National Institute for Health and Care Excellence

FINAL

Depression in adults

[E] Chronic depression

NICE guideline NG222

Evidence review underpinning recommendations 1.10.1 to 1.10.6 and 1.10.8 to 1.10.9 and research recommendations in the NICE guideline

June 2022

Final

May 2024: We have simplified the guideline by removing recommendations on general principles of care that are covered in other NICE guidelines (for example, the NICE guideline on service user experience in adult mental health).

This is a presentational change only, and no changes to practice are intended.

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-4622-8

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Chronic depression

Review question

For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Introduction

In reviewing the evidence for further-line treatment (see Evidence review D), the committee agreed that it was not meaningful to separate out chronic depression from inadequate response to first-line treatment and treatment-resistant depression. Therefore, a single category was formed 'further-line treatment' which combined all these groups where participants are randomised at the point of non-response and treatment strategies include increasing dose, augmenting or switching. However, the committee were also aware that there are people with chronic depression who have not received treatment for the current episode, or who have recovered following initial treatment, and that it was not appropriate to combine these groups with those who have shown an inadequate response to initial treatment. The committee therefore agreed to review the evidence for first-line treatment and relapse prevention of chronic depression in the current evidence review, and the evidence for further-line treatment of chronic depression is considered in the context of a broader evidence base in Evidence review D.

Depression is often viewed as a brief self-limiting disorder, however, evidence from longitudinal studies indicates that many cases follow a chronic, unremitting course with up to a third of patients still reporting depression at 1 year follow-up, 12% at 5 years, and 6% at 15 years.

This persistence of depression in adults is normally defined as 'chronic depression' when it has continued beyond 2 years, and although this convention is to some extent arbitrary, it has been used as the definition for this evidence review.

Within the period of persistence, evidence indicates considerable variability in the nature of 'chronic depression'. It may present as a persistent major depressive episode that waxes and wanes without ever reaching the prior state of wellbeing (remission); it may be a persistent depressed state that never quite fully meets criteria for a major depressive episode, taking a milder, chronic form called 'dysthymia'; or it may be an alternating state of dysthymia and major depression (sometimes called 'double depression'). For the purposes of this evidence review all these forms of long-standing depressive symptoms are considered as chronic depression.

The onset of chronic depression can be relatively early in a lifetime and it can lead to a substantial impact on people's lives: studies have associated chronic depressive symptoms with particularly high rates of hospitalisation, functional impairment and suicide, and once depression has become chronic the outcome tends to be poor. In addition, the associated economic costs remain high throughout the working lifespan, largely related to lost productivity.

Despite evidence on the persistence, cost, and poor prognosis of chronic depressive symptoms, there is little consensus on the most effective way to treat chronic depression. The aim of this review is to identify what are the most effective treatments for chronic depression, both for its initial management and for the prevention of relapse (as described above, further-line treatment, which will often but not always include people with chronic depression, is considered in Evidence review D).

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with chronic depression. Chronic depression was defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales, for at least 2 years; persistent subthreshold symptoms (dysthymia); double depression (an acute episode of MDD superimposed on dysthymia). For this review, adults with chronic depression needed to be receiving first-line treatment or relapse prevention. If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review.
Intervention	**Psychological interventions:** • Behavioural therapies • Cognitive and cognitive behavioural therapies • Counselling • Interpersonal psychotherapy • Psychodynamic psychotherapies • Art therapy • Music therapy • Eye movement desensitization and reprocessing **Psychosocial interventions:** • Peer support • Mindfulness, meditation or relaxation **Pharmacological interventions:** • SSRIs o Citalopram o Escitalopram o Fluoxetine o Fluvoxamine o Paroxetine o Sertraline • TCAs o Amineptine o Amitriptyline o Clomipramine o Desipramine o Imipramine o Lofepramine o Nortriptyline • MAOIs o Phenelzine

	• TeCAs
	  ○ Mianserin
	
	• SNRIs
	  ○ Duloxetine
	  ○ Venlafaxine
	
	• Other antidepressant drugs
	  ○ Bupropion
	  ○ Mirtazapine
	  ○ Moclobemide
	  ○ Nefazodone
	
	• Antipsychotics
	  ○ Amisulpride
	  ○ Aripiprazole
	  ○ Olanzapine
	  ○ Quetiapine
	  ○ Risperidone
	  ○ Ziprasidone
	
	Physical interventions:
	• Acupuncture
	• Exercise
	• Yoga
	• ECT
	• Light therapy

Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcome	**Critical:** • Depression symptomatology • Remission • Response • Relapse (for relapse prevention trials) • Discontinuation due to side effects (for pharmacological interventions) • Discontinuation due to any reason **Important:** • Quality of life • Personal, social, and occupational functioning

DSM: Diagnostic and statistical manual of mental disorders; ECT: electroconvulsive therapy; ICD: international classification of diseases; MAOIs: monoamine oxidase inhibitor; MDD: major depressive disorder; SNRIs: serotonin noradrenaline reuptake inhibitor SSRIs: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant

For further details see the review protocol in appendix A.

Methods and processes

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.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Forty-six RCTs were included in this review: (Agosti 1997; Amore 2001; Anisman 1999; Bakish 1993a; Bellino 1997; Boyer 1996 (study 1); Boyer 1996 (study 2)/Lecrubier 1997; Browne 2002; Butler 2008; Clayton 2003; de Mello 2001; Duarte 1996; Dunner 1996; Gastpar 2006; Gelenberg 2003; Hamidian 2013; Hellerstein 1993; Hellerstein 2010; Hellerstein 2012; Hellerstein 2019; Jarrett 1999; Keller 1998a; Klein 2004; Kocsis 1988a/Kocsis 1988b; Kocsis 1996; Markowitz 2005; Markowitz 2008; Perlis 2002; Rapaport 2003; Ravindran 2000; Ravindran 2013; Ravizza 1999; Rocca 2002a; Rudolph 1998; Schatzberg 2006; Schneider 2003; Smeraldi 1998; Stewart 1989/1993; Stewart 1997; Thase 1996/Kocsis 1997; Thompson 2001; Tourian 2009; Vallejo 1987; Vanelle 1997; Versiani 1997; Williams 2000).

Five of the included studies provided evidence on relapse prevention (Gelenberg 2003, Klein 2004, Kocsis 1996, Perlis 2002, Stewart 1997).

Evidence was found for psychological interventions for the following comparisons:

Cognitive and cognitive behavioural therapies (CBT):

Comparison 1. CBT (individual) versus pill placebo for chronic depression (MDD ≥ 2 years)

Comparison 2. CBT (individual) versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Comparison 3. CBT (individual) versus IPT for chronic depression (MDD ≥ 2years)

Comparison 4: Cognitive-behavioural analysis system for psychotherapy (CBASP) versus assessment-only for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Comparison 5: CBT individual + desipramine versus desipramine for chronic depression (MDD ≥2 years)

Comparison 6: Mindfulness-based cognitive therapy (MBCT) group + medication versus medication for dysthymia or double depression

Comparison 7. CBT individual + fluoxetine versus fluoxetine for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Comparison 8. Problem solving versus pill placebo for dysthymia

Comparison 9. Problem solving versus paroxetine for dysthymia

Interpersonal therapy (IPT):

Comparison 10. IPT versus pill placebo for chronic depression (MDD ≥ 2 years)

Comparison 11. IPT versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Comparison 12. IPT versus counselling for dysthymia

Comparison 13: IPT + antidepressant versus antidepressant-only for dysthymia or double depression

Counselling:

Comparison 14. Counselling versus sertraline for dysthymia

Evidence was found for pharmacological interventions for the following comparisons:

Selective serotonin reuptake inhibitors (SSRIs):

Comparison 15. SSRIs versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Comparison 16: Sertraline versus imipramine for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Comparison 17. Fluoxetine versus venlafaxine for chronic depression (MDD ≥2 years)

Comparison 18: SSRI versus amisulpride for dysthymia or double depression

Comparison 19. Sertraline + IPT versus IPT-only for dysthymia

Tricyclic antidepressants (TCAs):

Comparison 20. TCAs versus pill placebo for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Comparison 21. TCA versus amisulpride for dysthymia or double depression

Comparison 22. TCAs versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia, or double depression)

Monoamine oxidase inhibitors (MAOIs):

Comparison 23. Phenelzine versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Comparison 24. Phenelzine versus imipramine for dysthymia

Comparison 25. Phenelzine versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Serotonin-noradrenaline reuptake inhibitors (SNRIs):

Comparison 26. SNRIs versus pill placebo for chronic depression (MDD ≥2 years, dysthymia)

Other antidepressant drugs:

Comparison 27. Moclobemide versus pill placebo for dysthymia or double depression

Comparison 28. Moclobemide versus fluoxetine for double depression

Comparison 29. Moclobemide versus imipramine for dysthymia or double depression

Comparison 30: Nefazodone versus pill placebo for relapse prevention in chronic depression

Antipsychotics:

Comparison 31: Amisulpride versus pill placebo for dysthymia or double depression

Evidence was found for physical interventions for the following comparisons:

Yoga:

Comparison 32: Yoga + TAU versus TAU for chronic depression (MDD ≥ 2 years)

The included studies are summarised in Table 2

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies for comparison 1: CBT (individual) versus pill placebo for chronic depression (MDD ≥ 2 years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT US	N=31 Mean age in years (range): 31.3 (NR) Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous	CBT (followed the manual by Beck et al. 1979) 16x weekly 50-min sessions (13.3 hours)	Pill placebo	MDD ≥2 years	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	depressive episodes: NR Baseline severity: HAMD 19 (more severe)				
Jarrett 1999 RCT US	N=72 Mean age in years (range): 40 (NR) Gender (% female): 66.7 Ethnicity (% BME): 8.3 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 62.7 (95) Number (SD) of previous depressive episodes: 2.1 (1.2) Baseline severity: HAMD 17.9 (more severe)	CBT individual 20x twice-weekly sessions (mean sessions 17.4 [SD=0.9])	Pill placebo	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 10 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 3: Summary of included studies for comparison 2: CBT (individual) versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT	N=36	CBT (followed the manual by Beck et al. 1979)	Imipramine (dose not reported)	MDD ≥2 years	The study is a four-armed trial. Demographics could not be

Study	Population	Intervention	Comparison	Definition of chronic	Comments
US	Mean age in years (range): 31.3 (NR) Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.9 (more severe)	16x weekly 50-min sessions (13.3 hours)			extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason
Dunner 1996 RCT US	N=31 Mean age in years (range): 35.7 (19-50) Gender (% female): 46 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current	CBT (followed the manual by Beck et al. 1979) 16x weekly sessions	Fluoxetine 20mg/day	Dysthymia	Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	episode: 200 (134.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 16 (more severe)				
Jarrett 1999 RCT US	N=72 Mean age in years (range): 39.2 (NR) Gender (% female): 70.8 Ethnicity (% BME): 8.3 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 61.1 (85.5) Number (SD) of previous depressive episodes: 2.0 (1.4) Baseline severity: HAMD 17.60 (Less severe)	CBT individual 10x twice-weekly sessions (20 sessions total; mean sessions 17.4 [SD=0.9])	Phenelzine (dosed to achieve a therapeutic response to approximately 0.85 mg/kg or 1 mg/kg in all patients not responding to a lower dose)	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 10 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason
Thompson 2001 RCT US	N=64 Mean age in years (range): 66.6 (NR) Gender (% female): 65.6	CBT individual (over 15 sessions) 16-20x 50-60-minute sessions	Desipramine (mean stable daily dose 90mg/day [SD=63mg])	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR (mean duration > 2 years) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.8 (more severe)				Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; kg: kilograms; MDD: major depressive disorder; mg: milligrams; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 4: Summary of included studies for comparison 3: CBT (individual) versus IPT for chronic depression (MDD ≥ 2years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT US	N=30 Mean age in years (range): 31.3 (NR) Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR	CBT (followed the manual by Beck et al. 1979) 16x weekly 50-min sessions (13.3 hours)	IPT (following manual by Klerman et al. 1984) 16x weekly 50-min sessions (13.3 hours)	MDD ≥2 years	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 19.03 (more severe)				• Remission • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; MDD: major depressive disorder; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 5: Summary of included studies for comparison 4: Cognitive-behavioural analysis system for psychotherapy (CBASP) versus assessment-only for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Klein 2004 RCT US	N=82 Mean age in years (range): 45.1 (NR) Gender (% female): 67 Ethnicity (% BME): 8 Mean age (SD) at first onset of depression: 28.2 (12.9) Mean months (SD) since onset of current episode: 88.8 (117.6) Number (SD) of previous depressive	Cognitive-behavioural analysis system for psychotherapy (CBASP); followed the manual by McCullough 2000 13 sessions (1 every 4 weeks; mean attended 11.1 sessions [SD=3.8])	Assessment-only (13 sessions [1 every 4 weeks])	Mixed (39% chronic major depression, 39% double depression and 22% recurrent depression with incomplete remission between episodes)	Treatment length (weeks): 52 Outcomes: • Depression symptomatology • Relapse • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	episodes: 2.4 (1.6) Baseline severity: HAMD 6.4 (less severe)				

