94** (0.06 to 13.68)	**4 fewer per 1,000** (from 63 fewer to 845 more)	⨁◯◯◯ VERY LOW	CRITICAL

Discontinuation (at 34 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	2/16 (12.5%)	2/16 (12.5%)	**RR 1.00** (0.16 to 6.25)	**0 fewer per 1,000** (from 105 fewer to 656 more)	⨁◯◯◯ VERY LOW	CRITICAL

Mean daily dose in the past week (mg; at 22 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	18	17	-	MD **42.9 lower** (92.42 lower to 6.62 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent taper support + taper	usual prescribing	Relative (95% CI)	Absolute (95% CI)		
Mean daily dose in the past week (mg; at 34 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	18	17	-	MD **26.71 lower** (83.04 lower to 29.62 higher)	⨁⨁◯◯ LOW	CRITICAL
Opioid dose reduction by 50% or more (at 22 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	7/18 (38.9%)	2/16 (12.5%)	**RR 3.11** (0.75 to 12.87)	**264 more per 1,000** (from 31 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Opioid dose reduction by 50% or more (at 34 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	9/16 (56.3%)	5/16 (31.3%)	**RR 1.80** (0.77 to 4.19)	**250 more per 1,000** (from 72 fewer to 997 more)	⨁◯◯◯ VERY LOW	CRITICAL
Pain severity (at 22 weeks; BPI)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	18	17	-	MD **0.68 lower** (2.01 lower to 0.65 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Pain severity (at 34 weeks; BPI)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	18	17	-	MD **0.91 lower** (2.3 lower to 0.48 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent taper support + taper	usual prescribing	Relative (95% CI)	Absolute (95% CI)		
Insomnia severity (at 22 weeks; ISI). Protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	18	17	-	MD **3.13 lower** (7.22 lower to 0.96 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Insomnia severity (at 34 weeks; ISI). Protocol outcome: Improvements in adverse effects commonly associated with long-term prescribed substance use												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	18	17	-	MD **1.19 lower** (5.49 lower to 3.11 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments as the evidence was at very high risk of bias
b. Downgraded by 1 increment as the control group stayed on medication ('usual prescribing')
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes;0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows. Mean daily dose in the past week 154.18, Pain severity 0.71, Insomnia severity 3.54*

Table 73: Clinical evidence profile: Electroacupuncture + taper (taper schedule or taper as part of PMM) vs sham electroacupuncture + taper (taper schedule or taper as part of PMM) for opioid withdrawal

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + taper (PMM)	Sham electroacupuncture + taper (PMM)	Relative (95% CI)	Absolute (95% CI)		
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	48	29	-	MD **2.3 higher** (5.48 lower to 10.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + taper (PMM)	Sham electroacupuncture + taper (PMM)	Relative (95% CI)	Absolute (95% CI)		
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	48	29	-	MD **0.7 higher** (6.53 lower to 7.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	48	29	-	MD **3.6 higher** (5.14 lower to 12.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Opioid consumption (mg/week; post-intervention: week 8/average of weeks 11-14))												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	65	47	-	MD **3.77 lower** (76.38 lower to 68.84 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Opioid consumption (mg/week; at 12-week to 3-month follow-up)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	42	38	-	MD **48.99 lower** (120.46 lower to 22.47 higher)	⨁⨁◯◯ LOW	CRITICAL
50% OM reduction (at end of treatment: average of weeks 11-14)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	9/48 (18.8%)	8/29 (27.6%)	**RR 0.68** (0.30 to 1.56)	**88 fewer per 1,000** (from 193 fewer to 154 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + taper (PMM)	Sham electroacupuncture + taper (PMM)	Relative (95% CI)	Absolute (95% CI)		
Non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	48	29	-	MD **0.3 higher** (2.91 lower to 3.51 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	29	-	MD **0.1 higher** (0.88 lower to 1.08 higher)	⨁⨁◯◯ LOW	IMPORTANT
Average pain (VAS; 0-10; post-intervention: week 8/average of weeks 11-14)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	65	47	-	MD **0.61 lower** (1.46 lower to 0.25 higher)	⨁⨁◯◯ LOW	IMPORTANT
Duration of pain (hr/day; post-intervention)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	17	18	-	MD **1.8 higher** (1.65 lower to 5.25 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
OM-related adverse events per person (at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	29	-	MD **1.8 lower** (3.44 lower to 0.16 lower)	⨁⨁◯◯ LOW	IMPORTANT
Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + taper (PMM)	Sham electroacupuncture + taper (PMM)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	29	-	MD **7.3 lower** (15.18 lower to 0.58 higher)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 74: Clinical evidence profile: Electroacupuncture + PMM vs PMM alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	48	31	-	MD **5.8 higher** (2.9 lower to 14.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	48	31	-	MD **4.4 higher** (3.28 lower to 12.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	31	-	MD **7.4 higher** (2.71 lower to 17.51 higher)	⨁⨁◯◯ LOW	CRITICAL
Opioid dosage (mg; end of treatment: average of weeks 11-14)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	48	31	-	MD **58.6 lower** (133.75 lower to 16.55 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
50% OM reduction (at end of treatment: average of weeks 11-14)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/48 (18.8%)	4/31 (12.9%)	**RR 1.45** (0.49 to 4.31)	**58 more per 1,000** (from 66 fewer to 427 more)	⨁◯◯◯ VERY LOW	CRITICAL
Non-OM dosage (Medication quantification scale III; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	48	31	-	MD **0.5 lower** (3.56 lower to 2.56 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Intensity of the highest pain (VAS; 0-10; end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	31	-	MD **0.6 lower** (1.58 lower to 0.38 higher)	⨁⨁◯◯ LOW	IMPORTANT
Intensity of the average pain (VAS; 0-10; end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	31	-	MD **0.7 lower** (1.68 lower to 0.28 higher)	⨁⨁◯◯ LOW	IMPORTANT
OM-related adverse events per person (at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	31	-	MD **1.1 lower** (2.49 lower to 0.29 higher)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	31	-	MD **5.8 lower** (13.07 lower to 1.47 higher)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 75: Clinical evidence profile: Sham electroacupuncture + PMM vs PMM alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sham electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
QoL (SF-36; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	MD **3.5 higher** (5.68 lower to 12.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (SF-36-Physical health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	MD **3.7 higher** (4.49 lower to 11.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QoL (SF-36-Mental health; 0-100; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	MD **3.8 higher** (6.67 lower to 14.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sham electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
Opioid dosage (mg; at end of treatment; average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	29	31	-	MD **47.8 lower** (131.79 lower to 36.19 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
50 % OM reduction (at end of treatment: average of weeks 11-14)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	8/29 (27.6%)	4/31 (12.9%)	**RR 2.14** (0.72 to 6.35)	**147 more per 1,000** (from 36 fewer to 690 more)	⨁◯◯◯ VERY LOW	CRITICAL
Non-OM dosage (Medication quantification scale III; at end of treatment (average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [a]	none	29	31	-	MD **0.8 lower** (4.27 lower to 2.67 higher)	⨁⨁◯◯ LOW	IMPORTANT
Intensity of the highest pain (VAS; 0-10; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	29	31	-	MD **0.7 lower** (1.81 lower to 0.41 higher)	⨁⨁◯◯ LOW	IMPORTANT
Intensity of the average pain (VAS; 0-10; at end of treatment: average of weeks 11-14)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	29	31	-	MD **0.4 lower** (1.65 lower to 0.85 higher)	⨁⨁◯◯ LOW	IMPORTANT
OM-related adverse events per person (at end of treatment: average of weeks 11-14)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sham electroacupuncture + PMM	PMM alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	29	31	-	MD **0.7 higher** (1.16 lower to 2.56 higher)	⨁⨁◯◯ LOW	IMPORTANT

Severity of OM-related adverse events (at end of treatment: average of weeks 11-14)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29	31	-	MD **1.5 higher** (8.39 lower to 11.39 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs

G.2 Benzodiazepines

Table 76: Clinical evidence profile: CBT + tapered withdrawal vs CBT + abrupt withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	CBT + abrupt withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: post-intervention)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	9/23 (39.1%)	11/19 (57.9%)	**RR 0.68** (0.36 to 1.28)	**185 fewer per 1,000** (from 371 fewer to 162 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 15 months)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	5/23 (21.7%)	8/19 (42.1%)	**RR 0.52** (0.20 to 1.32)	**202 fewer per 1,000** (from 337 fewer to 135 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduced benzodiazepine use (follow up: post-intervention; assessed with: 50% reduction in BZD plasma level)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	3/23 (13.0%)	3/19 (15.8%)	**RR 0.83** (0.19 to 3.63)	**27 fewer per 1,000** (from 128 fewer to 415 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduced benzodiazepine use (follow up: 12 months; assessed with: 50% reduction in BZD plasma level)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	4/23 (17.4%)	1/19 (5.3%)	**RR 3.30** (0.40 to 27.13)	**121 more per 1,000** (from 32 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	CBT + abrupt withdrawal	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow up: post-intervention; assessed with: mean per patient)												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	21	19	-	MD **6.2 lower** (8.99 lower to 3.41 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptom severity score (follow up: post-intervention; Scale from: 0 to 10)												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	21	19	-	MD **4.8 lower** (6.6 lower to 3 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse (follow up: post-intervention; assessed with: additional use of own BZD supply)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	1/23 (4.3%)	7/19 (36.8%)	**RR 0.12** (0.02 to 0.88)	**324 fewer per 1,000** (from 361 fewer to 44 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. The majority of the evidence had an indirect population. For Sanchez-craig 1987, 4/9 dose equivalences reported in study are for drugs not in protocol.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: withdrawal symptoms - 2.1, withdrawal severity - 1.45.*

Table 77: Clinical evidence profile: CBT + tapered withdrawal vs Tapered withdrawal only for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Tapered withdrawal only	Relative (95% CI)	Absolute (95% CI)		
Quality of life - Physical function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Tapered withdrawal only	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **3 higher** (6.42 lower to 12.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Social function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **4 higher** (4.72 lower to 12.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Role limitation (physical) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **3 higher** (12.59 lower to 18.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Role limitation (emotional) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **9 lower** (23.5 lower to 5.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Mental health (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **5 lower** (15.87 lower to 5.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Vitality (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **2 higher** (5.25 lower to 9.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Tapered withdrawal only	Relative (95% CI)	Absolute (95% CI)		
Quality of life - Pain (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **6 higher** (3.6 lower to 15.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - General health (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	59	-	MD **5 higher** (2.07 lower to 12.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: post-intervention)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	49/61 (80.3%)	23/54 (42.6%)	**RR 1.89** (1.36 to 2.64)	**379 more per 1,000** (from 153 more to 699 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	33/57 (57.9%)	37/60 (61.7%)	**RR 0.94** (0.70 to 1.26)	**37 fewer per 1,000** (from 185 fewer to 160 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: range 12 months to 15 months)												
3	randomised trials	serious [a]	very serious [d]	serious [b]	very serious [c]	none	59/124 (47.6%)	45/118 (38.1%)	**RR 1.30** (0.68 to 2.47)	**114 more per 1,000** (from 122 fewer to 561 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: post-intervention; assessed with: weekly BZD use - diazepam eqv (mg))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Tapered withdrawal only	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	27	25	-	MD **10.1 mg lower** (28.21 lower to 8.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 12 months; assessed with: weekly BZD use - diazepam eqv (mg))												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	27	25	-	MD **8.85 mg lower** (27.86 lower to 10.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: (postintervention); assessed with: >50% dose reduction)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	33/34 (97.1%)	20/29 (69.0%)	**RR 1.41** (1.09 to 1.81)	**283 more per 1,000** (from 62 more to 559 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 12 months; assessed with: >50% dose reduction)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	26/32 (81.3%)	15/29 (51.7%)	**RR 1.57** (1.06 to 2.32)	**295 more per 1,000** (from 31 more to 683 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse into drug use (follow up: 24 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	7/21 (33.3%)	4/13 (30.8%)	**RR 1.09** (0.39 to 2.99)	**28 more per 1,000** (from 188 fewer to 612 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal symptoms (follow up: 3 months; assessed with: BWSQ; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Tapered withdrawal only	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	73	73	-	MD **0.6 higher** (1.72 lower to 2.92 higher)	⨁⨁◯◯ LOW	CRITICAL
Increase in symptoms for which the medication was originally prescribed - insomnia (follow up: post intervention; assessed with: Insomnia severity index; Scale from: 0 to 28)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	27	25	-	MD **1.54 lower** (4.56 lower to 1.48 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Increase in symptoms for which the medication was originally prescribed - insomnia (follow up: 12 months; assessed with: Insomnia severity index; Scale from: 0 to 28)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	27	25	-	MD **1.09 higher** (2.09 lower to 4.27 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Patients using alcohol (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	40/73 (54.8%)	42/73 (57.5%)	**RR 0.95** (0.71 to 1.27)	**29 fewer per 1,000** (from 167 fewer to 155 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. The majority of the evidence had an indirect population. For Oude Voshaar 2003, Oude Voshaar 2006 & Baillargeon 2003, the specific benzodiazepine used by patients was not reported.

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.33, insomnia severity: 2.68, reduction of BZD 27.69mg.*

d. Heterogeneity, I2=50%, unexplained by subgroup analysis (unable to perform subgroup analysis insufficient reporting detail of BZD half-life)

Table 78: Clinical evidence profile: CBT + tapered withdrawal vs Group work + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Group work + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Quality of life (follow up: 3 months; assessed with: systemic QoL inventory)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	11	10	-	MD **0.05 higher** (1.15 lower to 1.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	15/23 (65.2%)	11/22 (50.0%)	**RR 1.30** (0.78 to 2.18)	**150 more per 1,000** (from 110 fewer to 590 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: post-intervention; assessed with: BWSQ; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	14	12	-	MD **1.07 lower** (4.38 lower to 2.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 3 months; assessed with: BWSQ; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	11	10	-	MD **0.45 higher** (3.25 lower to 4.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse into drug use (follow up: 11 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Group work + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	1/10 (10.0%)	1/10 (10.0%)	**RR 1.00** (0.07 to 13.87)	**0 fewer per 1,000** (from 93 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Increase in symptoms - Anxiety (follow up: post-intervention; assessed with: Spielberger state; Scale from: 0 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	14	12	-	MD **0.11 higher** (8.28 lower to 8.5 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Increase in symptoms - Anxiety (follow up: 3 months; assessed with: Spielberger state; Scale from: 0 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	11	10	-	MD **6.57 lower** (14.99 lower to 1.85 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Increase in symptoms - Anxiety (follow up: post-intervention; assessed with: Spielberger trait; Scale from: 0 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	14	12	-	MD **3.33 lower** (11.42 lower to 4.76 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Increase in symptoms - Anxiety (follow up: 3 months; assessed with: Spielberger trait; Scale from: 0 to 80)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	11	10	-	MD **3.56 lower** (11.75 lower to 4.63 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Group work + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Distress - Psychological Distress (follow up: post-intervention; assessed with: Psychological Distress Inventory; Scale from: 0 to 100; high = poor outcome)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	14	12	-	MD **3.07 higher** (5.07 lower to 11.21 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Distress - Psychological Distress (follow up: 3 months; assessed with: Psychological Distress Inventory; Scale from: 0 to 100; high = poor outcome)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	11	10	-	MD 9.96 **lower** (20.85 lower to 0.93 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. O'Connor 2008, the specific benzodiazepine used by patients was not reported.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: systemic QoL inventory 1.8, BWSQ: 3.09, anxiety - state: 5.5; anxiety - trait: 5.26; distress 7.91.*

Table 79: Clinical evidence profile: CBT + tapered withdrawal vs Usual care for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life - Physical function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	26	-	MD **4 lower** (16.03 lower to 8.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life - Social function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	26	-	MD **1 lower** (10.24 lower to 8.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Role limitation (physical) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	58	26	-	MD **19 lower** (36.88 lower to 1.12 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Role limitation (emotional) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	58	26	-	MD 14 **lower** (29.35 lower to 1.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Mental health (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	58	26	-	MD 10 **lower** (21.97 lower to 1.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Vitality (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	26	-	MD **0** (10.56 lower to 10.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Pain (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	58	24	-	MD 2 **lower** (12.78 lower to 8.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - General health (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	58	59	-	MD **7 higher** (0.44 lower to 14.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	33/57 (57.9%)	5/34 (14.7%)	**RR 3.94** (1.70 to 9.11)	**432 more per 1,000** (from 103 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 15 months)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	20/68 (29.4%)	5/33 (15.2%)	**RR 1.94** (0.80 to 4.71)	**142 more per 1,000** (from 30 fewer to 562 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 3 months; assessed with: BWSQ; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	73	34	-	MD **1 higher** (2 lower to 4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patients using alcohol (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	40/73 (54.8%)	18/34 (52.9%)	**RR 1.04** (0.71 to 1.51)	**21 more per 1,000** (from 154 fewer to 270 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Oude Voshaar 2003 & Oude Voshaar 2006, the specific benzodiazepine used by patients was not reported.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.13.*

Table 80: Clinical evidence profile: Tapered withdrawal vs Usual care for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
Quality of life - Physical function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD **7 lower** (19 lower to 5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Social function (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD **5 lower** (14.87 lower to 4.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - Role limitation (physical) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD 22 **lower** (41 lower to 3 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Quality of life - Role limitation (emotional) (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD **5 lower** (19.94 lower to 9.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Quality of life - Mental health (follow up: 18; assessed with: SF36; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD **5 lower** (19.94 lower to 9.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Quality of life - Vitality (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	26	-	MD **2 lower** (12.54 lower to 8.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Quality of life - Pain (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	serious [b,d]	serious [c]	none	59	24	-	MD 8 **lower** (18.91 lower to 2.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Quality of life - General health (follow up: 18 months; assessed with: SF36; Scale from: 0 to 100)

1	randomised trials	serious [a]	not serious	serious [b,d]	very serious [c]	none	59	59	-	MD **2 higher** (5.59 lower to 9.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tapered withdrawal	Usual care	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b,d]	not serious	none	37/60 (61.7%)	5/34 (14.7%)	**RR 4.19** (1.82 to 9.65)	**469 more per 1,000** (from 121 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 12 months)												
1	randomised trials	serious [a]	not serious	serious [b,d]	serious [c]	none	25/69 (36.2%)	5/33 (15.2%)	**RR 2.39** (1.01 to 5.68)	**211 more per 1,000** (from 2 more to 709 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms score (follow up: 3 months; assessed with: BWSQ; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	serious [b,d]	serious [c]	none	73	34	-	MD **0.4 higher** (2.51 lower to 3.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Patients using alcohol (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	serious [b,d]	very serious [c]	none	42/73 (57.5%)	18/34 (52.9%)	**RR 1.09** (0.75 to 1.58)	**48 more per 1,000** (from 132 fewer to 307 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Oude Voshaar 2003 & Oude Voshaar 2006, the specific benzodiazepine used by patients was not reported.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group; published MIDs). MIDs for continuous outcomes were as follows: SF36 - Physical functioning: 3; Social functioning: 3; Role-physical: 3; Role-emotional: 4; Mental health: 3; Vitality: 2; Bodily pain: 3; General health: 2, BWSQ: 3.25.*
d. The majority of the evidence had an indirect comparison of usual care (unclear whether there was an intention to withdrawal from benzodiazepines in this group)

Table 81: Clinical evidence profile: Lorazepam substitution + tapered withdrawal vs Diazepam substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam substitution + tapered withdrawal	Diazepam substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Mortality - suicide (follow up: 14 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/23 (4.3%)	0/22 (0.0%)	**Peto OR 7.07** (0.14 to 356.89)	**40 more per 1,000 [c] (from 70 fewer to 160 more)**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 14 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	13/23 (56.5%)	16/22 (72.7%)	**RR 0.78** (0.50 to 1.21)	**160 fewer per 1,000** (from 364 fewer to 153 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).
c. Calculated from risk difference due to zero events in control arm.

