

National Institute for Health and Care Excellence

Final

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

[F] Evidence review: Monitoring: content and frequency

NICE guideline NG215

Evidence reviews underpinning recommendations 1.3.4, 1 .4.1, 1.4.2, 1.4.3, 1.4.4, 1.4.5, 1.4.6 in the NICE guideline

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Final

*These evidence reviews were developed
by the National Guideline Centre*

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1 Monitoring content

1.1 Review question: What should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms?

1.1.1 Introduction

People should not be put at risk from medicines they are taking so it is important to monitor the effects of medicines regularly to be sure that they are giving benefit and not producing unwanted effects. Additionally, monitoring of medicines associated with dependence needs to promptly identify if the person taking the medicines is developing problems of dependence or withdrawal. Discussions about dependence and related problems are necessary at the initial consultation when these medicines are prescribed but this information isn't always shared or retained by the people using them, so medicines reviews are an important opportunity to discuss risks and identify emerging concerns.

It is important to identify the components of the medicine review that are most likely to identify problems and the best way this information is given to the person taking dependence forming medicines. The monitoring review should also give people taking medicines a better understanding of potential future problems and how these might be identified, as well as agreeing the appropriate interval before the next review, and the actions that need to be taken if problems develop between reviews.

Each clinical interaction is unique and there are many prescriber, patient and system influences on how monitoring of medicines happens in practice. This review question aims to identify the essential questions that need to be asked, to minimise medicine related problems and in particular, the challenges of dependence and withdrawal.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A section A.1.

Table 1: PICO characteristics of review question

Population and setting	Adults (≥ 18 years) taking prescribed medicines that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants). Prescribers of the above (for the qualitative review).
Intervention/ Phenomena of interest	Intervention data: Different elements included in a monitoring review (i.e., inclusion of different items assessed during review of prescribed medicines associated with dependence or withdrawal symptoms) and alteration of treatment according to study. Qualitative data: Perceptions and experiences of healthcare professionals of the information that they require during a review of prescribed medicines associated with dependence or withdrawal symptoms AND perceptions and experiences of patients of the information they think should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms to help prevent dependence or withdrawal symptoms occurring.
Comparator	Intervention data:

	<p>Different content within a monitoring review compared with each other or with usual care (as defined by the study) and alteration of treatment according to study.</p> <p>Qualitative data: Not applicable.</p>
Outcomes	<p>Intervention data:</p> <ul style="list-style-type: none">• HRQOL• Mortality• Dependence to the prescribed medicine• Withdrawal symptoms• Non-fatal overdose• Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs• Patient Satisfaction• Self-harm or harm to others• Increase in symptoms for which the medication was originally prescribed <p>Qualitative data: Themes emerging from qualitative data (themes will be derived from the evidence identified for this review and not pre-specified)</p>
Types of study to be included	<p>Intervention studies: Randomised controlled trials Comparative non-randomised or cohort studies Systematic review of randomised controlled trials and non-randomised comparative studies.</p> <p>Qualitative studies: Qualitative studies (e.g., transcript data collected from focus groups/semi structured interviews)</p>

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](#).

1.1.4 Quantitative evidence

1.1.4.1 Included studies

No relevant quantitative intervention studies were identified.

See also the study selection flow chart in Appendix C section C.1.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix F section F.1.

1.1.5 Qualitative evidence

1.1.5.1 Included studies

Ten qualitative studies were included in the review^{24, 37, 46, 56, 62, 63, 72, 77, 95, 102}; these are summarised in Table 2 to Table 4 below. Key findings from these studies are summarised in the clinical evidence summaries below (Table 5 to Table 7). See also Appendix E (Table 11 to Table 24) for full qualitative evidence tables. See also the study selection flow chart in Appendix C section C.1 and study evidence tables in Appendix D section D.2.

It was agreed that evidence on different drug classes would be stratified and summarised separately as prespecified in the review protocol. Six of the ten studies identified and included in this review were specific to opioids, 3 to antidepressants and one to benzodiazepines and Z-drugs. No evidence specifically relevant to gabapentinoids was identified.

Both the views of people being prescribed medicines associated with dependence or withdrawal symptoms and the health professionals working with them were included in the evidence. The majority of studies used semi-structured interviews and thematic analysis.

1.1.5.2 Excluded studies

See the excluded studies list in Appendix F section F.1.

1.1.6 Summary of studies included in the qualitative evidence

Table 2: Summary of studies included in the evidence review: opioids

Study	Design	Population	Research aim	Comments
Chang 2017 ²⁴	Semi-structured interviews and coded thematic analysis.	<p>Primary care providers from six safety net primary health care settings who provided longitudinal primary care to a panel of patients (patients cared for by this population and discussed in this study had a history of substance abuse).</p> <p>n=23; 18 physicians, 4 nurse practitioners, 1 physician assistant; most of the providers were physicians (78%), four were nurse practitioners, and one was a physician assistant; 65% of the providers were women.</p> <p>Setting: USA (six safety net* primary health care settings)</p>	To report primary care provider experiences in the safety net*, interpreting and implementing guideline recommendations for patients with chronic non-cancer pain (CNCP) and substance use.	<p>Substance abuse is defined as any reported personal or family history of alcohol or drug abuse (APS/AAPM guidelines).</p> <p>*Safety net settings are defined as healthcare settings that care for a substantial share of patients who are uninsured, use Medicaid, or are otherwise vulnerable.</p> <p>Recommendations being implemented are from the American Pain Society and American Academy of Pain Medicine (APS/AAPM).</p>
Hamilton 2021 ⁴⁶	Semi-structured interviews and thematic analysis.	General practitioners (GPs) with authority to prescribe opioid analgesics in Australia who had prescribed or deprescribed opioids in at least one patient with chronic (>12 weeks) non-cancer pain within the last six months.	To investigate the perspectives of Australian GPs on the barriers, facilitators and resources for deprescribing opioids in patients with chronic non-cancer pain; to inform safe, effective and sustainable methods of opioid deprescribing in Australia.	

Study	Design	Population	Research aim	Comments
		N=22; male/female: 9/13; majority aged 55 years and older (45%) and most had >20 years of clinical experience (50%). Setting: primary care setting in Australia		
Liebschutz 2018 ⁶³	Observational study of nurse care manager-patient interactions.	Nurse care managers and patients with chronic non-cancer pain under their care. n=2 nurse care managers, n=41 patients. Setting: USA (four primary care settings)	To describe strategies nurse care managers (NCMs) used with patients when discussing aberrancies encountered during opioid monitoring.	Part of an interventional study in which participating patients' primary care providers had been randomized to the treatment arm, of which nurse care managers were a part.
Matthias 2020 ⁷²	Observation of clinical visits and qualitative interviews analysed using a constant comparison method (thematic analysis)	Primary care providers practicing in primary care clinics serving primarily low-income patients. N=9; male/female: 1/9; mean age (range): 45 (30-62) years; n=5 internal medicine physicians, n=2 family medicine clinicians, n=1 physician assistant, n=1 did not provide this information. Patients of participating primary care providers with chronic musculoskeletal pain who were taking prescribed opioids	To understand how decisions about pain management are made between patients prescribed opioids and their primary care providers, including the degree to which these decisions are shared.	

Study	Design	Population	Research aim	Comments
		<p>N=37; n=22 of which were interviewed; male/female: 12/25; mean age (range): 58 (22 to 74) years.</p> <p>Setting: four primary care clinics at academic medical centre serving primary low-income patients; USA</p>		
Stumbo 2016 ⁹⁵	Semi-structured interviews and thematic analysis.	<p>Patients who survived overdose or poisoning events and family members of deceased patients.</p> <p>n=69 patients, n=18 family members. 55% were female; mean age 42.9 years (SD 16.4).</p> <p>Setting: USA (recruitment from members of Kaiser Permanente Northwest")</p>	To document family involvement in opioid medication monitoring, and to provide preliminary descriptions of acceptability and helpfulness to patients.	<p>Of the patients, 58.6% held an active prescription for opioids at the time of the event; the remaining 41.4% involved heroin, prescription opioids not obtained by prescription, or expired prescriptions.</p> <p>*KPNW provides integrated medical, mental health, pain management, and addiction care to about 500,000 members in Oregon and Washington.</p>
Wyse 2019 ¹⁰²	Semi-structured interviews and thematic analysis.	<p>Physicians and nurse practitioners caring for people prescribed long-term opioid therapy in Veterans Affairs (VA) medical centres.</p> <p>N=24 (20 physicians, 4 nurse practitioners); male/female: 9/15; mean age (SD): 49.5 (10) years; average number of years since completion of training (SD, range): 17 (10, 2-37) years.</p>	<p>The primary goal of the interviews was to learn about the methods primary care providers used to address prescription opioid misuse and aberrant opioid-related behaviours among their patients.</p> <p>This paper describes the strategies providers have developed to meet new guidelines regarding opioid</p>	<p>This study is part of a larger, mixed-methods project that aimed to investigate the use of, and response to, urine drug testing (UDT) among providers caring for patients prescribed long term opioid therapy for the treatment of chronic pain.</p>

Study	Design	Population	Research aim	Comments
		Setting: USA (22 VA Medical Centres across the country)	management and address common challenges they face in caring for patients prescribed long term opioid therapy.	

Table 3: Summary of studies included in the evidence review: benzodiazepines & Z-drugs

Study	Design	Population	Research aim	Comments
Lefebvre-Durel 2021 ⁶²	Semi-structured interviews and thematic analysis.	Healthcare professionals from different professions caring for elderly patients in psychogeriatric unit. N=8 (n=4 nurses, n=2 doctors, n=1 psychologist, n=1 medical student); male/female: 1/7 median age (range): 30 (24 to 59) years. Setting: psychogeriatric unit; France	To understand the perception of healthcare providers towards BZD or Z-drug withdrawal within a psychogeriatric unit and to provide insights from advanced practice nurses on this topic.	The inpatient psychogeriatric unit provided care to elderly patients with severe behavioural and psychosomatic symptoms, 50% of whom had associated BZD withdrawal issues.

Table 4: Summary of studies included in the evidence review: antidepressants

Study	Design	Population	Research aim	Comments
Donald 2021 ³⁷	Semi-structured interviews and (reflexive) thematic analysis.	GPs in Australia N=22; male/female: 13/9; mean age (range) 47 years (33 to 73); years since graduation: 5 to 34.	To explore GPs' insights about long-term antidepressant prescribing and discontinuation.	

Study	Design	Population	Research aim	Comments
Kelly 2021 ⁵⁶	Semi-structured interviews and thematic analysis	Australia GPs practising in both urban and rural practices and providing care for patients from diverse social and cultural backgrounds N=10; male/female: 7/3; mean age (SD) not specified; practice type: urban (n=6), rural (n=3), both (n=1); years of experience <5 years (n=3), 5-10 years (n=4), >25 years (n=3) Ireland	To explore general practitioners' perceptions and experiences of discontinuing antidepressants in primary care.	
Nolan 2005 ⁷⁷	Semi-structured interviews and thematic analysis.	Patients who had experienced a first episode of depression in the past 18 months and had been prescribed antidepressants. N=60; male/female: 23/37; mean age (range): 42 (24 to 67) years. Setting: UK (four GP practices in the West Midlands)	To explore what factors, lead patients to consider they have a satisfactory relationship with their prescribing clinician, and what kind of information they find reassuring and helpful. To examine how medication regimens are monitored, and what kind of follow-up patients appreciate, and to identify pointers for establishing effective therapeutic relationships between patients and prescribing clinicians.	To be eligible, participants should have been treated in primary care, should have been prescribed antidepressant medication, should have no other significant diagnosed physical or mental health problem.

See Appendix D section D.2 for full evidence tables.

1.1.7 Summary of the qualitative evidence

Table 5: Review findings (Opioids)

Main findings	Statement of finding
Agreed management plans ^{24,46,72,95, 102}	Collaborative-decision making about opioid prescribing was important for both people taking opioids and health-care professionals; opioid management plans allow agreement of adherence expectations, a structured framework for educating the patient and opportunity to involve family or carers in the monitoring process.
Therapeutic relationship between patient and health care professional ^{46,63}	Creating a positive relationship between the patient and health care professional creates an environment allowing honest discussions about opioid monitoring. Also, building a rapport allows health professionals to provide patient education, support and reassurance.
Education around adherence ⁶³	Communication around potential opioid misuse should include education about proper use of the medication and how to recognise the influence of other factors that can contribute to pain before relying on opioids.
Assessing adherence and misuse risk ^{46, 63, 72}	Healthcare professionals highlighted the need to ensure people adhere to their medication prescription and prescribing guidelines; routine questions can help assess a patient's misuse risk, combining information about their medication use and pain with their personal and medical history.
Weighing up the benefits and harms of discontinuation ⁴⁶	When making decisions about deprescribing opioids GPs highlighted the importance of weighing the benefits and risks of discontinuation for each person including, how well they function on opioids, the availability of alternatives, the likelihood of the person experiencing withdrawal symptoms.

Table 6: Review findings (Benzodiazepines and Z-drugs)

Main findings	Statement of finding
Reassessment of treatment needs and dependence ⁶²	Healthcare professionals highlighted the importance of reassessing the indication, dosage, duration of treatment, as well as dependence, in order to provide appropriate care to people taking benzodiazepines and/or Z-drugs.

Table 7: Review findings (Antidepressants)

Main findings	Statement of finding
Agreed monitoring programs ^{37, 77}	Monitoring schedules should be clear and initially agreed between the patient and health care provider, and so should personalised plans for discontinuation.
Clarity around reasons for monitoring ⁷⁷	It should be clearly communicated to people taking antidepressants why they are being asked to attend regular monitoring check-ups.
Encouraging self-monitoring ⁷⁷	People benefit from being encouraged to self-monitor, which can empower them to take control of their own recovery and potentially improve their self-esteem.
Asking specific questions ⁷⁷	Simple, direct questions about a person's experience and quality of life help the patient better understand and monitor the effects of their medication and illness.

Main findings	Statement of finding
Reviewing the functional response to treatment and benefits and risks of discontinuation ^{37, 56}	GPs acknowledged the benefits of discontinuation but expressed concern about the risk involved for some people and highlighted the importance of assessing an individual's functional response to treatment and weighing up the benefits and risks when making decisions about discontinuation for each individual.
Regular symptom monitoring and adherence during discontinuation ³⁷	Regular review during discontinuation to allow monitoring of symptoms, adherence to lifestyle changes, discontinuation progress and, provide support, was considered important by GPs
Review of personal and social circumstances ^{37, 56}	Reviewing an individuals' personal and social circumstances including: the availability of social support, and their financial or relationship status, was considered critical by GPs when making decisions about the discontinuation of antidepressants.
Patient preference ^{37, 56}	GPs highlighted the importance of making decisions about discontinuation of antidepressants in conjunction with patients, respecting patient preference to remain on antidepressants, and reassessing patient preference in the next scheduled review.

See Appendix E section E.2 for full qualitative evidence tables.

1.1.7.1 Narrative summary of review findings for Opioids

Review finding 1: Collaborative decision making and agreed management plans

Primary care providers expressed a desire for collaborative decision-making, patient involvement in treatment decisions about opioids, but also acknowledged that there are limitations on patient input into pain treatment decisions. Caveats related to discussions about opioids and the safety and effectiveness of opioids and the need to follow rules as a condition of opioid prescribing.

Opioid management agreements can be used to emphasise to the patient the risks and expectations of opioid therapy. These plans could include conditions such as patients agreeing, not to use illicit drugs or alcohol while on opioids, to receive opioids from a single provider or pharmacy, and to only take opioids as prescribed. This management agreement was in some cases used as a condition for initiating or continuing opioid therapy.

Acceptance and agreement to a management plan was also viewed as a key opportunity to involve a family member in the opioid monitoring process. To do this health care providers could make a request or requirement for family member engagement part of the agreement. This could also apply to carer involvement; it was beneficial for carers to attend clinical appointments and to help the patient adhere to their management plan.

Management plans were seen to aid communication with the patient about the expectations and risks about opioid therapy in a structured and systematic way. However, some health care professionals thought that management plans had the potential to create tension in clinical interaction, particularly when prohibiting drug and alcohol use while taking opioids and could hinder honest dialogue about the patient's drug or alcohol intake. Both patients and primary care providers were aware that lack of agreement between them, with regard to opioid prescribing, could have an adverse effect on the patient-provider relationship, but some providers were unwilling to agree on a course of action that they perceived harmful for the patient.

GPs also mentioned incorporating individualised management plans, patient education and goal setting into deprescribing regimens. They found it useful to compile individualized deprescribing plans which encourages slow weaning in a structured way, while involving the patient in the planning process.