BME: black and minority ethnic; CBASP: cognitive behavioural analysis system of psychotherapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 6: Summary of included studies for comparison 5: CBT individual + desipramine versus desipramine for chronic depression (MDD ≥2 years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Thompson 2001 RCT US	N=69 Mean age in years (range): 67 (NR) Gender (% female): 66.7 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR (mean duration > 2 years) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.7 (more severe)	CBT individual (over 15 sessions) + desipramine 16-20x 50-60minute sessions + desipramine starting dose 10mg/day, increased as tolerated	Desipramine Starting dose 10mg/day, increased as tolerated (mean stable daily dose 90mg/day [SD=63mg])	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligrams; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 7: Summary of included studies for comparison 6: Mindfulness-based cognitive therapy (MBCT) group + medication versus medication for dysthymia or double depression <Insert Table Title here>

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Hamidian 2013 RCT Iran	N=50 Mean age in years (range): NR Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: BDI-II 29.4 (less severe)	MBCT (followed the manual by Segal et al. 2002) + medication 8x weekly 2.5-hour sessions	Medication (no further detail reported)	Dysthymia or double depression	Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Discontinuation due to any reason

BDI: beck depression inventory; BME: black and minority ethnic; K: number of studies; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 8: Summary of included studies for comparison 7: CBT individual + fluoxetine versus fluoxetine for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Perlis 2002 RCT US	N=132 Mean age in years (range): 39.9 (NR) Gender (% female): 55	CBT individual (over 15 sessions) following unpublished manual that followed a modified version of Beck cognitive therapy,	Fluoxetine (dose increase) 40mg/day	Mixed (chronic depressive symptoms [≥3 years], history of poor inter-episode recovery or both MDD	Treatment length (weeks): 28 Previous treatment: Remitted following 8-week open-label fluoxetine (20mg/day)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): 6 Mean age (SD) at first onset of depression: 23.9 (13.9) Mean months (SD) since onset of current episode: 39 (67.4) Number (SD) of previous depressive episodes: 5 (7.7) Baseline severity: HAMD 4.6 (less severe)	combined with fluoxetine dose increase from continuation phase 19 sessions of CBT: 12x weekly sessions + 7x alternate-week sessions; Fluoxetine: 40mg/day		and dysthymia)	treatment (relapse prevention study) Outcomes: • Depression symptomatology • Relapse • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligrams; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 9: Summary of included studies for comparison 8: Problem solving versus pill placebo for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Williams 2000 RCT US	N=145 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean time (months) since onset of	Problem-Solving Treatment-Primary Care (PST-PC); followed method of Mynors-Wallis 1996 6 sessions (1 hour for first session and 30-min subsequently)	Pill placebo (equivalent 10-40mg/day)	DSM-III-R dysthymia (confirmed with PRIME-MD; trial also included minor depression but data only extracted for subgroup with dysthymia)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Data only extracted for dysthymia subgroup and as a result demographic details limited (not reported by diagnostic subgroup)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: NR				Treatment length (weeks): 11 Outcome: • Remission

BME: black and minority ethnic; DSM: diagnostic and statistical manual of mental disorders; K: number of studies; mg: milligrams; N: number of participants; NR: not reported; PRIME-MD: primary care evaluation of mental disorders; PST-PC: problem-solving treatment-primary care; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 10: Summary of included studies for comparison 9: Problem solving versus paroxetine for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Williams 2000 RCT US	N=139 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean time (months) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: NR	Problem-Solving Treatment-Primary Care (PST-PC); followed method of Mynors-Wallis 1996 6 sessions (1 hour for first session and 30-min subsequently)	Paroxetine 10-40mg/day	DSM-III-R dysthymia (confirmed with PRIME-MD; trial also included minor depression but data only extracted for subgroup with dysthymia)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Data only extracted for dysthymia subgroup and as a result demographic details limited (not reported by diagnostic subgroup) Treatment length (weeks): 11 Outcome: • Remission

BME: black and minority ethnic; DSM: diagnostic and statistical manual of mental disorders; K: number of studies; mg: milligrams; N: number of participants; NR: not reported; PRIME-MD: primary care evaluation of mental disorders; PST-PC: problem-solving treatment-primary care; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 11: Summary of included studies for comparison 10: IPT versus pill placebo for chronic depression (MDD ≥ 2 years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT US	N=29 Mean age in years (range): 31.3 (NR) Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.5 (more severe)	IPT (following manual by Klerman et al. 1984) 16x weekly 50-min sessions (13.3 hours)	Pill placebo	MDD ≥2 years	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; MDD: major depressive disorder; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 12: Summary of included studies for comparison 11: IPT versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT US	N=34 Mean age in years (range): 31.3 (NR) Gender (% female): NR	IPT (following manual by Klerman et al. 1984) 16x weekly 50-min sessions (13.3 hours)	Imipramine (dose not reported)	MDD ≥2 years	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.5 (more severe)				Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason
Browne 2002 RCT Canada	N=374 Mean age in years (range): 42.4 (NR) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR	IPT (followed the manual by Weissman and Klerman 1993 and Klerman et al. 1984) 12x 1-hour sessions (mean attended 8.6 sessions [sd=3.2])	Sertraline 50-200mg/day	Dysthymia	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Discontinuation not reported by group Treatment length (weeks): 26 Outcomes: • Depression symptomatology • Response

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Baseline severity: MADRS 24.7 (more severe)				
Markowitz 2005 RCT US	N=47 Mean age in years (range): 42.3 (NR) Gender (% female): 63 Ethnicity (% BME): 37 Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.3 (more severe)	IPT for dysthymic disorder (IPT-D; followed manual by Markowitz 1998) 16-18 x 50-min sessions (mean attended 13.2 sessions [SD=4.0])	Sertraline 50-200mg/day (mean daily dose 111.9 mg/day [SD=56.3]) + clinical management (10 x clinical management sessions [mean attended 7.5 sessions [SD=3.3])	DSM-IV early-onset (<21 years) dysthymic disorder (confirmed with SCID)	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason

BME: black and minority ethnic; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SCID: structured clinical interview for DSM disorders; SD: standard deviation; US: United States

Table 13: Summary of included studies for comparison 12: IPT versus counselling for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Markowitz 2005 RCT US	N=49 Mean age in years (range): 42.3 (NR)	IPT for dysthymic disorder (IPT-D; followed manual by Markowitz 1998)	Brief supportive psychotherapy (BSP). 16-18 x 50-min sessions (mean	DSM-IV early-onset (<21 years) dysthymic disorder (confirmed with SCID)	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Gender (% female): 63 Ethnicity (% BME): 37 Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 19.3 (more severe)	16-18 x 50-min sessions (mean attended 13.2 sessions [SD=4.0])	attended 9.6 sessions [SD=6.3])		are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason
Markowitz 2008 RCT US	N=26 Mean age in years (range): 38.4 (NR) Gender (% female): 31 Ethnicity (% BME): 31 Mean age (SD) at first onset of depression: NR (77% reported early onset <21 years) Mean months (SD) since onset of current episode: NR	IPT for dysthymic disorder (IPT-D) 16-18x 50-minute sessions	Brief supportive psychotherapy (BSP) 16-18x 50-minute sessions	Dysthymia	Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Response

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 21.3 (more severe)				

BME: black and minority ethnic; BSP: brief supportive psychotherapy; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; N: number of participants; NR: not reported; RCT: randomised controlled trial; SCID: structured clinical interview for DSM disorders; SD: standard deviation; US: United States

Table 14: Summary of included studies for comparison 13: IPT + antidepressant versus antidepressant-only for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
de Mello 2001 RCT Brazil	N=35 Mean age in years (range): NR Gender (% female): 80 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 19.4 (less severe)	IPT (adapted to dysthymic disorder) + moclobemide 16 sessions + 300-600mg/day (mean dose 460.71 mg/day [SD=124.71])	Moclobemide 300-600mg/day (mean dose 490.90 mg/day [SD=117.93]) + clinical management	Double depression (91%; + 9% dysthymic disorder)	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Discontinuation due to any reason
Browne 2002 RCT	N=408	IPT (followed the manual by Weissman	Sertraline 50-200mg/day	Dysthymia	The study is a three-armed trial.

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Canada	Mean age in years (range): 42.4 (NR) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 25.5 (more severe)	and Klerman 1993 and Klerman et al. 1984) + sertraline 12x 1-hour sessions (mean attended 8.9 sessions [sd=2.6]) + 50-200g/day of sertraline			Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Discontinuation not reported by group Treatment length (weeks): 26 Outcomes: • Depression symptomatology • Response
Markowitz 2005 RCT US	N=45 Mean age in years (range): 42.3 (NR) Gender (% female): 63 Ethnicity (% BME): 37 Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years) Mean months (SD) since onset of	IPT for dysthymic disorder (IPT-D; followed manual by Markowitz 1998) + sertraline 16-18 x 50-min sessions (mean attended 12.8 sessions [SD=4.01]) + 50-200mg/day (mean daily dose 116.3 mg/day [SD=43.9)	Sertraline 50-200mg/day (mean daily dose 111.9 mg/day [SD=56.3]) + clinical management (10 x clinical management sessions [mean attended 7.5 sessions [SD=3.3])	DSM-IV early-onset (<21 years) dysthymic disorder (confirmed with SCID)	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.7 (more severe)				

BME: black and minority ethnic; BSP: brief supportive psychotherapy; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SCID: structured clinical interview for DSM disorders; SD: standard deviation; US: United States

Table 15: Summary of included studies for comparison 14: Counselling versus sertraline for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Markowitz 2005 RCT US	N=50 Mean age in years (range): 42.3 (NR) Gender (% female): 63 Ethnicity (% BME): 37 Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity:	Brief supportive psychotherapy (BSP). 16-18 x 50-min sessions (mean attended 9.6 sessions [SD=6.3])	Sertraline 50-200mg/day (mean daily dose 111.9 mg/day [SD=56.3])	DSM-IV early-onset (<21 years) dysthymic disorder (confirmed with SCID)	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	HAMD 18.8 (more severe)				

BME: black and minority ethnic; BSP: brief supportive psychotherapy; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SCID: structured clinical interview for DSM disorders; SD: standard deviation; US: United States

Table 16: Summary of included studies for comparison 15: SSRIs versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Anisman 1999 RCT Canada	N=68 Mean age in years (range): Range NR 40.5 (NR) Gender (% female): 51 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 17.8 (more severe)	Sertraline 50-200mg/day	Pill placebo	Dysthymia	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Response • Discontinuation due to any reason
Clayton 2003 RCT US	N=300 Mean age in years (range): 40.2 (18-64) Gender (% female): 63	Fluoxetine 20-40mg/day	Pill placebo	MDD ≥2 years	Data not extracted for reboxetine Treatment length (weeks): 8 Outcomes: • Response