Table 82: Clinical evidence profile: Buspirone substitution + tapered withdrawal vs Imipramine substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone substitution + tapered withdrawal	Imipramine substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	19/28 (67.9%)	19/23 (82.6%)	**RR 0.82** (0.60 to 1.13)	**149 fewer per 1,000** (from 330 fewer to 107 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Rickles 2000, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 83: Clinical evidence profile: Buspirone substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: post-intervention)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/25 (44.0%)	12/23 (52.2%)	**RR 0.71** (0.29 to 1.69)	**151 fewer per 1,000** (from 370 fewer to 360 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	19/28 (67.9%)	9/24 (37.5%)	**RR 1.81** (1.02 to 3.22)	**304 more per 1,000** (from 8 more to 833 more)	⨁⨁◯◯ LOW	CRITICAL
Cessation of benzodiazepine (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	6/11 (54.5%)	11/12 (91.7%)	**RR 0.60** (0.34 to 1.05)	**367 fewer per 1,000** (from 605 fewer to 46 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms - anxiety (follow up: 16 weeks; assessed with: HADS anxiety; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4	8	-	MD **2.75 higher** (2.83 lower to 8.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms – patients with insomnia (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	3/12 (25.0%)	1/12 (8.3%)	**RR 3.00** (0.36 to 24.92)	**167 more per 1,000** (from 53 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal symptom score (follow up: 16 weeks; assessed with: tool unclear; Scale from: 0 to 147)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4	11	-	MD **1.34 lower** (14.31 lower to 11.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: giddiness (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/12 (58.3%)	4/12 (33.3%)	**RR 1.75** (0.69 to 4.44)	**250 more per 1,000** (from 103 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: GI symptoms (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	6/12 (50.0%)	3/12 (25.0%)	**RR 2.00** (0.65 to 6.20)	**250 more per 1,000** (from 88 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms: headache (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/12 (8.3%)	2/12 (16.7%)	**RR 0.50** (0.05 to 4.81)	**83 fewer per 1,000** (from 158 fewer to 635 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: HADS anxiety 2.51, withdrawal symptoms score 6.92.*

Table 84: Clinical evidence profile: Imipramine substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imipramine substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	19/23 (82.6%)	9/24 (37.5%)	**RR 2.20** (1.27 to 3.82)	**450 more per 1,000** (from 101 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Rickels 2000, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

Table 85: Clinical evidence profile: Melatonin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: post-intervention)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	12/20 (60.0%)	9/18 (50.0%)	**RR 1.20** (0.67 to 2.15)	**100 more per 1,000** (from 165 fewer to 575 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	8/19 (42.1%)	7/17 (41.2%)	**RR 1.02** (0.47 to 2.22)	**8 more per 1,000** (from 218 fewer to 502 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 86: Clinical evidence profile: Dothiepin substitution + tapered withdrawal vs Placebo substitution + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dothiepin substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 14 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	11/36 (30.6%)	17/41 (41.5%)	**RR 0.74** (0.40 to 1.36)	**108 fewer per 1,000** (from 249 fewer to 149 more)	⨁◯◯◯ VERY LOW	
Patient satisfaction (follow up: 14 weeks; assessed with: Satisfaction analogue scale; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dothiepin substitution + tapered withdrawal	Placebo substitution + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	19	21	-	MD **22.9 higher** (3.19 higher to 42.61 higher)	⨁◯◯◯ VERY LOW	

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Tyrer 1996, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: satisfaction 15.63.*

Table 87: Clinical evidence profile: Valproate substitution + tapered withdrawal vs Tapered withdrawal alone for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate substitution + tapered withdrawal	Tapered withdrawal alone	Relative (95% CI)	Absolute (95% CI)		
Withdrawal symptoms (follow up: post-intervention; assessed with: CIWA-B; Scale from: 0 to 18)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	14	15	-	MD **1.1 lower** (3.87 lower to 1.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Use of illicit drugs (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	1/14 (7.1%)	1/16 (6.3%)	**RR 1.14** (0.08 to 16.63)	**9 more per 1,000** (from 58 fewer to 977 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Vorma 2011, 2 out of the 7 benzodiazepines listed (that people could be on) are not included in review protocol list, but no breakdown provided. Unclear if >80% were on relevant study drug.
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: CIWA-B 1.55.*

Table 88: Clinical evidence profile: Propranolol substitution + abrupt withdrawal vs Tapered withdrawal alone for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propranolol substitution + abrupt withdrawal	Tapered withdrawal alone	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	4/15 (26.7%)	11/16 (68.8%)	**RR 0.39** (0.16 to 0.96)	**419 fewer per 1,000** (from 578 fewer to 28 fewer)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal symptoms (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14/15 (93.3%)	11/16 (68.8%)	**RR 1.36** (0.95 to 1.94)	**248 more per 1,000** (from 34 fewer to 646 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 89: Clinical evidence profile: Patient advice & biofeedback guided information + tapered withdrawal vs Patient advice + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice & biofeedback guided information + tapered withdrawal	Patient advice + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: post-intervention)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	1/3 (33.3%)	0/3 (0.0%)	**Peto OR 7.39** (0.15 to 372.38)	**320 more per 1,000** [d] (from 240 fewer to 910 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Nathan 1986, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

d. Calculated from risk difference due to zero events in control arm.

Table 90: Clinical evidence profile: Psychological intervention, education and training + tapered withdrawal vs Psychological intervention, education and advice + tapered withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological intervention, education and training + tapered withdrawal	Psychological intervention, education and advice + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
Reduction of benzodiazepine (mg) (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological intervention, education and training + tapered withdrawal	Psychological intervention, education and advice + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	24	29	-	MD **4.4 mg higher** (0.01 lower to 8.81 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse (follow up: 6 months; assessed with: Weeks of taper suspension)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	24	29	-	MD **2.2 higher** (1.01 lower to 5.41 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Relapse (follow up: 6 months; assessed with: illicit use of benzodiazepine)												
1	randomised trials	serious [b]	not serious	not serious	very serious [a]	none	10/19 (52.6%)	12/20 (60.0%)	**RR 0.88** (0.50 to 1.53)	**72 fewer per 1,000** (from 300 fewer to 318 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal symptoms - anxiety (follow up: 6 months; assessed with: HADS - anxiety; Scale from: 0 to 21)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	19	20	-	MD **2.4 lower** (5.35 lower to 0.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal symptoms -depression (follow up: 6 months; assessed with: HADS - depression; Scale from: 0 to 21)												
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	19	20	-	MD **5.1 lower** (8.69 lower to 1.51 lower)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal symptoms - Sleep quality (follow up: 6 months; assessed with: PSQI; Scale from: 0 to 21)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychological intervention, education and training + tapered withdrawal	Psychological intervention, education and advice + tapered withdrawal	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [a]	none	19	20	-	MD **2.7 lower** (5.49 lower to 0.09 higher)	⨁⨁◯◯ LOW	CRITICAL

*a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of BZD 5.9, weeks of taper suspension 2.95, HADS anxiety 2, HADS depression 2.8, PSQI 2.1.*
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 91: Clinical evidence profile: Patient advice, education & support + gradual withdrawal vs Patient advice, education & support + abrupt withdrawal for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice, education & support + gradual withdrawal	Patient advice, education & support + abrupt withdrawal	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: post-intervention; assessed with: unauthorised use of benzodiazepine)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	7/21 (33.3%)	16/19 (84.2%)	**RR 0.40** (0.21 to 0.75)	**505 fewer per 1,000** (from 665 fewer to 211 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 92: Clinical evidence profile: Patient advice & information vs Patient advice for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice & information	Patient advice	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 6 months)												
2	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	20/170 (11.8%)	24/153 (15.7%)	**RR 0.74** (0.43 to 1.29)	**41 fewer per 1,000** (from 89 fewer to 45 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	37/75 (49.3%)	24/65 (36.9%)	**RR 1.34** (0.90 to 1.98)	**126 more per 1,000** (from 37 fewer to 362 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 6 months; assessed with: diazepam eqv (mg))												
1	randomised trials	not serious	not serious	not serious	not serious	none	95	88	-	MD **2.16 lower** (29.44 lower to 25.12 higher)	⨁⨁⨁⨁ HIGH	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

b. The majority of the evidence had an indirect population. For Cormack 1994, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of BZD 53.55.*

Table 93: Clinical evidence profile: Patient advice & information vs Usual care for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice & information	Usual care	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 6 months)												
2	randomised trials	not serious	not serious	serious [d]	serious [a]	none	20/170 (11.8%)	10/158 (6.3%)	**RR 1.86** (0.90 to 3.85)	**54 more per 1,000** (from 6 fewer to 180 more)	⨁⨁◯◯ LOW	CRITICAL
Cessation of benzodiazepine (follow up: 12 months; assessed with: ≤1 use in previous 15 days)												
1	randomised trials	very serious [b]	not serious	not serious	not serious	none	33/71 (46.5%)	6/64 (9.4%)	**RR 4.96** (2.22 to 11.05)	**371 more per 1,000** (from 114 more to 942 more)	⨁⨁◯◯ LOW	CRITICAL
Reduction of benzodiazepine (follow up: 6 months)												
1	randomised trials	serious [b]	not serious	serious [c,d]	not serious	none	37/75 (49.3%)	11/69 (15.9%)	**RR 3.09** (1.72 to 5.57)	**333 more per 1,000** (from 115 more to 729 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 6 months; assessed with: diazepam eqv (mg))												
1	randomised trials	not serious	not serious	serious [d]	not serious	none	95	89	-	MD **5.75 lower** (34.93 lower to 23.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Reduction of benzodiazepine (follow up: 12 months; assessed with: ≥50% reduction)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Patient advice & information	Usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	very serious [a]	none	16/71 (22.5%)	11/64 (17.2%)	**RR 1.31** (0.66 to 2.61)	**53 more per 1,000** (from 58 fewer to 277 more)	⨁◯◯◯ VERY LOW	CRITICAL

*a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of BZD 57.73 mg.*
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
c. The majority of the evidence had an indirect population. For Cormack 1994, the specific benzodiazepine used by patients was not reported. Unclear if >80% were on relevant study drug.
d The majority of the evidence had an indirect comparison. For Cormack 1994 & Heather 2004, the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 94: Clinical evidence profile: Brief advice, education & support vs Usual care for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief advice, education & support	Usual care	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 1 months)												
1	randomised trials	serious [a]	not serious	serious [c]	very serious [b]	none	6/11 (54.5%)	7/11 (63.6%)	**RR 0.86** (0.43 to 1.73)	**89 fewer per 1,000** (from 363 fewer to 465 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of benzodiazepine (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief advice, education & support	Usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious [c]	serious [b]	none	24/153 (15.7%)	10/158 (6.3%)	**RR 2.49** (1.23 to 5.02)	**94 more per 1,000** (from 15 more to 254 more)	⨁⨁◯◯ LOW	CRITICAL
Reduced benzodiazepine use (follow up: 6 months)												
2	randomised trials	very serious [a]	not serious	serious [c]	not serious	none	44/111 (39.6%)	22/113 (19.5%)	**RR 2.02** (1.30 to 3.13)	**199 more per 1,000** (from 58 more to 415 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction of benzodiazepine (follow up: 6 months; assessed with: diazepam eqv (mg))												
1	randomised trials	not serious	not serious	serious [c]	not serious	none	88	89	-	MD **3.59 mg lower** (34.61 lower to 27.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Increase in symptoms - psychiatric morbidity (follow up: 6 months; assessed with: increase of ≥2 on GHQ)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	24/46 (52.2%)	19/47 (40.4%)	**RR 1.29** (0.83 to 2.01)	**117 more per 1,000** (from 69 fewer to 408 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Withdrawal symptom score (follow up: 6 months; assessed with: scoring tool unclear)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	46	47	-	MD **1.6 higher** (0.86 lower to 4.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: reduction of BZD 55.31 mg, withdrawal symptom score 2.58.*
c. The majority of the evidence had an indirect comparison. For Bashir 1994, Cormack 1994, Heather 2004, & Gnjidic 2019 the study included control group who received usual care/no intervention. Unclear if there was any intention to withdraw from benzodiazepine in this group.

Table 95: Clinical evidence profile: Brief advice, education & support (multiple letters) vs Brief advice, education & support (single letter) for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief advice, education & support (multiple letters)	Brief advice, education & support (single letter)	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	44/186 (23.7%)	40/163 (24.5%)	**RR 0.96** (0.66 to 1.40)	**10 fewer per 1,000** (from 83 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 96: Clinical evidence profile: Brief advice, education & support (multiple letters) vs Brief advice, education & support (GP letter) for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief advice, education & support (multiple letters)	Brief advice, education & support (GP letter)	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	44/186 (23.7%)	23/159 (14.5%)	**RR 1.64** (1.03 to 2.58)	**93 more per 1,000** (from 4 more to 229 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

Table 97: Clinical evidence profile: Brief advice, education & support (single letter) vs Brief advice, education & support (GP letter) for benzodiazepines

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Brief advice, education & support (single letter)	Brief advice, education & support (GP letter)	Relative (95% CI)	Absolute (95% CI)		
Cessation of benzodiazepine (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	40/163 (24.5%)	23/159 (14.5%)	**RR 1.70** (1.07 to 2.70)	**101 more per 1,000** (from 10 more to 246 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
b. The majority of the evidence had an indirect population. For Ten Wolde 2008, 67.9% were taking oxazepam/temazepam/ diazepam, remaining 32.1% not reported. Unclear if >80% were on relevant study drug.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes).

G.3 Z-drugs

Table 98: Clinical evidence profile: acupuncture vs CBT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acupuncture	CBT	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 4-6 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	17/24 (70.8%)	21/25 (84.0%)	**RR 0.84** (0.62 to 1.15)	**134 fewer per 1,000** (from 319 fewer to 126 more)	⨁⨁◯◯ LOW	CRITICAL
Anxiety post intervention (Protocol outcome: withdrawal symptoms) (follow up: 4-6 weeks; assessed with: Hospital Anxiety and Depression Scale; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	25	25	-	MD **0.22 lower** (1.61 lower to 1.17 higher)	⨁⨁◯◯ LOW	CRITICAL
Anxiety (Protocol outcome: withdrawal symptoms) (follow up: 6 months; assessed with: Hospital Anxiety and Depression Scale; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	23	-	MD **0.25 higher** (1.29 lower to 1.79 higher)	⨁⨁◯◯ LOW	CRITICAL
Depression (Protocol outcome: withdrawal symptoms) (follow up: 4-6 weeks; assessed with: Hospital Anxiety and Depression Scale; Scale from: 0 to 21)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acupuncture	CBT	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	25	25	-	MD **0.1 higher** (1.36 lower to 1.56 higher)	⨁⨁◯◯ LOW	CRITICAL
Depression (Protocol outcome: withdrawal symptoms) (follow up: 6 months; assessed with: Hospital Anxiety and Depression Scale; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	23	-	MD **0.29 higher** (0.91 lower to 1.49 higher)	⨁⨁◯◯ LOW	CRITICAL
Insomnia (Protocol outcome: increase in symptoms for which the medication was originally prescribed) (follow up: 4-6 weeks; assessed with: Insomnia Severity Index; Scale from: 0 to 28)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	25	25	-	MD **6.09 higher** (3.32 higher to 8.86 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Insomnia (Protocol outcome: increase in symptoms for which the medication was originally prescribed) (follow up: 6 months; assessed with: Insomnia Severity Index; Scale from: 0 to 28)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	23	-	MD **2.82 higher** (0.25 lower to 5.89 higher)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment as the evidence was at high risk of bias.
b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 median of baseline SDs of intervention and control groups. MIDs were calculated as follows: ISI: 1.83, HADS anxiety 1.42 and HADS depression 1.42*