Explanation of quality assessment: minor concerns about methodological limitations with very minor concerns in two studies due to the role of the researcher not being explored and minor concerns in one study due to the study's semi-structured interview guide being adapted from a larger overall study with indirect research aims to this review and moderate concerns in one study due to the role of the researcher not being discussed and lack of sufficient detail on the recruitment process; no or very minor concerns about coherence; moderate concerns about relevance due to one study being specific to the implementation of new USA guidelines (American Pain Society and Academy of Pain Medicine (APS/AAPM) guideline for patients with chronic non-cancer pain), and the fact that the setting is specifically a safety net setting which mostly cares for patients who are uninsured, use Medicaid or are otherwise vulnerable, moderate concerns in one study due to the study recruiting only participants who had overdosed, or were family members of those who had died of an overdose, interviews being designed according to the aims of a larger study (to understand changes in circumstances surrounding overdose events prior to and following the introduction of an abuse-deterring formulation of a long-acting opioid), and setting within the USA healthcare system, minor concerns in two studies due to setting within the USA healthcare system and one study within the Australian healthcare system; no concerns about adequacy. The overall assessment of confidence was low.

Review finding 2: Therapeutic relationship between patient and HCP

Building a positive relationship with the patient was seen as an important supportive element of opioid reviews. Furthermore, GPs stated that the deprescribing process is easier when they have been managing the patient for a long time, whereby the relationship is well-established. Rapport building involves ensuring the patient does not feel abandoned to manage this task on their own and that they can consult with their GP wherever needed. Having rapport allows GPs to provide patient education as well as support and reassurance.

Explanation of quality assessment: minor concerns about methodological limitations with moderate concerns in one study due to its observational and descriptive approach rather than gathering qualitative evidence about effectiveness and a lack of patient perspective but very minor concerns in the other contributing study due to the role of the researcher not being discussed; no or very minor concerns about coherence; moderate concerns about relevance with moderate concerns in one study due to the population being specific to nurse care managers in the US healthcare system and the population in the other study being limited to GPs in Australia; and minor concerns about adequacy due to the research finding being based on only one study. The overall assessment of confidence was low.

Review finding 3: Education around adherence

When health care professionals discovered aberrance from opioid prescriptions it was seen as an important opportunity to educate the patient about how to appropriately use their medication. This could include clarifying clinical recommendations about the patient's health and opioid medications, how the opioids work in the context of the patient's specific situation and the impact of psychosocial factors on chronic pain. In the latter case, health care professionals should make clear the interaction of the patient's social circumstances and their physical symptoms so that the patient can improve the understanding of their pain and to encourage effective and adherent use of their medication.⁶³

Explanation of quality assessment: moderate concerns about methodological limitations with moderate concerns in one study due to its observational and descriptive approach rather than gathering qualitative evidence about effectiveness and a lack of patient perspective; no or very minor concerns about coherence; moderate concerns about relevance with moderate

concerns in one study due to the population being specific to nurse care managers in the US healthcare system; and moderate concerns about adequacy due to the research finding being based on only one study. The overall assessment of confidence was very low.

Review finding 4: Assessing adherence and misuse risk

Healthcare professionals highlighted that an opioid prescription came with rules and requirements and failure to comply with these requirements could result in discontinuation of a patient's opioid prescription. They expressed the need to feel they can trust their patient to be compliant with the deprescribing plan and the need to ensure patients were complying by the rules/guidelines for prescribing. When they prescribed opioids they had expectations for patients, which included submitting to regular urine drug screens and reporting to them if opioids were prescribed by another healthcare provider. Past history of patient adherence also influenced how providers approached decisions about opioids.

Health care professionals could obtain information about a patient's medication use, pain and risk for opioid misuse through risk assessment by, routine, probing or clarifying questions. This risk assessment could include questions about substance abuse history, psychiatric history, current medication use practices and aberrant behaviours such as diversion. As well as identifying potential for misuse, these questions allowed for open communication with the patient on how to use their medication safely.⁶³

Explanation of quality assessment: moderate concerns about methodological limitations with moderate concerns in two studies due to the role of the researcher not being discussed and lack of sufficient detail on the recruitment process in one study and concerns in the other study being due to the observational and descriptive approach rather than gathering qualitative evidence about effectiveness and a lack of patient perspective; no or very minor concerns about coherence; moderate concerns about relevance due to the population of one study being specific to nurse care managers in the US healthcare system and the population in the other study being specific to primary care providers in the US and in Australia in the third study; no concerns about adequacy. The overall assessment of confidence was low.

Review finding 5: Weighing up the benefits and harms of discontinuation

GPs raised many complex considerations when weighing up the harms versus the benefits of deprescribing opioids, particularly when there is a lack of time and insufficient alternatives to offer. For example, people who had been on opioids for a prolonged period seemed more likely to experience withdrawal symptoms upon tapering or people with comorbidities, traumatic injuries or who have a history of abuse are more challenging to initiate deprescribing as opioids form part of their coping mechanism. For patients who are medically complicated, GPs were concerned that deprescribing may drive their patients to undesirable options to manage their pain such as alcohol or buying opioids off the street and therefore GPs said they hesitate to deprescribe with patients who are responsible and functioning well on opioids. The effect of chronic pain and opioid use on an individual's mental health was raised as vital consideration as conditions such as depression or anxiety, tend to influence a patient's level of resilience needed to deprescribe.

Explanation of quality assessment: very minor concerns about methodological limitations due to the role of the researcher not being discussed in the contributing study; no concerns about coherence; minor concerns about relevance with the findings emerging from one study limited to GPs in Australia; minor concerns about adequacy with rich information to support the theme but only emerging from one study. The overall assessment of confidence was moderate with the concerns identified being minor.

1.1.7.2 Narrative summary of review finding for benzodiazepines and Z-drugs

Review finding 1: Reassessment of treatment needs and dependence

Healthcare professionals highlighted the importance of considering a reassessment of the indication, dosage and duration of treatment. They raised that the question of dependence should always be asked in order to seek advice or refer the patient to a specialised structure.

Explanation of quality assessment: very minor concerns over methodological limitations due to the role of the researcher not being discussed; no concerns about coherence; minor concerns over relevance due to the study being limited to healthcare professionals providing care to elderly people at a psychogeriatric unit; moderate concerns over adequacy with limited information from one study supporting the theme. The overall assessment of confidence was low.

1.1.7.3 Narrative summary of review findings for Antidepressants

Review finding 1: Agreed monitoring programs

People who were taking prescribed antidepressants expressed desire for a mutually agreed monitoring program. This practice varies between health care professionals; while some agree a monitoring plan with the patient at first consultation, others did not address this, leaving patients just assuming that their treatment was being monitored. Regularity of monitoring contact also varied, with some GPs asking to see patients every 2-3 days at the start of treatment then every 2-3 weeks once there were signs of patient improvement. Other patients were given a prescription and simply asked to return in a month; in these cases, patients were left to assume that this was the time it would take for their medication to start working.

GPs also recognised the importance of co-designing a personalized plan with people who had been taking prescribed antidepressants (when it comes to discontinuation). They expressed that tapering plans need to be personalised as weaning periods are hard to establish due to variation in antidepressant type and dose; and that it was important to go as slow as needed and generally slower than withdrawal regimens suggest. Being proactive about relapse planning was considered central, talking to patients about how they will recognise if they are not doing well, possible warning signs and what they might do if they notice them such as calling on social supports, returning to the GP or re-engaging with mental health support. GPs felt inadequate discontinuation planning meant patients may mistake withdrawal for relapse, so preparing patients for the possibility that ceasing long-term use may be uncomfortable was important.

Explanation of quality assessment: minor concerns about methodological limitations with moderate concerns in one study due to lack of sufficient detail on the data collection and data analysis methods used but very minor concerns in the other contributing study due to the role of the researcher not being discussed; minor concerns about coherence with findings from one study relating to a mutually agreed plan for discontinuation while findings from the other study relating to an agreed plan for while taking the medicine; no or very minor concerns about relevance; and no concerns about adequacy with sufficient information from two studies supporting the theme. Overall assessment of confidence was moderate.

Review finding 2: Clarity around reasons for monitoring

Some people taking antidepressants could misinterpret the reasons for regular check-ups, thinking that the frequency of their appointments indicated that they were more ill than they first thought. Explanations given by health care professionals of why repeated appointments are necessary, including explaining that they wanted to see how they were coping and whether the treatment was helpful, are important to patients. Being asked to return in order to review how the treatment was progressing was often viewed by patients as positive and indicative that the health care professional was interested in their well-being. In other cases, GPs tended to assume that if things were not going well patients would report this; however,

some patients are unlikely to come back and make an appointment unless asked specifically to do so.

Explanation of quality assessment: moderate concerns about methodological limitations with moderate concerns in one study due to lack of sufficient detail on the data collection and data analysis methods used; no or very minor concerns about coherence; no or very minor concerns about relevance; and moderate concerns about adequacy due to the research finding being supported by only one study. Overall assessment of confidence was low.

Review finding 3: Encourage self-monitoring

Health care professionals sometimes told patients that they themselves were the best people to observe the effects of their antidepressant medication. Patients found it helpful when they were encouraged to monitoring themselves and keep their own progress under review. This could help build their self-esteem and made them feel that they were in control of their own recovery.

Explanation of quality assessment: moderate concerns about methodological limitations with moderate concerns in one study due to lack of sufficient detail on the data collection and data analysis methods used; no or very minor concerns about coherence; no or very minor concerns about relevance; and moderate concerns about adequacy due to the research finding being supported by only one study. Overall assessment of confidence was low.

Review finding 4: Asking specific questions

People taking antidepressants found monitoring and review appointments easier when health care professionals asked specific questions, such as whether they had lost any weight, experienced panic attacks, or had problems with early morning waking or getting off to sleep at night. These kinds of questions helped the patient to better understand their illness and monitor themselves in response to the medication they were taking.

Explanation of quality assessment: moderate concerns about methodological limitations with moderate concerns in one study due to lack of sufficient detail on the data collection and data analysis methods used; no or very minor concerns about coherence; no or very minor concerns about relevance; and moderate concerns about adequacy due to the research finding being supported by only one study. Overall assessment of confidence was low.

Review finding 5: Reviewing the functional response to treatment and benefits and risks of discontinuation

Weighing up the benefits and risks of discontinuation for each individual was considered important by GPs when assessing peoples' preparedness for discontinuation. GPs mentioned that the reversal or removal of side effects, the removal of emotional numbness, reduced medication burden, reducing polypharmacy risks and the burden of cost were all important motivators for discontinuation. However, a few GPs expressed concerns about the risk of suicide and the risk of relapse and noted risks need to be weighed up when making decisions. The length of time the patient was taking antidepressants was considered by GPs when deciding about deprescribing. Decisions around the length of treatment were based on individual patient needs such as patient age and whether it was a first episode or recurrence of depression with GPs noting they would leave elderly people on their medication and that for a recurrent depressive episode they would give a longer course of treatment. All GPs took into account patients' functional responses to treatment when deciding to discontinue antidepressant medication, whether people were functioning better within their lives and their families and their work contexts, whether they felt they had fully recovered or had been well for a significant number of months.

Explanation of quality assessment: very minor concerns about methodological limitations due to the role of the researcher not being discussed in both contributing studies; no concerns about coherence; no concerns about relevance; no concerns about adequacy with the

sufficient information from two studies supporting the theme. Overall assessment of confidence was high with methodological limitations being very minor and no further concerns to lower our confidence.

Review finding 6: Regular symptom monitoring and adherence during discontinuation

GPs emphasised discontinuation of long-term use was about: finding the appropriate strategy for each patient and was described as a journey taken together with ongoing discussions over time to review progress and better prepare patients, to optimise outcomes. Making clear to patients that they were not doing this alone was considered to be key and to require being fluid and responsive to patients and their circumstances. GPs stressed the value of frequent and regular reviews (e.g., every two weeks or even weekly) as regular reviews during discontinuation enables symptom monitoring and reinforcing the importance of adhering to lifestyle measures such as exercise, diet, sleep hygiene, social supports and possibly psychological support.

Explanation of quality assessment: very minor concerns about methodological limitations due to the role of the researcher not being discussed; no concerns about coherence; no concerns about relevance; minor concerns about adequacy with the theme supported by sufficient information but coming from one study. Overall assessment of confidence was moderate.

Review finding 7: Review of personal and social circumstances

In assessing patient readiness for discontinuation, personal and social circumstances were viewed by GPs as equally important as recovery from depression. Having a stable relationship, employment, presence of social support, low financial stress, awareness of triggers, upcoming stressful events, engagement in self-care and healthy lifestyle were repeatedly advocated as critical. A few GPs indicated that for older patients who have been on antidepressants for a long-time 'getting depressed again is usually not worth the risk'; others suggested dose reduction, rather than discontinuation, was an adequate outcome in some circumstances; particularly when a patient is reluctant to cease, is in an unsafe or unstable environment, has inadequate social support or has experienced significant trauma. Being aware of the person's current life circumstances was central in decision making, particularly regarding the timing of antidepressant discontinuation.

Explanation of quality assessment: very minor concerns about methodological limitations due to the role of the researcher not being discussed in both contributing studies but with no further limitations to lower our confidence; no concerns about coherence; no concerns about relevance; no concerns about adequacy with sufficient information from two studies to support the theme. Overall assessment of confidence was high with methodological limitations being very minor to lower our confidence.

Review finding 8: Patient preference

GPs acknowledged the 'nebulous nature of depression' and that many of the patients had complex reasons not wanting to stop; they mentioned that if someone does not want to come off their medicine, they should not be forced and that this should be revisited when they see them, as decisions to stop the medication should be in conjunction with patients and sometimes led by them. GPs emphasised the importance of respecting patients' preferences to remain on their medication and that there were circumstances where they would not attempt discontinuation even if indicated. They noted patients need to want to stop and failed previous attempts can moderate patients' future readiness, thus GPs raised a level of concern about enabling unsuccessful attempts and stopping antidepressants at the wrong time and that patient readiness was important.

Explanation of quality assessment: very minor concerns about methodological limitations due to the role of the researcher not being discussed in both contributing studies but with no further limitation to lower our confidence; no concerns about coherence; no concerns about

relevance; no concerns about adequacy with sufficient information from two studies to support the theme. Overall assessment of confidence was high with methodological limitations being very minor to lower our confidence.

1.1.8 Economic evidence

1.1.8.1 Included studies

No health economic studies were included.

1.1.8.2 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 C.3.

1.1.9 Summary of included economic evidence

None

1.1.10 Economic model

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

2 Monitoring: frequency

2.1 What is the optimal frequency of review of prescribed medicines associated with dependence or withdrawal symptoms?

2.1.1 Introduction

Clinicians have a duty to monitor all medicines they prescribe to ensure that people continue to derive benefit without developing unacceptable side effects. Monitoring medicines with a risk of dependence and withdrawal relies on subjective measures of benefit and harm, rather than objective standardised biomarkers. Monitoring may change over time, from initial prescribing and maintenance of a medication regimen, through to the monitoring that may be required during a planned reduction or stopping of medicines. Prescribers and patients may have different views about who should be involved in medicines monitoring and how often; the frequency, content and format of planned reviews; and which symptoms and perspectives to prioritise as part of monitoring. This review explores the evidence for how best to monitor prescribed medicines associated with increased risk of dependence and withdrawal.

2.1.2 Summary of the protocol

For full details see the review protocol in Appendix A section A.2.

Table 8: 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).
Intervention	Different frequencies of monitoring/review and alteration of treatment according to study.
Comparison	Different frequencies of review compared with each other.
Outcomes	<ul style="list-style-type: none">• HRQoL• Mortality• Dependence to the prescribed medicine• Withdrawal symptoms• Non-fatal overdose• Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs• Patient Satisfaction• Self-harm or harm to others• Increase in symptoms for which the medication was originally prescribed
Study design	Randomised controlled trials, comparative non-randomised or cohort studies and systematic reviews of randomised controlled trials and non-randomised studies.

2.1.3 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](#).

2.1.4 Effectiveness evidence

2.1.4.1 Included studies

No relevant studies comparing different frequencies of monitoring/review were identified.

See also the study selection flow chart in Appendix C section C.2.

2.1.4.2 Excluded studies

See the excluded studies list in Appendix F section F.2.

2.1.5 Economic evidence

2.1.5.1 Included studies

No health economic studies were included.

2.1.5.2 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 J.

2.1.6 Summary of included economic evidence

None

2.1.7 Economic model

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

2.1.8 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness. These costs do not include qualification cost.

Resource	Unit costs	Source
GP - Prescription costs per consultation	£33.10	PSSRU 2020 ³⁵
GP cost per surgery consultation (excluding direct costs)	£28	PSSRU 2020 ³⁵

2.1.9 Evidence statements

2.1.9.1 Economic

No relevant economic evaluations were identified.

2.2 The committee's discussion and interpretation of the evidence

2.2.1 The outcomes that matter most

2.2.1.1 Monitoring content

Quantitative evidence

This was a mixed methods review, with quantitative and qualitative review sections. No quantitative evidence was identified for the evidence review of monitoring content

For the quantitative review, the committee were interested in determining the content that should be included within the person's review with a health care practitioner, that would lead to better treatment outcomes. One of the key reasons for monitoring was specified as, to look out for signs of dependence. Therefore, dependence was a critical outcome. When setting the protocol, the committee acknowledged that an outcome of dependence might not be commonly reported, as it is difficult to measure dependence per se. Therefore, any definition as described in the study was accepted, which could also include measures indicating problems with dependence or addiction, such as early refill requests, shopping behaviour, or measures of medicine misuse. The other critical outcomes for this review were mortality and health related quality of life.