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 27 (NR) Number (SD) of previous depressive episodes: 4.2 Baseline severity: HAMD 25.75 (more severe)				• Discontinuation due to any reason
Gastpar 2006 RCT Germany	N=257 Mean age in years (range): 49.3 (18-74) Gender (% female): 69 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 35.7 (46.2) Number (SD) of previous depressive episodes: NR	Citalopram 20mg/day	Pill placebo	MDD ≥2 years	Treatment length (weeks): 6 Outcomes: • Depression symptomatology • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Baseline severity: HAMD 21.9 (more severe)				
Hellerstein 1993 RCT US	N=35 Mean age in years (range): 36.2 (NR) Gender (% female): 50 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years: by self-report 62.5% began in childhood, 25% in teens and 12.5% in early 20s) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 19 (more severe)	Fluoxetine 20mg/day (actual doses taken 10-60mg/day; mean final dose 32.7mg [SD=13.8])	Pill placebo	Early-onset (<21 years) dysthymia	Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason
Hellerstein 2010 RCT US	N=36 Mean age in years (range): 44.7 (23-65) Gender (% female): 50	Escitalopram 10-20mg/day (mean final dose 15.3mg [SD=5.1])	Pill placebo 10-20mg/day (mean final dose 16.7 mg [SD=4.9])	Dysthymia	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Remission • Response

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): 28 Mean age (SD) at first onset of depression: NR (75% had early-onset dysthymic disorder) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: Mean NR (39% no previous major depressive episodes, 19% one prior major depression, and 42% ≥2 earlier episodes of major depression) Baseline severity: HAMD 23.4 (more severe)				• Discontinuation due to side effects • Discontinuation due to any reason
Rapaport 2003 RCT US & Canada	N=323 Mean age in years (range): 70 (60-88) Gender (% female): 56 Ethnicity (% BME): 2 Mean age (SD) at first onset of	Paroxetine 10-50mg/day (mean daily dose 28.03 mg/day)	Pill placebo	MDD ≥2 years	Data for controlled and immediate release paroxetine were combined into 1 paroxetine arm Treatment length (weeks): 12 Outcomes:

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	depression: NR Mean months (SD) since onset of current episode: 41.6 (79.7) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 22.2 (more severe)				• Depression symptomatology • Remission • Discontinnuatio ndue to side effects • Discontinuation due to any reason
Ravindran 2000 RCT Canada, France, Italy, Spain, Sweden, and UK	N=310 Mean age in years (range): NR (49% 18-44; 44% 45-64; 7% ≥65) Gender (% female): 67 Ethnicity (% BME): 20 Mean age (SD) at first onset of depression: 28.5 (13.1) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: 197.5 (122.6) Baseline severity: MADRS 23.3 (more severe)	Sertraline 50-200mg/day (mean final dose 127.8mg [SD=53.4])	Pill placebo 50-200mg/day (mean final dose equivalent 139.8mg [SD=55.3])	Dysthymia	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Ravindran 2013 RCT Canada	N=40 Mean age in years (range): 41.5 (19-59) Gender (% female): 48 Ethnicity (% BME): 8 Mean age (SD) at first onset of depression: 25.8 (12.9) Mean months (SD) since onset of current episode: 223.8 (140.2) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.8 (more severe)	Paroxetine 10-40mg/day (mean final dose 33.33 mg/day)	Pill placebo 10-40mg/day (mean final dose 35.25 mg/day)	Dysthymia	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason
Schatzberg 2006 RCT US	N=196 Mean age in years (range): 71 (NR) Gender (% female): 46 Ethnicity (% BME): 7 Mean age (SD) at first onset of depression: NR Mean months (SD) since	Fluoxetine 20-60mg/day	Pill placebo	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Remission • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	onset of current episode: 49.3 (NR) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 23.51 (more severe)				
Schneider 2003 RCT US	N=752 Mean age in years (range): 69.8 (59-97) Gender (% female): 56 Ethnicity (% BME): 7 Mean age (SD) at first onset of depression: 54.3 (18.6) Mean months (SD) since onset of current episode: 27.7 (54) Number (SD) of previous depressive episodes: 3.95 Baseline severity: HAMD 21.4 (more severe)	Sertraline 50-100mg/day	Pill placebo	MDD ≥2 years	Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason • Quality of life
Thase 1996/Kocsis 1997 RCT	N=274 Mean age in years (range): 42.1 (NR)	Sertraline 50-200mg/day (mean final dose 139.6mg [SD=58.5])	Pill placebo	Early-onset (<21 years) dysthymia	The study is a three-armed trial and demographics reported here are for the two

Study	Population	Intervention	Comparison	Definition of chronic	Comments
US	Gender (% female): 65 Ethnicity (% BME): 5.1 Mean age (SD) at first onset of depression: 12.1 (4.8) Mean months (SD) since onset of current episode: 359.9 (127.9) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 12.7 (less severe)				relevant arms only Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason • Quality of life • Global functioning • Fuctional impairment
Vanelle 1997 RCT France	N=140 Mean age in years (range): 43 (NR) Gender (% female): 75 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (23% early-onset and 77% late-onset dysthymia) Mean months (SD) since onset of current	Fluoxetine 20mg/day	Pill placebo	Dysthymia	Treatment length (weeks): 13 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason • Global functioning

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	episode: 73.0 (NR) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20.6 (more severe)				
Williams 2000 RCT US	N=210 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean time (months) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: NR	Paroxetine 10-40mg/day	Pill placebo 10-40mg/day	DSM-III-R dysthymia (confirmed with PRIME-MD; trial also included minor depression but data only extracted for subgroup with dysthymia)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Data only extracted for dysthymia subgroup and as a result demographic details limited (not reported by diagnostic subgroup) Treatment length (weeks): 11 Outcome: • Remission

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; UK: United Kingdom; US: United States

Table 17: Summary of included studies for comparison 16: Sertraline versus imipramine for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Keller 1998a	N=635	Sertraline 50-200mg/day (mean final	Imipramine 50-300mg/day (mean final	Mixed (54% double depression;	Treatment length (weeks): 12

Study	Population	Intervention	Comparison	Definition of chronic	Comments
RCT US	Mean age in years (range): 41.1 (NR) Gender (% female): 63 Ethnicity (% BME): 9 Mean age (SD) at first onset of depression: MDD: 24.8 (12.1); Dysthymia: 17 (13.1) Mean months (SD) since onset of current episode: 72.3 (98.4) Number (SD) of previous depressive episodes: Mean NR (64% ≥1 previous episodes of major depression) Baseline severity: HAMD 25.1 (more severe)	dose 141mg [SD=59.4])	dose 200.2mg [SD=82.1])	46% chronic MDD ≥2 years)	Outcomes: • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason
Thase 1996/Kocsis 1997 RCT US	N=270 Mean age in years (range): 41.8 (NR) Gender (% female): 67 Ethnicity (% BME): 4.1 Mean age (SD) at first	Sertraline 50-200mg/day (mean final dose 139.6mg [SD=58.5])	Imipramine 50-300mg/day (mean final dose 198.9mg [SD=91.2])	Early-onset (<21 years) dysthymia	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 12 Outcomes:

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	onset of depression: 12.2 (4.7) Mean months (SD) since onset of current episode: 353.3 (125.9) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 13 (less severe)				• Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason • Quality of life • Global functioning • Functional impairment

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; US: United States

Table 18: Summary of included studies for comparison 17: Fluoxetine versus venlafaxine for chronic depression (MDD ≥2 years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Schatzberg 2006 RCT US	N=204 Mean age in years (range): 71 (NR) Gender (% female): 51 Ethnicity (% BME): 7 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 33.6 (NR)	Fluoxetine 20-60mg/day	Venlafaxine 75-225mg/day	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Remission • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 24 (more severe)				

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; US: United States

Table 19: Summary of included studies for comparison 18: SSRI versus amisulpride for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Amore 2001 RCT Italy	N=313 Mean age in years (range): 47.1 (19-75) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (22% early onset <21 years) Mean months (SD) since onset of current episode: 153.5 (134.2) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 17.7 (more severe)	Sertraline 50-100mg/day	Amisulpride 50mg/day	Dysthymia or double depression	Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Bellino 1997 RCT Italy	N=49 Mean age in years (range): 70.6 (NR >65) Gender (% female): 65 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 18.7 (more severe)	Sertraline 50mg/day	Amisulpride 50mg/day	Dysthymia	Treatment length (weeks): 26 Outcomes: • Response • Discontinuation due to side effects • Discontinuation due to any reason
Rocca 2002a RCT Italy	N=118 Mean age in years (range): 45.0 (NR) Gender (% female): 67 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: 35.9 (16.3) Mean months (SD) since onset of	Paroxetine 20mg/day	Amisulpride 50mg/day	Dysthymia	Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	current episode: 109.8 (68.9) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20.6 (more severe)				
Smeraldi 1998 RCT US	N=281 Mean age in years (range): 49.4 (19-70) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 21.4 (less severe)	Fluoxetine 20mg/day	Amisulpride 50mg/day	Dysthymia	Treatment length (weeks): 13 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason • Functional impairment

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; US: United States

Table 20: Summary of included studies for comparison 19: Sertraline + IPT versus IPT-only for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Browne 2002 RCT Canada	N=390 Mean age in years (range): 42.4 (NR) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 25.3 (more severe)	Sertraline + IPT (followed the manual by Weissman and Klerman 1993 and Klerman et al. 1984) 50-200g/day of sertraline + 12x 1-hour sessions (mean attended 8.9 sessions [sd=2.6])	IPT (followed the manual by Weissman and Klerman 1993 and Klerman et al. 1984) 12x 1-hour sessions (mean attended 8.6 sessions [sd=3.2])	Dysthymia	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Discontinuation not reported by group Treatment length (weeks): 26 Outcomes: • Depression symptomatology • Response
Markowitz 2005 RCT US	N=44 Mean age in years (range): 42.3 (NR) Gender (% female): 63 Ethnicity (% BME): 37 Mean age (SD) at first onset of depression: NR (inclusion criteria <21 years)	Sertraline + IPT for dysthymic disorder (IPT-D; followed manual by Markowitz 1998) 50-200mg/day (mean daily dose 116.3 mg/day [SD=43.9) + 16-18 x 50-min sessions (mean attended 12.8 sessions [SD=4.01])	IPT for dysthymic disorder (IPT-D; followed manual by Markowitz 1998) 16-18 x 50-min sessions (mean attended 13.2 sessions [SD=4.0])	DSM-IV early-onset (<21 years) dysthymic disorder (confirmed with SCID)	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 19.3 (more severe)				• Response • Discontinuation due to any reason

BME: black and minority ethnic; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton Depression Rating Scale; IPT: interpersonal therapy; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SCID: structured clinical interview for DSM disorders; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; US: United States

Table 21: Summary of included studies for comparison 20: TCAs versus pill placebo for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Agosti 1997 RCT US	N=35 Mean age in years (range): 31.3 (NR) Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 190.8 (94.8) Number (SD) of previous depressive episodes: NR	Imipramine (dose not reported)	Pill placebo	MDD ≥2 years	The study is a four-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all four arms combined Treatment length (weeks): 16 Outcomes: • Depression symptomatology • Remission • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Baseline severity: HAMD 18.5 (more severe)				
Bakish 1993a RCT Canada	N=33 Mean age in years (range): NR Gender (% female): NR Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 15.6 (less severe)	Imipramine 50mg/day	Pill placebo	Dysthymia	Study has three arms but data has not been extracted for Ritanserin Treatment length (weeks): 7 Outcomes: • Discontinuation due to side effects • Discontinuation due to any reason
Boyer 1996 (study 1) RCT France	N=219 Mean age in years (range): 48.3 (NR) Gender (% female): 77 Ethnicity (% BME): NR Mean age (SD) at first onset of	Amineptine 200mg/day	Pill placebo	Dysthymia or double depression	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 13 Outcomes: • Depression symptomatology