G.4 Antidepressants

Table 99: Clinical evidence profile: TCAs: CBT + taper vs clinical management + taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	clinical management + taper	Relative (95% CI)	Absolute (95% CI)		
Discontinuation of antidepressants (follow up: 20 weeks; assessed with: calculated from the information on the number of people in whom discontinuation was not feasible)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	40/44 (90.9%)	40/44 (90.9%)	**RR 1.00** (0.88 to 1.14)	**0 fewer per 1,000** (from 109 fewer to 127 more)	⨁⨁◯◯ LOW	CRITICAL
Relapse (episode of major depression): protocol outcome: increase in symptoms for which the medication was originally prescribed (follow up: 2 years; assessed with: occurrence of a Research Diagnostic Criteria-defined episode of major depression during follow up)[b]												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	9/41 (22.0%)	25/42 (59.5%)	**RR 0.37** (0.20 to 0.68)	**375 fewer per 1,000** (from 476 fewer to 190 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Residual symptoms score (follow up: 20 weeks; assessed with: Total score on the modified version of the Paykel Clinical Interview for Depression – range of values not reported, assumed to be 133 (based on 19 symptom areas and a 1-7 point scale) Top=High is poor outcome)[c]												
2	randomised trials	very serious [a]	serious [d]	not serious	serious [e]	none	40	40	-	MD **2.61 lower** (3.92 lower to 1.29 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. For Fava 1994 this is including the people who were unable to discontinue during the taper stage, as it specifically states that these people were withdrawn because of relapse during the medication tapering phase. For Fava 1998, this does not include the people who were unable to discontinue during the taper stage, as does not specifically state that these people were unable to discontinue due to taper, and the study excluded these from further analysis.

c. people in the study had residual symptoms after successful treatment with antidepressants (baseline) - this score was assessed again after CBT or CM + taper.

d. Heterogeneity, I2=50%, unexplained by subgroup analysis (unable to perform subgroup analysis due to only 2 studies)

*e. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: residual symptoms 1.64*

Table 100: Clinical evidence profile: Other antidepressants (desvenlafaxine): abrupt discontinuation vs 1 week taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abrupt discontinuation	1 week taper	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	0/146 (0.0%)	0/139 (0.0%)	not estimable	**0 fewer per 1,000** (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
Completing the double-blind phase (i.e., antidepressant discontinuation) (follow up: 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	138/148 (93.2%)	127/140 (90.7%)	**RR 1.03** (0.96 to 1.10)	**27 more per 1,000** (from 36 fewer to 91 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Discontinuation Emergent Signs and Symptoms score: protocol outcome withdrawal symptoms (follow up: 2 weeks; assessed with: DESS total score (unclear if there is a range of values, suggests this is the number of DESS) Top=High is poor outcome) [f]												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	146	139	-	MD **0.5 higher** (0.88 lower to 1.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Discontinuation syndrome (increase in DESS score of ≥4): protocol outcome withdrawal symptoms (follow up: 2 weeks) [f]												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	31/146 (21.2%)	30/139 (21.6%)	**RR 0.98** (0.63 to 1.54)	**4 fewer per 1,000** (from 80 fewer to 117 more)	⨁◯◯◯ VERY LOW	CRITICAL
Taper/post-therapy–emergent adverse events (TPAEs): protocol outcome withdrawal symptoms (follow up: 4 weeks; assessed with: any adverse event that started or increased in severity during the double-blind phase)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abrupt discontinuation	1 week taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [d]	serious [c]	none	75/146 (51.4%)	54/139 (38.8%)	**RR 1.32** (1.02 to 1.72)	**124 more per 1,000** (from 8 more to 280 more)	⨁◯◯◯ VERY LOW	CRITICAL
Suicidal ideation: protocol outcome withdrawal symptoms (judged by reviewer) (follow up: 6 weeks; assessed with: C-SSRS)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	1/146 (0.7%)	1/139 (0.7%)	**RR 0.95** (0.06 to 15.07)	**0 fewer per 1,000** (from 7 fewer to 101 more)	⨁◯◯◯ VERY LOW	CRITICAL
Suicide attempt (intentional drug overdose of a non-study medication): protocol outcome, self-harm or harm to others (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	1/146 (0.7%)	0/139 (0.0%)	Peto OR 7.04 (0.14 to 355.37)	**10 more per 1,000** [g] (from 10 fewer to 30 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Depressive symptoms (QIDS-SR16): protocol outcome increase in symptoms for which the medication was originally prescribed (follow up: 4 weeks; assessed with: Quick Inventory of Depressive Symptomatology Self-Report 0-27 Top=High is poor outcome)[e]												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	146	139	-	MD **0.3 higher** (0.77 lower to 1.37 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Only one study with zero events in both arms, sample size >70<350
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS score 0.9; QIDS-SR16 2.15*
d. Downgraded for outcome indirectness
e. Range of the QIDS-SR16 not reported by the study. Online resources suggest this is a 16 item self-report measure of depression, with a total range of scores from 0-27 (0-5 no depression, 6-10 mild depression, 11-15 moderate depression, 16-20 severe depression, 21-27 very severe depression)
f. DESS reported at 2-week timepoint. This would have been 2 weeks of drug-free wash-out for the abrupt discontinuation arm, but only 1 week of drug-free wash-out for the taper arm. This was taken into account within the risk of bias assessment for the DESS outcomes.
g. Calculated from risk difference due to zero events in control arm.

Table 101: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs abrupt (placebo)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist)[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	57	98	-	MD **2.96 lower** (5.02 lower to 0.9 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	17/57 (29.8%)	41/98 (41.8%)	**RR 0.71** (0.45 to 1.13)	**121 fewer per 1,000** (from 230 fewer to 54 more)	⨁◯◯◯ VERY LOW	CRITICAL
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	11/57 (19.3%)	28/98 (28.6%)	**RR 0.68** (0.36 to 1.25)	**91 fewer per 1,000** (from 183 fewer to 71 more)	⨁◯◯◯ VERY LOW	CRITICAL
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	10/57 (17.5%)	35/98 (35.7%)	**RR 0.49** (0.26 to 0.92)	**182 fewer per 1,000** (from 264 fewer to 29 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	9/57 (15.8%)	26/98 (26.5%)	**RR 0.60** (0.30 to 1.18)	**106 fewer per 1,000** (from 186 fewer to 48 more)	⨁◯◯◯ VERY LOW	CRITICAL
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	not serious	none	5/57 (8.8%)	28/98 (28.6%)	**RR 0.31** (0.13 to 0.75)	**197 fewer per 1,000** (from 249 fewer to 71 fewer)	⨁⨁◯◯ LOW	CRITICAL
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	4/57 (7.0%)	22/98 (22.4%)	**RR 0.31** (0.11 to 0.86)	**155 fewer per 1,000** (from 200 fewer to 31 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	19/57 (33.3%)	44/98 (44.9%)	**RR 0.74** (0.48 to 1.14)	**117 fewer per 1,000** (from 233 fewer to 63 more)	⨁◯◯◯ VERY LOW	CRITICAL
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	13/57 (22.8%)	37/98 (37.8%)	**RR 0.60** (0.35 to 1.04)	**151 fewer per 1,000** (from 245 fewer to 15 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	35/52 (67.3%)	37/54 (68.5%)	**RR 0.98** (0.76 to 1.28)	**14 fewer per 1,000** (from 164 fewer to 192 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; placebo (abrupt): week 1).
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.85*

Table 102: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper) vs abrupt (placebo)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50 every other	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist)[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	59	98	-	MD **3.85 lower** (5.72 lower to 1.98 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	13/59 (22.0%)	41/98 (41.8%)	**RR 0.53** (0.31 to 0.90)	**197 fewer per 1,000** (from 289 fewer to 42 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50 every other	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	not serious	none	4/59 (6.8%)	28/98 (28.6%)	**RR 0.24** (0.09 to 0.64)	**217 fewer per 1,000** (from 260 fewer to 103 fewer)	⨁⨁◯◯ LOW	CRITICAL

Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	not serious	none	7/59 (11.9%)	35/98 (35.7%)	**RR 0.33** (0.16 to 0.70)	**239 fewer per 1,000** (from 300 fewer to 107 fewer)	⨁⨁◯◯ LOW	CRITICAL

Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	11/59 (18.6%)	26/98 (26.5%)	**RR 0.70** (0.38 to 1.32)	**80 fewer per 1,000** (from 164 fewer to 85 more)	⨁◯◯◯ VERY LOW	CRITICAL

Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	not serious	none	5/59 (8.5%)	28/98 (28.6%)	**RR 0.30** (0.12 to 0.73)	**200 fewer per 1,000** (from 251 fewer to 77 fewer)	⨁⨁◯◯ LOW	CRITICAL

Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	7/59 (11.9%)	22/98 (22.4%)	**RR 0.53** (0.24 to 1.16)	**106 fewer per 1,000** (from 171 fewer to 36 more)	⨁◯◯◯ VERY LOW	CRITICAL

Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50 every other	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	21/59 (35.6%)	44/98 (44.9%)	**RR 0.79** (0.53 to 1.19)	**94 fewer per 1,000** (from 211 fewer to 85 more)	⨁◯◯◯ VERY LOW	CRITICAL

Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	12/59 (20.3%)	37/98 (37.8%)	**RR 0.54** (0.31 to 0.95)	**174 fewer per 1,000** (from 261 fewer to 19 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)

1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	26/53 (49.1%)	37/54 (68.5%)	**RR 0.72** (0.52 to 0.99)	**192 fewer per 1,000** (from 329 fewer to 7 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-eo taper: week 3; placebo (abrupt): week 1).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.48*

Table 103: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper) vs abrupt (placebo)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-placebo	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	79	98	-	MD **2.61 lower** (4.61 lower to 0.61 lower)	⨁⨁◯◯ LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	21/79 (26.6%)	41/98 (41.8%)	**RR 0.64** (0.41 to 0.98)	**151 fewer per 1,000** (from 247 fewer to 8 fewer)	⨁⨁◯◯ LOW	CRITICAL
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	8/79 (10.1%)	28/98 (28.6%)	**RR 0.35** (0.17 to 0.73)	**186 fewer per 1,000** (from 237 fewer to 77 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	not serious	none	10/79 (12.7%)	35/98 (35.7%)	**RR 0.35** (0.19 to 0.67)	**232 fewer per 1,000** (from 289 fewer to 118 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	18/79 (22.8%)	26/98 (26.5%)	**RR 0.86** (0.51 to 1.45)	**37 fewer per 1,000** (from 130 fewer to 119 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-placebo	abrupt (placebo)	Relative (95% CI)	Absolute (95% CI)		
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	15/79 (19.0%)	28/98 (28.6%)	**RR 0.66** (0.38 to 1.15)	**97 fewer per 1,000** (from 177 fewer to 43 more)	⨁⨁◯◯ LOW	CRITICAL
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	very serious [c]	none	18/79 (22.8%)	22/98 (22.4%)	**RR 1.01** (0.59 to 1.76)	**2 more per 1,000** (from 92 fewer to 171 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	23/79 (29.1%)	44/98 (44.9%)	**RR 0.65** (0.43 to 0.98)	**157 fewer per 1,000** (from 256 fewer to 9 fewer)	⨁⨁◯◯ LOW	CRITICAL
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	22/79 (27.8%)	37/98 (37.8%)	**RR 0.74** (0.48 to 1.14)	**98 fewer per 1,000** (from 196 fewer to 53 more)	⨁⨁◯◯ LOW	CRITICAL
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	29/40 (72.5%)	37/54 (68.5%)	**RR 1.06** (0.81 to 1.38)	**41 more per 1,000** (from 130 fewer to 260 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-placebo taper: week 2; placebo (abrupt): week 1).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 3.01*

Table 104: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50 every other	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	57	59	-	MD **0.89 higher** (1.05 lower to 2.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	17/57 (29.8%)	13/59 (22.0%)	**RR 1.35** (0.73 to 2.53)	**77 more per 1,000** (from 59 fewer to 337 more)	⨁◯◯◯ VERY LOW	CRITICAL
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	11/57 (19.3%)	4/59 (6.8%)	**RR 2.85** (0.96 to 8.42)	**125 more per 1,000** (from 3 fewer to 503 more)	⨁◯◯◯ VERY LOW	CRITICAL
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	10/57 (17.5%)	7/59 (11.9%)	**RR 1.48** (0.60 to 3.62)	**57 more per 1,000** (from 47 fewer to 311 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50 every other	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	9/57 (15.8%)	11/59 (18.6%)	**RR 0.85** (0.38 to 1.89)	**28 fewer per 1,000** (from 116 fewer to 166 more)	⨁◯◯◯ VERY LOW	CRITICAL

Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	5/57 (8.8%)	5/59 (8.5%)	**RR 1.04** (0.32 to 3.39)	**3 more per 1,000** (from 58 fewer to 203 more)	⨁◯◯◯ VERY LOW	CRITICAL

Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	4/57 (7.0%)	7/59 (11.9%)	**RR 0.59** (0.18 to 1.91)	**49 fewer per 1,000** (from 97 fewer to 108 more)	⨁◯◯◯ VERY LOW	CRITICAL

Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	19/57 (33.3%)	21/59 (35.6%)	**RR 0.94** (0.57 to 1.55)	**21 fewer per 1,000** (from 153 fewer to 196 more)	⨁◯◯◯ VERY LOW	CRITICAL

Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms[a]

1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	13/57 (22.8%)	12/59 (20.3%)	**RR 1.12** (0.56 to 2.25)	**24 more per 1,000** (from 89 fewer to 254 more)	⨁◯◯◯ VERY LOW	CRITICAL

Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50 every other	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	35/52 (67.3%)	26/53 (49.1%)	**RR 1.37** (0.98 to 1.91)	**182 more per 1,000** (from 10 fewer to 446 more)	⊕◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; Desvenlafaxine 50-eo taper: week 3).
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.14*

Table 105: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d for 7 days then 25 mg/d for 7 days (Desvenlafaxine 50-25 taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50-placebo	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist) [a]												
1	randomised trials	very serious [b]	not serious	not serious	not serious	none	57	79	-	MD **0.35 lower** (2.41 lower to 1.71 higher)	⊕⊕◯◯ LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	17/57 (29.8%)	21/79 (26.6%)	**RR 1.12** (0.65 to 1.93)	**32 more per 1,000** (from 93 fewer to 247 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50-placebo	Relative (95% CI)	Absolute (95% CI)		
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	11/57 (19.3%)	8/79 (10.1%)	**RR 1.91** (0.82 to 4.43)	**92 more per 1,000** (from 18 fewer to 347 more)	⨁◯◯◯ VERY LOW	CRITICAL
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. [a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	10/57 (17.5%)	10/79 (12.7%)	**RR 1.39** (0.62 to 3.11)	**49 more per 1,000** (from 48 fewer to 267 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	9/57 (15.8%)	18/79 (22.8%)	**RR 0.69** (0.34 to 1.43)	**71 fewer per 1,000** (from 150 fewer to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	5/57 (8.8%)	15/79 (19.0%)	**RR 0.46** (0.18 to 1.20)	**103 fewer per 1,000** (from 156 fewer to 38 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	4/57 (7.0%)	18/79 (22.8%)	**RR 0.31** (0.11 to 0.86)	**157 fewer per 1,000** (from 203 fewer to 32 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50-25	Desvenlafaxine 50-placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	19/57 (33.3%)	23/79 (29.1%)	**RR 1.14** (0.69 to 1.89)	**41 more per 1,000** (from 90 fewer to 259 more)	⨁◯◯◯ VERY LOW	CRITICAL
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	13/57 (22.8%)	22/79 (27.8%)	**RR 0.82** (0.45 to 1.48)	**50 fewer per 1,000** (from 153 fewer to 134 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	35/52 (67.3%)	29/40 (72.5%)	**RR 0.93** (0.71 to 1.21)	**51 fewer per 1,000** (from 210 fewer to 152 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-25 taper: week 3; Desvenlafaxine 50-placebo taper: week 2).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.67*

Table 106: Clinical evidence profile: Other antidepressants: Desvenlafaxine 50 mg/d every other day for 14 days (Desvenlafaxine 50-eo taper) vs Desvenlafaxine 50 mg/d for 7 days then placebo for 7 days (Desvenlafaxine 50-placebo taper)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50 every other	Desvenlafaxine 50-placebo	Relative (95% CI)	Absolute (95% CI)		
Discontinuation-Emergent Signs & Symptoms (DESS) total score (post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms. Range of values unclear (DESS 43-item checklist)[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	59	79	-	MD **1.24 lower** (3.12 lower to 0.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Dizziness, light-headedness, spinning sensation (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	13/59 (22.0%)	21/79 (26.6%)	**RR 0.83** (0.45 to 1.52)	**45 fewer per 1,000** (from 146 fewer to 138 more)	⨁◯◯◯ VERY LOW	CRITICAL
Headaches (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	4/59 (6.8%)	8/79 (10.1%)	**RR 0.67** (0.21 to 2.12)	**33 fewer per 1,000** (from 80 fewer to 113 more)	⨁◯◯◯ VERY LOW	CRITICAL
Increased dreaming/nightmare (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	7/59 (11.9%)	10/79 (12.7%)	**RR 0.94** (0.38 to 2.32)	**8 fewer per 1,000** (from 78 fewer to 167 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	11/59 (18.6%)	18/79 (22.8%)	**RR 0.82** (0.42 to 1.60)	**41 fewer per 1,000** (from 132 fewer to 137 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desvenlafaxine 50 every other	Desvenlafaxine 50-placebo	Relative (95% CI)	Absolute (95% CI)		
Nausea (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	5/59 (8.5%)	15/79 (19.0%)	**RR 0.45** (0.17 to 1.16)	**104 fewer per 1,000** (from 158 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sudden worsening of mood (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	7/59 (11.9%)	18/79 (22.8%)	**RR 0.52** (0.23 to 1.16)	**109 fewer per 1,000** (from 175 fewer to 36 more)	⨁◯◯◯ VERY LOW	CRITICAL
Sweating more than usual (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	21/59 (35.6%)	23/79 (29.1%)	**RR 1.22** (0.75 to 1.99)	**64 more per 1,000** (from 73 fewer to 288 more)	⨁◯◯◯ VERY LOW	CRITICAL
Trouble sleeping/insomnia (incidence of symptom on the DESS, post-taper: 1 week after last dose in the taper). Protocol outcome: withdrawal symptoms.[a]												
1	randomised trials	very serious [b]	not serious	not serious	very serious [c]	none	12/59 (20.3%)	22/79 (27.8%)	**RR 0.73** (0.39 to 1.35)	**75 fewer per 1,000** (from 170 fewer to 97 more)	⨁◯◯◯ VERY LOW	CRITICAL
Patient Satisfaction (number of people responded satisfied or very satisfied, week 3)												
1	randomised trials	very serious [b]	not serious	not serious	serious [c]	none	26/53 (49.1%)	29/40 (72.5%)	**RR 0.68** (0.48 to 0.95)	**232 fewer per 1,000** (from 377 fewer to 36 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

a. For those outcomes at the 'post-intervention/post-taper' timepoint, this was different for each group, due to the different length taper - the post-intervention timepoint was taken as the timepoint 1 week after the last dose of desvenlafaxine (Desvenlafaxine 50-eo taper: week 3; Desvenlafaxine 50-placebo taper: week 2).