This evidence review could also identify studies comparing monitoring content during a person's reduction or withdrawal period, as the committee were also interested in identifying the most effective monitoring review to avoid withdrawal symptoms. Withdrawal symptoms were therefore included as an important outcome. Other important outcomes for this review were use of illicit drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose, patient satisfaction, self-harm or harm to others and symptoms for which the medication was originally prescribed.

Qualitative evidence

The qualitative review looked at perceptions and experiences of healthcare professionals of the information that they require during a review of prescribed medicines associated with dependence or withdrawal symptoms. It also looked at patients' perceptions and experiences of the information they think should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms to help prevent dependence or withdrawal symptoms occurring. Information emerging from qualitative data regarding the information required during a review of prescribed medicines associated with dependence or withdrawal symptoms by healthcare professionals and patients was summarised into different themes. Themes were derived from the evidence identified and were not pre-specified by the committee.

Qualitative evidence was identified for opioids, antidepressants and very limited qualitative evidence from one study was identified for benzodiazepines and Z-drugs. No evidence was identified for gabapentinoids.

2.2.1.2 Monitoring frequency

No quantitative evidence was identified for the evidence review of monitoring frequency. This was an interventional review looking for quantitative evidence only, comparing studies using different frequencies of review.

As with the quantitative review on monitoring content described above, one of the key reasons for monitoring was specified as to look out for signs of dependence. The most effective frequency of review should show a reduction in dependence. Therefore, the outcome of dependence was a critical outcome. Again, when setting the protocol, the committee acknowledged that an outcome of dependence might not be commonly reported, as it is difficult to measure dependence per se. Therefore, any definition as defined by the study was accepted, which could also include measures indicating problems with dependence or addiction, such as early refill requests, shopping behaviour, or measures of medicine misuse. The other critical outcomes for this review were mortality and health related quality of life.

This evidence review also included studies comparing different monitoring frequencies during a person's reduction or withdrawal period. Therefore, the committee were also interested in the most effective monitoring frequency to avoid withdrawal symptoms, and included withdrawal symptoms as an important outcome. Other important outcomes were use of illicit drugs or alcohol as a replacement to prescribed drugs, non-fatal overdose, patient satisfaction, self-harm or harm to others and symptoms for which the medication was originally prescribed.

2.2.2 The quality of the evidence

2.2.2.1 Monitoring content:

Quantitative evidence

No evidence was identified for the quantitative review.

Qualitative evidence

Evidence was identified for opioids, antidepressants, benzodiazepines and Z-drugs (the latter 2 examined in the same study). No evidence was identified for gabapentinoids.

Overall, confidence in the evidence base informing the review for content of a monitoring review ranged from high to very low, with confidence in the evidence for 3 out of 14 themes being high, confidence for a further 3 themes being moderate and confidence in 1 theme being very low. The primary reason for downgrading was the context of the evidence; in particular, most opioid-specific studies were conducted in a USA healthcare setting with one further study conducted in Australia. The committee agreed that evidence taken from USA or Australian opioid studies is less relevant to the UK and the NHS, and that caution should be taken when extrapolating from such literature. Specific examples identified by the committee of differences between these settings in the evidence base included prevalence of opiate contracts and urine testing due to national issues around opioid misuse. The confidence in the evidence was also occasionally downgraded due to concerns over adequacy when a small number of studies with limited information supported the emergent theme.

2.2.2.2 Monitoring frequency

No evidence was identified for the review of monitoring frequency.

2.2.3 Findings identified in the evidence synthesis

2.2.3.1 Monitoring content:

Quantitative evidence

No evidence was identified for the quantitative review.

Qualitative evidence

The committee agreed that the review provided limited detail on the specific content of reviews that was most effective, but that primary conclusion from the qualitative evidence was that the effectiveness of the monitoring process relies on creating a strong and ongoing relationship between patient and prescriber based on mutual trust. This was also a central theme in the committee's discussion of monitoring reviews, alongside the finding that prescribing should be considered an ongoing process and not just the initiation of medication. The committee agreed that monitoring reviews should be organised to reflect this and create an ongoing relationship between prescriber and patient. This was in line with the evidence within the information and support review of this guideline, and the committee agreed that, at all stages of prescribing and withdrawal management (including when considering prescribing), the aim should be to foster collaborative, trusting and supportive relationships with people. It was also agreed that shared decision making should be applied to all stages of prescribing and monitoring, not just at initiation of prescribing. The committee highlighted that a strategy for regular review and monitoring should be thought about before starting treatment and included within the management plan at the start of treatment, this was included within the recommendations.

The committee discussed that prescribing and monitoring may differ between the drug classes reviewed here, and in particular noted that most evidence was available for opioids and antidepressants, with very limited evidence available for benzodiazepines and Z-drugs examined by the same study. The committee agreed that this guideline should be used alongside relevant condition specific guidelines and the NICE guideline for [medicines optimisation](#) and [medicines adherence](#).

Evidence from people taking antidepressants and opioids highlighted the importance of reviewing the persons' functional response to treatment and the benefits and risks of discontinuation. The committee agreed this was very important and that prescribing decisions across drug classes should be based on the consideration of the benefits and risks of continuing or stopping the medicine for each person. Evidence from studies relevant to opioids and limited evidence from one study in people taking benzodiazepines and Z-drugs also highlighted the importance of assessing adherence and dependence/risk of misuse. It was agreed that, at each review, it is important to discuss the benefits and risks of continuing or stopping the medicine with the person. This would take into account whether any problems associated with dependency are developing. The committee highlighted that some people may be deriving benefit from the medicine and should continue taking the medicine, this should also be considered. It would also include any side effects (both patient-reported and through proactive clinical investigation). It was the committee's view that, during the treatment period, the patient should also be made aware of any new evidence arising about the medicine.

The importance of reviewing an individual's personal and social circumstances such as the availability of support when making decisions about discontinuation of antidepressants was another theme that emerged from the evidence. The committee acknowledged this was important and that individual circumstances should be taken into account when making decisions about the timing, the frequency and content of reviews as well as in decisions about discontinuation of the medicine. Evidence also highlighted the importance of

considering patient preference when making decisions about the discontinuation and the reassessment of this in subsequent appointments. The committee agreed on the importance of the persons' preference and incorporated this throughout the monitoring recommendations.

Limited evidence highlighted the importance of regular monitoring of symptoms and adherence to the medicine. The committee agreed on the importance of regular monitoring and considered this to be important during discontinuation but also during dose adjustments at any stage of treatment.

As well as monitoring during treatment, the importance of developing a personalised plan for discontinuation was identified as an important theme. This was in line with the committee's clinical experience and there was consensus on the importance of developing a mutually agreed management plan that was not of limited applicability to discontinuation but was important throughout the stages of prescribing. Based on their clinical experience, the committee agreed that after each review, the management plan should be agreed and updated, with a copy given to the person, so that all relevant parties have a record. A recommendation was made to highlight that this should be done at each review.

The committee discussed whether a face-to-face review should be offered periodically. It was agreed that current practice had shifted to an increased use of online, phone or video consultations as a result of the COVID pandemic. It was thought that this was likely to remain in place and providing the means of consultation was appropriate for the issue being considered, there was no justification for stating that a face-to-face review had to be held at any particular frequency.

2.2.3.2 Monitoring frequency

No evidence was identified for the review of monitoring frequency.

The committee agreed that although there was no evidence to inform the optimal frequency of review, their clinical experience was that people should be offered regular reviews. This is particularly important for the classes of medicines included in this guideline, in order to avoid running into problems with dependency. They noted this was supported by some themes that emerged from the qualitative review of the content of the monitoring review (discussed above). It was noted that many of the medicines included in this guideline treat the symptoms and not the underlying pathology of a condition, and their effectiveness in the long-term is debated. Therefore, regular reviews are necessary in order to avoid people getting stuck on a medicine for which they are no longer deriving benefit. The committee decided that they could not recommend a specific monitoring frequency, as each individual's circumstances will differ and required frequency will also be dependent on the type of medicine they are taking. It was agreed that the frequency of review should be tailored to the person's preferences and circumstances, the type of medicine being prescribed and the dosage, and any risk factors that might indicate a need for frequent reviews. Risk factors may include the potential for misuse of the medicine, the potential for adverse effects and problems associated with dependence, whether it is the first use of the medicine by the person or use of a medicine outside its licenced indication. Due to the need for an individualised approach, the committee also agreed that future research comparing different monitoring frequencies would not be useful. The committee also highlighted that if the person is taking an antidepressant, there is guidance on frequency of reviews within the NICE guidelines on [depression in adults](#) and [depression in adults with a chronic physical health problem](#).

The committee highlighted that this evidence review wasn't just aimed at finding the most effective monitoring frequency for ongoing treatment, but also for how frequently a person should be monitored during a reduction or withdrawal in their medicines. As no evidence was identified, the committee made recommendations based on consensus. It was highlighted that people can often quickly or unexpectedly run into problems during dose reductions, and

that additional monitoring was essential. The committee agreed that this was equally important when starting a medicine when doses may be, being increased. A consensus recommendation was made to consider increasing the frequency of reviews during dose adjustments. This was also supported by some qualitative evidence arising from the review of monitoring content. The committee agreed that increasing the frequency of reviews would allow for early identification of any problems with withdrawal symptoms or re-emergence of symptoms. The committee discussed that everyone would have a different experience, and that the person's clinical and support needs should be taken into account. The committee agreed from their experience, that there were other factors that were equally important to consider as a need for more frequent reviews, including the potential for the adverse effects to lead to problems associated with dependence, if someone is starting a new medicine for the first time or if the person has additional care needs, such as someone with a learning disability or dementia. They agreed to include these as factors that should be considered to indicate a need for increasing frequency of reviews.

The committee agreed that there are certain scenarios when extra, unscheduled reviews would be necessary. These may include if a person reports adverse effects from a medicine, becomes pregnant or is planning pregnancy, has a change in their condition or psychosocial circumstances (for example, a person may lose their job or suffer a bereavement), starts taking additional medicines, or requests a change in dosage.

In order to ensure continuity of care and to stop situations where people's prescription is not reviewed for a long period of time, it was discussed whether there should be a backstop of a maximum acceptable period between reviews. However, the committee agreed that each individual's circumstances differ, and it is also dependent on the type of medicine they are taking, therefore recommending a universal backstop would be inappropriate.

2.2.4 Cost effectiveness and resource use

No economic evidence was found for the frequency or content of monitoring review. The committee was presented with the unit cost of a GP consultation.

Due to the absence of clinical evidence, the committee did not make a specific recommendation on the optimal frequency of review and instead listed a range of characteristics that should be taken into consideration when setting the frequency of review. This is in line with current practice, as monitoring is already based on patients' needs. The committee agreed that current practice had shifted to increased use of online, phone or video consultations which were explicitly mentioned as potential tools in the recommendations. It is likely, therefore, that more reviews will be conducted in this form, leading to savings for the NHS and potentially reducing the cost of any increase in the frequency of reviews resulting from the recommendations.

Overall, the recommendations should improve the relationship between patients and physicians and ensure tailored care, thus enhancing the effectiveness of monitoring and leading to a reduction of the frequency of reviews on people who do not need to be monitored while increasing the frequency for those in need of regular monitoring. This should ultimately improve the efficiency of the NHS.

2.2.5 Other factors the committee took into account

The committee emphasised that monitoring is not only concerned with adherence to a prescription, which is often what the qualitative studies included in this evidence review focussed on and is of relevance to all medicines, not just those associated with dependence or withdrawal symptoms, but that problems around safe prescribing are also to do with how drugs are being prescribed, including prescriptions beyond medical guidance. Monitoring in this case should help prevent cases in which people are being left on inappropriate prescriptions without proper reviews and without the monitoring that would allow prescriber

and patient to question whether the drug is still effective and worthwhile. The committee commented that monitoring should be proactive, not only reacting to patients reporting side effects but also the silent side effects that may be associated with prescribed medications.

It was noted that this review and this guideline do not cover how medicines should be prescribed for different conditions. Existing NICE guidance should be followed where available.

2.2.6 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.4., 1.4.1, 1.4.2, 1.4.3, 1.4.4, 1.4.5., 1.4.6. No research recommendations were made from this evidence review. Other evidence supporting these recommendations can be found in the evidence review B on Prescribing Strategies.

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Appendices – Monitoring

Appendix A Review protocols

A.1 Review protocol for monitoring content

Field	Content
PROSPERO registration number	CRD42020187763
Review title	What should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms?
Review question	What should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms?
Objective	To identify what should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms? Intervention: To identify any comparative evidence of different monitoring review strategies (i.e., the items assessed during review of prescribed medicines associated with dependence or withdrawal symptoms). Qualitative: To identify information deemed to be important (either by the patient or the healthcare professional) to include in a review of prescribed medicines associated with dependence or withdrawal symptoms.
Searches	The following databases (from inception) will be searched: <ul style="list-style-type: none">• Cochrane Central Register of Controlled Trials (CENTRAL)• Cochrane Database of Systematic Reviews (CDSR)• Embase• MEDLINE• Epistemonikos

	<ul style="list-style-type: none">• Health and Evidence• HTA• CINAHL, Cumulative Index to Nursing and Allied Health Literature• PsycINFO• ASSIA <p>Searches will be restricted by:</p> <ul style="list-style-type: none">• English language studies• Human studies• Letters and comments are excluded <p>Other searches:</p> <p>Inclusion lists of relevant systematic reviews will be checked by the reviewer.</p> <p>The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant.</p> <p>For full search strategies see Appendix B</p>
Condition or domain being studied	Dependence and/or withdrawal symptoms associated with prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants.
Population	<p>Inclusion: adults (≥ 18 years) taking prescribed medicines that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants)</p> <p>Prescribers of the above (for the qualitative review)</p> <p>Stratification</p> <p>Drug class</p> <ul style="list-style-type: none">• Opioids• Benzodiazepines,• Z-drugs• Gabapentinoids• Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others).

	<p>No other population strata</p> <p>Exclusions:</p> <p>Children and young people (<18 years)</p> <p>People taking opioids prescribed for end-of-life care, acute pain, cancer pain</p> <p>Use of gabapentinoids when prescribed for epilepsy</p> <p>People taking the above drugs that have not been prescribed for their own use</p> <p>Decision rules for inclusion of primary studies</p> <p>If study includes prescribed medicines and non-prescribed/OTC medicines, the study will only be included if at least 80% were prescribed.</p> <p>If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old.</p>
Intervention/Exposure/Test/ Phenomena of interest	<p>Intervention data:</p> <p>Different elements included in a monitoring review (i.e., inclusion of different items assessed during review of prescribed medicines associated with dependence or withdrawal symptoms) and alteration of treatment according to study.</p> <p>Qualitative data</p> <p>Perceptions and experiences of healthcare professionals of the information that they require during a review of prescribed medicines associated with dependence or withdrawal symptoms AND perceptions and experiences of patients of the information they think should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms to help prevent dependence or withdrawal symptoms occurring.</p>
Comparator/Reference standard/Confounding factors	<p>Intervention data:</p> <p>Different content within a monitoring review compared with each other or with usual care (as defined by the study) and alteration of treatment according to study.</p> <p>Qualitative data:</p> <p>Not applicable.</p>
Types of study to be included	<p><u>Intervention studies:</u></p>

	<p>Randomised controlled trials</p> <p>Comparative non-randomised or cohort studies</p> <p>Systematic review of randomised controlled trials and non-randomised comparative studies. 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.</p> <p>Exclusions:</p> <p>Before and after studies</p> <p>Non-comparative cohort studies</p> <p>Other non-comparative evidence</p> <p><u>Qualitative studies:</u></p> <p>Qualitative studies (e.g., transcript data collected from focus groups/semi structured interviews)</p> <p>Exclusions:</p> <p>Quantitative studies (i.e., closed questionnaire surveys; surveys will only be included if they contain open ended free text answers)</p>
Other exclusion criteria	<p>Non-NHS prescribed medicines (for the full list of medicines to be included in the guideline see Appendix K)</p> <p>Medicines prescribed for end-of-life care, cancer pain or acute pain</p> <p>Over-the-counter medicines</p> <p>Antipsychotic and stimulant medicines.</p> <p>Use of gabapentinoids when prescribed for epilepsy.</p> <p>Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs).</p> <p>Non-English language studies.</p> <p>Conference abstracts will be excluded as they will not provide enough information to inform analysis.</p>

Context	This will cover any setting in which one of the above-mentioned medicines are being prescribed. As this is an overarching guideline covering many different conditions, it needs to cover all settings.
Primary outcomes (critical outcomes)	<p><u>Intervention data:</u></p> <p>Validated HRQOL (continuous outcome), including:</p> <ul style="list-style-type: none">• Physical health• Psychological health• Social functioning <p>Mortality (dichotomous or time-to-event outcome, all-cause mortality and breakdown of overdose or suicide related mortality)</p> <p>Dependence to the prescribed medicine (dichotomous outcome, accept any definition as defined by the study (may also include measures suggesting dependence or addiction, examples to include early refill requests, loss of prescriptions, drug shopping behaviour, prescription misuse))</p> <p><u>Qualitative data:</u></p> <p>Themes emerging from qualitative data (themes will be derived from the evidence identified for this review and not pre-specified)</p>
Secondary outcomes (important outcomes)	<p><u>Intervention data:</u></p> <p>Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome (dichotomous or continuous outcome, as defined by the study)</p> <p>Non-fatal overdose (dichotomous outcome)</p> <p>Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs (dichotomous outcome)</p> <p>Patient Satisfaction (dichotomous or continuous outcome)</p> <p>Self-harm or harm to others (dichotomous outcome)</p> <p>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)</p> <p><u>Qualitative data:</u></p> <p>n/a</p>