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 17.9 (less severe)				• Response • Discontinuation due to side effects • Discontinuation due to any reason
Boyer 1996 (study 2)/Lecrubier 1997 RCT France	N=146 Mean age in years (range): 43.4 (18-73) Gender (% female): 54 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 24.7 (more severe)	Imipramine 50-100mg/day	Pill placebo	Mixed (41% dysthymic disorder; 18% double depression and 40% major depression in partial remission)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Data cannot be extracted for depression symptomatology (no measures of variance reported) Treatment length (weeks): 26 Outcomes: • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason
Kocsis 1988a/1988b RCT	N=76	Imipramine 100-300mg/day	Pill placebo	Double depression (96%; + 4%	Treatment length (weeks): 6

Study	Population	Intervention	Comparison	Definition of chronic	Comments
US	Mean age in years (range): 39 (NR) Gender (% female): 70 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: 20 (13) Mean months (SD) since onset of current episode: 228 (192) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 22.8 (more severe)			dysthymic disorder)	Outcomes: • Remission • Discontinuation due to side effects • Discontinuation due to any reason • Functional impairment
Thase 1996/Kocsis 1997 RCT US	N=276 Mean age in years (range): 41.3 (NR) Gender (% female): 64 Ethnicity (% BME): 5 Mean age (SD) at first onset of depression: 12.4 (4.8) Mean months (SD) since onset of current	Imipramine 50-300mg/day (mean final dose 198.9mg [SD=91.2])	Pill placebo	Early-onset (<21 years) dysthymia	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 12 Outcomes: • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason • Quality of life

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	episode: 342 (130.1) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 13.0 (less severe)				• Global functioning • Functional impairment
Versiani 1997 RCT Unclear (3 countries)	N=207 Mean age in years (range): 41.5 (18-65) Gender (% female): 73 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (36% early onset) Mean months (SD) since onset of current episode: 138 (114) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20 (more severe)	Imipramine 25-250mg/day (mean final dose 204mg [SD=64])	Pill placebo 2-5 tablets/day (final mean dose 4.5 tablets [SD=1.0])	Dysthymia (68%) or double depression (32%)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; CBT: cognitive behavioural therapy; HAMD: Hamilton Depression Rating Scale; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TCA: tricyclic antidepressant; US: United States

Table 22: Summary of included studies for comparison 21: TCA versus amisulpride for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Boyer 1996 (study 1) RCT France	N=215 Mean age in years (range): 48.2 (NR) Gender (% female): 74 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 17.9 (less severe)	Amineptine 200mg/day	Amisulpride 50mg/day	Dysthymia or double depression	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 13 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason
Boyer 1996 (study 2)/Lecrubier 1997 RCT France	N=146 Mean age in years (range): 42.9 (18-73) Gender (% female): 52 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR	Imipramine 50-100mg/day	Amisulpride 50mg/day	Mixed (41% dysthymic disorder; 18% double depression and 40% major depression in partial remission)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Data cannot be extracted for depression symptomatology (no measures of variance reported) Treatment length (weeks): 26

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 24.6 (more severe)				Outcomes: • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason
Ravizza 1999 RCT Italy	N=253 Mean age in years (range): 47.1 (20-69) Gender (% female): 64 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 21.2 (less severe)	Amitriptyline 25-75mg/day (mean daily dose 50mg/day)	Amisulpride 50mg/day	Dysthymia (98%) or single episode of major depression in partial remission (2%)	Treatment length (weeks): 26 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason • Functional impairment

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TCA: tricyclic antidepressant

Table 23: Summary of included studies for comparison 22: TCAs versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia, or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Kocsis 1996 RCT US	N=53 Mean age in years (range): 36.9 (NR) Gender (% female): 59 Ethnicity (% BME): 14 Mean age (SD) at first onset of depression: 12.6 (7) Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 21.9 (more severe)	Desipramine 50-200mg/day	Pill placebo	Mixed (40% dysthymic disorder, 50% double depression, 10% chronic major depression)	Treatment length (weeks): 104 Outcome: • Relapse
Stewart 1997 RCT US	N=47 Mean age in years (range): 39 (23-58) Gender (% female): 57 Ethnicity (% BME): 13 Mean age (SD) at first onset of depression: 14 (11)	Imipramine 150-400mg/day. Mean entry doses were 253 mg/day (SD=67) and mean final dose 279 mg/day (SD=61)	Pill placebo	Mixed: MDD>2 years (35%), dysthymia (36%) or double depression (28%)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Treatment length (weeks): 26 Outcomes: • Relapse

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Mean months (SD) since onset of current episode: 226 (163) Number (SD) of previous depressive episodes: NR Baseline severity: NR				• Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TCA: tricyclic antidepressant; US: United States

Table 24: Summary of included studies for comparison 23: Phenelzine versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Jarrett 1999 RCT US	N=72 Mean age in years (range): 39.5 (NR) Gender (% female): 65 Ethnicity (% BME): 6 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 51.1 (68.1) Number (SD) of previous depressive episodes: 2 (1.3) Baseline severity:	Phenelzine (dosed to achieve a therapeutic response to approximately 0.85 mg/kg or 1 mg/kg in all patients not responding to a lower dose)	Pill placebo	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 10 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	HAMD 17.10 (more severe)				
Stewart 1989/1993 RCT US	N=39 Mean age in years (range): 37.3 (NR) Gender (% female): 30 Ethnicity (% BME): 9 Mean age (SD) at first onset of depression: 20.9 (11.8) Mean months (SD) since onset of current episode: 90.0 (102.7) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 13.0 (less severe)	Phenelzine ≤90mg/day (mean dose 73mg [SD=14])	Pill placebo ≤6 tablets (mean dose NR for dysthymia subgroup but across broader depression sample: 5.7 tablets [SD=0.6])	Dysthymia (sub-analysis of broader depressive disorder sample)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Treatment length (weeks): 6 Outcome: • Response

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; MAOI: monoamine oxidase inhibitor; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 25: Summary of included studies for comparison 24: Phenelzine versus imipramine for dysthymia

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Stewart 1989/1993 RCT US	N=45 Mean age in years (range): 37.3 (NR) Gender (% female): 30	Phenelzine ≤90mg/day (mean dose 73mg [SD=14])	Imipramine ≤300mg/day (mean dose NR for dysthymia subgroup but across broader depression sample:	Dysthymia (sub-analysis of broader depressive disorder sample)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): 9 Mean age (SD) at first onset of depression: 20.9 (11.8) Mean months (SD) since onset of current episode: 90.0 (102.7) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 13.0 (less severe)		265mg [SD=47])		Treatment length (weeks): 6 Outcome: • Response
Vallejo 1987 RCT Spain	N=39 Mean age in years (range): 40.2 (NR) Gender (% female): 88 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 36.6 (4.1) Number (SD) of previous depressive episodes: NR	Phenelzine 30-75mg/day	Imipramine 100-250mg/day	Dysthymia (sub-analysis of broader depressive disorder sample)	The study included participants with major depression with melancholia but data is only extracted for the dysthymic disorder subgroups for this review Treatment length (weeks): 6 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Baseline severity: HAMD 20.5 (more severe)				

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; MAOI: monoamine oxidase inhibitor; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 26: Summary of included studies for comparison 25: Phenelzine versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Stewart 1997 RCT US	N=43 Mean age in years (range): 39 (23-58) Gender (% female): 57 Ethnicity (% BME): 13 Mean age (SD) at first onset of depression: 14 (11) Mean months (SD) since onset of current episode: 226 (163) Number (SD) of previous depressive episodes: NR Baseline severity: NR	Phenelzine 7.5-105mg, Mean dose at entry 62 mg/day (SD=21) and mean final dose 73 mg/day (SD=24)	Pill placebo	Mixed: MDD>2 years (35%), dysthymia (36%) or double depression (28%)	The study is a three-armed trial. Demographics could not be extracted for the two relevant arms only and are reported for all three arms combined Treatment length (weeks): 26 Outcomes: • Relapse • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; MAOI: monoamine oxidase inhibitor; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 27: Summary of included studies for comparison 26: SNRIs versus pill placebo for chronic depression (MDD ≥2 years, dysthymia)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Hellerstein 2012 RCT US	N=57 Mean age in years (range): 41.6 (19-70) Gender (% female): 42 Ethnicity (% BME): 30 Mean age (SD) at first onset of depression: 19.9 (15) Mean months (SD) since onset of current episode: 95.2 (199.9) Number (SD) of previous depressive episodes: Mean NR (51% reported no previous major depressive episodes, 21% 1 prior major depression and 28% ≥2 prior episodes of major depression) Baseline severity: HAMD 14.5 (less severe)	Duloxetine 30-120mg/day (final mean dose 88.97mg [SD=28.33])	Pill placebo 30-120mg/day (final mean dose 100.71mg [SD=27.34])	DSM-IV-TR diagnosis of dysthymic disorder or depression NOS	Treatment length (weeks): 10 Outcomes: • Depression symptomatology • Remission • Response
Hellerstein 2019 RCT US	N=61 Mean age in years (range): 37.9 (20-63)	Desvenlafaxine 50mg/day (Mean final dose 96.5mg/day [SD=12])	Pill placebo (Mean final dose equivalent 93mg/day [SD=17.6])	MDD ≥2 years	Treatment length (weeks): 12 Outcomes:

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Gender (% female): 54 Ethnicity (% BME): 38 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20.16 (more severe)				• Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason • Functional impairment
Rudolph 1998 RCT US	N=358 Mean age in years (range): 42.9 (19-65) Gender (% female): 37 Ethnicity (% BME): 15 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 108 (200.6) Number (SD) of previous	Venlafaxine 75-375mg/day	Pill placebo	MDD ≥2 years	Data for 75mg/day, 225mg/day and 375mg/day doses were combined into 1 venlafaxine arm Treatment length (weeks): 6 Outcomes: • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	depressive episodes: NR Baseline severity: NR (more severe)				
Schatzberg 2006 RCT US	N=200 Mean age in years (range): 71 (NR) Gender (% female): 51 Ethnicity (% BME): 7 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: 42.8 (NR) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 23.5 (more severe)	Venlafaxine 75-225mg/day	Pill placebo	MDD ≥2 years	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Remission • Discontinuation due to side effects • Discontinuation due to any reason
Tourian 2009 RCT US	N=638 Mean age in years (range): 39.5 (NR) Gender (% female): 65 Ethnicity (% BME): 26 Mean age (SD) at first	Desvenlafaxine 50mg/day Desvenlafaxine 100mg/day Duloxetine 60mg/day	Pill placebo	MDD ≥2 years	Desvenlafaxine (50mg/day and 100mg/day) and duloxetine arms combined Treatment length (weeks): 8 Outcomes: • Remission • Response

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	onset of depression: NR Mean months (SD) since onset of current episode: 33.5 (56.8) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 23.3 (more severe)				• Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; MDD: major depressive disorder; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake Inhibitors; US: United States

Table 28: Summary of included studies for comparison 27: Moclobemide versus pill placebo for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Versiani 1997 RCT Unclear (3 countries)	N=212 Mean age in years (range): 40.5 (18-65) Gender (% female): 68 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (34% early onset) Mean months (SD) since onset of current episode: 125.9 (107.9)	Moclobemide 75-750mg/day (mean final dose 633mg [SD=158])	Pill placebo 2-5 tablets/day (final mean dose 4.5 tablets [SD=1.0])	Dysthymia (68%) and double depression (32%)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20.5 (more severe)				

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 29: Summary of included studies for comparison 28: Moclobemide versus fluoxetine for double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Duarte 1996 RCT Unclear (2 countries)	N=42 Mean age in years (range): 45.9 (21-60) Gender (% female): 40 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 24 (more severe)	Moclobemide 300mg/day	Fluoxetine 200mg/day	Double depression	Treatment length (weeks): 6 Outcomes: • Response • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 30: Summary of included studies for comparison 29: Moclobemide versus imipramine for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Versiani 1997 RCT Unclear (3 countries)	N=211 Mean age in years (range): 41.2 (18-65) Gender (% female): 73 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR (32.5% early onset) Mean months (SD) since onset of current episode: 131.8 (114.6) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 20.5 (more severe)	Moclobemide 75-750mg/day (mean final dose 633mg [SD=158])	Imipramine 25-250mg/day (mean final dose 204mg [SD=64])	Dysthymia (68%) and double depression (32%)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 8 Outcomes: • Depression symptomatology • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; RIMA: reversible inhibitors of monoamine oxidase-A; SD: standard deviation