b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group). MIDs for continuous outcomes were as follows: DESS 2.29*

Table 107: Clinical evidence profile: Mixed antidepressants: longer (14 day) taper vs shorter (3 day) taper week taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	longer (14 day) taper	shorter (3 day) taper	Relative (95% CI)	Absolute (95% CI)		
Discontinuation syndrome (≥3 new symptoms on the DESS checklist) post-taper: protocol outcome withdrawal symptoms (follow up: 5-7 days)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	6/13 (46.2%)	7/15 (46.7%)	**RR 0.99** (0.45 to 2.20)	**5 fewer per 1,000** (from 257 fewer to 560 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded for population indirectness: population differs from others included in this review, as the included population are discontinuing antidepressants in order to switch to another antidepressant, not because they no longer require to be on the antidepressant

*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).*

Table 108: Clinical evidence profile: Mixed antidepressants: CBT + taper vs taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
Suicide (follow up: 16 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/42 (2.4%)	0/45 (0.0%)	Peto OR 7.94 (0.16 to 400.89)	**20 more per 1,000** [d] (from 40 fewer to 90 more)	⨁◯◯◯ VERY LOW	CRITICAL
Recurrence of the previous anxiety disorder. Protocol outcome: increase in symptoms for which the medication was originally prescribed (follow up: 16 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	18/42 (42.9%)	20/45 (44.4%) [c]	**HR 1.04** (0.53 to 2.06)	**13 more per 1,000** (from 177 fewer to 258 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).*

c. Study only provides HR summary statistic and % of people with the outcome. Numbers in each group calculated from these percentages (assumed all people analysed)

d. Calculated from risk difference due to zero events in control arm

Table 109: Clinical evidence profile: Mixed antidepressants: Mindfulness-based cognitive therapy + taper vs placebo substitution taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness-based cognitive therapy (MBCT) + taper	placebo substitution taper	Relative (95% CI)	Absolute (95% CI)		
Relapse (recurrence of major depressive episode): protocol outcome: increase in symptoms for which the medication was originally prescribed (follow up: 18 months; assessed with: DSM-IV major depressive episode, using the depression module of the SCID)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness-based cognitive therapy (MBCT) + taper	placebo substitution taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	10/26 (38.5%)	18/30 (60.0%)	**RR 0.64** (0.36 to 1.13)	**216 fewer per 1,000** (from 384 fewer to 78 more)	⨁⨁◯◯ LOW	IMPORTANT

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).*

Table 110: Clinical evidence profile: Mixed antidepressants: advice to GP to discontinue patient's antidepressants vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advice to GP to discontinue patient's antidepressants	usual care	Relative (95% CI)	Absolute (95% CI)		
Antidepressant discontinuation (follow up: 1 years)[a]												
1	randomised trials	very serious [b]	not serious	serious [c]	very serious [d]	none	17/70 (24.3%)	15/76 (19.7%)	**RR 1.23** (0.67 to 2.27)	**45 more per 1,000** (from 65 fewer to 251 more)	⨁◯◯◯ VERY LOW	CRITICAL
Antidepressant restart. Protocol outcome: relapse into medication use (follow up: 1 years)												
1	randomised trials	very serious [b]	not serious	serious [c]	very serious [d]	none	8/70 (11.4%)	5/76 (6.6%)	**RR 1.74** (0.60 to 5.06)	**49 more per 1,000** (from 26 fewer to 267 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advice to GP to discontinue patient's antidepressants	usual care	Relative (95% CI)	Absolute (95% CI)		
Relapse (depressive or anxiety disorder during follow-up). Protocol outcome: increase in symptoms for which the medication was originally prescribed. (follow up: 1 years; assessed with: CIDI)												
1	randomised trials	very serious [b]	not serious	serious [c]	serious [d]	none	18/70 (25.7%)	10/76 (13.2%)	**RR 1.95** (0.97 to 3.94)	**125 more per 1,000** (from 4 fewer to 387 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. regardless of intention to comply with recommendation to discontinue or not in the intervention group
b. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c. Downgraded for comparison indirectness: : usual care group had no specific aim to taper or discontinue
*d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group).*

G.5 Mixed medicines

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Table 111: Clinical evidence profile: MBRP + initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal vs initial psychoeducation group session + individualised guidance on gradual voluntary withdrawal

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MBRP	control	Relative (95% CI)	Absolute (95% CI)		
Equivalent hypnotic dosage (DDD/DME); protocol outcome: reduction in prescribed medication use; at post-intervention (8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	36	34	-	MD **1.01 lower** (2.29 lower to 0.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MBRP	control	Relative (95% CI)	Absolute (95% CI)		
Equivalent hypnotic dosage (DDD/DME); protocol outcome: reduction in prescribed medication use; at 6 months follow-up												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	36	34	-	MD **0.2 higher** (0.48 lower to 0.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia (Insomnia Severity Index; range 0-28; higher values = worse outcome); protocol outcome: symptoms for which the medication was originally prescribed; at post-intervention (8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	36	34	-	MD **1.28 lower** (3.95 lower to 1.39 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Insomnia (Insomnia Severity Index; range 0-28; higher values = worse outcome); protocol outcome: symptoms for which the medication was originally prescribed; at 6 months follow-up												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c]	none	36	34	-	MD **4.82 lower** (7.45 lower to 2.19 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
b. Downgraded for population indirectness: breakdown of benzodiazepines used not provided and unclear if on guideline medicine list
*c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of intervention and control groups). Calculated MIDs for continuous outcomes were as follows: hypnotic dosage: 1.45; ISI: 2.94*

Table 112: Clinical evidence profile: CBT+taper vs taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
HRQOL (follow up: 8 weeks; assessed with: SF-36-Physical health component score; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23	25	-	MD **10.42 lower** (20.9 lower to 0.06 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
HRQOL (follow up: 6 months; assessed with: SF-36-physical health component)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	20	23	-	MD **8.32 lower** (19.52 lower to 2.88 higher)	⨁⨁◯◯ LOW	CRITICAL
HRQOL (follow up: 8 weeks; assessed with: SF-36-mental health component)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	23	25	-	MD **3.72 lower** (12.91 lower to 5.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HRQOL (follow up: 6 months; assessed with: SF-36-mental health component)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	20	23	-	MD **1.09 lower** (10.82 lower to 8.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug post intervention (follow up: 8/13 weeks)												
2	randomised trials	very serious [a]	not serious	serious [c]	not serious	none	23/36 (63.9%)	10/39 (25.6%)	**RR 2.50** (1.39 to 4.49)	**385 more per 1,000** (from 100 more to 895 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	9/19 (47.4%)	13/24 (54.2%)	**RR 0.87** (0.48 to 1.59)	**70 fewer per 1,000** (from 282 fewer to 320 more)	⨁◯◯◯ VERY LOW	CRITICAL

BZD usage post intervention, lorazepam equivalent, mg. Protocol outcome: reduction of prescribed drug use (follow up: 8 weeks; assessed with: Daily hypnotic dose)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	23	25	-	MD **0.08 higher** (0.1 lower to 0.26 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
BZD usage post intervention, lorazepam equivalent, mg. Protocol outcome: reduction of prescribed drug use (follow up: 6 months; assessed with: Daily hypnotic dose)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	20	23	-	MD **0.04 lower** (0.47 lower to 0.39 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Decrease in prescribed drug use: Reduction of prescribed drug use (follow up: 13 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	13/14 (92.9%)	10/14 (71.4%)	**RR 1.30** (0.91 to 1.87)	**214 more per 1,000** (from 64 fewer to 621 more)	⨁◯◯◯ VERY LOW	CRITICAL
'Responder'. Protocol outcome : increase in symptoms for which the medication was originally prescribed (follow up: 13 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	9/14 (64.3%)	5/14 (35.7%)	**RR 1.80** (0.81 to 4.02)	**286 more per 1,000** (from 68 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Proportion of medication taken post-treatment relative to pre-treatment. Protocol outcome: reduction of prescribed drug (follow up: 13 weeks; assessed with: post-treatment dose divided by pre-treatment dose)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [b]	none	14	14	-	MD **0.12 lower** (0.72 lower to 0.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Depression post intervention. Protocol outcome: withdrawal symptoms (follow up: 8 weeks; assessed with: BDI; Scale from: 0 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23	25	-	MD **3.11 higher** (0.16 higher to 6.06 higher)	⨁⨁◯◯ LOW	CRITICAL
Depression. Protocol outcome: withdrawal symptoms (follow up: 6 months; assessed with: BDI; Scale from: 0 to 63)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	20	23	-	MD **0.43 lower** (2.81 lower to 1.95 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Anxiety post intervention. Protocol outcome: withdrawal symptoms (follow up: 8 weeks; assessed with: STAI-state; Scale from: 20 to 80)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23	25	-	MD **0.86 lower** (7.31 lower to 5.59 higher)	⨁⨁◯◯ LOW	CRITICAL
Anxiety Protocol outcome: withdrawal symptoms (follow up: 6 months; assessed with: STAI-state; Scale from: 20 to 80)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	20	23	-	MD **4.13 lower** (9.65 lower to 1.39 higher)	⨁⨁◯◯ LOW	CRITICAL
Withdrawal symptoms post intervention (follow up: 8 weeks; assessed with: CIWA-B; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	23	25	-	MD **1.18 higher** (7.37 lower to 9.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Withdrawal symptoms (follow up: 6 months; assessed with: CIWA-B; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + taper	taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	20	23	-	MD **1.62 higher** (5.51 lower to 8.75 higher)	⨁⨁◯◯ LOW	CRITICAL
Insomnia post intervention. Protocol outcome: increase in symptoms for which the medication was originally prescribed (follow up: 8 weeks; assessed with: Insomnia Severity Index; Scale from: 0 to 28)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23	25	-	MD **2.52 lower** (5.69 lower to 0.65 higher)	⨁⨁◯◯ LOW	IMPORTANT
Insomnia. Protocol outcome: increase in symptoms for which the medication was originally prescribed (follow up: 6 months; assessed with: Insomnia Severity Index; Scale from: 0 to 28)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	20	23	-	MD **0.78 lower** (4.81 lower to 3.25 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment if the evidence was at high risk of bias and by 2 increments if the evidence was at very high risk of bias.
*b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of intervention and control groups). Calculated MIDs for continuous outcomes were as follows: daily hypnotic dose 0.65, BDI 3.28, STAI 5.39, CIWA-B 4.99, Insomnia Severity Scale 2.13. Published MIDs were: SF-36 physical 2, SF-36: mental 3.*
c. Possibly indirect population- no breakdown of BZDs used.

Table 113: Clinical evidence profile: Patient advice+ relaxation vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	patient advice/education	usual care	Relative (95% CI)	Absolute (95% CI)		
No hypnotic use. Protocol outcome: cessation of drug (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	patient advice/education	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	7/10 (70.0%)	1/10 (10.0%)	**RR 7.00** (1.04 to 46.95)	**600 more per 1,000** (from 4 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

No hypnotic use. Protocol outcome: cessation of drug (follow up: 12 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	6/10 (60.0%)	1/10 (10.0%)	**RR 6.00** (0.87 to 41.21)	**500 more per 1,000** (from 13 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

Resumption of nightly hypnotic use. Protocol outcome: relapse into medication use. (follow up: 4 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	1/10 (10.0%)	7/10 (70.0%)	**RR 0.14** (0.02 to 0.96)	**602 fewer per 1,000** (from 686 fewer to 28 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Resumption of nightly hypnotic use. Protocol outcome: relapse into medication use. (follow up: 12 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	2/10 (20.0%)	8/10 (80.0%)	**RR 0.25** (0.07 to 0.90)	**600 fewer per 1,000** (from 744 fewer to 80 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Sleep latency. Protocol outcome: increase in symptoms for which the medicine was originally prescribed. (follow up: 4 weeks)

1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	10	10	-	MD **43 higher** (17.29 higher to 68.71 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Sleep latency. Protocol outcome: increase in symptoms for which the medicine was originally prescribed. (follow up: 12 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	patient advice/education	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	10	10	-	MD **2 lower** (24.39 lower to 20.39 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 1 increment as the evidence was at high risk of bias
b. Possibly indirect population- no breakdown of drugs was provided.
*c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of the intervention and control groups). MID for sleep latency was calculated to be 19.*

Table 114: Clinical evidence profile: Melatonin + support + taper vs placebo + support + taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	melatonin + support + taper	placebo + support + taper	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug post intervention (follow up: 1 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	36/45 (80.0%)	41/45 (91.1%)	**RR 0.88** (0.74 to 1.04)	**109 fewer per 1,000** (from 237 fewer to 36 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cessation of drug (follow up: 6 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	14/44 (31.8%)	20/45 (44.4%)	**RR 0.72** (0.42 to 1.23)	**124 fewer per 1,000** (from 258 fewer to 102 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Cessation of drug (follow up: 3 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	melatonin + support + taper	placebo + support + taper	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	12/42 (28.6%)	14/41 (34.1%)	**RR 0.84** (0.44 to 1.59)	**55 fewer per 1,000** (from 191 fewer to 201 more)	⨁⨁◯◯ LOW	CRITICAL
BZD usage. Protocol outcome: reduction of prescribed drug use (follow up: 6 months)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	44	45	**OR 2.50** (1.12 to 5.58)	**Unable to calculate**	⨁⨁⨁◯ MODERATE	CRITICAL

a. *Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crosses 2 MIDs (0.8 and 1.25 for dichotomous outcomes)*

Table 115: Clinical evidence profile: Prescriber education vs written manual for prescribers

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive support	written manual	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 0-3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	998/11423 (8.7%)	659/7975 (8.3%)	**RR 1.06** (0.96 to 1.16)	**5 more per 1,000** (from 3 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 4-6 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	1129/11423 (9.9%)	810/7975 (10.2%)	**RR 0.97** (0.89 to 1.06)	**3 fewer per 1,000** (from 11 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive support	written manual	Relative (95% CI)	Absolute (95% CI)		
50% reduction in BZD use (follow up: 0-3 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	1793/11423 (15.7%)	1179/7975 (14.8%)	**RR 1.06** (0.99 to 1.14)	**9 more per 1,000** (from 1 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL
50% reduction in BZD use (follow up: 4-6 months)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	1820/11423 (15.9%)	1331/7975 (16.7%)	**RR 0.95** (0.89 to 1.02)	**8 fewer per 1,000** (from 18 fewer to 3 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 2 increments as the evidence was at very high risk of bias.
b. Downgraded by 1 increment as the population may have been indirect (no breakdown of drugs provided.)

Table 116: Clinical evidence profile: Structured intervention with follow-up vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up	usual care	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	71/191 (37.2%)	25/173 (14.5%)	**RR 2.58** (1.77 to 3.75)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	86/191 (45.0%)	26/173 (15.0%)	**RR 3.00** (2.04 to 4.40)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 36 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	79/191 (41.4%)	45/173 (26.0%)	**RR 1.59** (1.15 to 2.19)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Mortality at 36 months												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	1/159 (0.6%)	2/149 (1.3%)	**RR 0.47** (0.04 to 5.11)	**7 fewer per 1,000** (from 13 fewer to 55 more)	⨁◯◯◯ VERY LOW	CRITICAL
Tremor. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	30/186 (16.1%)	9/170 (5.3%)	**RR 3.05** (1.49 to 6.23)	**109 more per 1,000** (from 26 more to 277 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	42/186 (22.6%)	15/170 (8.8%)	**RR 2.56** (1.47 to 4.44)	**138 more per 1,000** (from 41 more to 304 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	87/186 (46.8%)	30/170 (17.6%)	**RR 2.65** (1.85 to 3.80)	**291 more per 1,000** (from 150 more to 494 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up	usual care	Relative (95% CI)	Absolute (95% CI)		
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	72/186 (38.7%)	21/170 (12.4%)	**RR 3.13** (2.02 to 4.86)	**263 more per 1,000** (from 126 more to 477 more)	⨁◯◯◯ VERY LOW	CRITICAL
Convulsions. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	3/186 (1.6%)	1/170 (0.6%)	**RR 2.74** (0.29 to 26.11)	**10 more per 1,000** (from 4 fewer to 148 more)	⨁◯◯◯ VERY LOW	CRITICAL
Tremor. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [c]	very serious [c]	none	13/184 (7.1%)	11/164 (6.7%)	**RR 1.05** (0.49 to 2.29)	**3 more per 1,000** (from 34 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	26/184 (14.1%)	20/164 (12.2%)	**RR 1.16** (0.67 to 2.00)	**20 more per 1,000** (from 40 fewer to 122 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	66/184 (35.9%)	47/164 (28.7%)	**RR 1.25** (0.92 to 1.71)	**72 more per 1,000** (from 23 fewer to 203 more)	⨁◯◯◯ VERY LOW	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	48/184 (26.1%)	33/164 (20.1%)	**RR 1.30** (0.88 to 1.91)	**60 more per 1,000** (from 24 fewer to 183 more)	⨁◯◯◯ VERY LOW	CRITICAL

Convulsions. Protocol outcome: withdrawal symptoms (follow up: 12 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	0/184 (0.0%)	0/164 (0.0%)	**not estimable**	**0 per 1,000** [d] (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL

Attempted suicide. Protocol outcome: self-harm or harm to others (follow up: 12 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	0/180 (0.0%)	0/160 (0.0%)	**not estimable**	**0 fewer per 1,000** [d] (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 2 increments as the evidence was at very high risk of bias
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing BZDs.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed 2 MIDs (0.8 and 1.25 for dichotomous outcomes).
d. Calculated from risk difference due to zero events in both arms.