Data extraction (selection and coding)	<p>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.</p> <p><u>Intervention review:</u></p> <p>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.</p> <p><u>Qualitative review:</u></p> <p>Once saturation is considered to have been reached (all the themes are already covered in the data extraction) data from other included papers will not be extracted or critically appraised, but the paper will still be read to check for any additional themes and will be noted in the included studies. The point at which data extraction is reached will be noted within the review.</p> <p>A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality.</p>
Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <p><u>Intervention:</u></p> <p>For Intervention reviews the following checklist will be used according to study design being assessed:</p> <ul style="list-style-type: none">• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)• Randomised Controlled Trial: Cochrane RoB (2.0) <p>Nonrandomised study, including cohort studies: Cochrane ROBINS-I</p> <p><u>Qualitative:</u></p> <p>For this review the Critical Appraisal Skills Programme (CASP) qualitative checklist will be used to assess risk of bias of individual studies.</p> <p><u>Intervention and qualitative review:</u></p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p>

	<ul style="list-style-type: none">• 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 <p>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.</p>
Strategy for data synthesis	<p>Drugs will be pooled within classes stated in the population and antidepressants pooled by sub-class of type of antidepressant.</p> <p><u>Intervention:</u></p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Publication bias is tested for when there are more than 5 studies for an outcome.</p> <p>Other bias will only be taken into consideration in the quality assessment if it is apparent.</p> <p>Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.</p> <p>If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis. However, we don't expect an NMA to be feasible for this question as we expect there to be limited quantitative data available, and instead have planned to do a mixed methods review.</p> <p><u>Qualitative:</u></p>

	<p>The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings.</p> <p>GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.</p> <p><u>Mixed methods synthesis</u></p> <p>A segregated approach will be used for the review. The committee will synthesise the findings of the two through their discussions of the evidence and interpret the relationship between the qualitative and quantitative evidence.</p>
Analysis of sub-groups	None
Type and method of review	<input type="checkbox"/> Intervention <input type="checkbox"/> Diagnostic <input type="checkbox"/> Prognostic <input type="checkbox"/> Qualitative <input type="checkbox"/> Epidemiologic <input type="checkbox"/> Service Delivery <input checked="" type="checkbox"/> Mixed Methods
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

	<p>Alfredo Mariani, Health economist Elizabeth Pearton, Information specialist Tamara Diaz, Project Manager</p>
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=CRD42020187763
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: <ul style="list-style-type: none">• 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
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A.2 Review protocol for monitoring frequency

Field	Content
PROSPERO registration number	CRD42020187757
Review title	Optimal frequency of review of prescribed medicines associated with dependence or withdrawal symptoms
Review question	What is the optimal frequency of review of prescribed medicines associated with dependence or withdrawal symptoms?
Objective	To identify the optimal frequency of review of prescribed medicines associated with dependence or withdrawal symptoms, in order to identify and minimise the risk of dependence and symptoms of withdrawal.
Searches	<p>The following databases (from inception) will be searched:</p> <ul style="list-style-type: none">• Cochrane Central Register of Controlled Trials (CENTRAL)• Cochrane Database of Systematic Reviews (CDSR)• Embase• MEDLINE• Epistemonikos• Health and Evidence• HTA <p>Searches will be restricted by:</p> <ul style="list-style-type: none">• English language studies• Human studies• Letters and comments are excluded <p>Other searches:</p> <p>Inclusion lists of relevant systematic reviews will be checked by the reviewer.</p>

	<p>The searches may be re-run 6 weeks before the final committee meeting, and further studies retrieved for inclusion if relevant.</p> <p>For full search strategies see Appendix B</p>
Condition or domain being studied	Dependence to and/or withdrawal symptoms associated with prescribed opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants
Population	<p>Inclusion: adults (≥ 18 years) taking prescribed medicines that are associated with dependence or withdrawal symptoms (opioids, benzodiazepines, Z-drugs, gabapentinoids, or antidepressants)</p> <p>Stratification</p> <p>Drug class</p> <ul style="list-style-type: none">• Opioids• Benzodiazepines,• Z-drugs• Gabapentinoids• Antidepressants (further stratified by SSRIs, MAOIs, tricyclics, others). <p>Other</p> <ul style="list-style-type: none">• Opioids: immediate release, slow release (including slow-release routes such as transdermal patches)• Benzodiazepines: short half-life, long half-life <p>Exclusions:</p> <p>Children and young people (< 18 years)</p> <p>People taking opioids prescribed for end-of-life care, acute pain, cancer pain</p> <p>Use of gabapentinoids when prescribed for epilepsy</p> <p>People taking the above drugs that have not been prescribed for their own use</p> <p>Decision rules for inclusion of primary studies</p>

	<p>If study includes prescribed medicines and non-prescribed/OTC medicines, the study will only be included if at least 80% were prescribed.</p> <p>If the study includes people <18 years old, the study will only be included if at least 80% of people were ≥18 years old.</p>
Intervention	Different frequencies of monitoring/review and alteration of treatment according to study
Comparator	Different frequencies of review compared with each other
Types of study to be included	<p>Randomised controlled trials</p> <p>Comparative non-randomised or cohort studies</p> <p>Systematic review of randomised controlled trials and non-randomised comparative studies. 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.</p> <p>Exclusions:</p> <p>Before and after studies</p> <p>Non-comparative cohort studies</p> <p>Other non-comparative evidence</p>
Other exclusion criteria	<p>Non-NHS prescribed medicines (for the full list of medicines to be included in the guideline see Appendix K)</p> <p>Medicines prescribed for end-of-life care, cancer pain or acute pain</p> <p>Over-the-counter medicines</p> <p>Use of gabapentinoids when prescribed for epilepsy</p> <p>Antipsychotic and stimulant medicines.</p> <p>Medicines to treat drug misuse disorders (e.g., methadone and buprenorphine when prescribed for withdrawal from illicit drugs).</p> <p>Non-English language studies.</p>

	Conference abstracts will be excluded.
Context	This will cover any setting in which one of the above-mentioned medicines are being prescribed. As this is an overarching guideline covering many different conditions, it needs to cover all settings.
Primary outcomes (critical outcomes)	<p>Validated HRQOL (continuous outcome), including:</p> <ul style="list-style-type: none">• Physical health• Psychological health• Social functioning <p>Mortality (dichotomous or time-to-event outcome, all-cause mortality and breakdown of overdose or suicide related mortality)</p> <p>Dependence to the prescribed medicine (dichotomous outcome, accept any definition as defined by the study (may also include measures suggesting dependence or addiction, examples to include early refill requests, loss of prescriptions, drug shopping behaviour, prescription misuse))</p>
Secondary outcomes (important outcomes)	<p>Withdrawal symptoms including rebound symptoms/intensity or duration of withdrawal syndrome (dichotomous or continuous outcome, as defined by the study)</p> <p>Non-fatal overdose (dichotomous outcome)</p> <p>Use of illicit or over the counter drugs or alcohol as a replacement to prescribed drugs (dichotomous outcome)</p> <p>Patient Satisfaction (dichotomous or continuous outcome)</p> <p>Self-harm or harm to others (dichotomous outcome)</p> <p>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)</p>
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.

	<p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.</p> <p>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.</p>
Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <p>For Intervention reviews the following checklist will be used according to study design being assessed:</p> <ul style="list-style-type: none">• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)• Randomised Controlled Trial: Cochrane RoB (2.0)• Non-randomised study, including cohort studies: Cochrane ROBINS-I <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none">• 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 <p>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.</p>
Strategy for data synthesis	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.

	<p>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.</p> <p>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.</p> <p>Publication bias is tested for when there are more than 5 studies for an outcome.</p> <p>Other bias will only be taken into consideration in the quality assessment if it is apparent.</p> <p>Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.</p> <p>If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.</p>												
Analysis of sub-groups	<p>Subgroups that will be investigated if heterogeneity is present:</p> <p>Settings: prisons and secure environments, care homes</p> <p>People with a history of substance misuse</p> <p>Inpatient/outpatient</p>												
Type and method of review	<table border="1"><tr><td><input checked="" type="checkbox"/></td><td>Intervention</td></tr><tr><td><input type="checkbox"/></td><td>Diagnostic</td></tr><tr><td><input type="checkbox"/></td><td>Prognostic</td></tr><tr><td><input type="checkbox"/></td><td>Qualitative</td></tr><tr><td><input type="checkbox"/></td><td>Epidemiologic</td></tr><tr><td><input type="checkbox"/></td><td>Service Delivery</td></tr></table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic	<input type="checkbox"/>	Service Delivery
<input checked="" type="checkbox"/>	Intervention												
<input type="checkbox"/>	Diagnostic												
<input type="checkbox"/>	Prognostic												
<input type="checkbox"/>	Qualitative												
<input type="checkbox"/>	Epidemiologic												
<input type="checkbox"/>	Service Delivery												

	<input type="checkbox"/>	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/proposed/gid-qs10106

Other registration details	n/a
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020187757
Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none">• 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

A.3 Review protocol for health economics

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • 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 B below.
Review strategy	<p>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.</p> <p>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).⁷⁵</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • 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. <p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <ul style="list-style-type: none"> • 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 reviews:

- What should be included in a review of prescribed medicines associated with dependence or withdrawal symptoms?
- What is the optimal frequency of review 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.⁷⁵

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

B.1 Monitoring 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.

The below searches cover 2 questions. It should be noted that qualitative studies were only used for reviewing the monitoring content question, as outlined in the protocols (please see appendix A). All other study design search filters listed in Table 23 were used for both questions.

Table 9: 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 Qualitative studies Exclusions (animal studies, letters, comments)
Embase (OVID)	1974 - 15 June 2021	Randomised controlled trials Systematic review studies Observational studies Qualitative 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 - 15 June 2021	None

Database	Dates searched	Search filter used
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception - 15 June 2021	Qualitative studies
PsycINFO (ProQuest)	Inception - 15 June 2021	Qualitative studies
ASSIA, Applied Social Sciences Index and Abstracts (ProQuest)	Inception - 15 June 2021	Qualitative studies

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 depresrib* or de-presrib*).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 presrib*) 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.	Qualitative research/ or Narration/ or exp Interviews as Topic/ or exp Questionnaires/ or Health care surveys/
96.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
97.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or

	grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaietti* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
98.	or/95-97
99.	60 and (68 or 79 or 94 or 98)

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.

Medicines associated with dependence or withdrawal symptoms: Final Monitoring: frequency

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 *dihydromorphone/ 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 cocodamol* or dextromoramide* or dextropropoxyphene* or diamorphine* or dihydrocodeine* or dihydromorphone* 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 SNRI* 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/61-69
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/71-80
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.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
102.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
103.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
104.	or/101-103
105.	60 and (70 or 81 or 100 or 104)

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 SNRI* 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

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*
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	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*)))))
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Health and evidence

1.	I(("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
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	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*))]
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CINAHL (EBSCO) search terms

S1.	(MH "Substance Use Disorders") OR (MH "Substance Withdrawal Syndrome") OR (MH "Inappropriate Prescribing") OR (MH "Drugs, Prescription")
S2.	TI ((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*) n2 (drug* or medicine* or medicat* or medical* or pharm*))
S3.	AB ((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*) n2 (drug* or medicine* or medicat* or medical* or pharm*))
S4.	TI ((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 innappropriate) n3 (prescription* or prescrib*))
S5.	AB ((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 innappropriate) n3 (prescription* or prescrib*))
S6.	TI (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*))
S7.	AB (addict* n3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*))
S8.	TI (deprescription* or de-prescription* or depresrib* or de-presrib*)
S9.	AB (deprescription* or de-prescription* or depresrib* or de-presrib*)
S10.	TI ((therap* or treat*) n2 (manag* or substit*))

S11.	AB ((therap* or treat*) n2 (manag* or substit*))
S12.	TI ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*)
S13.	AB ((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) n2 symptom*)
S14.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S16.	S14 NOT S15
S17.	(MH "Narcotics+") OR (MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Antidepressive Agents+") OR (MH "Antidepressive Agents, Second Generation+") OR (MH "Antidepressive Agents, Tricyclic+") OR (MH "Zolpidem") OR (MH "Eszopiclone") OR (MH "Analgesics, Opioid+")
S18.	TI ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*))
S19.	AB ((analgesic* n3 narcotic n3 agent*) or (opioid* or opiate*))
S20.	TI (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*)
S21.	AB (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*)
S22.	TI (Z-drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon)
S23.	AB (Z-drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines or cyclopyrrolones or pyrazolopyrimidines or zolpidem or zopiclone or eszopiclone or zaleplon)
S24.	TI (generation n3 hypnotic*)
S25.	AB (generation n3 hypnotic*)
S26.	TI (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)
S27.	AB (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)
S28.	TI (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*)

S29.	AB (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*)
S30.	TI (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)
S31.	AB (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)
S32.	TI (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)
S33.	AB (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)
S34.	TI (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)
S35.	AB (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)
S36.	(MH "Gabapentin") OR (MH "Pregabalin")
S37.	TI (gabapentin* or pregabalin*)
S38.	AB (gabapentin* or pregabalin*)
S39.	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S40.	S16 AND S39
S41.	TI ((withdraw* or prescription* or prescrib*) n2 opi*) OR AB ((withdraw* or prescription* or prescrib*) n2 opi*)
S42.	S40 OR S41
S43.	(MH "Qualitative Studies+")
S44.	(MH "Qualitative Validity+")
S45.	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S46.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S47.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S48.	S42 OR S43 OR S44 OR S45 OR S46
S49.	S42 and S48

PsycINFO (ProQuest) search terms

1.	"Substance Use Disorder"/ or "Substance Related and Addictive Disorders"/ or Prescription Drug Misuse/ or Drug Withdrawal/
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Medicines associated with dependence or withdrawal symptoms: Final Monitoring: frequency

2.	((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.
3.	((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 innappropriate) adj3 (prescription* or prescrib*)).ti,ab.
4.	(addict* adj3 (prescription* or prescrib* or medicat* or medicine* or medical* or pharm*)).ti,ab.
5.	(deprescription* or de-prescription* or depresrib* or de-presrib*).ti,ab.
6.	((therap* or treat*) adj2 (manag* or substit*)).ti,ab.
7.	((drug* or medic*) adj2 (prescription* or presrib*)).ti,ab.
8.	((withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu*) adj2 symptom*).ti,ab.
9.	or/1-8
10.	((withdraw* or prescription* or presrib*) adj2 opi*).ti,ab.
11.	"opioid use disorder"/
12.	10 or 11
13.	exp narcotic drugs/
14.	((analgesic* adj3 narcotic) or (opioid* or opiate*)).ti,ab.
15.	(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.
16.	(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.
17.	(generation adj3 hypnotic*).ti,ab.
18.	exp Benzodiazepines/
19.	(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.
20.	exp antidepressant drugs/
21.	(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 SNRI* 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.
22.	(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.
23.	(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.