Table 31: Summary of included studies for comparison 30: Nefazodone versus pill placebo for relapse prevention in chronic depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Gelenberg 2003 RCT US	N=108 Mean age in years (range): 39.6 (NR) Gender (% female): 68	Nefazodone 300-600mg/day (Mean final dose 485.9mg/day [SD=115.6])	Pill placebo (Mean final dose 504mg/day [SD=115.9])	Mixed (MDD ≥ 2 years, double depression, or recurrent MDD with incomplete inter-episode	Maintenance phase following Keller 2000 Treatment length (weeks): 52 Outcomes:

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	Ethnicity (% BME): 7 Mean age (SD) at first onset of depression: 25.99 Mean months (SD) since onset of current episode: 93.8 (110.4) Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 5.74 (less severe)			recovery of ≥ 2 years duration)	• Relapse • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; US: United States

Table 32: Summary of included studies for comparison 31: Amisulpride versus pill placebo for dysthymia or double depression

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Boyer 1996 (study 1) RCT France	N=212 Mean age in years (range): 48 (NR) Gender (% female): 73 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of	Amisulpride 50mg/day	Pill placebo	Dysthymia or double depression	The study is a three-armed trial and demographics reported here are for the two relevant arms only Treatment length (weeks): 13 Outcomes: • Depression symptomatology • Response • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Definition of chronic	Comments
	current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 17.9 (less severe)				• Discontinuation due to any reason
Boyer 1996 (study 2)/Lecrubier 1997 RCT France	N=146 Mean age in years (range): 42.3 (18-73) Gender (% female): 58 Ethnicity (% BME): NR Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: MADRS 24 (more severe)	Amisulpride 50mg/day	Pill placebo	Mixed (41% dysthymic disorder; 18% double depression and 40% major depression in partial remission)	The study is a three-armed trial and demographics reported here are for the two relevant arms only Data cannot be extracted for depression symptomatology (no measures of variance reported) Treatment length (weeks): 26 Outcomes: • Remission • Response • Discontinuation due to side effects • Discontinuation due to any reason

BME: black and minority ethnic; K: number of studies; MADRS: Montgomery-Asberg Depression Rating Scale; mg: milligram; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation

Table 33: Summary of included studies for comparison 32: Yoga + TAU versus TAU for chronic depression (MDD ≥ 2 years)

Study	Population	Intervention	Comparison	Definition of chronic	Comments
Butler 2008 RCT US	N=35 Mean age in years (range): 50.4 (22-80) Gender (% female): 74 Ethnicity (% BME): 13 Mean age (SD) at first onset of depression: NR Mean months (SD) since onset of current episode: NR Number (SD) of previous depressive episodes: NR Baseline severity: HAMD 15.84 (less severe)	Yoga + treatment as usual (TAU; psychoeducation) 8x weekly 2-hour sessions plus 1x 4-hour retreat and 1x booster session	TAU (psychoeducation)	MDD ≥2 years	Data has not been extracted for hypnosis arm Treatment length (weeks): 12 Outcomes: • Depression symptomatology • Remission

BME: black and minority ethnic; HAMD: Hamilton Depression Rating Scale; K: number of studies; N: number of participants; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; TAU: treatment as usual; US: United States

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of studies included in the evidence review

See the evidence profiles in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

A list of excluded economic and utility studies, with reasons for exclusion, is provided in supplement 3 - Health economic included & excluded studies.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

PSYCHOLOGICAL INTERVENTIONS

Comparison 1. CBT (individual) versus pill placebo for chronic depression (MDD ≥ 2 years)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=103) shows a statistically significant but not clinically important benefit of an individual CBT intervention relative to pill placebo on depression symptomatology change score, for adults with chronic depression.

Remission

- Very low quality evidence from 2 RCTs (N=103) shows a clinically important and statistically significant benefit of an individual CBT intervention, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=103) shows a clinically important and statistically significant difference with a lower rate of discontinuation (due to any reason) associated with an individual CBT intervention relative to pill placebo, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 2. CBT (individual) versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 4 RCTs (N=194) shows neither a clinically important nor statistically significant difference between an individual CBT intervention and

antidepressants on depression symptomatology change score, for adults with chronic depression.

Remission

- Very low quality evidence from 2 RCTs (N=102) shows neither a clinically important nor statistically significant difference between an individual CBT intervention and antidepressants on the rate of remission, for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 4 RCTs (N=203) shows a lower rate of discontinuation (due to any reason) associated with an individual CBT intervention relative to antidepressants for adults with chronic depression, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 3. CBT (individual) versus IPT for chronic depression (MDD ≥ 2years)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=30) shows neither a clinically important nor statistically significant difference between individual CBT and IPT on depression symptomatology change score, for adults with chronic depression.

Remission

- Very low quality evidence from 1 RCT (N=30) shows neither a clinically important nor statistically significant difference between individual CBT and IPT on the rate of remission, for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=30) shows neither a clinically important nor statistically significant difference between individual CBT and IPT on discontinuation due to any reason, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 4. Cognitive-behavioural analysis system for psychotherapy (CBASP) versus assessment-only for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=82) shows a clinically important and statistically significant benefit of CBASP, relative to assessment-only, for depression symptomatology change scores in adults with remitted chronic depression.

Relapse

- Very low quality evidence from 1 RCT (N=82) shows a clinically important and statistically significant benefit of CBASP, relative to assessment-only, on the rate of relapse in adults with remitted chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=82) shows neither a clinically important nor statistically significant difference between CBASP and assessment-only on discontinuation due to any reason, for adults with remitted chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 5. CBT individual + desipramine versus desipramine for chronic depression (MDD ≥2 years)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=69) shows neither a clinically important nor statistically significant difference between combined individual CBT and desipramine relative to desipramine-only on depression symptomatology change score, for adults with chronic depression.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=69) shows neither a clinically important nor statistically significant difference between combined individual CBT and desipramine relative to desipramine-only on discontinuation due to any reason, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 6. Mindfulness-based cognitive therapy (MBCT) group + medication versus medication for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=44) shows a clinically important and statistically significant benefit of combined mindfulness-based cognitive therapy (MBCT) group and medication, relative to medication-only, on depression symptomatology change score for adults with dysthymia or double depression.

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=50) shows neither a clinically important nor statistically significant difference between a combined mindfulness-based cognitive therapy (MBCT) group and medication intervention relative to medication-only on discontinuation due to any reason, for adults with dysthymia or double depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 7. CBT individual + fluoxetine versus fluoxetine for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=132) shows neither a clinically important nor statistically significant difference between combined CBT and fluoxetine relative to fluoxetine-only on depression symptomatology change score, for adults with depression whose chronic depression has remitted following open-label fluoxetine treatment.

Relapse

- Very low quality evidence from 1 RCT (N=132) shows neither a clinically important nor statistically significant difference between combined CBT and fluoxetine relative to fluoxetine-only on the rate of relapse, for adults with depression whose chronic depression has remitted following open-label fluoxetine treatment.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=132) shows a higher rate of discontinuation due to side effects associated with combined CBT and fluoxetine relative to fluoxetine-only for adults with depression whose chronic depression has remitted following open-label fluoxetine treatment, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=132) shows neither a clinically important nor statistically significant difference between combined CBT and fluoxetine relative to fluoxetine-only on discontinuation due to any reason, for adults with depression whose chronic depression has remitted following open-label fluoxetine treatment.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 8. Problem solving versus pill placebo for dysthymia

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=125) shows a clinically important but not statistically significant benefit of problem solving relative to pill placebo on the rate of remission for adults with dysthymia.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 9. Problem solving versus paroxetine for dysthymia

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=120) shows neither a clinically important nor statistically significant difference between problem solving and paroxetine on the rate of remission for adults with dysthymia.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 10. IPT versus pill placebo for chronic depression (MDD ≥ 2 years)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=29) shows neither a clinically important nor statistically significant difference between IPT and pill placebo on depression symptomatology change score, for adults with chronic depression.

Remission

- Very low quality evidence from 1 RCT (N=29) shows a clinically important but not statistically significant benefit of IPT, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=29) shows neither a clinically important nor statistically significant difference between IPT and pill placebo on discontinuation due to any reason, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 11. IPT versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 3 RCTs (N=455) shows a statistically significant but not clinically important benefit of antidepressants, relative to IPT, on depression symptomatology change score for adults with chronic depression.

Remission

- Very low quality evidence from 2 RCTs (N=75) shows a clinically important and statistically significant benefit of antidepressants, relative to IPT, on the rate of remission for adults with chronic depression.

Response

- Very low quality evidence from 2 RCTs (N=421) shows a clinically important and statistically significant benefit of sertraline, relative to IPT, on the rate of response for adults with chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=81) shows a lower rate of discontinuation due to any reason associated with IPT relative to antidepressants for adults with chronic depression, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 12. IPT versus counselling for dysthymia

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=75) shows neither a clinically important nor statistically significant difference between IPT and brief supportive psychotherapy on depression symptomatology change score, for adults with dysthymia.

Remission

- Very low quality evidence from 2 RCTs (N=75) shows neither a clinically important nor statistically significant difference between IPT and brief supportive psychotherapy on the rate of remission, for adults with dysthymia.

Response

- Very low quality evidence from 2 RCTs (N=75) shows a clinically important but not statistically significant benefit of IPT relative to brief supportive psychotherapy on the rate of response, for adults with dysthymia.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=49) shows lower discontinuation due to any reason associated with IPT relative to brief syupportive psychotherapy for adults with dysthymia, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 13. IPT + antidepressant versus antidepressant-only for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 3 RCTs (N=477) shows neither a clinically important nor statistically significant difference between a combined IPT and antidepressant intervention, relative to antidepressants-only, on depression symptomatology change score for adults with dysthymia or double depression.

Remission

- Very low quality evidence from 1 RCT (N=45) shows a clinically important but not statistically significant benefit of combined IPT and sertraline, relative to sertraline-only, on the rate of remission for adults with dysthymia.

Response

- Very low quality evidence from 2 RCTs (N=453) shows neither a clinically important nor statistically significant difference between combined IPT and sertraline, relative to sertraline-only, on the rate of response for adults with dysthymia.

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=80) shows a lower rate of discontinuation (due to any reason) associated with a combined IPT and antidepressant intervention relative to antidepressants-only for adults with dysthymia or double depression, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 14. Counselling versus sertraline for dysthymia

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=50) shows a clinically important and statistically significant benefit of sertraline, relative to brief supportive psychotherapy, on depression symptomatology change score for adults with dysthymia.

Remission

- Very low quality evidence from 1 RCT (N=50) shows a clinically important and statistically significant benefit of sertraline, relative to brief supportive psychotherapy, on the rate of remission for adults with dysthymia.

Response

- Very low quality evidence from 1 RCT (N=50) shows a clinically important but not statistically significant benefit of sertraline, relative to brief supportive psychotherapy, on the rate of response for adults with dysthymia.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=50) shows lower discontinuation (due to any reason) associated with sertraline relative to brief supportive psychotherapy for adults with dysthymia, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

PHARMACOLOGICAL INTERVENTIONS

Comparison 15. SSRIs versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 10 RCTs (N=2,170) shows a statistically significant but not clinically important benefit of SSRIs, relative to pill placebo, on depression symptomatology change from baseline to endpoint for adults with chronic depression.

Remission

- Very low quality evidence from 7 RCTs (N=1,092) shows a clinically important and statistically significant benefit of SSRIs, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

- Very low quality evidence from 9 RCTs (N=1,896) shows a clinically important and statistically significant benefit of SSRIs, relative to pill placebo, on the rate of response for adults with chronic depression.

Discontinuation due to side effects

- Very low quality evidence from 8 RCTs (N=1,957) shows a clinically important and statistically significant difference with a higher rate of discontinuation due to side effects associated with SSRIs, relative to pill placebo, for adults with chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 12 RCTs (N=2,722) shows neither a clinically important nor statistically significant difference between SSRIs and pill placebo on discontinuation due to any reason, for adults with chronic depression.