Table 117: Clinical evidence profile: Structured intervention with written instructions vs usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with written instructions	usual care	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	72/168 (42.9%)	25/173 (14.5%)	**RR 2.97** (2.09 to 4.23)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	76/168 (45.2%)	26/173 (15.0%)	**RR 3.01** (2.03 to 4.45)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 36 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [b]	none	66/168 (39.3%)	45/173 (26.0%)	**RR 1.51** (1.11 to 2.06)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Mortality (follow up: 36 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [b]	none	4/145 (2.8%)	2/149 (1.3%)	**RR 2.06** (0.38 to 11.05)	**14 more per 1,000** (from 8 fewer to 135 more)	⨁◯◯◯ VERY LOW	CRITICAL
Tremor. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	18/159 (11.3%)	9/170 (5.3%)	**RR 2.14** (0.99 to 4.62)	**60 more per 1,000** (from 1 fewer to 192 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability. Protocol outcome: withdrawal symptoms (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with written instructions	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	42/159 (26.4%)	15/170 (8.8%)	**RR 2.99** (1.73 to 5.18)	**176 more per 1,000** (from 64 more to 369 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	83/159 (52.2%)	30/170 (17.6%)	**RR 2.96** (2.07 to 4.23)	**346 more per 1,000** (from 189 more to 570 more)	⨁◯◯◯ VERY LOW	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	64/159 (40.3%)	21/170 (12.4%)	**RR 3.26** (2.09 to 5.07)	**279 more per 1,000** (from 135 more to 503 more)	⨁◯◯◯ VERY LOW	CRITICAL
Convulsions. Protocol outcome: withdrawal symptoms (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	1/159 (0.6%)	1/170 (0.6%)	**RR 1.07** (0.07 to 16.95)	**0 fewer per 1,000** (from 5 fewer to 94 more)	⨁◯◯◯ VERY LOW	CRITICAL
Tremor. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	11/159 (6.9%)	11/164 (6.7%)	**RR 1.03** (0.46 to 2.31)	**2 more per 1,000** (from 36 fewer to 88 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability. Protocol outcome: withdrawal symptoms (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with written instructions	usual care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	23/159 (14.5%)	20/164 (12.2%)	**RR 1.19** (0.68 to 2.07)	**23 more per 1,000** (from 39 fewer to 130 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	53/159 (33.3%)	47/164 (28.7%)	**RR 1.16** (0.84 to 1.61)	**46 more per 1,000** (from 46 fewer to 175 more)	⨁◯◯◯ VERY LOW	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	47/159 (29.6%)	33/164 (20.1%)	**RR 1.47** (1.00 to 2.17)	**95 more per 1,000** (from 0 fewer to 235 more)	⨁◯◯◯ VERY LOW	CRITICAL
Convulsions. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	0/159 (0.0%)	0/164 (0.0%)	**not estimable**	**0 per 1,000** [d] (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
Attempted suicide Protocol outcome: self-harm or harm to others (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	1/157 (0.6%)	0/160 (0.0%)	**Peto OR 7.53** (0.15 to 379.64)	**10 more per 1,000** [e] (from 10 fewer to 20 more	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 2 increments as the evidence was at high risk of bias
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing BZDs.
c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed 2 MIDs (0.8 and 1.25 for dichotomous outcomes).
d. Calculated from risk difference due to zero events in both arms.

e. Calculated from risk difference due to zero events in control arm.

Table 118: Clinical evidence profile: Structured intervention with follow-up vs Structured intervention with written instructions

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up visits	Structured intervention with written instructions	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	71/191 (37.2%)	72/168 (42.9%)	**RR 0.87** (0.67 to 1.12)	**56 fewer per 1,000** (from 141 fewer to 51 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	86/191 (45.0%)	26/173 (15.0%)	**RR 1.00** (0.98 to 1.02)	**Unable to calculate**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 36 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	79/191 (41.4%)	66/168 (39.3%)	**RR 1.05** (0.82 to 1.36)	**20 more per 1,000** (from 71 fewer to 141 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality (follow up: 36 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	1/159 (0.6%)	4/145 (2.8%)	**RR 0.23** (0.03 to 2.02)	**21 fewer per 1,000** (from 27 fewer to 28 more)	⨁◯◯◯ VERY LOW	CRITICAL
Tremor. Protocol outcome: withdrawal symptoms (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up visits	Structured intervention with written instructions	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	30/186 (16.1%)	18/159 (11.3%)	**RR 1.42** (0.83 to 2.46)	**48 more per 1,000** (from 19 fewer to 165 more)	⨁◯◯◯ VERY LOW	CRITICAL

Irritability. Protocol outcome: withdrawal symptoms (follow up: 6 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	42/186 (22.6%)	42/159 (26.4%)	**RR 0.85** (0.59 to 1.24)	**40 fewer per 1,000** (from 108 fewer to 63 more)	⨁◯◯◯ VERY LOW	CRITICAL

Insomnia. Protocol outcome: withdrawal symptoms (follow up: 6 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	87/186 (46.8%)	83/159 (52.2%)	**RR 0.90** (0.72 to 1.11)	**52 fewer per 1,000** (from 146 fewer to 57 more)	⨁◯◯◯ VERY LOW	CRITICAL

Anxiety. Protocol outcome: withdrawal symptoms (follow up: 6 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	72/186 (38.7%)	64/159 (40.3%)	**RR 0.96** (0.74 to 1.25)	**16 fewer per 1,000** (from 105 fewer to 101 more)	⨁◯◯◯ VERY LOW	CRITICAL

Convulsions. Protocol outcome: withdrawal symptoms (follow up: 6 months)

1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	3/186 (1.6%)	1/170 (0.6%)	**RR 2.74** (0.29 to 26.11)	**10 more per 1,000** (from 4 fewer to 148 more)	⨁◯◯◯ VERY LOW	CRITICAL

Tremor. Protocol outcome: withdrawal symptoms (follow up: 12 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up visits	Structured intervention with written instructions	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	13/184 (7.1%)	11/159 (6.9%)	**RR 1.02** (0.47 to 2.22)	**1 more per 1,000** (from 37 fewer to 84 more)	⨁◯◯◯ VERY LOW	CRITICAL
Irritability. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	26/184 (14.1%)	23/159 (14.5%)	**RR 0.98** (0.58 to 1.64)	**3 fewer per 1,000** (from 61 fewer to 93 more)	⨁◯◯◯ VERY LOW	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	66/184 (35.9%)	53/159 (33.3%)	**RR 1.08** (0.80 to 1.44)	**27 more per 1,000** (from 67 fewer to 147 more)	⨁◯◯◯ VERY LOW	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	48/184 (26.1%)	47/159 (29.6%)	**RR 0.88** (0.63 to 1.24)	**35 fewer per 1,000** (from 109 fewer to 71 more)	⨁◯◯◯ VERY LOW	CRITICAL
Convulsions. Protocol outcome: withdrawal symptoms (follow up: 12 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	0/184 (0.0%)	0/159 (0.0%)	not estimable	**0 fewer per 1,000** [d] (from 10 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
Attempted suicide. Protocol outcome: self-harm or harm to others (follow-up: 12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured intervention with follow-up visits	Structured intervention with written instructions	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	0/180 (0.0%)	1/157 (0.6%)	**Peto OR 0.12** (0.00 to 5.95)	**10 fewer per 1,000** [e] (from 20 fewer to 10 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by 2 increments as the evidence was at very high risk of bias
b. Downgraded by 2 increments as the population may have been indirect (no drug breakdown provided) and it was unclear if the usual care group involved decreasing BZDs.
*c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of the intervention and control groups for continuous outcomes).*
d. Calculated from risk difference due to zero events in both arms.
e. Calculated from risk difference due to zero events in intervention arm.

Table 119: Clinical evidence profile: Motivational interviewing vs brief advice (information booklet)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	motivational interview	information booklet	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	0/55 (0.0%)	1/62 (1.6%)	**P**eto O**R 0.15** (0.00 to 7.69)	**20 fewer per 1,000** [d] (from 60 fewer to 30 more)	⨁◯◯◯ VERY LOW	CRITICAL
Cessation of drug (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	very serious [c]	none	10/55 (18.2%)	6/62 (9.7%)	**RR 1.88** (0.73 to 4.83)	**85 more per 1,000** (from 26 fewer to 371 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction>25% of drug (follow up: 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	motivational interview	information booklet	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	very serious [b]	serious [c]	none	29/55 (52.7%)	21/62 (33.9%)	**RR 1.56** (1.01 to 2.39)	**190 more per 1,000** (from 3 more to 471 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mean defined daily dosage difference. Protocol outcome: reduction of prescribed drug use (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	very serious [b]	not serious	none	55	62	-	MD **0.3 higher** (0.49 lower to 1.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 2 increments as the evidence was at very high risk of bias.
b. Downgraded by 2 increments as the population may have been indirect (no breakdown of drugs provided) and the comparison group was indirect (no specific aim to decrease medication in the control group).
*c. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SDs of the intervention and control groups for continuous outcomes).MID for daily dosage difference was calculated to be 1.18.*
d. Calculated from risk difference due to zero events in intervention arm.

Table 120: Clinical evidence profile: Electroacupuncture + taper vs Sham acupuncture + taper

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electroacupuncture	sham acupuncture	Relative (95% CI)	Absolute (95% CI)		
Cessation of drug (follow up: 6 weeks; assessed with: 14-day prospective daily record)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	72	72	**OR 1.03** (0.26 to 4.06)	**Could not be calculated**	⨁◯◯◯ VERY LOW	CRITICAL
Cessation at 16 weeks (follow up: 16 weeks; assessed with: with day prospective daily record)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electroacupuncture	sham acupuncture	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	72/0	72/0	**OR 0.87** (0.29 to 2.61)	**Could not be calculated**	⨁◯◯◯ VERY LOW	CRITICAL
Equivalent dose of usage in diazepam mg/d. Protocol outcome: reduction of prescribed drug use. (follow up: 6 weeks)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.06 lower** (0.37 lower to 0.25 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Equivalent dose of usage in diazepam mg/d. Protocol outcome: reduction of prescribed drug use. (follow up: 16 weeks)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.1 lower** (0.4 lower to 0.2 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal symptoms (follow up: 6 weeks; assessed with: Benzodiazepine Withdrawal Symptom Questionnaire; Scale from: 0 to 40)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.21 higher** (0.1 lower to 0.52 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal Symptoms (follow up: 16 weeks; assessed with: Benzodiazepine Withdrawal symptom Questionnaire; Scale from: 0 to 40)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.11 higher** (0.21 lower to 0.43 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 6 weeks; assessed with: Insomnia Severity Index; Scale from: 0 to 28)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.04 higher** (0.29 lower to 0.37 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Insomnia. Protocol outcome: withdrawal symptoms (follow up: 16 weeks; assessed with: Insomnia Severity Scale; Scale from: 0 to 28)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electroacupuncture	sham acupuncture	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.06 lower** (0.3 lower to 0.18 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 6 weeks; assessed with: Hospital Anxiety and Depression Scale- Anxiety subset; Scale from: 0 to 21)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.03 lower** (0.45 lower to 0.39 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Anxiety. Protocol outcome: withdrawal symptoms (follow up: 16 weeks; assessed with: Hospital Anxiety and Depression Scale- anxiety subset; Scale from: 0 to 21)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.09 higher** (0.28 lower to 0.46 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Depression. Protocol outcome: withdrawal symptoms (follow up: 6 weeks; assessed with: Hospital Anxiety and Depression Scale- depression subset; Scale from: 0 to 21)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.06 higher** (0.22 lower to 0.34 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Depression. Protocol outcome: withdrawal symptoms (follow up: 16 weeks; assessed with: Hospital Anxiety and Depression Scale- depression subset; Scale from: 0 to 21)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	72	72	-	MD **0.14 higher** (0.18 lower to 0.46 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

a. No breakdown of drugs used was provided.
*b. Downgraded by 1 increment if the confidence interval crossed 1 MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5*median baseline SD of the intervention and control groups). MID for equivalent dose of usage was 4.46, 2.12 for BWSQ, 2.55 for ISI, 1.27 for HADS anxiety and HADS depression*

Appendix H Economic evidence tables

H.1 Opioids

None.

H.2 Benzodiazepines

Study	Godfrey 2008[94]			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes:**	**Cost effectiveness**
Economic analysis: Cost Comparison analysis (No health outcome) **Study design:** Within trial analysis (RCT) Heather 2004[111] **Approach to analysis:** As the companion paper [111] found no difference in health outcomes between the interventions, the economic design chosen was cost minimisation **Perspective:** UK NHS	**Population:** Long-term benzodiazepine users who had taken benzodiazepine continuously for at least 6 months **Cohort settings:** Mean age: 69 Male: 23% N: 184 **Intervention 1:** Control: patients in the control group receive usual care but no intervention **Intervention 2:**	**Total cost change (before and after the intervention):** Intervention 1: £140.53 Intervention 2: £-242.70 Intervention 3: £180.54 Incremental (2−1): -£383.23 (95% CI:-NR; p=NR) Incremental (3−1): £40.1 (95% CI:-NR; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:**	n/a	Letter intervention is cost saving if compared with control or consultation intervention **Analysis of uncertainty:** No exploration of uncertainty

Time horizon/Follow-up: 6 months **Discounting:** Costs=n/a Outcomes=n/a	Letter: patients received a letter recommending tapering and stop their benzodiazepine medication signed by their GP **Intervention 3:** Consultation: patients were invited to see their GP for a medication review of 12 minutes. Written guidelines on BDZ discontinuation benefits and a booklet were provided to the patients during the consultation	Intervention cost, GP consultation, prescription, practice nurse, district nurse, health visitor, accident & emergency, outpatient, inpatient, day cases, benzodiazepines		
Data sources				
Health outcome: n/a **Quality-of-life weights** n/a **Cost sources:** PSSRU unit cost of health and social care and department of health reference cost.				
Comments				
Source of funding: The study was funded by the Northern and Yorkshire Regional Health Authority R&D Programme **Limitations:** The time horizon of 6 months might be too short to capture long-term outcomes. Effectiveness data were collected from a single RCT rather than from a systematic review. No exploration of uncertainty through a sensitivity analysis was attempted. The assumption that there is not difference in health outcomes between the intervention is partially contradicted by the companion study which found an improvement in SF-36 mental score for patients undergoing a reduction of 25% or more of benzodiazepine **Other:**				
Overall applicability:[a] Directly applicable **Overall quality:**[b] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CCA= cost comparison analysis; NR= not reported.
(a) Directly applicable/Partially applicable/Not applicable
(b) Minor limitations/Potentially serious limitations/Very serious limitations

Study	Oude Voshaar 2006[203]			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes:**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis (successful benzodiazepine discontinuation) **Study design:** Within trial analysis (RCT) Oude Voshaar 2003[202] **Approach to analysis:** The analysis was based on a randomized controlled trial with two tapering-off strategies and one usual care control group. **Perspective:** Netherlands health care perspective[(a)] **Time horizon/Follow-up:** 18 months **Discounting:** Costs=n/a Outcomes=n/a	**Population:** Long-term benzodiazepine users who had not discontinued 3 months after receiving a letter of discontinuation by their GP **Cohort settings:** Mean age: 63 Male: 30% N: 180 **Intervention 1** Patients received care as usual from their GP without specific attention paid to their benzodiazepine use behavioural therapy starting half-way through the taper program **Intervention 2:** Tapering off alone: patients in this group had benzodiazepine use tapered-off in six visits to their GP by dosage reduction in steps of 25% a week. **Intervention 3:**	**Total costs:** Intervention 1: £204 Intervention 3: £380 Intervention 2: £551 Incremental (3−1): £176 Incremental (2-3): £171 **Currency & cost year:** 2001 Euros (presented here as 2001 UK pounds[(a)]) **Cost components incorporated:** Pharmaceutical costs (benzodiazepine and non-benzodiazepine), intervention cost, medical specialist, psychologist/social worker, physiotherapist, non-regular medicine	**Benzodiazepine discontinuation:** Intervention 1: 15% Intervention 3:29% Intervention 2: 36% Incremental (3-1): 14% Incremental (2-3): 7% **HUI-3 utility health score (mean difference):** Intervention 1: 0.08 (95% CI: -0.06 to 0.2; p=NR) Intervention 3: 0.05 (95% CI: -0.04 to 0.14; p=NR) Intervention 2: -0.06 (95% CI: -0.17 to 0.05; p=NR)	**Cost effectiveness analysis: ICER (intervention 3 vs intervention 1)** TO+CBT costs £1300 for every extra successful discontinuation compared with usual care **ICER (Intervention 2 vs intervention 3)** TOA costs £2400 for every extra successful discontinuation compared with TO+CBT **Cost-utility analysis** Usual care dominates TO+CBT and TOA **Analysis of uncertainty:** Not conducted.

Study	Oude Voshaar 2006[203]			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes:**	**Cost effectiveness**
	Tapering off + CBT: patients, in addition of having their benzodiazepine use tapered-off in six visits to their GP, attended five weekly 2-hour sessions of group cognitive			
Data sources				
Health outcome: The effectiveness data came from a randomized controlled trial [202] **Quality-of-life weights:** Utility valuations were obtained from the questionnaire Health Utility Index Mark III (HUI-3) completed by patient at baseline and 18 months follow-up **Cost sources:** costs were based on case record forms, the drug prescription database of the GP and obtained from the cost diaries				
Comments				
Source of funding: The study was supported by the Dutch Health Care Insurance Council, The Hague, The Netherlands. **Limitations:** Effectiveness data were collected from a single RCT rather than from a systematic review. The ICER is hard to interpret as there is no threshold value that can be used as a comparison. Baseline characteristics and costs are heavily unbalanced across the 3 groups, although the authors focused on change over time. The time horizon may be too short. No sensitivity analysis was conducted. **Other:**				
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations				

Abbreviations: CBT = Cognitive behavioural therapy; CI= 95% confidence interval; CEA= cost–effectiveness analysis; 95% HUI-3= Health utility index Mark III; ICER= incremental cost-effectiveness ratio; NR= not reported; TO= Tapering-off; TOA= Tapering-off alone.