24.	(Amitriptyline or Amoxapine or Clomipramine or Desipramine or Dothiepin or Dosulepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nefazodone or Nortriptyline or Opiplamol or Protriptyline or Trimipramine).ti,ab.
25.	Gabapentin/ or pregabalin/
26.	(gabapentin* or pregabalin*).ti,ab.
27.	or/13-26
28.	9 and 27
29.	12 or 28
30.	exp Qualitative Methods/ or Narratives/ or exp Questionnaires/ or exp Interviews/ or exp Health Care Services/
31.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
32.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
33.	or/30-32
34.	29 and 33
35.	limit 34 to English language

ASSIA (ProQuest) search terms

1.	((TI,AB:withdraw* or abstinen* or abstain* or stop* or cessat* or reduc* or taper* or discontinu* N/2 symptom*) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(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 ti,ab(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 ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(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)) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) NOT (((MAINSUBJECT.EXACT("Substance dependency") OR MAINSUBJECT.EXACT("Substance abuse disorders") OR MAINSUBJECT.EXACT("Overprescribing") OR MAINSUBJECT.EXACT("Withdrawal symptoms") OR MAINSUBJECT.EXACT("Withdrawal")) OR ti,ab(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 addict* or depend*)) OR ti,ab(prescription* OR prescrib*) OR
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	ti,ab(deprescription* OR de-prescription* OR depresrib* OR de-presrib*)) AND (MAINSUBJECT.EXACT("Gabapentin") OR MAINSUBJECT.EXACT.EXPLODE("Narcotics") OR MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR MAINSUBJECT.EXACT.EXPLODE("Antidepressant drugs") OR MAINSUBJECT.EXACT("Zolpidem") OR ti,ab(opioid* OR opiate*) OR ti,ab(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 ti,ab(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 ti,ab(generation NEAR/3 hypnotic*) OR ti,ab(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))) AND (MAINSUBJECT.EXACT.EXPLODE("Interviews") OR MAINSUBJECT.EXACT.EXPLODE("Qualitative research") OR MAINSUBJECT.EXACT.EXPLODE("Questionnaires") OR MAINSUBJECT.EXACT.EXPLODE("Narratives") OR ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaiuzzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)))
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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 10: 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
	Quality of Life 1946 – 17 June 2021	Exclusions (animal studies, letters, comments)
	Modelling 1946 – 17 June 2021	
Embase	Health Economics 1 January 2014 – 17 June 2021	Health economics studies Quality of life studies Modelling studies

Database	Dates searched	Search filter used
	Quality of Life 1974 – 17 June 2021	Exclusions (animal studies, letters, comments)
	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 Opiplamol 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 hq1* 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)

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 depresrib* or de-presrib*).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 presrib*) 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/

Medicines associated with dependence or withdrawal symptoms: Final Monitoring: frequency

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 cocodamol* 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)

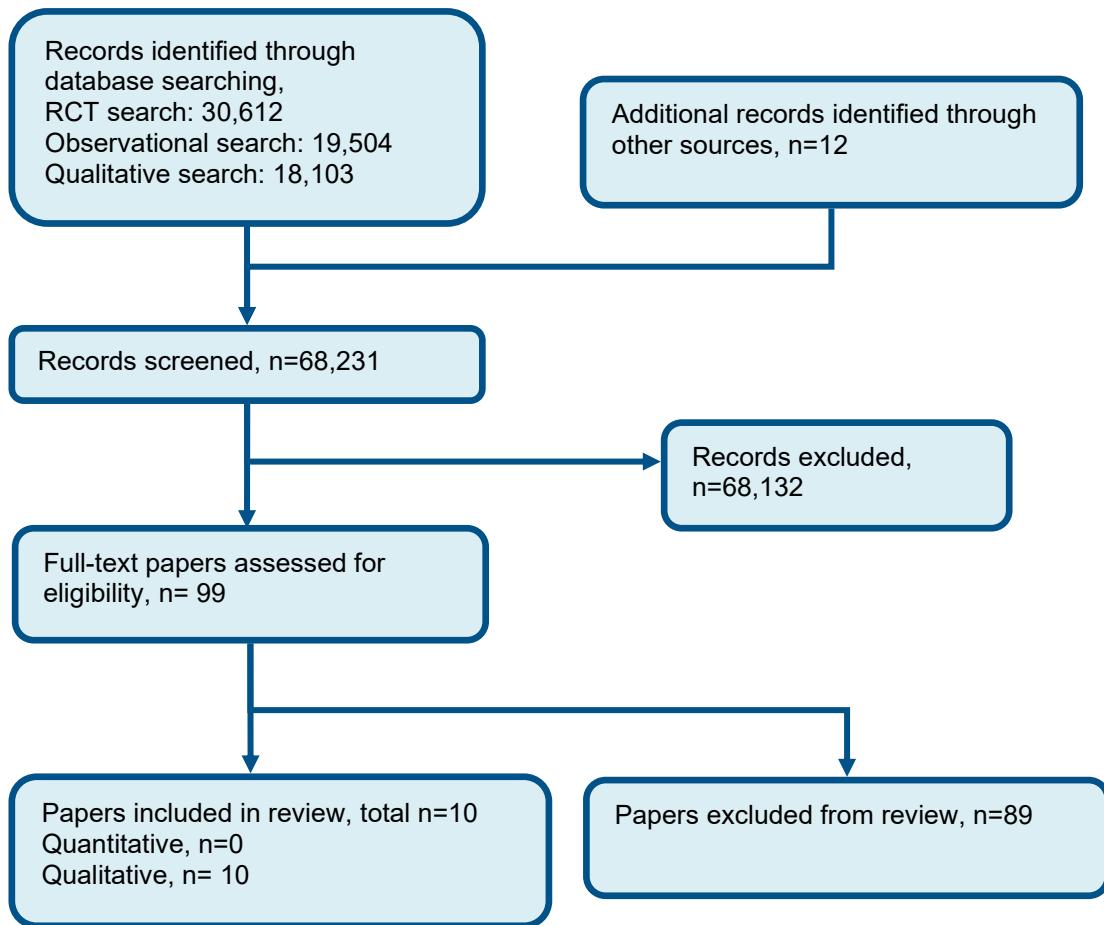
NHS EED and HTA (CRD) search terms

#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 depresrib* 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

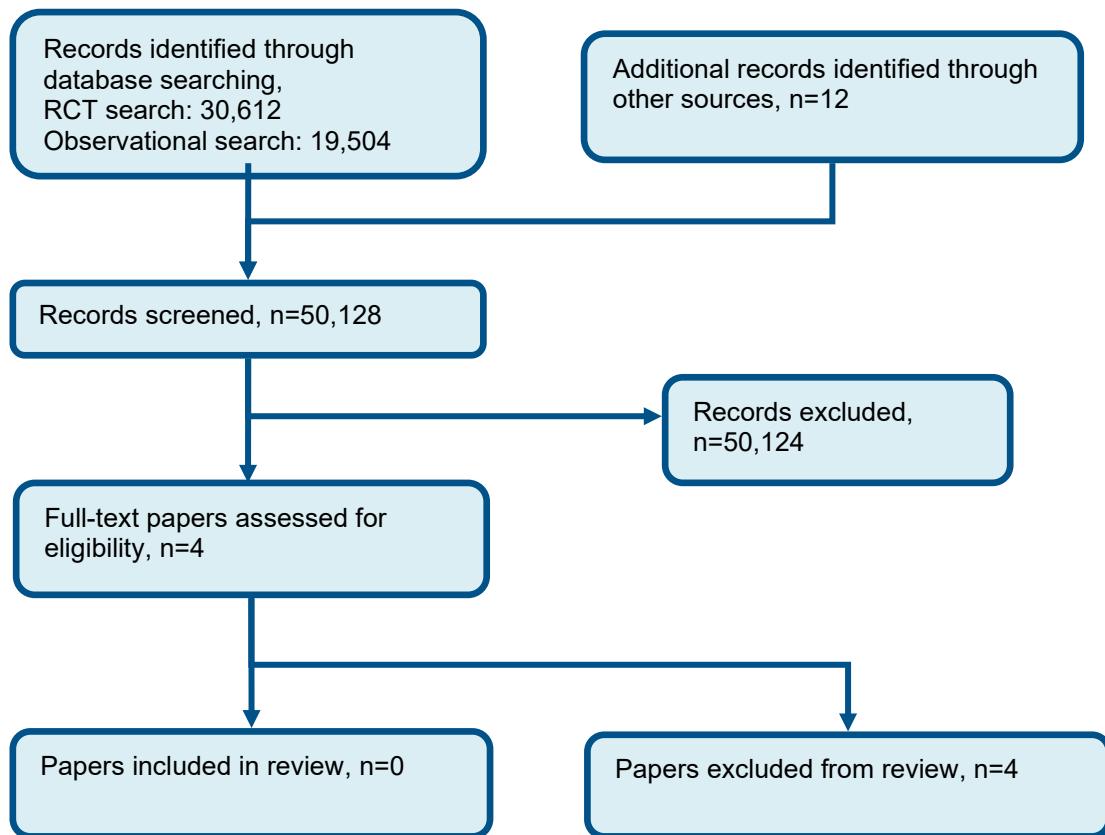
	meptazinol* or methadone* or morphine* or oxycodone* or oxymorphone* or papaveretum* or pentazocine* or pethidine* or phenazocine* or promedol* or remifentanil* or sufentanil* or tapentadol* or tilidine* or tramadol*))
#20.	((Z-drug* or z hypnotic* or non-benzodiazepin* or nonbenzodiazepin* or imidazopyridines 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 SNRI* 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

Appendix C Evidence study selection

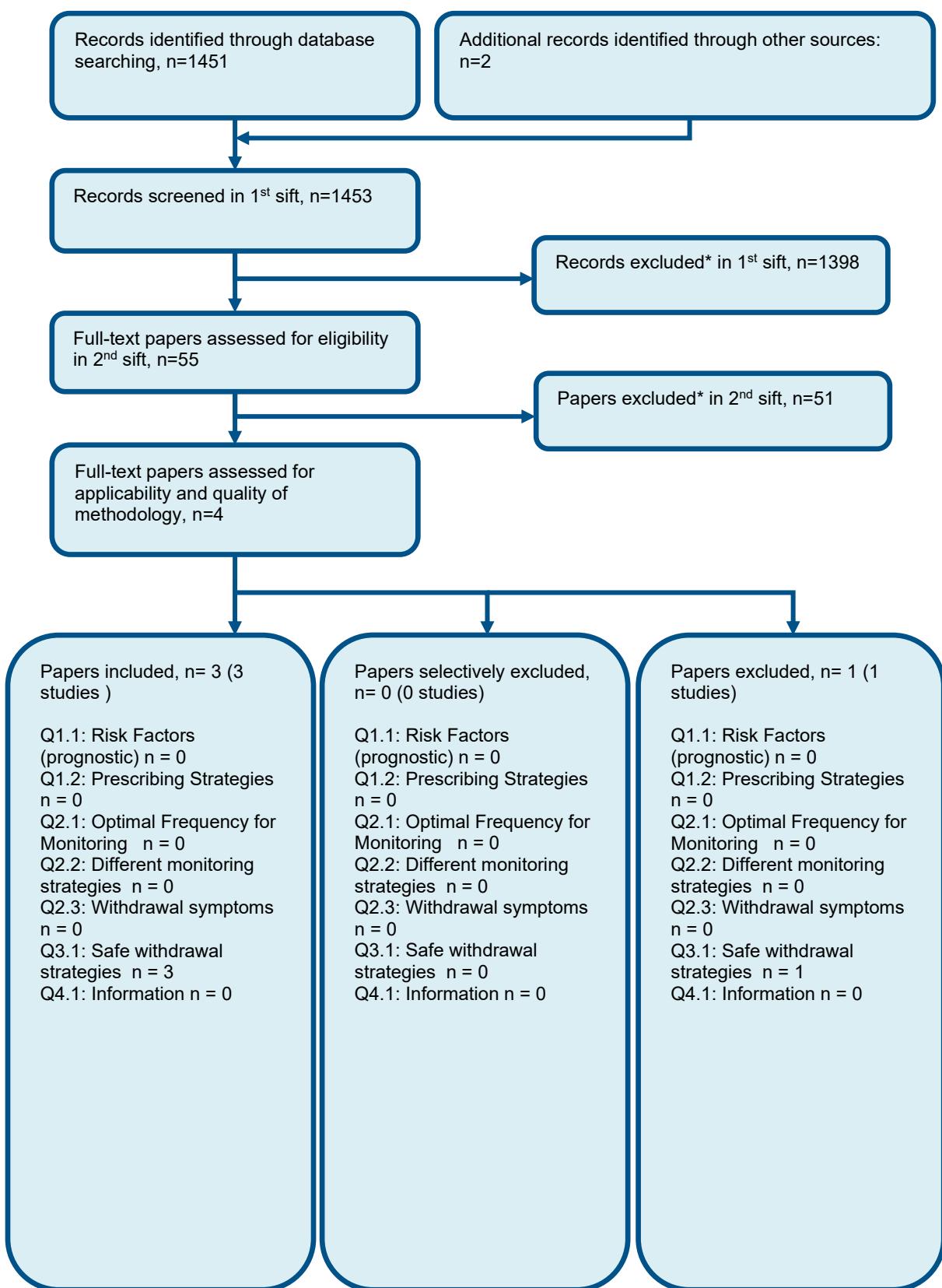
C.1 Flow chart of clinical study selection for the review of monitoring content (quantitative and qualitative)



C.2 Flow chart of clinical study selection for the review of monitoring frequency



C.3 Flow chart of economic study selection for the review



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

Appendix D Evidence

D.1 Monitoring content: quantitative evidence

No evidence identified.

D.2 Monitoring content: qualitative evidence

Study	Chang 2017 ²⁴
Aim	To report primary care provider experiences in the safety net interpreting and implementing guideline recommendations for patients with chronic non-cancer pain (CNCP) and substance use. Safety net settings are defined as healthcare settings that care for a substantial share of patients who are uninsured, use Medicaid, or are otherwise vulnerable. The recommendations being implemented are from the American Pain Society and American Academy of Pain Medicine (APS/AAPM). Substance abuse is defined as any reported personal or family history of alcohol or drug abuse (APS/AAPM guidelines).
Population	Health care providers from six safety net primary health care settings. All were primary care providers (physician, nurse practitioner, or physician assistant) who provided longitudinal primary care to a panel of patients. Note: patients cared for by this population and discussed in this study had a history of substance abuse. n=23; most of the providers were physicians (78%), four were nurse practitioners, and one was a physician assistant; 65% of the providers were women.
Setting	Primary health care settings in the USA.
Study design	Semi-structured interviews and thematic analysis.
Methods and analysis	Providers were interviewed using a semi-structured interview guide that focused on their experiences with the management of co-occurring CNCP and SU history. Interviews were 1-2 hours in duration and audio recorded. Participants received a \$50 gift card. All audio-recorded material was transcribed verbatim. The coding scheme was developed through an iterative process, with coders working independently before cross-checking and developing a final code list. This was followed by content analysis.
Findings	Methods of identifying opioid misuse/illicit substance use:

Study	Chang 2017²⁴
	Health care providers identified opioid misuse and illicit substance use through 1) the use of a substance use or opioid risk screening tool, 2) use of urine toxicity screening, and/or 3) patient disclosure.
	Use of management plans.
	Management plans – referred to by the providers as “pain agreements”, “pain contracts”, or “informed consent” – were used to give patients with CNCP an overview of the risks and expectations of opioid therapy. These management plans routinely included the following conditions: 1) patients would not use illicit drugs or alcohol while on opioids; 2) patients would only receive opioids from a single provider and single pharmacy; and 3) patients would take opioids as prescribed. Typically, patients were asked to sign the management plan as a condition of initiating or continuing opioid therapy.
	Improved communication (management plans).
	Providers described management plans and urine toxicity screening as useful tools for working with CNCP patients because they aided communication about the expectations of opioid therapy. They helped providers systematically inform CNCP patients about the risks of opioid use, as well as the requirement to abstain from illicit substances.
	Negative aspects (management plans).
	However, management plans also created tension in the clinical interaction. Several providers expressed concern that these tools might hinder conversations with patients about substance use and treatment. Management plans often prohibited drug and alcohol use while on opioid therapy, and as such providers worried this prohibition could impede an honest dialogue about a patient’s drug or alcohol use.
Limitations and applicability of evidence	Overall CASP rating: No concerns. Serious concerns about relevance due to the study being specific to the implementation of new USA guidelines (American Pain Society and Academy of Pain Medicine (APS/AAPM) for patients with chronic non-cancer pain), and the fact that the setting is specifically a safety net setting which mostly cares for patients who are uninsured, use Medicaid or are otherwise vulnerable.

Study	Donald 2020³⁷
Aim	To explore GPs’ insights about long-term antidepressant prescribing and discontinuation.
Population	A convenience sample of GPs was recruited through advertising in two Australian Primary Health Networks’ newsletters, emails to professional networks and flyers distributed through university teaching networks. Characteristics: n=22; male/female: 13/9; mean age (range): 47 (33 to 73) years; number of years since graduation ranged from 5 to 34 years; n=11 worked in urban settings and n=11 in inner-regional settings.
Setting	Primary care
Study design	Semi-structured interviews and thematic analysis.