Important outcomes:

Quality of life

- Very low quality evidence from 2 RCTs (N=939) shows a statistically significant but not clinically important benefit of sertraline, relative to pill placebo, on quality of life for adults with chronic depression.

Personal, social, and occupational functioning

- Very low quality evidence from 2 RCTs (N=368) shows a statistically significant but not clinically important benefit of SSRIs, relative to pill placebo, on global functioning for adults with dysthymia.
- Very low quality evidence from 1 RCT (N=246) shows a clinically important and statistically significant benefit of sertraline, relative to pill placebo, on functional impairment for adults with dysthymia.

Comparison 16. Sertraline versus imipramine for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=270) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on depression symptomatology change scores, for adults with dysthymia.

Remission

- Very low quality evidence from 2 RCTs (N=893) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on the rate of remission for adults with chronic depression.

Response

- Very low quality evidence from 2 RCTs (N=893) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on the rate of response for adults with chronic depression.

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=905) shows a clinically important and statistically significant difference with a higher rate of discontinuation due to side effects associated with imipramine relative to sertraline, for adults with chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=905) shows a clinically important and statistically significant difference with a higher rate of discontinuation due to any reason associated with imipramine relative to sertraline, for adults with chronic depression.

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=208) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on quality of life for adults with dysthymia.

Personal, social, and occupational functioning

- Very low quality evidence from 1 RCT (N=253) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on global functioning for adults with dysthymia.
- Very low quality evidence from 1 RCT (N=245) shows neither a clinically important nor statistically significant difference between sertraline and imipramine on functional impairment for adults with dysthymia.

Comparison 17. Fluoxetine versus venlafaxine for chronic depression (MDD ≥2 years)

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=192) shows a clinically important but not statistically significant benefit of venlafaxine, relative to fluoxetine, on the rate of remission for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=204) shows a higher rate of discontinuation due to side effects associated with venlafaxine relative to fluoxetine for adults with chronic depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=204) shows neither a clinically important nor statistically significant difference between fluoxetine and venlafaxine on discontinuation due to any reason, for adults with chornic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 18. SSRI versus amisulpride for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Low quality evidence from 3 RCTs (N=692) shows a statistically significant but not clinically important benefit of amisulpride, relative to SSRIs, on depression symptomatology change scores for adults with dysthymia or double depression.

Remission

- Very low quality evidence from 2 RCTs (N=431) shows neither a clinically important nor statistically significant difference between SSRIs and amisulpride on the rate of remission, for adults with dysthymia or double depression.

Response

- Low quality evidence from 4 RCTs (N=761) shows neither a clinically important nor statistically significant difference between SSRIs and amisulpride on the rate of response, for adults with dysthymia or double depression.

Discontinuation due to side effects.

- Very low quality evidence from 4 RCTs (N=761) shows neither a clinically important nor statistically significant difference between SSRIs and amisulpride on discontinuation due to side effects, for adults with dysthymia or double depression.

Discontinuation due to any reason

- Low quality evidence from 4 RCTs (N=761) shows a higher rate of discontinuation due to any reason associated with SSRIs relative to amisulpride for adults with dysthymia or double depression, however this effect is not statistically significant.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Moderate quality evidence from 1 RCT (N=268) shows neither a clinically important nor statistically significant difference between fluoxetine and amisulpride on functional impairment, for adults with dysthymia.

Comparison 19. Sertraline + IPT versus IPT-only for dysthymia

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=434) shows a clinically important and statistically significant benefit of a combined sertraline and IPT intervention, relative to IPT-only, on depression symptomatology change scores for adults with dysthymia.

Remission

- Very low quality evidence from 1 RCT (N=44) shows a clinically important but not statistically significant benefit of a combined sertraline and IPT intervention, relative to IPT-only, on the rate of remission for adults with dysthymia.

Response

- Very low quality evidence from 2 RCTs (N=434) shows a clinically important and statistically significant benefit of a combined sertraline and IPT intervention, relative to IPT-only, on the rate of response for adults with dysthymia.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=44) shows neither a clinically important nor statistically significant difference between a combined sertraline and IPT intervention and IPT-only on discontinuation due to any reason, for adults with dysthymia.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 20. TCAs versus pill placebo for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 4 RCTs (N=714) shows a clinically important and statistically significant benefit of TCAs, relative to pill placebo, on depression symptomatology change scores for adults with chronic depression.

Remission

- Very low quality evidence from 5 RCTs (N=696) shows a clinically important and statistically significant benefit of TCAs, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

- Very low quality evidence from 5 RCTs (N=831) shows a clinically important and statistically significant benefit of TCAs, relative to pill placebo, on the rate of response for adults with chronic depression.

Discontinuation due to side effects

- Very low quality evidence from 6 RCTs (N=935) shows a clinically important and statistically significant difference with a higher rate of discontinuation due to side effects associated with TCAs, relative to pill placebo, for adults with chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 7 RCTs (N=970) shows neither a clinically important nor statistically significant difference between TCAs and pill placebo on discontinuation due to any reason for adults with chronic depression.

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=207) shows a statistically significant but not clinically important benefit of imipramine, relative to pill placebo, on quality of life for adults with dysthymia.

Personal, social, and occupational functioning

- Very low quality evidence from 1 RCT (N=256) shows a statistically significant but not clinically important benefit of imipramine, relative to pill placebo, on global functioning for adults with dysthymia.
- Very low quality evidence from 1 RCT (N=256) shows a statistically significant but not clinically important benefit of imipramine, relative to pill placebo, on functional impairment change scores for adults with dysthymia.
- Very low quality evidence from 1 RCT (N=24) shows a clinically important and statistically significant benefit of imipramine, relative to pill placebo, on functional impairment at endpoint for adults with double depression.

Comparison 21. TCA versus amisulpride for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=458) shows neither a clinically important nor statistically significant difference between a TCA and amisulpride on depression symptomatology change scores, for adults with dysthymia or double depression.

Remission

- Very low quality evidence from 1 RCT (N=146) shows neither a clinically important nor statistically significant difference between a TCA and amisulpride on the rate of remission for adults with dysthymia or double depression.

Response

- Low quality evidence from 3 RCTs (N=565) shows neither a clinically important nor statistically significant difference between a TCA and amisulpride on the rate of response for adults with dysthymia or double depression.

Discontinuation due to side effects

- Low quality evidence from 3 RCTs (N=614) shows a higher rate of discontinuation due to side effects associated with TCAs relative to amisulpride for adults with dysthymia or double depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Low quality evidence from 3 RCTs (N=614) shows neither a clinically important nor statistically significant difference between a TCA and amisulpride on discontinuation due to any reason, for adults with dysthymia or double depression.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Moderate quality evidence from 1 RCT (N=250) shows neither a clinically important nor statistically significant difference between amitriptyline and amisulpride on functional impairment for adults with dysthymia.

Comparison 22. TCAs versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia, or double depression)

Critical outcomes:

Relapse

- Very low quality evidence from 2 RCTs (N=82) shows a clinically important but not statistically significant benefit of TCAs, relative to pill placebo, for relapse prevention in adults with chronic depression.

Discontinuation due to side effects

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=32) shows a higher rate of discontinuation (due to any reason) associated with imipramine (used for relapse prevention) relative to pill

placebo in adults with chronic depression, however this effect is not statisticaly significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 23. Phenelzine versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=72) shows a clinically important and statistically significant benefit of phenelzine, relative to pill placebo, on depression symptomatology change scores for adults with chronic depression.

Remission

- Very low quality evidence from 1 RCT (N=72) shows a clinically important and statistically significant benefit of phenelzine, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

- Low quality evidence from 1 RCT (N=39) shows a clinically important but not statistically significant benefit of phenelzine, relative to pill placebo, on the rate of response for adults with dysthymia.

Discontinuation due to side effects

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=72) shows a clinically important and statistically significant difference with a lower rate of discontinuation due to any reason associated with phenelzine, relative to pill placebo, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 24. Phenelzine versus imipramine for dysthymia

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=32) shows a clinically important and statristically significant benefit of phenelzine, relative to imipramine, on depression symptomatology at endpoint for adults with dysthymia.

Remission

No evidence was identified for this outcome.

Response

- Very low quality evidence from 1 RCT (N=30) shows a clinically important but not statistically significant benefit of imipramine, relative to phenelzine, on the rate of response for adults with dysthymia.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=39) shows a higher rate of discontinuation due to side effects associated with imipramine relative to phenelzine for adults with dysthymia, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=39) shows a higher rate of discontinuation due to any reason associated with imipramine relative to phenelzine for adults with dysthymia, however this effect is not statistically significant.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 25. Phenelzine versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Critical outcomes:

Relapse

- Very low quality evidence from 1 RCT (N=28) shows a clinically important and statistically significant benefit of phenelzine, relative to pill placebo, for preventing relapse in adults with chronic depression.

Discontinuation due to side effects

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=28) shows neither a clinically important nor statistically significant difference between phenelzine (used for relapse prevention) and pill placebo in discontinuation due to any reason, for adults with chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 26. SNRIs versus pill placebo for chronic depression (MDD ≥2 years, dysthymia)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=109) shows a clinically important but not statistically significant benefit of SNRIs, relative to pill placebo, on depression symptomatology change scores for adults with chronic depression.

Remission

- Very low quality evidence from 4 RCTs (N=943) shows a clinically important but not statistically significant benefit of SNRIs, relative to pill placebo, on the rate of remission for adults with chronic depression.

Response

- Very low quality evidence from 4 RCTs (N=1070) shows a clinically important but not statistically significant benefit of SNRIs, relative to pill placebo, on the rate of response for adults with chronic depression.

Discontinuation due to side effects

- Very low quality evidence from 4 RCTs (N=1222) shows a clinically important and statistically significant difference with a higher rate of discontinuation due to side effects associated with SNRIs relative to pill placebo for adults with chronic depression.

Discontinuation due to any reason

- Very low quality evidence from 4 RCTs (N=1222) shows neither a clinically important nor statistically significant difference between SNRIs and pill placebo on discontinuation due to any reason, for adults with chronic depression.

Important outcomes

Quality of life

No evidence was identified for this outcome.

Personal, social and occupational functioning

- Very low quality evidence from 1 RCT (N=52) shows neither a clinically important nor statistically significant difference between desvenlafaxine and pill placebo on functional impairment for adults with chronic depression.

Comparison 27. Moclobemide versus pill placebo for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=201) shows a clinically important and statistically significant benefit of moclobemide, relative to pill placebo, on depression symptomatology change scores for adults with dysthymia or double depression.

Remission

- Very low quality evidence from 1 RCT (N=201) shows a clinically important and statistically significant benefit of moclobemide, relative to pill placebo, on the rate of remission for adults with dysthymia or double depression.

Response

- Very low quality evidence from 1 RCT (N=201) shows a clinically important and statistically significant benefit of moclobemide, relative to pill placebo, on the rate of response for adults with dysthymia or double depression.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=212) shows a higher rate of discontinuation due to side effects associated with moclobemide relative to pill placebo for adults with dysthymia or double depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=212) shows neither a clinically important nor statistically significant difference between moclobemide and pill placebo on discontinuation due to any reason, for adults with dysthymia or double depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 28. Moclobemide versus fluoxetine for double depression

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

No evidence was identified for this outcome.

Response

- Very low quality evidence from 1 RCT (N=42) shows a clinically important and statistically significant benefit of moclobemide, relative to fluoxetine, on the rate of response for adults with double depression.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=42) shows neither a clinically important nor statistically significant difference between moclobemide and fluoxetine on discontinuation due to side effects, for adults with double depression.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=42) shows neither a clinically important nor statistically significant difference between moclobemide and fluoxetine on discontinuation due to any reason, for adults with double depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 29. Moclobemide versus imipramine for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=198) shows neither a clinically important nor statistically significant difference between moclobemide and imipramine on depression symptomatology change scores, for adults with dysthymia or double depression.