(a) Study used societal perspective, but results are presented disaggregated and so results have been recalculated to only include health care system costs in line with NICE reference case

(b) Converted using 2001 purchasing power parities[196]

(c) Directly applicable/Partially applicable/Not applicable

(d) Minor limitations/Potentially serious limitations/Very serious limitations

H.3 Z-drugs

None.

H.4 Antidepressants

Study	Eveleigh 2014[69]			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes:**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Within trial analysis (RCT) Muskens 2013[177] **Approach to analysis:** The analysis was based on a cluster-randomized controlled trial (PANDA). Missing values were handled using multiple imputation. **Perspective:** Netherlands health care perspective[(a)] **Time horizon/Follow-up:** 12 months	**Population:** Inappropriate long-term antidepressant users (9 months). Appropriateness of medication was defined by multidisciplinary guidelines for depressive and anxiety disorder. **Cohort settings:** Mean age: 56 Male: 22% N: 146 **Intervention 1:** Family physicians were asked to provide usual care **Intervention 2:** Antidepressant cessation advice: advice written by an experienced family	**Total costs:** Intervention 1: £1,821 Intervention 2: £1,772 Incremental (2−1): - £49 (95% CI:-1,084 to 1,184; p=NR) **Currency & cost year:** 2013 Euros (presented here as 2013 UK pounds[(b)]) **Cost components incorporated:** Use of health services and health resources collected through a questionnaire, including medicines.	**QALYs (mean per patient):** Intervention 1: 0.72 Intervention 2: 0.70 Incremental (2−1): -0.02 (95% CI: -0.05 to 0.10 NR; p=NR) **Antidepressant discontinuation:** Intervention 1: 8% Intervention 2: 6% Incremental (2-1): -2% **Relapse into depression rate:** Intervention 1: 14% Intervention 2: 18% Incremental (2-1): 4%	Usual care cost an extra £2,450 per QALY gained compared with the cessation advice **Analysis of uncertainty:** Confidence intervals were generated around the cost and outcome differences using non-parametric bootstrapping. A cost-effectiveness acceptability curve (CEAC) was used to present the probability that the intervention is cost-effective at different WTP threshold. Bootstrapped costs and effects lie in the Southwest quadrant. No one-way sensitivity analysis was attempted.

Discounting: Costs=n/a Outcomes=n/a	physician and a psychiatrist was sent to participants` family physician stating that the patients did not meet the requirements for ADM			
Data sources				
Health outcome: The effectiveness data came from a randomized control trial (PANDA) **Quality-of-life weights:** Utility valuations were obtained from the EQ-5D questionnaire which was completed by patients in the trial at baseline, 3, 6, 9 and 12 months**. Cost sources:** Costs were based on standard Dutch unit prices and, if not available, on tariffs. Costs of medication was based on the Dutch “pharmacotherapeutic compass”				
Comments				
Source of funding: The study was funded by Netherlands Organization for Health Research and Development (ZonMw), program Mental Health **Limitations:** The authors acknowledged that a time horizon of 1 year may be too short to catch important long-term effects. Effectiveness data were collected from a single RCT rather than from a systematic review. **Other:** None.				
Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= EuroQoL 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years.

(a) Study used societal perspective, but results are presented disaggregated and so results have been recalculated to only include health care system costs in line with NICE reference case

(b) Converted using 2013 purchasing power parities[196]

(c) Directly applicable/Partially applicable/Not applicable

(d) Minor limitations/Potentially serious limitations/Very serious limitations

H.5 Mixed medicines

None.

Appendix I Excluded studies

I.1 Clinical studies

Table 121: Studies excluded from the clinical review

Study	Exclusion reason
Aguiluz 2018[1]	Study type does not match protocol (narrative review)
Ahmadi 2018[2]	Population does not match protocol (inpatients abusing opium, heroin, and illicit or prescribed opioids for at least 1 year - no breakdown of those on prescribed opioids)
Alam 2020[3]	Population does not match protocol (majority heroin use)
Andersch 1991[4]	Intervention and comparison do not match protocol (comparison of an antidepressant with a benzodiazepine for panic disorder, not comparing withdrawal strategies).
Anon[147]	Trial registry record only
Anon[236]	Trial registry record only (I-WOTCH)
Ashton 2009[5]	Short review of a systematic review
Ashworth 2000[7]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for antidepressants already included in this review)
Avedisova 2007[8]	Not in English
Baandrup 2018[9]	Systematic review (population of review protocol does not match our review protocol - specified people who had been treated with benzodiazepines for at least 2 months and/or fulfilled criteria for benzodiazepine dependence; included people on benzodiazepines not on our review protocol list).
Baker 1997[11]	No relevant outcomes - audit of GP care provided
Bakhshani 2008[12]	Population does not match protocol (people with opiate dependency, prescribed opioids not specified).
Balbale 2017[13]	Systematic review (protocol does not match review protocol)
Baldessarini 2010[14]	Study type does not match protocol (not an RCT, randomised evidence already included for antidepressant stratum)
Beamish 2019[18]	Population does not match protocol (people with opioid use disorder, prescribed medicines not specified)
Beaulieu-Bonneau 2017[19]	Intervention and comparison do not match protocol (assessing efficacy of CBT with or without zolpidem for insomnia - only one withdrawal arm (CBT plus tapered withdrawal, in comparison to no withdrawal).
Belanger 2005[20]	Secondary analysis of a study already considered for inclusion in this review (#717). This secondary analysis contains no additional relevant outcomes to the primary study.
Belleville 2008[22]	Secondary analysis of a study already considered for inclusion in this review (#616). This secondary analysis contains no additional relevant outcomes to the primary study.
Berna 2015[25]	Review
Bhatia 2015[26]	Systematic review (protocol does not match our review protocol).
Bialos 1982[27]	Comparison does not match protocol (withdrawal of antidepressants compared to continuation of active medication).
Blondell 2007[29]	Population does not match protocol (people being treated for opioid detoxification - 45% heroin).
Blondell 2008[28]	Population does not match protocol (people with substance use disorders, majority alcohol or heroin, not prescribed medications).

Study	Exclusion reason
Bockting 2018[30]	Intervention and comparison do not match protocol (assessing efficacy of preventative cognitive therapy with tapered withdrawal of antidepressants - only one withdrawal arm, in comparison to continued antidepressants with or without PCT).
Boisseau 2018[31]	Protocol only (no published results found)
Bowman 2013[32]	Study type does not match protocol (narrative review)
Breedvelt 2021[33]	Systematic review (protocol does not match review protocol)
Brigo 2019[34]	Protocol only for a symptomatic review
Cadth 2014[38]	Systematic review (protocol does not match review protocol)
Cadth 2015[36]	Systematic review (protocol does not match review protocol)
Cadth 2015[37]	Rapid review (protocol does not match review protocol)
Cassano 1996[41]	Intervention does not match protocol (intervention (alpidem) not licenced in the UK or listed in the BNF).
Chu 2017[43]	Intervention does not match protocol (experimental withdrawal induced with intravenous naloxone, to assess the effect of intravenous ondansetron on withdrawal symptoms). Population does not match protocol (people with chronic pain, but not necessarily opioid users at the start of the study - all patients either begun or switched to sustained release oral morphine for 30 days).
Cochran 2018[46]	Protocol only (no published results found)
Cochran 2019[45]	Protocol only (no published results found)
Cohen 2019[47]	Systematic review (protocol does not match review protocol)
Curran 2003[50]	Intervention and comparison do not match protocol (not comparing 2 withdrawal strategies, comparing withdrawal vs continuation)
Darker 2015[53]	Systematic review (protocol does not match review protocol)
Day 2005[55]	Systematic review (protocol does not match review protocol)
Dhokia 2020[58]	Intervention does not match protocol (intervention for treatment of dependence, but not a withdrawal intervention per se)
Di costanzo 1992[59]	Not in English
Dou 2019[61]	Systematic review (protocol does not match review protocol)
Dreifuss 2013[62]	No relevant outcomes (secondary analysis of the POATS trial already excluded from this review).
Dunn 2015[63]	Population does not match protocol (people using prescription opioids illicitly (without a valid prescription)
Eccleston 2017[64]	Systematic review (intervention of review protocol does not match our review protocol - not only withdrawal interventions, also included studies with a treatment goal of dose reduction).
Eilender 2016[65]	Systematic review (protocol does not match review protocol)
Elarabi 2019[66]	Population does not match protocol (people with illicit or prescription opioid use disorder). Ongoing trial (STAR-T), no results reported
Elsesser 1996[68]	Population does not match protocol (>40% of people on benzodiazepines not on our review protocol list).
Eveleigh 2014[69]	Economic analysis of included RCT, clinical outcomes reported elsewhere
Feng 2021[73]	No relevant outcomes
Fernandes 2002[74]	No usable outcome data (outcome of decrease in daily codeine use matches protocol outcomes, however no variance measures are reported, therefore unable to report outcome).
Fiellin 2014[75]	Population does not match protocol (people with prescription opioid dependence, illicit or prescribed not specified but excluded people

Study	Exclusion reason
	requiring opioids for a pain-related diagnosis and focused on outcome of illicit opioid use).
Fluyau 2018[76]	Study type does not match protocol (narrative review)
Fontaine 1984[77]	Population does not match protocol (not all people were on benzodiazepines prior to inclusion).
Frank 2017[78]	Systematic review (protocol does not match review protocol)
Fux 1995[79]	Unable to obtain paper
Garcia-Borreguero 1991[81]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Garfinkel 1999[82]	Population does not match protocol (<80% of study population on a benzodiazepine on the guideline medicine list)
Garland 2014[86]	Intervention does not match protocol (intervention for treatment of dependence, but not a withdrawal intervention per se).
Garland 2019[85]	Intervention does not match protocol (intervention for treatment of dependence, but not a withdrawal intervention per se).
Garland 2017[83]	Secondary analysis of a study already excluded from this review, Garland 2014 #1053
Garland 2019[84]	Secondary analysis of a study already excluded from this review, Garland 2014 #1053
Garzon 2009[87]	Population does not match protocol (not all people were on benzodiazepines at inclusion).
Gerra 1993[88]	Population does not match protocol (50% of people on benzodiazepines not on our review protocol list).
Gerra 2002[89]	Population does not match protocol (66% of people on benzodiazepines not on our review protocol list).
Gilhooly 1998[91]	Brief report, full results not reported
Gimbel 2016[92]	Intervention does not match protocol (efficacy and safety of buprenorphine, but not as a withdrawal intervention)
Godfrey 2008[94]	Economic analysis of included RCT, clinical outcomes reported elsewhere
Goodman 1986[95]	Incorrect study type (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Gorgels 2005[98]	Incorrect study type (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Gorgels 2007[97]	No relevant outcomes (secondary analysis of a RCT already considered for inclusion in this review)
Gosselin 2006[99]	Population does not match protocol (25% of people on benzodiazepines not on our review protocol list).
Goudman 2021[100]	Incorrect study design (not an RCT, RCTs already included for opioid stratum)
Gould 2014[101]	Systematic review (protocol does not match review protocol)
Greenblatt 1987[102]	Population does not match protocol (people with insomnia recruited and put onto triazolam (benzodiazepine not included)).
Griffin 2014[103]	Secondary analysis of the POATS trial already excluded from this review.
Guaiana 2016[105]	Review
Guarino 2018[106]	Intervention does not match protocol (intervention for treatment of dependence, but not a withdrawal intervention per se).

Study	Exclusion reason
Habraken 1997[107]	Intervention and comparison do not match protocol (only one withdrawal arm vs continuation on prescribed medication)
Hallstrom 1988[108]	Unable to obtain paper
Hantouche 1998[109]	Not in English
Henningfield 2020[112]	Intervention does not match protocol (efficacy and safety of Oxycodegol (new analgesic NKTR-181), not on guideline medicine list)
Hodgkin 2021[113]	Incorrect study design (not an RCT, RCTs already included for opioid stratum)
Hruschak 2018[116]	Systematic review (protocol does not match review protocol)
Huijbers 2020[117]	No relevant comparison (all received MBCT)
Jamison 2010[119]	Comparison does not match protocol (control group were "maintained on their current opioid regimen" with no aim to withdraw).
Jureidini 2008[121]	Commentary
Just 2016[122]	Review
Kesten 2020[123]	Study type does not match protocol (qualitative study)
Kheirabadi 2019[125]	Population does not match protocol (illicit opioid use)
Klein 1994[127]	Population does not match protocol (all people on benzodiazepines not on our review protocol list).
Klein 1995[126]	Review summary of primary studies carried out by the research group
Kocsis 2007[128]	Intervention and comparison do not match protocol (only one withdrawal arm vs continuation on prescribed medication)
Kornowski 2002[129]	Not in English
Kowolczyk 2017[130]	Population does not match protocol (heroin or opioid prescription dependent and no breakdown)
Kristensen 2006[131]	Population does not match protocol (people with opioid dependence (illicit opioids and heroin)).
Kua 2014[132]	Systematic review (protocol does not match review protocol)
Kumar 2003[133]	Population does not match protocol (people abusing ampoules Pentazocine 6-10/day IV, SC, or IM, not stated that the medication was prescribed).
Kurita 2018[134]	Intervention and comparison do not match protocol (only one withdrawal arm vs continuation on prescribed medication)
Kurokawa 2011[135]	Population does not match protocol (people with delirium due to benzodiazepine withdrawal).
Lader 1993[136]	Intervention does not match protocol (intervention (alpidem) not licenced or listed in the BNF).
Lahteenmaki 2019[138]	No relevant outcomes (secondary analysis of a study already included in this review #698. In this secondary analysis, randomised treatment arms were combined for analysis).
Laughren[141]	No usable outcome data.
Lecrubier 2005[143]	Not in English
Lemoine 1997[145]	Population does not match protocol (66% of people on benzodiazepines not on our review protocol list).
Lemoine 1997[146]	Not in English
Lemoine 2006[144]	Population does not match protocol (64% of people on benzodiazepines not on our review protocol list).

Study	Exclusion reason
Lichstein 1999[148]	Population does not match protocol (25% of people on over-the-counter sleep aids and unclear whether these were medicines defined in the review protocol).
Ling 2010[149]	Population does not match protocol (63% heroin abuse)
Lofwall 2013[150]	Population does not match protocol (non-medical use of prescription opioids).
Malsch 2001[153]	Population does not match protocol (30% of people on benzodiazepines not on our review protocol list).
Mariani 2016[154]	Population does not match protocol (people with benzodiazepine abuse or dependence - unclear whether prescribed or illicit use, but discussion suggests a mixture of both).
Martin 2017[155]	No relevant outcomes (EMPOWER trial primary study assessed for inclusion in this review #782)
Martin 2017[156]	No relevant outcomes (post hoc analysis of the EMPOWER trial with no additional outcomes: primary study assessed for inclusion in this review #782)
Mathieson 2020[157]	Systematic review (quality assessment is inadequate)
Mauger 2014[159]	Review
Maund 2019[160]	Systematic review (protocol does not match review protocol)
Mcdermott 2015[161]	Secondary analysis of the POATS trial already excluded from this review.
Mcgregor 2003[162]	Population does not match protocol (illicit benzodiazepine use).
Mehl-Madrona 2016[163]	Incorrect study design (non-randomised study, RCTs already included for opioid stratum)
Mercier-guyon 2004[164]	Population does not match protocol (3 out of the 5 benzodiazepines people were on are not on our review protocol list (alprazolam, clobazam, bromazepam), no breakdown in study).
Messina 2019[165]	Unable to obtain paper
Mol 2006[166]	No relevant outcomes (secondary analysis of a study already included in this review #740).
Moore 2016[167]	Population does not match protocol (secondary analysis of a study recruiting people with opioid dependence (heroin or prescription opioids)). Illicit or prescribed use of prescription opioids not specified, and no breakdown reported, however the primary outcome is illicit opioid use.
Morgan 2004[168]	Intervention does not match protocol (aim of CBT intervention was to improve sleep quality, which could subsequently reduce hypnotics, however CBT was not specifically a dose reduction or withdrawal intervention – not all people in the intervention group had the aim to decrease or discontinue their hypnotics).
Mouland 1997[173]	Not in English
Mugunthan 2011[174]	Systematic review (protocol does not match review protocol)
Murnion 2020[175]	Population does not match protocol (on methadone or buprenorphine treatment presumably for illicit opioid use)
Naderi[178]	Population does not match protocol (on methadone maintenance therapy)
Nakao 2006[179]	Population does not match protocol (87% of people on benzodiazepines not on our review protocol list).
Naylor 2010[182]	Intervention does not match protocol (CBT and Therapeutic Interactive Voice Response interventions are pain management interventions which may subsequently reduce medicines, but not specifically a dose reduction or withdrawal intervention – not all