Study	Donald 2020³⁷
Methods and analysis	<p>Semi-structured interviews, informed by published literature on long-term antidepressant prescribing and the clinical experience of the research group, were conducted by telephone or face-to-face by four authors with previous experience. The interview guide was piloted with two GPs, the data of which was not included in the analysis. All interviews were audio-recorded and transcribed verbatim, checked and anonymised. Interviews lasted between 20 and 60 minutes (mean 35 minutes); 16 were by telephone and six face-to-face. Data were analysed using reflexive thematic analysis by two members of the research team who independently read a selection of transcriptions, coded and added notes. Initial codes were created through collaboration of the two principal coders who continued analysing the data ultimately generating prototype themes.</p>
Findings	<p>Considerations required to assess preparedness for discontinuation</p> <ul style="list-style-type: none"> a) Personal and social circumstances were viewed as equally important as recovery from depression in assessing patient readiness. Having a stable relationship, employment, presence of social support, low financial stress, awareness of triggers, engagement in self-care and healthy lifestyle were repeatedly advocated as critical. A few GPs indicated that for older patients who have been on antidepressants for a long-time (in some cases decades) 'getting depressed again is usually not worth the risk'; others suggested dose reduction rather than discontinuation was an adequate outcome in some circumstances. Particularly when a patient is reluctant to cease, is in an unsafe or unstable environment, has inadequate social support or has experienced significant trauma. Being aware of the persons' situation was central in decision making. b) Patient preference/ Assessing the timing of discontinuation: There were circumstances where GPs would not attempt discontinuation even if indicated. They mentioned the importance of respecting patients' preferences to remain on their medication. GPs noted patients need to want to stop and failed previous attempts can moderate patients' future readiness, thus GPs raised a level of concern about enabling unsuccessful attempts and stopping antidepressants at the wrong time and that patient readiness was important. Planning the timing and making sure it is a good time and not a stressful time in the life of the person was mentioned as the first step for discontinuation. c) Weighing up the benefits and risks of discontinuation: GPs mentioned the reversal or removal of side effects, the removal of emotional numbness, reduced medication burden, reducing polypharmacy risks and the burden of cost were important motivators for discontinuation. However, few GPs expressed concerns about the risk of suicide and the risk of relapse and noted risks need to be weighed up when making decisions. <p>Ongoing and regular review of discontinuation progress (symptom monitoring, adherence) and individualised support:</p> <p>GPs emphasised discontinuation of long-term use is about finding the appropriate strategy for each patient. They go on to describe this as a journey taken together with ongoing discussions over time to review progress and better prepare patients to optimise outcomes. Making clear to patients they are not doing this alone was considered to be key and to require being fluid and responsive to the patients and their circumstances. GPs stressed the value of frequent and regular review (e.g., every two weeks or even weekly) as regular review during discontinuation enables symptom monitoring and reinforcing the importance of adhering to lifestyle measures such as exercise, diet, sleep hygiene, social supports and possibly psychological support.</p>

Study	Donald 2020³⁷
	Co-designing a personalised plan for gradual discontinuation: Many GPs recognised that tapering plans need to be personalised as weaning periods are hard to establish due to variation in antidepressant type and dose; that it was important to go as slow as needed and generally slower than withdrawal regimens suggest. Being proactive about relapse planning was considered central; talking to patients about how they will recognise if they are not doing well, possible warning signs and what they might do if they notice them, such as: calling on social supports, returning to the GP or re-engaging with mental health support. GPs felt inadequate discontinuation planning meant patients may mistake withdrawal for relapse, so preparing patients for the possibility that ceasing long-term use may be uncomfortable.
Funding	The University of Queensland (through a Faculty of Health and Behavioural Sciences and Faculty of Medicine seeding grant).
Limitations and applicability of evidence	Overall CASP rating: Very minor concerns (due to the role of the researcher not being discussed). No concerns over relevance.

Study	Hamilton 2021⁴⁶
Aim	To investigate the perspectives of Australian GPs on the barriers, facilitators and resources for deprescribing opioids, in patients with chronic non-cancer pain, to inform safe, effective and sustainable methods of opioid deprescribing in Australia.
Population	A purposive sample of general practitioners (GPs) with authority to prescribe opioid analgesics in Australia, who had prescribed or deprescribed opioids in at least one patient with chronic (>12 weeks) non-cancer pain within the last six months. N=22; male/female: 9/13; majority aged 55 years and older (45%) and most had >20 years of clinical experience (50%).
Setting	Primary care.
Study design	Semi-structured interviews and thematic analysis.
Methods and analysis	Semi-structured telephone interviews were conducted using an established interview guide, developed based on discussion with experts in the field with experience in qualitative design, quality use of medicines, pharmacy and opioid stewardship. Interviews lasted between 25 to 60 minutes, were audio-recorded and transcribed verbatim by a professional transcription service. Interviews were analysed using a five-step framework and thematic analysis method
Findings	<p>Factors to consider when making deprescribing decisions about opioids: individual patient factors and weighing up the benefits and harms of deprescribing for each individual</p> <p>GPs raised many complex considerations when weighing up the harms versus the benefits of deprescribing opioids, particularly when there is a lack of time and insufficient alternatives to offer. For example, patients who had been on opioids for a prolonged period seemed more likely to experience withdrawal symptoms upon tapering, or patients with comorbidities, traumatic injuries or who have a history of abuse are more challenging to initiate deprescribing as opioids form part of their coping mechanism. For patients who are medically complicated, GPs were concerned that deprescribing may drive their patients to undesirable options to manage their pain</p>

Study	Hamilton 2021⁴⁶
	such as alcohol misuse or buying opioids off the street, and therefore GPs said they hesitate to deprescribe with patients who are responsible and functioning well on opioids. The effect of chronic pain and opioid use on an individual's mental health was raised as vital consideration as conditions such as depression or anxiety, tend to influence a patients' level of resilience needed to deprescribe. GPs emphasized that psychological support is essential part of an effective deprescribing plan as opioid misuse is more common in patients with coexisting mental health conditions.
	Individualised management plan GPs mentioned incorporating individualized management plans, patient education and goal setting into deprescribing regimens. They found it useful to compile individualized deprescribing plans which encourages slow weaning in a structured way, while involving the patient in the planning process.
	Establishing a relationship with the patient GPs stated that the deprescribing process is easier when they have been managing the patient for a long time, whereby the relationship is well-established. Rapport building involves ensuring the patient does not feel abandoned to manage this task on their own and that they can consult with their GP wherever they need. GPs also expressed the need to feel they can also trust their patient to be compliant with the deprescribing plan. Having rapport allows GPs to provide patient education as well as support and reassurance.
Funding	Australian and New Zealand Musculoskeletal Clinical Trials Network.
Limitations and applicability of evidence	Overall CASP rating: Very minor concerns (due to the role of the researcher not being discussed). Minor concerns over applicability due to the population being limited to GPs in Australia.

Study	Kelly 2021⁵⁶
Aim	To explore general practitioners' perceptions and experiences of discontinuing antidepressants in primary care.
Population	A purposive sample of GPs with a broad range of experience, practising in both urban and rural practices and providing care for patients from diverse social and cultural backgrounds were recruited via a network of GP tutors affiliated with the ULEARN_GP network (a nationally represented network of GP practices). N=10; male/female: 7/3; mean age (SD) not specified; practice type: urban (n=6), rural (n=3), both (n=1); years of experience <5 years (n=3), 5-10 years (n=4), >25 years (n=3).
Setting	Primary care.
Study design	Exploratory qualitative design using semi-structured interviews and thematic analysis.

Study	Kelly 2021⁵⁶
Methods and analysis	<p>Semi-structured interviews were guided by a pilot-tested structured interview consisting of open-ended questions and probes developed after a preliminary review of the literature and through discussion with the research team which included GPs. GPs were asked to discuss their experiences of deprescribing antidepressants in general practice. Interviews took place at a time and venue that suited the GP, were recorded digitally and lasted 20-60 minutes (mean length 28 min) and were conducted by two researchers. Data collection ceased after 10 interviews as data saturation occurred after eight interviews with the final two interviews serving to test the evolving themes.</p> <p>Codes and themes iteratively derived from the data were discussed and agreed by authors who met biweekly to review and compare summaries. The iterative process of data analysis involved three researchers in coding and confirmation of themes. Two GPs participated in a reflective session to review and refine themes and to ensure that the findings captured a GP perspective.</p>
Findings	<p>Factors considered in GPs' decision making around discontinuing antidepressants</p> <ul style="list-style-type: none"> a) Patient willingness to stop the medicine: Decisions to stop the medication were in conjunction with the patient and sometimes led by them. GPs acknowledged the 'nebulous nature of depression' and that many of the patients had complex reasons not wanting to stop; they mentioned that if someone does not want to come off their medicine, they should not be forced and that this should be revisited when they see them. b) Medical factors: The length of time the patient was taking antidepressants was considered by GPs when deciding about deprescribing. Decisions around the length of treatment were based on individual patient needs such as patient age and whether it was a first episode or recurrence of depression with GPs noting they would leave elderly people on their medication and that for a recurrent depressive episode they would give a longer course of treatment. All GPs took into account the patients' functional response to treatment when deciding to discontinue antidepressant medication, whether people are functioning better within their life and their family and their work context, whether they feel they have fully recovered or have been well for a significant number of months. c) Psychological factors: when making decisions about the timing of antidepressant discontinuation, participants considered the persons' current life circumstances such as changes in employment, upcoming events (e.g., stressful events) and support networks.
Funding	Not declared.
Limitations and applicability of evidence	<p>Overall CASP rating: Very minor concerns (due to the role of the researcher not being discussed).</p> <p>No concerns over relevance.</p>

Study	Lefebvre-Durel 2021⁶²
Aim	To understand the perception of healthcare providers towards BZD or Z-drug withdrawal within a psychogeriatric unit and to provide insights from advanced practice nurses on this topic.
Population	Healthcare professionals from different professions caring for elderly patients in psychogeriatric unit. N=8; male/female: 1/7; median age (range): 30 (24 to 59) years; n=4 nurses, n=2 doctors, n=1 psychologist, n=1 medical student.
Setting	Inpatient psychogeriatric unit.
Study design	Semi-structured interviews and thematic analysis.
Methods and analysis	Interviews were conducted by the first author, an advance practice nurse student with experience in qualitative research. The guide for the semi-structured interviews contained open questions pertaining to the experience and evolution of BZD withdrawal (length, incidence, symptoms), management techniques, medical management of BZDs and history of substance use). Interviews were recorded and transcribed verbatim; median duration was 25 minutes. Eight interviews were performed, taking place on the psychogeriatric unit. Interviews began with small talk and then the open-ended questions of: 'can you please tell me about your experiences of BZD and Z-related drugs?'. Interviews were transcribed and analysed thematically by two authors, using an open-coding procedure based on themes on the interview guide.
Findings	Reassessment of treatment needs and dependence Healthcare professionals highlighted the importance of considering a reassessment of the indication, dosage and duration of treatment. They raised that the question of dependence should always be asked in order to seek advice or refer the patient to a specialised structure.
Funding	Advanced practice nurse master funding from the AP-HP Assistance Publique Hopiteaux de Paris and Agence Regionale de Sante (ARS) Ile de France
Limitations and applicability of evidence	Overall CASP rating: Very minor concerns (due to the role of the researcher not being discussed). Serious concerns over applicability with study sample being limited to health professionals providing care to elderly people at psychogeriatric unit.

Study	Liebschutz 2018⁶³
Aim	To describe strategies nurse care managers (NCMs) used with patients when discussing aberrancies encountered during opioid monitoring.
Population	Nurse care managers and patients with chronic non-cancer pain under their care. n=2 nurse care managers, n=41 patients

Study	Liebschutz 2018⁶³
Setting	Four primary care settings (USA)
Study design	Observational study of NCM-patient interactions. Part of an interventional study in which participating patients' primary care providers had been randomized to the treatment arm, of which nurse care managers were a part.
Methods and analysis	<p>This study employed direct observation methods to gather information about NCM and patient interactions during both initial and follow-up appointments; these NCM visits were part of a multicomponent intervention designed to change opioid prescribing patterns in primary care. Trained research assistants recorded direct observations in detailed field notes to capture the context in which, and the nonverbal communication with which, individuals interacted and events that may have escaped the awareness of others in that setting.</p> <p><u>Intervention:</u> The TOPCARE study was a cluster randomized controlled trial conducted at four sites: one hospital based primary care centre and three federally qualified community health centres. The subjects of the trial were PCPs (either attending physicians or nurse practitioners) and their patients. PCPs received either a four-component intervention or a control condition. The four-component intervention consisted of (1) care management with a NCM, (2) NCM use of a Web-based electronic registry of patients with chronic pain on long-term opioid therapy, (3) academic detailing with an expert in opioid prescribing for pain, and (4) electronic clinical decision support tools. The control condition provided PCPs access only to the electronic support tools. Academic detailing consisted of one 30-minute visit between a PCP and a chronic pain management expert physician 6-8 weeks after study enrolment to review guideline care and any patient cases the PCP identified as most challenging to manage. The electronic clinical decision support tools consisted of a Web site, mytopcare.org, which contained information for providers, patients, and pharmacists about opioids and chronic pain (e.g., the "For Providers" section included information on how to interpret urine screening tests). The intervention study is published as follows: Lasser KE, Shanahan C, Parker V, et al.: A multicomponent intervention to improve primary care provider adherence to chronic opioid therapy guidelines and reduce opioid misuse: A cluster randomized controlled trial protocol. J Subst Abuse Treat. 2016; 60: 101-109. doi:10.1016/j.jsat.2015.06.018.</p> <p>A convenience sample of 41 observations of NCM appointments with 41 unique patients was selected. Four members of the analysis team participated in the collection of observational data, after training in how to unobtrusively observe and take detailed field notes. All observers recorded notes by hand into the observation guide during the appointments and then typed their (deidentified) observations into an electronic version of the guide later that same day, along with additional observer recollections of the appointments. Data were analysed using conventional content analysis. Coding was complete and saturation reached when no new codes were generated from the data. Codes were grouped into themes which were refined by all authors into a final list.</p>
Note on study	This paper describes practical nurse care manager approaches to patient consultations. The themes below highlight approaches but discussion in the paper goes into more depth on actual person-to-person patient management strategies.
Themes with findings	<p>Intensive opioid management strategy</p> <p>Here intensive opioid management included short opioid prescription intervals, pill counts, urine drug screening, and nursing assessments. These monitoring strategies were what often revealed aberrancies.</p> <p>Developing a therapeutic relationship with the patient</p>

Study	Liebschutz 2018 ⁶³
	<p>This was done by implementing strategies to increase comfort through social conversations about family and giving encouragement on progress. This helps neutralize the potential strain in the relationship with the patient after identification of aberrancies, which lead to repeated explanations or justifications from the patient, and even disagreement in some appointments. Trust- and rapport-building strategies used with the patient allow the NCM to accomplish the planned goals of collecting information, teaching, and providing recommendations.</p>
	<p>Encouraging adherence through a collaborative approach</p> <p>The NCMs encouraged adherence to monitoring strategies by explaining their role in the patient's care and the importance of safety with opioid medications. In this intervention, for established patients these elements were new or occurred more frequently than their prior monitoring schedule. The NCM explains the change by framing their role in the patient's health care team at the beginning of their initial appointments and by explaining how they work with the PCP. The contextualized statements from the NCM explained their role in the patient's care, in part so the patient feels comfortable reaching out if they need anything, further emphasizing the collaborative team-based care approach.</p>
	<p>Emphasising the importance of safety</p> <p>The NCM also framed the importance of safety with opioids in the context of a discrepancy. The NCM used safety framing to explain that the goals of the appointment were to facilitate pain treatment for the patient while keeping the patient safe on opioids.</p>
	<p>Inquire into discrepancies between patient narrative and objective data</p> <p>The NCM and the patient discussed discrepancies between the patient's narrative and objective data to further understand the aberrancy, identify potential opioid misuse, and guide changes to opioid management. The NCMs communicated unexpected findings such as an incorrect pill count, a nonprescribed substance on a urine drug test, or absence of a prescribed substance on a urine drug test by making observations about the inconsistencies to the patient in a neutral, non-judgmental way.</p> <p>In response to the NCM's observations about discrepancies, a patient may offer explanations, either with an admission of behaviour outside of their opioid treatment agreement or an explanation of behaviour inside the treatment agreement. In such cases, presenting factual data from the NCM's observations uncovers unsafe medication-taking behaviours and possible undertreatment of pain. The NCM's observations enabled exploration of the reasons behind the patient's actions.</p> <p>In cases where a patient admits to behaviour outside of the treatment agreement and potential misuse or aberrancy is identified, the NCM has an opportunity to <u>provide clinical education</u> or to <u>utilize other monitoring tools (such as shorter prescription intervals or more frequent urine drug screens)</u>.</p>
	<p>Assess patient's medication use and pain to determine opioid misuse risk</p> <p>The NCM collected information about the patient's medication use and pain to obtain more information about the aberrancy and determine risk for opioid misuse. The NCM had multiple strategies to collect information to assess and mitigate risk for opioid misuse when a discrepancy is revealed, including a risk assessment of routine questions, and probing or clarifying questions. The NCM's risk assessment included routine questions to identify the patient's risk level for opioid misuse by asking about SUD history, psychiatric history, current medication use practices, and aberrant behaviours, such as diversion.</p>

Study	Liebschutz 2018⁶³
	<p>In another appointment, the NCM used the risk assessment questions when the patient stated their last dose of opioids to be two days ago to ask about diversion of opioid medication. The risk assessment questions uncovered an unsafe pattern: the patient had been taking more medication than prescribed early in the month, running out of medication before the next refill, and then taking a girlfriend's medication. These questions allowed for open communication with the patient on using medication safely.</p> <p>Educate patients and guide appropriate medication use</p> <p>When aberrancy is encountered, the NCM educated the patient and made recommendations to help the patient appropriately use their medication. The NCM educated and made clinical recommendations about the patient's health and opioid medications after aberrancies were identified. Often in response to a question from the patient or as a part of the visit, the NCM educated the patient about their health and how opioid medications work in the context of the patient's specific situation. The NCM educates the patient about the impact of psychosocial factors on chronic pain by explaining the interaction of the patient's social circumstances and physical symptoms in a clear way so that the patient can improve their understanding of the experience of chronic pain.</p> <p>In conjunction with patient education, the NCM also made clinical recommendations regarding opioid medications and the patient's health, such as recommending counselling to address psychosocial issues. The education and recommendations individualized to the specific situation are aimed at improving the patient's understanding of chronic pain and opioids and empowering effective use of the medication.</p>
Limitations and applicability of evidence	<p>Overall CASP rating: Moderate concerns (due to observational and descriptive approach, rather than gathering qualitative evidence about what approaches were effective, no patient perspective).</p> <p>Moderate concerns about relevance due to the population being nurse care managers, a role specific to the health care setting in which the study was conducted (USA).</p>