Remission

- Very low quality evidence from 1 RCT (N=198) shows a clinically important but not statistically significant benefit of moclobemide, relative to imipramine, on the rate of remission for adults with dysthymia or double depression.

Response

- Very low quality evidence from 1 RCT (N=198) shows neither a clinically important nor statistically significant difference between moclobemide and imipramine on the rate of response, for adults with dysthymia or double depression.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=211) shows a higher rate of discontinuation due to side effects associated with imipramine relative to moclobemide for adults with dysthymia or double depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=211) shows neither a clinically important nor statistically significant difference between moclobemide and imipramine on discontinuation due to any reason, for adults with dysthymia or double depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 30. Nefazodone versus pill placebo for relapse prevention in chronic depression

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Relapse

- Very low quality evidence from 1 RCT (N=160) shows a clinically important but not statistically significant benefit of nefazodone, relative to pill placebo, on the rate of relapse for adults with remitted chronic depression.

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=160) shows a higher rate of discontinuation due to side effects associated with nefazodone (used for relapse prevention) relative to pill placebo for adults with remitted chronic depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=160) shows a clinically important and statistically significant difference with a lower rate of discontinuation due to any reason associated with nefazodone (used for relapse prevention), relative to pill placebo, for adults with remitted chronic depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Comparison 31. Amisulpride versus pill placebo for dysthymia or double depression

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=206) shows a clinically important and statistically significant benefit of amisulpride, relative to pill placebo, on depression symptomatology change scores for adults with dysthymia or double depression.

Remission

- Low quality evidence from 1 RCT (N=146) shows a clinically important but not statistically significant benefit of amisulpride, relative to pill placebo, on the rate of remission for adults with dysthymia or double depression.

Response

- Very low quality evidence from 2 RCTs (N=307) shows a clinically important and statistically significant benefit of amisulpride, relative to pill placebo, on the rate of response for adults with dysthymia or double depression.

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=358) shows a higher rate of discontinuation due to side effects associated with amisulpride relative to pill placebo for adults with dysthymia or double depression, however this effect is not statistically significant.

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=358) shows neither a clinically important nor statistically significant difference between amisulpride and pill placebo on discontinuation due to any reason, for adults with dysthymia or double depression.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

PHYSICAL INTERVENTIONS

Comparison 32. Yoga + TAU versus TAU for chronic depression (MDD ≥ 2 years)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=27) shows a clinically important and statistically significant benefit of yoga in addition to TAU, relative to TAU-only, on depression symptomatology at endpoint for adults with chronic depression.

Remission

- Very low quality evidence from 1 RCT (N=27) shows a clinically important but not statistically significant benefit of yoga in addition to TAU, relative to TAU-only, on the rate of remission for adults with chronic depression.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Important outcomes:

No evidence for quality of life or functioning outcomes for this comparison.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the most effective treatments for chronic depression so the committee prioritised depression symptomatology, remission and response as critical outcomes. Where interventions were targeted at keeping people who were in full or partial remission from chronic depression well, relapse was identified as a critical outcome. As a treatment can only be effective if it is utilised by the person with depression, discontinuation due to side effects and discontinuation due to any reason were also prioritised by the committee as critical outcomes.

The aim of treating depression is to improve people's life and so health-related quality of life and personal, social and occupational functioning were chosen as important outcomes. The committee were cognisant that for people with depression, quality of life may be the most valued outcome, however, it was not prioritised as a critical outcome as the committee were aware that the data for this outcome was very limited, and therefore was not as helpful in making decisions.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. The committee noted that all but two of the outcomes had been assessed as either low or very low quality. Most outcomes were downgraded due to imprecision (frequently associated with relatively small sample sizes) and risk of bias (common reasons for downgrading based on risk of bias included non-blind or unclear blinding of participants, intervention adminstrators, and outcome assessors, and high or unclear risk of selective reporting bias). The results of the evidence for chronic depression symptomatology were relatively consistent with interventions that have been found to be effective in other areas of the guideline and this increased the committee's confidence in the results from the evidence.

Benefits and harms

The committee considered the evidence for the first-line treatment of chronic depression, whilst bearing in mind the evidence from the further-line treatment review (Evidence review D) that included people with chronic depression who had shown limited or no response to at least one treatment. The evidence for chronic depression combined populations with major depressive disorder (MDD) for at least 2 years, those with persistent subthreshold symptoms (dysthymia) and people with double depression (an acute episode of MDD superimposed on dysthymia). The committee agreed that the distinction between these groups was not clinically meaningful, and that people with depression could be grouped based on chronicity or severity and both offered potential insights into the best treatment for people with depression.

The committee discussed the heterogeneity in the length of the current episode (where reported) in the evidence base. The committee were aware of the evidence suggesting that the length of the episode of depression is prognostic so that on average the longer the prior episode the less expected benefit there might be. However, they were cognisant of the uncertainties over whether this is a linear or non-linear relationship – for example, there may be a larger difference in expected benefit between a 6 month and a 24 month duration of depression relative to a 3 year and a 4.5 year duration of depression. Moreover, the committee agreed that the length of the episode does not appear to be prescriptive, in terms of differentiating between treatments, and as such considerations about duration of symptoms did not impact upon identifying the most effective treatments.

For people with chronic depressive symptoms who had not previously sought treatment, the committee discussed the need to consider why treatment had not been accessed before. A recommendation was added based on committee experience, to alert healthcare professionals to this group who may not be aware that they have chronic depression, and may need help in accessing treatment and services.

For acute treatment of chronic depression, there was some evidence that cognitive and cognitive behavioural therapies appeared to improve depression outcomes for adults with chronic depressive symptoms compared to pill placebo. There was also single-RCT evidence for improved efficacy with the addition of a mindfulness-based cognitive therapy (MBCT) group to ongoing medication, although this was a relatively small study and not based in the UK. Based on this limited evidence, the committee decided not to name individual interventions as specific examples of the cognitive behavioural class but considered it important to outline some key components that these interventions should include based on the content of the interventions in the evidence reviewed, the committee's knowledge and experience of factors that maintain and prolong depression, and the associated evidence from the further-line treatment review (Evidence review D).

There was consistent evidence for small but significant benefits on chronic depression symptomatology of SSRIs and TCAs. The committee therefore agreed that they should recommend SSRIs or TCAs alone for people with chronic depressive symptoms who may prefer to receive a pharmacological intervention. However, based on their experience the committee added additional guidance on which TCAs may be preferred, as there is the potential for cardiotoxicity and associated increased risk in overdose with some TCAs such as amitriptyline and dosulepin and so the committee included a warning about this. They also added, based on their knowledge and the BNF guidance that 'lofepramine has a lower incidence of side-effects and is less dangerous in overdose [than other tricyclic antidepressants' the fact that lofepramine has the best safety profile. Given the evidence on the acceptability, tolerability and safety of SSRIs was better than for other drugs, and based on their knowledge and experience, the committee agreed that if a person with chronic depression cannot tolerate an SSRI, an alternative SSRI should be considered. There was some evidence for SNRIs, and the committee considered that, due to the potential toxicity issues with TCAs, it may be logical to try an SNRI if treatment with a SSRI was not effective, before trying a TCA and so they added in SNRIs as another treatment option.The committee also considered that combination therapy may be an option for some people, although the evidence for this had been very limited.

The committee considered the further-line treatment of chronic depression in the context of a wider review on further-line treatment (see Evidence review D) and agreed that the recommendations that came from that review should be followed for people who present with chronic depressive symptoms and who have had, or are still receiving, treatment for depression.

The committee considered that although the balance of the evidence was in favour of a SSRI or TCA over alternative pharmacological interventions, some people may have failed to respond to previous SSRI/SNRI treatment, and for these people an alternative pharmacological intervention would be needed. Given that the evidence considered was for first-line treatment of chronic depressive symptoms and hence recommendations about further medication sequencing represented an extrapolation from the evidence, the committee agreed that it was appropriate to make this a 'consider' rather than an offer recommendation. There was some evidence for benefits of TCAs, phenelzine, low dose amisulpride, and moclobemide, and the committee agreed that these should be given as examples of pharmacological interventions that could be considered in circumstances where previous antidepressant treatment had failed. However, due to concerns around the tolerability of these drugs and potential drug interactions the committee agreed that these should only be prescribed in a specialist setting or after consultation with a specialist. The committee also agreed that a specialist setting was appropriate for people with chronic

depressive symptoms who have not responded to the interventions recommended for first-line and further-line treatment and therefore recommended referral to specialist mental health services for this group.

The committee were concerned that people with chronic depressive symptoms may remain on antidepressant medication for an extended period of time, even in the absence of significant clinical benefits. The committee agreed that for people on long-term antidepressant medication, who have not responded to the interventions recommended for first-line and further-line treatment, it is important to review the benefits of that medication, explore potential reasons why it might not be working and what other treatments may be helpful, and consider stopping the medication.

There was evidence from small single studies for benefits of cognitive-behavioural analysis system for psychotherapy (CBASP) or phenelzine in relapse prevention. However, this evidence was considered too limited to form the basis of a treatment recommendation for relapse prevention in people with chronic depressive symptoms.

The committee were aware of the high prevalence of chronic depressive symptoms in people aged over 75 years and the very limited evidence for the treatment of any type of depression in this age group. They therefore decided to develop a research recommendation to evaluate the effectiveness of psychological, pharmacological or a combination of these interventions in the treatment of older adults with chronic depressive symptoms.

The committee also discussed the fact that there had been some evidence for the role of MAOIs (phenelzine) for first-line treatment of chronic depression but none for further-line use and that further research was necessary to elucidate their role in chronic depression with anhedonia, and so they made a research recommendation.

The committee also discussed that in many people with chronic depression, there may be causal factors (such as loss of employment or relationship breakdown) which contribute to the chronicity but which are not addressed by standard treatments, and made a research recommendation to identify if focusing on these could enable more effective treatment.

Longer-term follow-up

There were no studies that reported outcomes after the end of treatment for first-line treatment, or relapse prevention, of chronic depression. When reviewing the endpoint evidence the committee were cognisant of the uncertainties around the sustainability of effects. However, the committee were able to draw on evidence from the further-line treatment review (Evidence review D) that suggested sustained benefits on depression outcomes associated with several psychological interventions including CBT, and given that CBT was shown to be effective for the first-line treatment of chronic depression, the committee had more confidence in their recommendations.

Quality of life and functioning outcomes

The committee also noted that there was very little data for quality of life or functioning outcomes. The committee considered the evidence for clinically important and statistically significant effects, and noted single-study analyses showing benefits of SSRIs and TCAs on functional impairment. Although the evidence was very limited, the committee agreed that given that the effects on functioning outcomes were generally in line with the benefits observed for critical outcomes, this strengthened their confidence in the recommendations.

Cost effectiveness and resource use

The committee considered the high healthcare costs and the burden associated with the presence of chronic depressive symptoms, and the benefits and cost-savings resulting from resolution of chronic depressive symptoms. Therefore, the committee focused the

interventions covered in this evidence review on people whose chronic depressive symptoms were having a significant impact on their overall personal and social functioning.

No evidence on the cost-effectiveness of interventions for adults with chronic depressive symptoms was identified and no further economic analysis was undertaken. The committee noted that evidence suggested that CBT, SSRIs and TCAs were effective in adults with chronic depressive symptoms and considered the results of the economic analysis for these treatments for adults with a new episode of depression that was undertaken for the guideline (evidence review B, appendix J). According to this, for populations with more severe depression, the combination of individual CBT with an antidepressant was likely to be one of the most cost-effective options for the treatment of new episodes, followed by a range of antidepressants (including SSRIs and TCAs) and psychological interventions (including individual CBT), all of which were more cost-effective than GP care alone. The committee expressed the view that effective combined treatment of an antidepressant (a SSRI or a TCA) with CBT that has a focus on chronic depressive symptoms and associated maintaining processes (avoidance, rumination, interpersonal difficulties), as well as antidepressants (SSRIs, TCAs) alone, and CBT with a focus on chronic depressive sympoms and associated maintaining processes alone, were likely to be cost-effective for people with chronic depressive symptoms too.