Study	Exclusion reason
	people in the intervention group had the aim to decrease or discontinue their opioid or NSAID use).
Neumann 2013[183]	Population does not match protocol (people with chronic pain and coexisting opioid addiction, but not clear if opioids prescribed or obtained illicitly).
Nielsen 2012[187]	Population does not match protocol (people with opioid dependence on heroin or prescription opioids (prescription opioid use included illicit use)).
Nielsen 2013[188]	Population does not match protocol (secondary analysis of a study recruiting people with opioid dependence (heroin or prescription opioids)). Illicit or prescribed use of prescription opioids not specified, but only a third of people on prescription opioids were taking any prescribed medicine for a physical problem.
Nielsen 2014[189]	Secondary analysis of the POATS trial already excluded from this review.
Nielsen 2015[186]	Population does not match protocol (secondary analysis of a study recruiting people with opioid dependence (heroin or prescription opioids)). Illicit or prescribed use of prescription opioids not specified, and no breakdown reported
Nielsen 2016[190]	Systematic review (review population does not match protocol - people dependent on pharmaceutical opioids - illicit or prescribed use of prescription opioids not specified, and no breakdown reported).
Nielsen 2017[185]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for opioids already included in this review)
Nielsen 2018[191]	Systematic review (protocol does not match review protocol)
Nosyk 2015[193]	Secondary analysis of the START trial and the POATS trial. Population does not match protocol for the POATS trial (already excluded from this review). Population does not match protocol for the START trial (already excluded from this review).
Onyett 1988[195]	Study type does not match protocol (unclear if all participants were randomised; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review).
Ostini 2011[197]	Systematic review (protocol does not match review protocol)
Otto 1993[200]	Population does not match protocol (>20% of people on benzodiazepines not on our review protocol list).
Otto 2009[198]	Population does not match protocol (people with problematic use of opioids, anxiolytics, hypnotics, sedatives, or caffeine - unclear breakdown and how many meet review protocol population).
Otto 2010[199]	Population does not match protocol (>20% of people on benzodiazepines not on our review protocol list).
Paquin 2014[205]	Systematic review (protocol does not match review protocol)
Pani 2000[204]	Population does not match protocol (illicit opioid use)
Parr 2009[206]	Systematic review (protocol does not match review protocol)
Parr 2013[207]	Randomised trial, but due to dropouts and low numbers the results are reported as case reports.
Parran 2002[208]	Population does not match protocol.
Pecknold 1982[209]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Pecknold 1982[210]	Population does not match protocol (people not on benzodiazepines on entry to the study and allocated to one of two

Study	Exclusion reason
	benzodiazepines (one of which, halazepam, is not on the guideline medicine list).
Peles 2007[211]	Population does not match protocol (non-prescribed benzodiazepine use).
Petrovic 1999[213]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Petrovic 2002[212]	Population does not match protocol (35% of people on benzodiazepines not on our review protocol list).
Pimlott 2003[214]	No relevant outcomes (physician prescribing behaviour outcomes).
Pollmann 2015[215]	Scoping review
Potter 2013[217]	Population does not match protocol, START trial (people with opioid dependence including both opioid analgesics and heroin. 170/1250, people who were dependent on opioid analgesics alone, but unclear if prescribed medication).
Potter 2015[216]	Population does not match protocol. 18-month outcomes for the POATS trial already excluded from this review.
Ray 1986[220]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)
Reeve 2017[221]	Systematic review (protocol does not match review protocol)
Ribeiro 2021[222]	Systematic review (quality assessment is inadequate)
Rickels 1990[224]	Review and interim analysis of 2 ongoing trials
Rickels 1999[226]	Population does not match protocol (>40% of people on benzodiazepines not on our review protocol list).
Riedel 1998[227]	Population does not match protocol (>20% of people on benzodiazepines not on our review protocol list).
Romach 1998[228]	Population does not match protocol (25% of people on benzodiazepines not on our review protocol list).
Roy-Byrne 1993[229]	Review
Ruetsch 2014[230]	Commentary on a trial excluded from this review.
Ruetsch 2010[231]	Methods paper for a study already excluded from review (Reutsch 2021)
Ruetsch 2012[232]	Population does not match protocol (methadone maintenance therapy; lifetime drug use statistics suggest methadone maintenance therapy for illicit drug use)
Rynn 2003[233]	Population does not match protocol (65% of people on benzodiazepines not on our review protocol list).
Salonoja 2010[234]	Population does not match protocol (elderly people, some of whom were on psychotropic drugs and other fall-risk increasing drugs (including drugs not specified in our review protocol). Not all people were on prescribed medicines at all at baseline). Aim of study to assess and intervention to reduce the use of fall-risk increasing drugs (not to withdrawal one class of drugs in particular).
Sandhu 2019[237]	Protocol only (study not yet published)
Sanger 2018[238]	Systematic review protocol only. Systematic review protocol does not match this review protocol.
Saul 1989[239]	Unable to obtain paper
Schweizer 1990[243]	Study type does not match protocol (not a randomised trial; excluded as per protocol, as RCT evidence for benzodiazepines already included in this review)

Study	Exclusion reason
Schweizer 1991[242]	Population does not match protocol (25% of people on benzodiazepines not on our review protocol list).
Schweizer 1995[241]	Population does not match protocol (>20% on benzodiazepines not on our review protocol list).
Shapiro 1995[245]	No useable outcomes (sleep quality only reported for one out of the three groups).
Sigmon 2013[246]	Population does not match protocol (people using prescription opioids illicitly).
Silverstone 1992[247]	Population does not match protocol (people with morphine dependence, unclear if prescribed and unclear if they have chronic pain).
Socias 2018[248]	Protocol for the OPTIMA trial. Population does not match protocol (people using prescription opioids illicitly).
Stella 2005[249]	Population does not match protocol (illicit opioid use)
Stewart 2007[250]	Nonrandomised comparative study with multivariate analysis (excluded as per protocol, as RCT evidence for benzodiazepines already included in this review).
Sullivan 1993[252]	Population does not match protocol (people on hypnotic sedatives, 5/6 were on benzodiazepines, but participants were also taking barbiturates and muscle relaxants (and all of these were included as part of the sedative dose calculated for the taper)
Sullivan 2017[251]	Population does not match protocol (illicit use: heroin and opioid dependence)
Sullivan 2020[152]	Incorrect study design (nested case control)
Tannenbaum 2014[254]	Comparison does not match protocol (control arm did not receive a withdrawal intervention and was described as being on a wait list to receive the intervention after 6 months. Therefore, it is reasonable to presume people in the control arm would not have attempted to withdraw from medicines).
Tham 1989[257]	No relevant outcomes.
Tint 2009[259]	Erratum
Turner 2019[260]	Protocol for the TAPERING trial (study not yet published)
Tyrer 1981[262]	Study type does not match protocol (no randomisation reported)
Vernieri 2020[264]	Population does not match protocol (withdrawal of medicine for medication overuse headache, medicine population on unclear)
Vicens 2019[267]	Protocol only for the BENZORED trial. No relevant outcomes (GP prescribing outcomes, not patient level)
Vorma 2002[274]	Population does not match protocol (76 people included in the study were on 114 medicines (some on multiple medicines). >20% of these medicines not on our review protocol list, therefore likely that >20% of people were on a medicine not on our protocol list).
Vorma 2003[272]	Long term follow-up of a study already excluded from this review (Vorma 2002#795)
Vorma 2004[273]	Long term follow-up of a study already excluded from this review (Vorma 2002#795)
Voshaar 2006[275]	Systematic review (protocol does not match review protocol)
Vowles 2020[276]	Intervention does not match protocol (intervention for treatment of dependence, but not a withdrawal intervention per se).
Webster 2016[277]	Intervention and comparison do not match protocol (switching from morphine to buprenorphine vs continuation on morphine).
Weiss 2010[279]	Methods paper for the POATS trial, already excluded from this review.

Study	Exclusion reason
Weiss 2010[282]	Population does not match protocol. People with prescription opioid dependence, but study includes those who had been prescribed opioids by a physician and those who had obtained them illicitly. Less than 80% had a legitimate prescription as their first source of prescription opioids (review protocol decision rules require at least 80% taking prescribed medications, not obtained illicitly). Study also excludes people taking opioid medication as prescribed, only those abusing their medication. Methodology paper for the POATS trial.
Weiss 2011[280]	Population does not match protocol. POATS trial already excluded from this review
Weiss 2014[278]	Secondary analysis of the POATS trial (already excluded from this review as the population does not match the protocol - included people with prescription opioid dependence, both those who had been prescribed opioids by a physician and those who had obtained them illicitly. People who were prescribed opioids is not a subgroup in this secondary analysis).
Weiss 2015[281]	Population does not match protocol. Long term outcomes for the POATS trial already excluded from this review.
Weiss 2017[283]	Summary of POATS trial and follow-up trial. POATS trial already excluded from this review.
Weizman 2003[284]	Population does not match protocol (patients abusing benzodiazepines - unclear if prescribed or illicit use). Comparison does not match protocol (maintenance on clonazepam).
Wentink 2019[285]	Protocol only (study not yet published)
Wilson 2015[286]	Review
Wilson 2015[287]	Intervention does not match protocol (Internet based self-management program intervention judged to be an alternative treatment which may subsequently reduce medicines, but not specifically a dose reduction or withdrawal intervention – not all people in the intervention group had the aim to decrease or discontinue their opioid use).
Winklbaur 2008[288]	Population does not match protocol (illicit drug use)
Woody 1995[290]	Population does not match protocol (illicit opioid use)
Worley 2015[291]	Secondary analysis of the POATS trial (already excluded from this review as the population does not match the protocol - included people with prescription opioid dependence, both those who had been prescribed opioids by a physician and those who had obtained them illicitly. People who were prescribed opioids is not a subgroup in this secondary analysis).
Worley 2017[292]	Secondary analysis of the POATS trial (already excluded from this review as the population does not match the protocol - included people with prescription opioid dependence, both those who had been prescribed opioids by a physician and those who had obtained them illicitly. People who were prescribed opioids is not a subgroup in this secondary analysis).
Zhang 2013[296]	Not in English
Zitman 2001[299]	Population does not match protocol (33% of people on benzodiazepines not on our review protocol list).

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 122: Studies excluded from the health economic review

Reference	Reason for exclusion
Moriarty 2019[169]	Excluded as rated partially applicable and with very serious limitations. The study focuses only on benzodiazepines adverse events, assumes no withdrawal symptoms and same quality of life with benzodiazepines or no drug.

Appendix J Research recommendations

J.1 What are the key components of an effective multicomponent intervention to support dose reduction during withdrawal of opioids?

Why this is important

Opioids are not recommended by NICE for chronic primary pain due lack of evidence of effectiveness when used long term, and it is likely that many people using them long-term are deriving little benefit. Doses are often escalated to unsafe levels due to a desire to achieve an effect. The harms of long-term use include problems associated with dependence, amongst others. Therefore, effective withdrawal interventions to help support people withdraw from or reduce the dose of prescribed opioids when their use is no longer appropriate or the dose has become unsafe, are of great importance to both people prescribed opioids, and healthcare professionals.

Multicomponent interventions may be an effective method that could be of benefit as they may help manage symptoms of the original condition that the medicine was prescribed for, as well as supporting the person with the withdrawal and/or dose reduction. There is increasing interest in such interventions, and therefore it is important to determine what components would make an effective multicomponent intervention for this population.

Rationale for research recommendation

Importance to 'patients' or the population	There is limited knowledge of the most effective method of supporting people to do a tapered withdrawal or reduction of prescribed opioid medicine. Withdrawal can be a difficult process and it is possible that a multicomponent intervention would best support this due to the various factors that contribute to the person's experience at the time. A multicomponent intervention may be able to support the person's wellbeing whilst also helping manage their original symptoms, minimising any problems with withdrawal and helping to successfully taper, therefore reducing the risk of long-term harms. However, which specific components would need to be required to make an effective intervention needs to be determined.
Relevance to NICE guidance	Methods of withdrawal were reviewed within this guideline. Recommendations could not be made on the most effective specific interventions to support withdrawal for each drug class and therefore research on this topic would help inform future updates of this guideline
Relevance to the NHS	The outcome would affect the interventions provided by the NHS to help those who need to taper their opioids. This would help reduce harm from inappropriate opioid use when no longer providing benefit and use at unsafe doses.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area:

	https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	The evidence review within the guideline identified 1 small study that compared multicomponent psychological opioid taper support (including motivational interviewing and CBT) together with a taper program to help people withdraw or reduce their opioid use. This demonstrated promising results in terms of quality of life and dose reduction, although not in the number of people discontinuing. The sample size of this study was very small (n=35) and there were further limitations including a relatively short follow-up post-intervention (only 12 weeks) meaning that firm conclusions could not be based on this alone. Further research is required to confirm whether such a component can be of benefit. The intervention studied had many components, not all fully described. It is possible that different components could be more/less effective, therefore research is required to determine the components of an effective multicomponent intervention.
Equality considerations	None known

Modified PICO table

Population	Adults (aged 18 or over) taking prescribed opioids (or those bought over the counter) for chronic non-cancer pain who would like to withdraw from the medicine or reduce the dose used.
Intervention	Multicomponent intervention(s) aimed to support people withdraw from opioids, consisting of defined components for each individual, provided alongside information and support to withdraw.
Comparator	Information and support to withdraw (consistent with concurrent treatment in the intervention group)
Outcome	• Health-Related Quality of life • Mortality • Reduction/cessation of opioid use • Withdrawal symptoms (including rebound symptoms) • Relapse into medicine use • Use of illicit or over the counter drugs (other than those the participant is tapering off) or alcohol as a replacement to prescribed drugs • Non-fatal overdose • Reduced tolerance • Patient satisfaction
Study design	Randomised control trial. May be best addressed by a multifactorial experiment design
Timeframe	A post-intervention follow-up, as well as a long term (1 year follow up), would be beneficial so as also to demonstrate long-term effects.
Additional information	None

J.2 What are the most effective psychological interventions to support withdrawal and help people cope with withdrawal symptoms?

Why this is important

One of the key areas to cover within the guideline was the most clinically and cost-effective strategies for the safe withdrawal of prescribed medicines associated with dependence or withdrawal symptoms. Psychological interventions were included within this area. Unfortunately, there was little evidence on psychological interventions other than group cognitive behavioural therapy, which was shown to be beneficial and cost-effective when used alongside tapering from a benzodiazepine. In the absence of clear evidence, there was some discussion amongst the committee as to whether the outcomes were directly attributable to the psychological intervention or whether this might have been as a result of developing a supportive therapeutic relationship during the intervention. There was some evidence to suggest that other psychological therapies (including CBT for insomnia and motivational interviewing) may have a positive benefit in the supporting withdrawal from medicines associated with dependence and withdrawal symptoms, however, this evidence was limited in quality and amount of available evidence and was insufficient to inform recommendations in this guideline. Based on the experience of committee members, it is understood that a number of psychological interventions are successfully used in substance misuse services to support the safe withdrawal of illicit substances and or/substitution medication. With all of this in mind and because of the lack of evidence for drug classes other than benzodiazepines, the committee agreed it was important to make a recommendation for research on the effectiveness of psychological interventions for all drug classes associated with dependence or withdrawal.

Rationale for research recommendation

Importance to ‘patients’ or the population	There is limited evidence in the use of psychological interventions to support people withdrawing from medicines associated with dependence or experiencing withdrawal symptoms of prescribed medications. Such interventions are routinely used in the field of substance misuse and seem to be associated with positive outcomes. If there were evidence to support the use of these interventions, across a range of prescribed medicines, these could be used to support people to reduce their medicine use and manage possible withdrawal symptoms.
Relevance to NICE guidance	The evidence reviewed within this guideline only enabled a recommendation to be made to consider group CBT during benzodiazepine withdrawal. High-quality research in this area would generate much-needed evidence which may enable future updates in this guideline to recommend psychological interventions to aid withdrawal from other medicines or enable recommendations to be made on other types of psychological therapies that can help support people withdrawing from medicines associated with dependence and withdrawal.
Relevance to the NHS	High-quality evidence in the effectiveness and cost-effectiveness of psychological interventions to support people withdrawing from medicines, would help to make the best use of finite

	resources whilst still prioritising patients and achieving the best outcomes. As it has been mentioned previously, it seems that such interventions are already in use in other areas of the NHS and further research may help identify the relevance of using the same or similar interventions for this population.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	The current evidence sufficient to base a recommendation on was limited to group CBT to support benzodiazepine withdrawal. There was also some evidence of benefit for CBT for insomnia as well as motivational interviewing for mixed medicine withdrawal, and mindfulness combined with CBT for antidepressant withdrawal, but all of these were limited by being single studies, small sample sizes ,and low to very low-quality evidence and a lack of cost-effectiveness evidence meaning they were insufficient to base a recommendation on. Other evidence was available of psychological interventions compared to each other, however, without proven efficacy of one or the other, these again could not inform a recommendation. Further research is therefore required.
Equality considerations	None known

Modified PICO table

Population	Adults (aged 18 years or over) who wish to withdraw from medicines associated with dependence or withdrawal symptoms; opioids, benzodiazepines, gabapentinoids, Z-drugs or antidepressants.
Intervention	Psychological therapies, for example (but not limited to) motivational interviewing, mindfulness, CBT (alongside tapered withdrawal).
Comparator	Tapered withdrawal alone, or usual care to aid withdrawal of medicines.
Outcome	• Quality of life • Mortality • Reduction/cessation of medicine use • Withdrawal symptoms
Study design	Randomised controlled trial (cluster randomised trials may also be appropriate).
Timeframe	Long-term follow-up is beneficial to demonstrate sustained benefits. Outcomes should also be reported at the end of the intervention period.
Additional information	None

J.3 What service models are most effective in supporting people withdrawal from medicines associated with dependence and withdrawal symptoms

Why this is important

Review of the evidence highlighted both the negative patient experiences in the qualitative reviews and a paucity of studies exploring organisational models supporting continuity of care in the intervention reviews of best methods for safe withdrawal from these medicines. At present, the provision of services to specifically support withdrawal from prescribed medicines (rather than illicit drug withdrawal) within the NHS is limited. Information and evidence are required to inform the best service model for this population.

Rationale for research recommendation

Importance to 'patients' or the population	The presence of services in the NHS for people withdrawing from prescribed medicines would help ensure continuity of care, could reduce the incidence of medical errors, might lead to a reduction of events of serious accidental or impulsive self-harm and would enhance the care and support for vulnerable people.
Relevance to NICE guidance	A robust evidence base about organisational factors supporting continuity of care will inform service delivery for patient groups with comparable needs (e.g., frailty). Recommendations on the best service model could not be informed from the current evidence base, and so further research in this area would inform future updates of this guideline.
Relevance to the NHS	The outcome would affect the services provided by the NHS to help those who need to withdraw from prescribed medicines. This would help reduce harm from inappropriate medicine use when no longer providing benefit or used at unsafe doses.
National priorities	High Organisational research as outlined above refers to the strategic aims of the White Paper "Integrating care: next steps to building strong and effective integrated care systems across England" This is also relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	Currently, there are few studies exploring management factors within and across the organisations that deliver services for people who taking prescribed medicines associated with dependence and withdrawal symptoms. No evidence on different service models was identified within the evidence review for this guideline.