Study	Matthias 2020⁷²
Aim	To understand how decisions about pain management are made between patients prescribed opioids and their primary care providers, including the degree to which these decisions are shared.
Population	<p>Primary care providers practicing in primary care clinics serving primarily low-income patients. N=9; male/female: 1/9; mean age (range): 45 (30-62) years; n=5 internal medicine physicians, n=2 family medicine clinicians, n=1 physician assistant, n=1 did not provide this information.</p> <p>Patients of participating primary care providers with chronic musculoskeletal pain who were taking prescribed opioids for their pain at the time of enrolment. N=37; n=22 of which were interviewed; male/female: 12/25; mean age (range): 58 (22 to 74) years;</p>

Study	Matthias 2020⁷²
Setting	Four primary care clinics at academic medical centre serving primary low-income patients.
Study design	Qualitative interviews analysed using a constant comparison method (thematic analysis)
Methods and analysis	<p>96 clinic visits and 31 interviews (9 primary care providers and 22 patient interviews). Data collection occurred over 20 months (2015-2017) at which point theoretical saturation was reached. Up to three of each patients' primary care visits were audio-recorded. Once a patient had completed at least two visits a qualitative interview was scheduled.</p> <p>Primary care providers were interviewed after most or all their patient visits had been recorded, based on availability.</p> <p>Interviews were conducted by an experienced qualitative interviewer, took place in person in a private room and were audio-recorded and transcribed. Participants were asked questions about the patient-provider relationship, pain and opioid management (including decision making), opioid monitoring practices and institutional policies or state laws governing opioid prescribing.</p> <p>Using the constant comparative method, data analysis occurred in an iterative process consisting of two broad phases: open coding and focused coding, during which themes were derived.</p>
Findings	<p>Shared decision making and caveats:</p> <p>primary care providers expressed a desire for collaborative decision-making patient involvement in treatment decisions about opioids, but also acknowledged that there are limitations on patient input into pain treatment decisions. Caveats related to discussions about opioids and the safety and effectiveness of opioids and the need to follow rules as a condition of opioid prescribing. Patients and PCPs were aware that lack of agreement between them in regard to opioid prescribing could have an adverse effect on the patient-provider relationship, but PCPs were unwilling to agree on a course of action that they perceived harmful for the patient.</p> <p>Checking adherence/Regular urine drug screens:</p> <p>Primary care providers the need to ensure patients were complying by the rules/guidelines for prescribing. When primary care providers prescribed opioids they had expectations for patients, which included submitting to regular urine drug screens and reporting to the PCP if opioids are prescribed by another healthcare provider. Past history of patient adherence also influenced how providers approached decisions about opioids. PCPs indicated that an opioid prescription came with rules and requirements and failure to comply with these requirements could result in discontinuation of a patient's opioid prescription</p>
Funding	The National Institute on Drug Abuse of the National Institutes of Health.
Limitations and applicability of evidence	<p>Overall CASP rating: Moderate concerns (due to lack sufficient detail on the recruitment strategy).</p> <p>Minor concerns over applicability with the study being limited to primary care providers and patients in the USA.</p>

Study	Nolan 2005⁷⁷
Aim	To explore what factors, lead patients to consider their relationship with their prescribing clinician to be satisfactory and what kind of information they find reassuring and helpful. To examine how medication regimens are monitored and what kind of follow-up patients appreciate, and to identify pointers for establishing effective therapeutic relationships between patients and prescribing clinicians.
Population	Patients who had experienced a first episode of depression in the past 18 months were recruited from four GP practices in the West Midlands, UK, two of which were located in urban settings and two in rural settings. To be eligible, participants should have been treated in primary care, should have been prescribed antidepressant medication, and should have no other significant diagnosed physical or mental health problem. N=60; male/female: 23/37; mean age (range): 42 (24 to 67) years.
Setting	Primary care: four GP practices in the West Midlands, UK
Study design	Semi-structured interviews and thematic analysis
Methods and analysis	Semi-structured interviews were conducted at the participants' homes or their GP practice. All interviews were undertaken by one of the authors (FB) to ensure consistency, they were audio recorded, transcribed and analysed. Transcripts were analysed by both authors independently, who then conferred to discuss and agree themes to prevent bias in the analysis arising from its being undertaken by the interviewer.
Themes with findings	<p>Mutually agreed monitoring program</p> <p>What constituted monitoring varied considerably from GP to GP. Some respondents stated that a programme of monitoring was agreed between them and their GP at the first consultation, while others simply assumed that their treatment was being monitored. Eight respondents stated their GP asked to see them every 2-3 days at the start of treatment and then every 2-3 weeks once there were signs of improvement. Others stated they were given a prescription and asked to return in a month and assumed this was the length of time their GP felt it would take for the medication to start working.</p> <p>Assessment of helpfulness of medication and coping</p> <p>The explanation given by GPs for frequent visits was that the doctor wanted to see how they were coping and whether the treatment was helpful. Respondents themselves tended to interpret the frequency of their visits as indicative of the fact that they were more ill than they thought they were or that the GP was taking a particular interest in them. Being asked to return in order to review how the treatment was progressing was seen as symbolizing interest in their well-being. It was reported that GPs tend to assume that if things are not going well, patients will come and tell them, however this may not be the case for some patients, who if not being asked specifically to come back, would not have done so.</p> <p>Encouragement and support with self-monitoring</p>

Study	Nolan 2005⁷⁷
	Some participants had been told that they themselves were the best people to observe the effects of medication and were encouraged to keep themselves under review. Respondents found being invited to monitor their own progress and difficulties very helpful in building their self-esteem and putting them in control of their own recovery.
	Specific questions Specific questions by GPs were generally easier to deal with. Questions such as whether they had noticed any changes, whether they had lost any weight, experienced panic attacks or had problems with early morning waking or getting off to sleep at night helped respondents understand their illness better and monitor for themselves, their response to medication and their progress towards recovery.
	Assessment of personal well-being Respondents valued having their treatment monitored because it meant the GP was interested in how they were progressing. Being asked how they were doing made them think about their life in general and to what extent they were improving. For some, being asked how they were feeling by the GP was difficult as they did not know how to respond. Also, respondents appreciated being asked how they were doing when they saw other members of the primary care team such as community psychiatric nurses (CPN) and practice nurses.
Limitations and applicability of evidence	Overall CASP rating: Moderate concerns (due to concerns over the lack of sufficient detail on the data collection method and the data analysis). No concerns over applicability.

Study	Stumbo 2016⁹⁵
Aim	To document family involvement in opioid medication monitoring, and to provide preliminary descriptions of acceptability and helpfulness to patients.
Population	Patients who survived overdose or poisoning events and family members of deceased patients. n=69 patients, n=18 family members. 55% were female; mean age 42.9 years (SD 16.4). Of the patients, 58.6% held an active prescription for opioids at the time of the event; the remaining 41.4% involved heroin, prescription opioids not obtained by prescription, or expired prescriptions. Of the 87 events, 61% were unintentional, 29% were suicide attempts, and 10% were of undetermined intentionality. 39% percent of participants who had events involving prescribed opioid medications described some form of family involvement in managing these medications, either before or after overdoses.
Setting	This study was conducted within the membership of Kaiser Permanente Northwest (KPNW), USA. KPNW provides integrated medical, mental health, pain management, and addiction care to about 500,000 members in Oregon and Washington.

Study	Stumbo 2016⁹⁵
Study design	Semi-structured interviews and thematic analysis.
Methods and analysis	<p>Recruitment: Potential participants were identified using diagnostic codes for opioid overdoses and poisonings and pharmacy dispense records in the electronic medical record (EMR), to determine whether or not a patient/decedent had an active opioid prescription at the time of the event. Recruitment included all individuals with an active oxycodone single-ingredient sustained-release prescription at the time of overdose. KPNW members with events (or decedents' family members) were recruited by letter, with follow-up telephone contacts, inviting participation. Data were collected from June 2012 through February 2014; events occurred between November 2008 and July 2013. Ninety individuals were interviewed, however following interviews, 3 were excluded; 1 due to miscoding in the EMR, 2 due to confounding by significant comorbid health factors that made it difficult to determine whether an overdose had occurred. Analysis and results were derived from interviews with a total of 87 individuals with confirmed overdose events.</p> <p>Interview & analysis: Semi-structured interviews were conducted according to an interview guide based on the qualitative aims of the larger study: to understand changes in circumstances surrounding overdose events prior to and following the introduction of an abuse-deterrent formulation of a long-acting opioid. Interviews lasted for an average of about 1 hour and were recorded then transcribed verbatim. Researchers reviewed transcripts and used Atlas.ti (Qualitative Data Analysis & Research Software) to code interviews. A modified grounded theory approach and constant comparative methods were used to elicit emerging subthemes.</p>
Themes with findings	<p>Patient involvement in the medication management plan</p> <p>The most important component we found for successfully engaging a family member in the opioid monitoring process was the degree to which the patient agreed to, and accepted, medication monitoring. This process often involved the clinician requesting or requiring the engagement of a family member, although it could also be established through direct negotiation between patients and carers. Patients may also agree to a post-overdose, clinician-required pain contract that explicitly outlines family member involvement. This appeared especially true for suicide attempts.</p> <p>Carer involvement</p> <p>Having a carer who is involved with the clinician, attends clinical encounters, maintains fidelity to the management plan even under pressure, and who does not succumb to emotional manipulation appears to foster success.</p>
Limitations and applicability of evidence	<p>Overall CASP rating: Minor concerns (due to the study's semi-structured interview guide being adapted from the larger study (to understand changes in circumstances surrounding overdose events prior to and following the introduction of an abuse-deterrent formulation of a long-acting opioid)).</p> <p>Moderate concerns about relevance due to the study recruiting only participants who had overdosed, or were family members of those who had died of an overdose; interviews being designed according to the aims of a larger study (to understand changes in circumstances surrounding overdose events prior to and following the introduction of an abuse-deterrent formulation of a long-acting opioid); and due to the setting of the study in the USA healthcare system.</p>

Study	Wyse 2019¹⁰²
Aim	<p>The primary goal of the interviews was to learn about the methods primary care providers used to address prescription opioid misuse and aberrant opioid-related behaviours among their patients.</p> <p>This paper describes strategies providers have developed to meet new guidelines regarding opioid management and address common challenges they face in caring for patients prescribed Long Term Opioid Therapy.</p> <p>This study was part of a larger, mixed-methods project that aimed to investigate the use of, and response to, urine drug testing (UDT) among providers caring for patients prescribed Long Term Opioid Therapy for the treatment of chronic pain.</p>
Population	<p>Physicians and nurse practitioners (n=24) caring for patients prescribed long-term opioid therapy, were recruited from the VA Portland Health Care System. They represented 22 Veterans Affairs (VA) Medical Centres across the USA i.e., diverse geographical regions.</p> <p>N=24 (20 physicians, 4 nurse practitioners); male/female: 9/15; mean age (SD): 49.5 (10) years; average number of years since completion of training (SD, range): 17 (10, 2-37) years.</p>
Setting	VA Portland Health Care System
Study design	Semi-structured interviews and thematic analysis.
Methods and analysis	<p>All interviews were conducted by the project investigators, lasted 30-40 min, and were audio-recorded and transcribed verbatim. The semi-structured interview guide used was developed by clinician researchers with expertise in the treatment of chronic pain, long term opioid therapy, substance use disorders and qualitative research methods. Questions included examined: 1) the methods clinicians utilise to reduce prescriptions opioid misuse and address aberrant opioid-related behaviours; 2) how clinicians responded to misuse; 3) resources and constraints they faced in managing and treating opioid misuse among their patients.</p> <p>A qualitative content analysis approach was used for data analysis. Six interviews were coded jointly by project investigators to establish mutually agreed upon codes and definitions which were then used to build a codebook. The remaining interviews were divided and first coded independently by project investigators and then exchanged for secondary coding (i.e., all interviews were coded by two investigators. Quotes pertaining to conversations between patients and clinicians were then further categorised into sub-themes, which were then further categorised into sub-themes. Quotes that exemplified key sub-themes were selected for inclusion in the manuscript.</p>
Themes with findings	<p>Urine drug testing (UDT)</p> <p>All providers interviewed reported that they utilised UDT with their patients who were prescribed opioid therapy, and many described the substantial time investments UDT required. Nurse time was extensively used for tracking the dates on which UDT was required, monitoring patient behaviour and clinical history to determine whether a test was needed, scheduling and administering the test, and in</p>

Study	Wyse 2019 ¹⁰²
	<p>some cases, calling patients to discuss aberrant results. Some clinics simplified the work processes surrounding UDT by routinising it – by conducting UDT at specified time intervals or linking a template with date of last UDT in the medical record with their prescription renewal.</p> <p>A frequently expressed concern regarding the UDT process was the timing of tests. Patients generally completed a UDT on the same day they came in for their prescription renewal appointment and as such providers renewed the opioid prescription without knowing the UDT result. This meant that not only did the patient already have a new monthly prescription at the time aberrant results were discovered, but providers might also need to schedule another patient visit.</p> <p>Providers described circumventing this issue by scheduling the patient's UDT several days before their scheduled prescription renewal visits, ensuring that laboratory results would be available by the time the provider saw the patient. Although this innovation solved the problem of not having results at the time of the visit, it remained potentially onerous for patients who needed to schedule and attend two clinic visits within just a few days.</p>
	<p>Informed consent procedures</p> <p>Opioid agreements and informed consents for long term opioid therapy are intended to educate patients about opioid safety, familiarize them with standard monitoring practices, and communicate behavioural expectations for continued prescribing. Some providers described time constraints and technological impediments to smoothly incorporating the consent process, into their care practices. Time constraints were faced both because the consent procedure could be lengthy and because the consent was embedded within the electronic medical record, making it difficult to access.</p>
	<p>Opioid review committees and groups</p> <p>An essential resource discussed in many of the interviews was reliance on within-facility collaboration to guide and support safe prescribing practices. A formal mechanism was that of an opioid review board/opioid safety committee, wherein providers drawn from diverse medical fields across a hospital would convene to perform tasks such as auditing charts, initiating specialised review of patients on high doses of opioids, reviewing patients at the behest of providers to “flag charts” (i.e., mark patients as not able to receive opioids), review flags already issued, and provide recommendations about opioid taper or discontinuation.</p>
Limitations and applicability of evidence	<p>Overall CASP rating: Very minor concerns (due to the role of the researcher not being explored).</p> <p>Minor concerns about relevance due to the setting within the US care system.</p>

D.3 Monitoring frequency

No evidence identified.

Medicines associated with dependence or withdrawal symptoms: Final
Monitoring: frequency

Appendix E GRADE tables

E.1 Monitoring content: quantitative evidence

No evidence identified.

E.2 Monitoring content: qualitative evidence

2.2.6.1 Opioids

Table 11: Summary of evidence: Opioids: Review Finding 1

Study design and sample size		Finding	Quality assessment		Overall assessment of confidence
Number of studies contributing to the finding	Design		Criteria	Rating	
Shared decision-making and agreed management plans					
5	Semi-structured interviews and thematic analysis (4); observation of clinical visits and qualitative interviews with thematic analysis (1)	Collaborative decision making about opioid prescribing was important for both people taking opioids and health-care professionals; opioid management plans allow agreement of adherence expectations, a structured framework for educating the patient and opportunity to involve family or carers in the monitoring process.	Limitations	Minor concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance ^b	
			Adequacy	Minor concerns about adequacy	

(a) Very minor concerns in two studies^{46, 102} due to the role of the researcher not being explored and minor concerns in one study⁹⁵ due to the study's semi-structured interview guide being adapted from a larger overall study with indirect research aims to this review; moderate concerns in one study due to lack of sufficient detail on the recruitment process.⁷²

(b) Serious concerns in one study²⁴ due to the study being specific to the implementation of new USA guidelines (American Pain Society and Academy of Pain Medicine (APS/AAPM) guideline for patients with chronic non-cancer pain), and the fact that the setting is specifically a safety net setting which mostly cares for patients who are uninsured, use Medicaid or are otherwise vulnerable. Moderate concerns in one study⁹⁵ due to: the study recruiting only participants who had overdosed, or were family members of those who had died of an overdose; interviews being designed according to the aims of a larger study (to understand changes in circumstances surrounding overdose events prior to and following the introduction of an abuse-deterrent formulation of a long-acting opioid); and setting within the USA healthcare system. Minor concerns in two studies^{72, 102} due to setting within the USA healthcare system and minor concerns in one study due to setting within the Australian healthcare system.⁴⁶

Table 12: Summary of evidence: Opioids: Review Finding 2

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Therapeutic relationship between patient and health care professional					
2	Observation of patient-HCP interactions (1); Semi-structured interviews and thematic analysis (1)	Creating a positive relationship between the patient and the health care professional creates an environment allowing honest discussions about opioid monitoring and building a rapport allows health professionals to provide patient education, support and reassurance.	Limitations	Minor concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance ^b	
			Adequacy	Minor concerns about adequacy ^c	

(a) Moderate concerns in one study⁶³ due to observational and descriptive approach, rather than gathering qualitative evidence about what approaches were effective; no patient perspective and very minor concerns in the other study due to the role of the researcher not being discussed.⁴⁶

(b) Moderate concerns in one study⁶³ due to the population being specific to nurse care managers in the US healthcare system; and minor concerns in one study due to setting within the Australian healthcare system.⁴⁶

(c) Minor concerns about adequacy due to research finding being based on relatively limited information coming from two studies.