Equality considerations	The research will address factors such as the digital exclusion of vulnerable population groups and poverty medicine. Aspects of intersectionality are bound up with social disadvantage. The experience of adverse childhood experiences (ACE) is common in these patient groups.

Modified PICO table

Population	Adults (aged 18 or over) who wish to withdraw from medicines associated with dependence and withdrawal symptoms.
Intervention	Implementation of service models with a focus on minimising fragmentation and lack of continuity of care
Comparator	Organisations serving similar populations
Outcome	• Health-Related Quality of life • Reduction/cessation of medicine use • Withdrawal symptoms (including rebound symptoms) • Relapse into medicine use • Use of illicit or over the counter drugs (other than those the participant is tapering off) or alcohol as a replacement for prescribed drugs • Non-fatal overdose • Reduced tolerance • Patient satisfaction • Staff satisfaction (time off sick, satisfaction surveys)
Study design	Cluster randomised trial
Timeframe	A long-term follow up would be required to demonstrate outcomes impacted by changes to the service design.
Additional information	None

J.4 What is the clinical and cost effectiveness of converting to medicines with a longer half-life to aid withdrawal from benzodiazepines or antidepressants?

Why this is important

There is some evidence that converting to a benzodiazepine with a longer half-life may aid withdrawal when benzodiazepines are used recreationally. It is not known if this practice is clinically or cost-effective when benzodiazepines are prescribed for a medical purpose in which the risk-benefit ratio is more finely balanced. There is limited evidence available for other interventions to support people withdrawing from prescribed benzodiazepine use, and therefore further research on areas thought to be beneficial experience in illicit drug use could help inform prescribed medicine withdrawal. It is also known that antidepressants with a short half-life can be more difficult to withdraw from, and therefore it would be beneficial to ascertain whether converting to a longer half-life would also help withdrawal from these medicines.

1 Rationale for research recommendation

Importance to 'patients' or the population	There is a biochemical basis for considering benzodiazepines with longer half-lives may reduce the likelihood of suffering withdrawal effects when withdrawn. If proven true in clinical settings in which benzodiazepines are prescribed for a medical purpose, then people may be better able to tolerate withdrawal with fewer adverse effects. It is also known that withdrawing from an antidepressant with a short half-life can be more difficult. Therefore, it is also possible that converting to a longer half-life may help people trying to withdraw from these medicines as well. At present there is little evidence for effective interventions to support prescribed benzodiazepine or antidepressant withdrawal, so increased research in this area would be beneficial to people wishing to withdraw from this medicine.
Relevance to NICE guidance	Further research on the use of benzodiazepines or antidepressants with a longer half-life may mean that updates of this guideline would be better able to support a consideration or more robust recommendations for conversion to benzodiazepines or antidepressants with longer half-life to aid withdrawal.
Relevance to the NHS	The outcome would support practical and practicable change in clinical practice across the NHS and determine if clinical practice currently undertaken in services for recreational benzodiazepine use can be extended to services for prescribed benzodiazepine use, thereby rationalising practice.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	No evidence was identified within the evidence review in this guideline specifically for conversion to medicines with a longer half-life to aid withdrawal from these when prescribed. All the evidence comes from clinical consensus and practice undertaken in drug and alcohol services for recreational benzodiazepine use.
Equality considerations	None known

2 Modified PICO table

Population	Adults (aged 18 or over) who wish to withdraw or reduce the dose of prescribed benzodiazepines or antidepressants
Intervention	Conversion to a longer-acting benzodiazepine or antidepressant preparation (as relevant to the medicine they are withdrawing from)
Comparator	Not converting to a longer-acting preparation

	Withdrawing with medicine currently prescribed (tapered withdrawal only)
Outcome	• Proportion of patients able to stop • Reduction in dose • Severity and frequency of withdrawal symptoms • Incidence of serious adverse effects such as withdrawal seizures or delirium tremens • Quality of life
Study design	Randomised controlled trial
Timeframe	Short to medium term. Long-term follow-up would be beneficial to demonstrate sustained benefit. Outcomes should also be reported at the end of the intervention period.
Additional information	None

J.5 What is the most effective model of CBT, including timing of CBT, to support withdrawal from benzodiazepines?

Why this is important

CBT is the most widely provided psychological therapy on the NHS and the most studied internationally, but it's role in supporting people's withdrawal from prescribed benzodiazepine use is less well studied. Evidence identified benefits from CBT in this regard, but the detail on the type of CBT and methods of delivery could not be informed from the available evidence. It is important to identify what the optimal model CBT is to assist people with withdrawal from benzodiazepine use.

Rationale for research recommendation

Importance to 'patients' or the population	CBT is the most studied psychological intervention. This is largely because of its design and approach (usually manualised and time-limited), so it is possible to replicate CBT in different forms, where other therapies usually cannot be replicated in the same way. CBT has also been shown to be generalisable and available to the entire population through the NHS Improving Access to Psychological Therapies (IAPT) model. Initial evidence suggests this may be beneficial to support people withdrawing from benzodiazepines, however further research on the best type of CBT would enable more defined interventions to be recommended for people withdrawing, as well as informing whether group or individual CBT is most effective.
Relevance to NICE guidance	CBT has been recommended in the guideline to support withdrawal from benzodiazepines, however, detail of the best type or timing of CBT could not be informed from the available evidence. Further research in this area could help refine recommendations in future updates of this guideline.
Relevance to the NHS	The outcome of future research would inform the most effective type(s) of CBT for benzodiazepine withdrawal provided by the NHS and improve the use of resources in this context.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	The current evidence base was limited only to group CBT and did not inform the type of CBT (e.g., whether it was CBT for withdrawal symptoms vs. CBT for original symptoms for which medicine was prescribed) or other aspects such as the best timing to provide the intervention.
Equality considerations	None known

Modified PICO table

Population	Adults (aged 18 or over) wishing to discontinue or reduce benzodiazepine use.
Intervention	Tapered withdrawal plus CBT: • in group setting or individually • to target withdrawal symptoms or symptoms for which medicine was originally prescribed • provided prior to commencing withdrawal, during withdrawal or toward end of withdrawal and beyond.
Comparator	Each compared to each other, or Tapered withdrawal alone
Outcome	• Proportion able to successfully stop benzodiazepine use • Reduction in benzodiazepine dose • Quality of life • Resumption and severity of original symptoms • Use of benzodiazepine (prescribed or otherwise) in medium to long-term • Withdrawal symptoms
Study design	Randomised controlled trial (may require a factorial design or separate trials)
Timeframe	Short-medium term. Long-term follow-up is beneficial to inform sustained benefits. Outcomes should also be reported at the end of the intervention period.
Additional information	None

J.6 What is the clinical and cost effectiveness of acupuncture (including electroacupuncture) as an adjunct to aid withdrawal from opioids?

Why this is important

Opioids are not recommended by NICE for the treatment of chronic primary pain due to a lack of evidence of effectiveness when used long-term, and long-term use is associated with harms. Doses are often escalated to unsafe levels due to a desire to achieve an effect. The harms of long-term use include problems associated with dependence, amongst others. Therefore, effective withdrawal interventions to help support people to withdraw from or reduce the dose of prescribed opioids when their use is no longer appropriate or the dose has become unsafe, are of great importance to both people prescribed opioids and healthcare professionals.

Acupuncture (including electroacupuncture) may be a useful non-pharmacological adjunct to facilitate withdrawal from opioids. The technique may work by treating the symptoms for which the opioids are being prescribed (e.g., pain –NICE recommend its use in chronic primary pain) but also by helping directly with symptoms of withdrawal or dose reduction. Current evidence is insufficient to demonstrate whether acupuncture has a role in supporting opioid withdrawal and it is, therefore, important to investigate this intervention.

Rationale for research recommendation

Importance to 'patients' or the population	There is limited knowledge of the most effective method of supporting people to do a tapered withdrawal, or reduction of prescribed opioid medicine. Withdrawal can be a difficult process not only because of unpleasant direct symptoms of withdrawal but because of emergence of symptoms which may have been controlled in part by opioids. Acupuncture might help support opioid withdrawal by helping to manage original presenting symptoms, minimising any problems withdrawal and helping to successfully taper, therefore reducing the risk of long-term harms. If the treatment is effective, the type of acupuncture treatment and dose of treatment needs to be determined.
Relevance to NICE guidance	Non-pharmacological techniques to facilitate opioid withdrawal were reviewed within this guideline. Recommendations could not be made on whether acupuncture is useful to support withdrawal from opioids and other drug classes. Research on this topic would therefore help inform future updates of this guideline
Relevance to the NHS	The outcome would affect the interventions provided by the NHS to help those who need to taper their opioids. This would help reduce harms from inappropriate opioid use when no longer providing benefit our used at unsafe doses.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area:

	https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	A small amount of evidence identified in the evidence review suggested some benefits of acupuncture and electroacupuncture for people withdrawing from opioids. However these benefits were inconsistent across outcomes and there were considerable limitations in the quality of evidence meaning firm conclusions could not be drawn from this evidence base to inform recommendations.
Equality considerations	None known

Modified PICO table

Population	Adults (aged 18 or over) taking prescribed opioids (or those bought over the counter) for chronic non-cancer pain who would like to withdraw from the medicine or reduce the dose used.
Intervention	Acupuncture techniques (including electroacupuncture) to support people withdraw from opioids, provided alongside information and support to withdraw.
Comparator	Information and support to withdraw, consistent with concurrent treatment in the intervention group (Tapered withdrawal alone)
Outcome	• Health-Related Quality of life • Mortality • Reduction/cessation of opioid use • Withdrawal symptoms (including rebound symptoms) • Relapse into medicine use • Use of illicit or over the counter drugs (other than those the participant is tapering off) or alcohol as a replacement for prescribed drugs • Non-fatal overdose • Reduced tolerance • Patient satisfaction
Study design	Randomised controlled trial
Timeframe	A post intervention follow-up as well as a long-term (1-year follow up) would be beneficial so as also to demonstrate long term effects.
Additional information	None

J.7 What are the most clinically and cost-effective strategies or interventions to aid withdrawal of gabapentinoids?

Why this is important

Manufacturer guidelines and national formulary recommendations suggest that gabapentinoids can be reduced over the course of one week however symptoms of withdrawal may emerge, and fixed dose tapering schedules have been used and recommended in other national guidance. There is currently no evidence base for clinical or cost-effectiveness of different withdrawal strategies or interventions to assist withdrawal of gabapentinoids.

Rationale for research recommendation

Importance to 'patients' or the population	Dependence on prescribed medicines including gabapentinoids is of public and political concern. There is currently no evidence on the clinical effectiveness of different strategies or interventions to assist withdrawal from gabapentinoids and research in this area could significantly improve acceptability to patients, health-related quality of life, and reduce morbidity associated with withdrawal of gabapentinoids.
Relevance to NICE guidance	Clinical and cost-effectiveness of different strategies or interventions to assist withdrawal from gabapentinoids has been considered in this guideline and although a fixed schedule taper is recommended in some guidelines, there is no evidence available for effective tapering strategies, schedules, or additional supportive interventions, such as CBT specifically for gabapentinoid withdrawal. Therefore, evidence in this area could help inform recommendations in future updates of this guideline.
Relevance to the NHS	The outcome of this research could impact on the cost of prescribing for tapering schedules, on prescriber experience, and on strategic planning of services if, for example, it was identified that specific interventions e.g., increased frequency of face-to-face clinical follow up, CBT, or peer support were found to be effective in supporting patient withdrawal from gabapentinoids.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	There is currently no evidence on gabapentinoid withdrawal schedules, strategies, or interventions.
Equality considerations	If research involved strategies with written information, considerations would need to be taken to ensure easy-read, pictorial or translated information was provided. If family, carer or peer support were investigated, provision or support

	for patients with minimal or no informal supportive networks would need to be taken into account. Variability of access to digital support would also need to be considered e.g., secure environments, homeless patients.

Modified PICO table

Population	Adults (aged 18 or over) prescribed gabapentinoids where they are not providing clinical benefit, or where they are causing harm or creating risk for the patient or others.
Intervention	Withdrawal schedules with i) proportional decrements ii) regular follow up with clinician (face-to-face, telephone, digital e.g., text) iii) additional CBT/other non-pharmacological support
Comparator	Withdrawal with fixed schedule (in line with current guidelines – 50-100mg/week pregabalin; 300mg every 4 days gabapentin with safety netting advice) and patient education with written leaflet provided
Outcome	Quality of life during and following withdrawal from gabapentinoid; rebound symptoms or adverse events during withdrawal from gabapentinoid; side effects and risk created by ongoing prescribing
Study design	Randomised controlled trial.
Timeframe	Long-term follow-up would be beneficial to demonstrate sustained benefits. Outcomes should also be reported at the end of the intervention period.
Additional information	None

J.8 What is the effectiveness of equipment, technologies, practical aids, and medicine formulations in supporting people to manage dose reductions, compared with usual practice?

Why this is important

People who have taken opioids, benzodiazepines, gabapentinoids, Z-drugs, or antidepressants may experience withdrawal symptoms when they try and stop the medicines. This reduces their chances of successful cessation. Usual practice on supporting people to manage these symptoms is not informed by reliable data. It is important to investigate what types of equipment, technologies, practical aids, and medicine formulations are most effective in supporting people to stop these medications.

Rationale for research recommendation

Importance to 'patients' or the population	There is a lack of evidence for what interventions are most effective in supporting people tapering off prescribed medicines and minimising withdrawal symptoms. This likely results in people experiencing withdrawal symptoms which may be unnecessary and thus experiencing more difficulty in stopping the medication. More information in this area would help support people when withdrawing from these medicines.
Relevance to NICE guidance	Withdrawal interventions have been considered in this guideline and there is little data on which are the most effective for prescribed medicines.
Relevance to the NHS	The outcome of this research would help inform the types of support that can be offered for those people who were experiencing withdrawal symptoms when they try to stop prescribed medicine use and would improve care for people.
National priorities	High This is relevant to Public Health England's Prescribed medicines review, which recommends further research is required in this area: https://www.gov.uk/government/publications/prescribed-medicines-review-report
Current evidence base	The evidence review identified a number of studies, but none were able to reliably inform recommendations for the best way to support people reducing the use of the medicines considered, due to limitations in the evidence base in terms of quality and size of the evidence base. No data were specifically available for particular types of equipment, technologies, or practical aids.
Equality considerations	None known

Modified PICO table

Population	Adults (aged 18 or over) who are attempting to stop medicines associated with withdrawal symptoms
Intervention	Dose reduction aids (for example practical aids or technologies) or use of low dose tablets or liquid formulations alongside tapering
Comparator	Tapering alone or tapering using standard formulations
Outcome	• Health-related quality of life • Mortality • Reduction/cessation of prescribed drug use • Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome • Relapse into medication use • Use of illicit or over the counter drugs or alcohol as a replacement for prescribed drugs • Non-fatal overdose • Increase in symptoms for which the medication was originally prescribed
Study design	Randomised trail
Timeframe	3 to 6 months. Long-term follow-up would also be beneficial to demonstrate sustained benefits.
Additional information	None

Appendix K List of medicines to be included

This list refers to codes from BNF version 68.

Drug class (for this analysis)	BNF chapter	Drugs included
Opioids	4.7.2	Buprenorphine
		Codeine*
		Dextromoramide
		Diamorphine
		Dihydrocodeine**
		Dipipanone (including with cyclizine)
		Fentanyl
		Hydromorphone
		Meptazinol
		Methadone
		Morphine (including with cyclizine)
		Oxycodone (including with naloxone)
		Papaveretum
		Pentazocine
		Pentazocine
		Pethidine
		Tapentadol
		Tramadol (including with paracetamol)
	4.7.1	Codeine with paracetamol = co-codamol*
		Dihydrocodeine with paracetamol = co-dydramol**
Z-drugs	4.1.1	Zaleplon[$]
		Zopiclone
		Zolpidem
Benzodiazepines[£]	4.1.1 (insomnia)	Flurazepam
		Loprazolam
		Lormetazepam
		Nitrazepam
		Temazepam

Drug class (for this analysis)	BNF chapter	Drugs included
	4.1.2 (anxiety)	Diazepam
		Chlordiazepoxide
		Lorazepam
		Oxazepam
		Clonazepam
Gabapentinoids	4.7.3	Gabapentin
	4.8.1	Pregabalin
Antidepressants	4.3.1 (Tricyclics)	Amitriptyline (including with perphenazine)
		Amoxapine
		Clomipramine
		Dosulepin
		Doxepin
		Imipramine
		Lofepramine
		Maprotiline
		Mianserin
		Nortriptyline
		Protriptyline
		Trazodone
		Trimipramine
	4.3.2 (MAOIs)	Isocarboxazid
		Moclobemide
		Phenelzine
		Tranylcypromine
	4.3.3 (SSRIs)	Citalopram
		Escitalopram
		Fluoxetine
		Fluvoxamine
		Paroxetine
		Sertraline

Drug class (for this analysis)	BNF chapter	Drugs included
	4.3.4 (Other antidepressants)	Agomelatine
		Duloxetine
		Flupentixol
		Mirtazapine
		Nefazodone
		Oxitriptan
		Reboxetine
		Tryptophan
		Venlafaxine
		Vortioxetine

List of medicines taken from the 2019 Public Health England review of prescribed medicines, and adapted where necessary.[218]

* Although they are captured within different BNF chapters, codeine and co-codamol will be regarded as a single drug when considering co-prescribing within the opioid class.

** Although they are captured within different BNF chapters, dihydrocodeine and co-dydramol will be regarded as a single drug when considering co-prescribing within the opioid class.

$ Zaleplon was initially included for consistency with the Public Health England (PHE) report on prescribed drug dependence and withdrawal. Subsequent to starting guideline development, Zaleplon was discovered to no longer have a marketing authorisation in the UK. Therefore, it was excluded from evidence reviews.

£ Alprazolam and clobazam are listed within the BNF, however, they are not prescribable in NHS primary care. Therefore, they were not included in this guideline. This is consistent with the Public Health England (PHE) report on prescribed drug dependence and withdrawal.