Table 13: Summary of evidence: Opioids: Review Finding 3

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Education around adherence					
1	Observation of patient-HCP interactions (1)	Communication around potential opioid misuse should include education about proper use of the medication and how to recognise the influence of other factors that can contribute to pain before relying on opioids.	Limitations	Moderate concerns about methodological limitations ^a	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance ^b	
			Adequacy	Moderate concerns about adequacy ^c	

(a) Moderate concerns in one study⁶³ due to observational and descriptive approach, rather than gathering qualitative evidence about what approaches were effective: no patient perspective.

(b) Moderate concerns in one study⁶³ due to the population being specific to nurse care managers in the US healthcare system.

(c) Moderate concerns about adequacy due to research finding being based on only one study.

Table 14: Summary of evidence: Opioids: Review Finding 4

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Assessing adherence and misuse risk					
3	Observation of patient-HCP interactions (1); observation of clinical visits and qualitative interviews with thematic analysis (1); semi-structured interviews and thematic analysis (1)	Healthcare professionals highlighted the need to ensure people adhere to their medication prescription and prescribing guidelines; routine questions can help assess a patient's misuse risk, combining information about their medication use and pain with their personal and medical history.	Limitations	Moderate concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance ^b	
			Adequacy	No concerns about adequacy ^c	

(a) Moderate concerns in one study⁶³ due to observational and descriptive approach, rather than gathering qualitative evidence about what approaches were effective; no patient perspective, moderate concerns in one study due to lack of sufficient detail on the recruitment process (Matthias 2021⁷²) and very minor concerns in one study due to the role of the researcher not being discussed.⁴⁶

(b) Moderate concerns over relevance due to the population in one study⁶³ being specific to nurse care managers in the US healthcare system, the population in the other study being specific to primary care providers in the US⁷² and the population in the third study due to setting within the Australian healthcare system.⁴⁶

Table 15: Summary of evidence: Opioids: Review Finding 5

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Weighing up the benefits and harms of discontinuation					
1	Semi-structured interviews and thematic analysis (1)	When making decisions about deprescribing opioids GPs highlighted the importance of weighing the benefits and risks of discontinuation for each person including how well they function on opioids, the availability of alternatives, the likelihood of the person experiencing withdrawal symptoms.	Limitations	Very minor concerns about methodological limitations ^a	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance ^b	
			Adequacy	Minor concerns about adequacy ^c	

(a) Very minor concerns in one study due to the role of the researcher not being discussed⁴⁶.

(b) Minor concerns over relevance due to the setting of the contributing study within the Australian healthcare system

(c) Minor concerns over adequacy with rich information to support the theme but only emerging from one study

2.2.6.2 Benzodiazepines and Z-drugs

Table 16: Summary of evidence: benzodiazepines and Z-drugs: Review Finding 1

Study design and sample size		Finding	Quality assessment		Overall assessment of confidence
Number of studies contributing to the finding	Design		Criteria	Rating	
Reassessment of treatment needs and dependence					
1	Semi-structured interviews and thematic analysis (1)	Healthcare professionals highlighted the importance of reassessing the indication, dosage, duration of treatment as well as dependence, in order to provide appropriate care to people taking benzodiazepines and/or Z-drugs.	Limitations	Very minor concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance ^b	
			Adequacy	Moderate concerns about adequacy ^c	

(a) Very minor concerns due to the role of the researcher not being discussed⁶²

(b) Minor concerns over relevance due to the study being limited to healthcare professionals providing care to elderly people at a psychogeriatric unit

(c) Moderate concerns over adequacy with limited information from one study supporting the theme

2.2.6.3 Antidepressants

Table 17: Summary of evidence: Antidepressants: Review Finding 1

Study design and sample size		Finding	Quality assessment		Overall assessment of confidence
Number of studies contributing to the finding	Design		Criteria	Rating	
Agreed monitoring programs					
2	Semi-structured interviews and thematic analysis (2).	Monitoring schedules should be clear and initially agreed between the patient and health care provider and so should personalised plans for discontinuation.	Limitations	Minor concerns about methodological limitations ^a	MODERATE
			Coherence	Minor concerns about coherence ^b	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No concerns about adequacy ^b	

(a) One study with moderate methodological limitations due to concerns over the lack of sufficient detail on the data collection method and the data analysis⁷⁷ and one study with very minor concerns due to the role of the researcher not being discussed³⁷.

(b) Minor concerns about coherence with findings from one study relating to a mutually agreed plan for discontinuation while findings from the other study relating to an agreed plan for while taking the medicine

Table 18: Summary of evidence: Antidepressants: Review Finding 2

Study design and sample size		Finding	Quality assessment		Overall assessment of confidence
Number of studies contributing to the finding	Design		Criteria	Rating	
Clarity around reasons for monitoring					
1	Semi-structured interviews and thematic analysis (1).	It should be clearly communicated to people taking antidepressants why they are being asked to attend regular monitoring check-ups.	Limitations	Moderate concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy ^b	

(a) One study with moderate methodological limitations due to concerns over the lack of sufficient detail on the data collection method and the data analysis.⁷⁷

(b) Moderate concerns about adequacy due to research finding being based on only one study.

Table 19: Summary of evidence: Antidepressants: Review Finding 3

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Encouraging self-monitoring					
1	Semi-structured interviews and thematic analysis (1).	People benefit from being encouraged to self-monitor, which can empower them to take control of their own recovery and potentially improve their self-esteem.	Limitations	Moderate concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy ^b	

(a) One study with moderate methodological limitations due to concerns over the lack of sufficient detail on the data collection method and the data analysis.⁷⁷

(b) Moderate concerns about adequacy due to research finding being based on only one study.

Table 20: Summary of evidence: Antidepressants: Review Finding 4

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Asking specific questions					
1	Semi-structured interviews and thematic analysis (1).	Simple, direct questions about a person's experience and quality of life help the patient better understand and monitor the effects of their medication and illness.	Limitations	Moderate concerns about methodological limitations ^a	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy ^b	

(a) One study with moderate methodological limitations due to concerns over the lack of sufficient detail on the data collection method and the data analysis.⁷⁷

(b) Moderate concerns about adequacy due to research finding being based on only one study.

Table 21: Summary of evidence: Antidepressants: Review Finding 5

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Reviewing the functional response to treatment and benefits and risks of discontinuation					
2	Semi-structured interviews and thematic analysis (2).	GPs acknowledged the benefits of discontinuation but expressed concerns about the risk involved for some people and highlighted the importance of assessing an individual's functional response to treatment and weighing up the benefits and risks when making decisions about discontinuation for each individual.	Limitations	Very minor concerns about methodological limitations ^a	HIGH
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) Two studies with very minor concerns over methodological limitations due to the role of the researcher not being discussed^{37, 56}

Table 22: Summary of evidence: Antidepressants: Review Finding 6

Study design and sample size		Finding	Quality assessment		Overall assessment of confidence
Number of studies contributing to the finding	Design		Criteria	Rating	
<u>Regular symptom monitoring and adherence during discontinuation</u>					
1	Semi-structured interviews and thematic analysis (1).	Regular review during discontinuation to allow monitoring of symptoms, adherence to lifestyle changes, discontinuation progress and provide support was considered important by GPs.	Limitations	Very minor concerns about methodological limitations ^a	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy ^b	

(a) One study with very minor concerns over methodological limitations due to the role of the researcher not being discussed³⁷

(b) Minor concerns about adequacy with the theme supported by sufficient information but coming from one study

Table 23: Summary of evidence: Antidepressants: Review Finding 7

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Review of personal and social circumstances					
2	Semi-structured interviews and thematic analysis (2).	Reviewing an individuals' personal and social circumstances including the availability of social support, their financial or relationship status was considered critical by GPs when making decisions about the discontinuation of antidepressants.	Limitations	Very minor concerns about methodological limitations ^a	HIGH
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) Two studies with very minor concerns over methodological limitations due to the role of the researcher not being discussed^{37, 56}

Table 24: Summary of evidence: Antidepressants: Review Finding 8

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Patient preference					
2	Semi-structured interviews and thematic analysis (2).	GPs highlighted the importance of making decisions about discontinuation of antidepressants in conjunction with patients, respecting patient preference to remain on antidepressants and reassessing patient preference in the next review.	Limitations	Very minor concerns about methodological limitations ^a	HIGH
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	No concerns about adequacy	

(a) Two studies with very minor concerns over methodological limitations due to the role of the researcher not being discussed^{37, 56}

E.3 Monitoring frequency

None.

Appendix F Excluded studies

F.1 Monitoring content: clinical studies excluded from the review (quantitative and qualitative)

Reference	Reason for exclusion
Alishashi 2021 ¹	Exclude: no relevant themes
Alley 2020 ²	Quantitative analysis; no relevant themes
Andersson 2020 ³	No relevant themes (relevant to substitution treatment for illicit drug use)
Andrilla 2018 ⁴	Quantitative analysis; no extractable themes
Andrilla 2020 ⁵	Incorrect population: prescribers of buprenorphine for opioid use disorder
Anonymous ³⁸	Incorrect setting: emergency departments; no relevant themes
Ayakta 2021 ⁶	No relevant themes
Baker 1997 ⁸	No relevant outcomes
Baker 2021 ⁷	Quantitative analysis; no relevant themes
Balbale 2017 ⁹	Incorrect study design (systematic scoping review of study types not compatible with this review)
Bergstein 2021 ¹⁰	Incorrect population: 95% heroin use
Bessen 2019 ¹¹	No relevant themes
Binswanger 2018 ¹²	Intervention does not match protocol; no relevant outcomes
Black 2020 ¹³	Quantitative analysis; no extractable themes
Blake 2007 ¹⁴	No relevant themes
Blanck 2015 ¹⁵	Incorrect study design: closed-question questionnaire.
Bornstein 2020 ¹⁶	Incorrect population: people with opioid use disorder on methadone treatment; no relevant themes
Bounthavong 2020 ¹⁷	Exclude: no relevant themes
Bowles 2021 ¹⁸	Incorrect population: non-prescription use
Brinkley-Rubinstein 2019 ¹⁹	Illicit opioids use
Brown 2020 ²⁰	Quantitative results; no extractable themes
Bunting 2021 ²¹	No relevant themes
Cadogan 2015 ²²	Incorrect study design (quantitative questionnaire/survey)
Castañeda 2020 ²³	No relevant themes
Chatterjee 2021 ²⁵	Incorrect population: use of opioids for recreational purposes; no relevant themes
Chau 2021 ²⁶	Incorrect population: acting representatives from local and regional drug use, community and advocacy organisations; no relevant themes
Choi 2021 ²⁷	No relevant themes
Chouinard 2018 ²⁸	Quantitatively analysed survey; no extractable themes
Clancy 2013 ²⁹	Unable to obtain paper
Cleveland 2020 ³⁰	Mixed sample of illicit and prescription opioids also obtained for non-medical use; no relevant themes
Cossette 2020 ³¹	Incorrect drugs: antipsychotics; no relevant themes
Coupland 2020 ³²	No relevant themes: prescriber views of a service for pregnant women with substance use disorders (alcohol and drugs) - no mention of prescription drug.

Reference	Reason for exclusion
Coyne 2021 ³³	Quantitatively analysed survey; no extractable themes
Coyne 2021 ³⁴	Quantitative analysis; no relevant themes
De Sola 2020 ³⁶	No relevant themes
Farrugia 2020 ³⁹	Incorrect population: illicit drug use; take home naloxone for overdose
Fatani 2021 ⁴⁰	Incorrect population: mixed sample of people using prescription and illicit substances reported to be taking them for non-medical use
Fernandez 2021 ⁴¹	Incorrect population: illicit and tobacco use
Gedde 2021 ⁴²	Incorrect population: mixed psychotropic drugs (including antidepressants and hypnotics but also including antipsychotics, and antidementia drugs)
Gibson 2014 ⁴³	Incorrect study design: narrative review
Goessling 2019 ⁴⁴	No relevant themes
Hassan 2021 ⁴⁷	No relevant themes
Huijbers 2020 ⁴⁸	No relevant themes
Jacobs 2016 ⁴⁹	Comparison does not match protocol (pilot study with no comparator)
Jamison 2010 ⁵⁰	Intervention does not match protocol; monitoring schedule combined with counselling ('cognitive behavioural substance misuse counselling')
Jamison 2016 ⁵¹	Comparison does not match protocol (no comparator)
Jeske 2019 ⁵²	No relevant themes
Kahler 2017 ⁵³	Intervention does not match protocol; protocol for transitioning opioid users from emergency department to an outpatient chronic pain programme program
Katon 1995 ⁵⁴	Reported outcomes not in an appropriate extractable format
Keller 2021 ⁵⁵	No relevant themes
Kim 2020 ⁵⁷	No qualitative analysis
Kosteniuk 2020 ⁵⁸	No relevant themes
Lai 2021 ⁵⁹	Incorrect population: people with a history on non-medical opioid use
Langford 2021 ⁶⁰	No relevant themes
Langford 2021 ⁶¹	No relevant themes
Liebschutz 2017 ⁶⁴	Intervention does not match protocol; care management intervention to improve guideline adherence
Lira 2019 ⁶⁵	Study protocol only
Magee 2021 ⁶⁶	No relevant themes
Marquez 2021 ⁶⁷	Quantitative analysis; no extractable themes
Martin 2018 ⁶⁸	No relevant themes: includes drugs not meeting protocol
Martirosyan 2012 ⁶⁹	Incorrect drugs: drugs for T2DM
Mathis 2019 ⁷¹	No relevant themes
Mathis 2020 ⁷⁰	No relevant themes
Mayock 2021 ⁷³	Incorrect population: people on long term methadone maintenance treatment; no relevant themes
Mazurenko 2020 ⁷⁴	No relevant themes; incorrect setting: acute care hospital
Navis 2019 ⁷⁶	No relevant themes
Oros 2021 ⁷⁸	No relevant themes
Ostrach 2019 ⁷⁹	No relevant themes
Park 2021 ⁸⁰	Incorrect population: 30.8% on benzodiazepines not prescribed
Parr 2006 ⁸¹	No relevant themes

Reference	Reason for exclusion
Paterson 2016 ⁸²	No relevant themes
Peacock-Chambers 2020 ⁸³	No relevant themes: about early intervention child development services for mothers in recovery of opioid use disorder; most likely not prescribed opioids
Penn 2019 ⁸⁴	No relevant themes
Pilkonis 2017 ⁸⁵	No relevant themes: thematic analysis not reported in full
Planelles 2018 ⁸⁶	Comparison does not match protocol (no comparator)
Potter 2001 ⁸⁷	Incorrect study design (quantitative closed survey of HCP attitudes)
Prathivadi 2021 ⁸⁹	No relevant themes
Prathivadi ⁸⁸	No relevant themes
Read 2020 ⁹¹	No relevant themes
Simon 2000 ⁹²	No relevant outcomes
Slat 2021 ⁹³	Exclude: no relevant themes
Solanki 2011 ⁹⁴	Incorrect study design (systematic scoping review of study types not compatible with this review)
Thakur 2020 ⁹⁶	No relevant themes
Tierce-Hazard 2014 ⁹⁷	Unable to obtain paper
Wiedemer 2007 ⁹⁸	Comparison does not match protocol (no comparator)
Wiles 2018 ⁹⁹	Intervention does not match protocol (CBT as adjunct to usual care); no relevant themes
Wilkinson 1993 ¹⁰⁰	Intervention does not match protocol; assignment of practice nurse vs GP alone
Wilson 2020 ¹⁰¹	No relevant themes
Young 2018 ¹⁰³	Intervention does not match protocol; online peer-support intervention

F.2 Monitoring frequency: clinical studies excluded from the review

Reference	Reason for exclusion
Gudin 2020 ⁴⁵	Incorrect study design: retrospective review of database (not comparative groups)
Jamison 2010 ⁵⁰	Intervention does not match protocol; monitoring schedule combined with counselling ('cognitive behavioural substance misuse counselling')
Jamison 2016 ⁵¹	Comparison does not match protocol (pilot study with no comparator)
Katon 1995 ⁵⁴	Reported outcomes not in an appropriate extractable format

F.3 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.

None.

Appendix G Forest plots

G.1 Monitoring content

None

G.2 Monitoring frequency

None

Appendix H Economic evidence tables

None

H.1 Monitoring content

None

H.2 Monitoring frequency

None

Appendix I Health economic model

None

Appendix J Research recommendations

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 ^f	4.1.1 (insomnia)	Flurazepam Loprazolam Lormetazepam

Drug class (for this analysis)	BNF chapter	Drugs included
		Nitrazepam
		Temazepam
	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

Drug class (for this analysis)	BNF chapter	Drugs included
		Fluvoxamine
		Paroxetine
		Sertraline
4.3.4 (Other antidepressants)	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 necessary⁹⁰.

* 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.