Therefore, the committee decided to recommend CBT, SSRIs, TCAs, or combination therapy of CBT with a SSRI or TCA for people who present with chronic depressive symptoms that significantly impair personal and social functioning and who have not received previous treatment for depression, as cost-effective treatment options, given the effectiveness results of the systematic review of treatments for adults with chronic depressive symptoms and the results of the guideline economic analysis for the treatment of adults with a new episode of depression (evidence review B, appendix J).

For people who have had, or are still receiving, treatment for depression and who present with chronic depressive symptoms, the committee decided to adopt the recommendations on further-line treatment (evidence review D), considering that the resource implications of those recommendations are not expected to be different in people with chronic depressive symptoms.

The committee acknowledged the additional costs associated with the provision of antidepressants such as SNRIs, phenelzine, moclobemide or amisulpride in specialist settings or after consultation with a specialist. These costs relate to specialist staff time, potentially higher drug acquisition costs (for example, moclobemide, although available in generic form, has higher acquisition costs compared with SSRIs and TCAs) and costs associated with treatment of side effects. However, the committee considered that these drugs may be the only or best option for a number of people who have not responded to SSRIs or TCAs, and that, due to their side effect profile, specialist support is needed for safe prescribing and monitoring. Based on the above considerations, the committee made a recommendation for alternative medication, for example SNRIs, phenelzine, moclobemide or amisulpride to be considered either in specialist settings or after consultation with a specialist, for people who have not responded to SSRIs or TCAs.

The committee were mindful that not all people with chronic depressive symptoms respond to treatment and as a consequence suffer considerable disability and social isolation. They therefore decided to modify the recommendation for this population in the 2009 guideline to offer social or vocational support to people with chronic depressive symptoms who would benefit from such support. Again given the low numbers to which this would apply and the fact that other non-health agencies may be involved in the provision of these interventions it should not have additional significant resource implications.

Other factors the committee took into account

No evidence was available for psychosocial interventions for chronic depressive symptoms as a study on befriending that had been included by the 2009 guideline did not meet the revised inclusion criteria in the protocol for this update, as this study had defined chronic depression as greater than 1 year instead of 2 years, and did not report the mean duration of depression. However, the committee recognised the potential benefit of additional social or vocational support, particularly given the lack of long-term data on psychological or pharmacological interventions and the potential for poor prognosis and long-term functional impairment, and on this basis the committee agreed to retain the recommendation from the 2009 guideline.

The committee were aware that a number of trials, often pragmatic trials, were excluded from the meta-analysis, typically because the samples in the trial were not first-line treatment or relapse prevention (but may also not have met criteria for the further-line treatment review if <80% were receiving further-line treatment): the committee used their knowledge of these trials in the round when interpreting the evidence from the systematic review and making recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.1 to 1.10.6 and 1.10.8 to 1.10.9 and research recommendations in the NICE guideline.

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Appendices

Appendix A – Review protocol

Review protocol for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Table 34: Review protocol

Field (based on PRISMA-P)	Content
Review question	For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?
Type of review question	Intervention review
Objective of the review	To identify the most effective strategy for the first-line treatment or relapse prevention of chronic depression or persistent subthreshold depression symptoms
Population	• Adults with chronic depression, defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales, for at least 2 years; persistent subthreshold symptoms (dysthymia); double depression (an acute episode of MDD superimposed on dysthymia) If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review.
Exclude	• Trials of women with antenatal or postnatal depression • Trials of children and young people (mean age under 18 years) • Trials of people with learning disabilities • Trials of people with bipolar disorder • Trials where more than 20% of the population have psychotic symptoms • Trials where more than 20% of the population have a coexisting personality disorder • Trials of further-line treatment following no/inadequate/limited response • Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) • Trials that specifically recruit participants with a physical health condition in addition to depression (e.g. depression in people with diabetes)

Field (based on PRISMA-P)	Content
Intervention	Interventions listed below are examples of interventions which may be included either alone or in combination: **Psychological interventions** • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) • Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT], third-wave cognitive therapies, Mindfulness-based Cognitive Therapy [MBCT] and Cognitive Behavioural Analysis System of Psychotherapy [CBASP]) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Interpersonal psychotherapy (IPT) • Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Psychoeducational interventions (including psychoeducational group programmes) • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) **Psychosocial interventions:** • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR]) **Pharmacological interventions** Antidepressants SSRIs • Citalopram • Escitalopram • Fluvoxamine • Fluoxetine • Paroxetine • Sertraline TCAs

Field (based on PRISMA-P)	Content
	• Amineptine[1] • Amitriptyline • Clomipramine • Desipramine[2] • Imipramine • Lofepramine • Nortriptyline MAOIs • Phenelzine TeCAs • Mianserin SNRIs • Duloxetine • Venlafaxine Other antidepressant drugs • Bupropion[3] • Mirtazepine • Moclobemide • Nefazodone[2] Antipsychotics • Amisulpride[3] • Aripiprazole[3] • Olanzapine[3] • Quetiapine[4] • Risperidone[3] • Ziprasidone[2] **Physical interventions**

Field (based on PRISMA-P)	Content
	• Acupuncture • Exercise • Yoga • ECT • Light therapy (for depression, not SAD)
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	**Critical outcomes:** Efficacy • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) • Relapse (number of participants who relapsed) The following depression scales will be included in the following hierarchy: • MADRS • HAMD • QIDS • PHQ • CGI (for dichotomous outcomes only) • CES-D • BDI • HADS-D (depression subscale) • HADS (full scale) Acceptability/tolerability • Discontinuation due to side effects (for pharmacological trials)

Field (based on PRISMA-P)	Content
	• Discontinuation due to any reason (including side effects) **Important outcomes:** • Quality of life: ○ Quality of life (as assessed with a validated scale, including the 12-item/36-item Short-Form Survey [SF-12/SF-36], 26-item short version of the World Health Organization Quality of Life assessment [WHOQOL-BRIEF], EuroQoL [EQ5D], Quality of Life Depression Scale [QLDS], Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q], Quality of Life Inventory [QoLI], and World Health Organization 5-item Well-Being Index [WHO-5]) • Personal, social, and occupational functioning: ○ Global functioning (as assessed with a validated scale, including Global Assessment of Functioning [GAF], Global Assessment Scale [GAS], and Social and Occupational Functioning Assessment Scale [SOFAS]) ○ Functional impairment (as assessed with a validated scale, including Sheehan Disability Scale [SDS], Social Adjustment Scale [SAS], and Work and Social Adjustment Scale [WSAS]) ○ Sleeping difficulties (as assessed with a validated scale, including Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI]) ○ Employment (for instance, % unemployed) ○ Interpersonal problems (as assessed with a validated scale, including Inventory of Interpersonal Problems [IIP]) Outcomes will be assessed at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, and >2 years).
Study design	Systematic reviews of RCTs RCTs
Include unpublished data?	Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted from elsewhere (for instance, from the previous guideline).
Restriction by date?	All relevant studies from existing reviews from the 2009 guideline and from previous searches (pre-2016) will be carried forward. No restriction on date for the updated search, studies published between database inception and the date the searches are run will be sought.
Minimum sample size	N = 10 in each arm

Field (based on PRISMA-P)	Content
	Studies with <50% completion data (drop out of >50%) will be excluded.
Study setting	Primary, secondary, tertiary and social care settings Non-English-language papers will be excluded (unless data can be obtained from an existing review).
The review strategy	**Data Extraction (selection and coding)** Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90%). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer. All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. **Data Analysis** A meta-analysis using a random-effects model will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible. Risk of bias will be assessed at the study level using the Cochrane risk of bias tool. This assessment includes: adequacy of randomisation (sufficient description of randomisation method, allocation concealment and any baseline difference between groups); blinding (of participants, intervention administrators and outcome assessors); attrition ('at risk of attrition bias' defined as a dropout of more than 20% and completer analysis used, or a difference of >20% between the groups); selective reporting bias (is the protocol registered, are all outcomes reported); other bias (for instance, conflict of interest in funding). Risk of bias will also be assessed at the outcome level using GRADE. For heterogeneity, outcomes will be downgraded once if I^2>50%, twice if I^2 >80%. For imprecision, outcomes will be downgraded using rules of thumb. If the 95% CI is imprecise i.e. crosses the line of no effect and the threshold for clinical benefit/harm, 0.8 or 1.25 (dichotomous) or -0.5 or 0.5 SMD (for continuous), the outcome will be downgraded. Outcomes will be downgraded one or two levels depending on how many lines it crosses. If the 95% CI is not imprecise, we will consider whether the criterion for Optimal Information Size is met (for dichotomous outcomes, 300 events; for continuous outcomes, 400 participants), if not we will downgrade one level.
Heterogeneity (sensitivity analysis and subgroups)	No planned sub-group analysis
Data management (software)	Endnote was used to sift through the references identified by the search, and for data extraction

Field (based on PRISMA-P)	Content
	Pairwise meta-analyses and production of forest plots was done using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome.
Notes	Studies investigating further-line treatment of chronic depression will be considered under RQ 2.4/2.5 and any differences in efficacy due to chronic depression will be examined through sub-analysis in that review. 1. Amineptine is not available to prescribe as a medicine (although it falls under Class C of the Misuse of Drugs Act 1971, and listed as Schedule 2 under the Controlled Drugs Regulations 2001). However, this drug is included in this review in order to assess the class effect of pharmacological interventions for depression 2. These drugs are not available in the UK to prescribe. However, they are included in this review in order to assess the class effect of pharmacological interventions for depression 3. None of these drugs are licensed for use in depression. However, they are included in the review in order to assess harms and efficacy for off-label use and to assess the class effect of pharmacological interventions for depression 4. Quetiapine is licensed for use as an adjunctive treatment of major depressive episodes with major depressive disorder but not as monotherapy
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Update of CG90 (2009)
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014

Field (based on PRISMA-P)	Content
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Navneet Kapur in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not applicable

BDI: beck depression inventory; CBASP: cognitive behavioural analysis system of psychotherapy; CBT: cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CG: clinical guideline; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: diagnostic and statistical manual of mental disorder; ECT: electroconvulsive therapy; EFT: emotion-focused therapy; EMDR: eye movement desensitization and reprocessing; EQ-5D: European quality of life-5 dimensions; GAF: global assessment of functioning; GAS: global assessment scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HAMD: Hamilton depression rating scale; ICD: international classification of diseases; IIP: inventory of interpersonal problems; IPT: interpersonal therapy; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–åsberg depression rating scale MAOI: monoamine oxidase inhibitor; MBCT: mindfulness-based cognitive therapy; MBSR: mindfulness-based stress reduction; MDD: major depressive disorder; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PHQ: patient health questionnaire; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depression symptomatology; QLDS: quality of life depression scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire; QOLI: Quality of life inventory; RCT: randomised controlled trial; REBT: rational, emotive behaviour therapy; RoB: risk of bias; SAD: seasonal affective disorder; SAS: social adjustment scale; SD: standard deviation; SDS: sheehan disability scale; SF12/36: 12-/36-item short form health survey ; SMD: standardised mean difference; SNRI: serotonin noradrenaline reuptake inhibitor; SOFAS: Social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant; WHOQOL-BRIEF: world health organization quality of life assessment (brief); WHO-5: world health organization 5-item wellbeing index; WSAS: work and social adjustment scale

Appendix B – Literature search strategies

Literature search strategies for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Clinical search

Database(s): Embase 1974 to 2019 Week 19, Emcare 1995 to present, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 14, 2019, PsycINFO 1806 to May Week 1 2019

Searched: 16/05/2019

Search updated: 04/06/2020

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use oemezd,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melanchol* or ((affective or mood) adj disorder*)).tw.
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	(exp psychotherapy/ or exp counseling/ or mindfulness/ or problem solving/ or psychiatric treatment/ or psychoeducation/ or self help/ or exp support group/) use oemezd,emcr
8	(exp Psychotherapy/ or Bibliotherapy/ or exp Cognitive Behavioral Therapy/ or exp Counseling/ or Problem Solving/ or Self Care/ or Self Efficacy/ or Self-Help Groups/) use ppez
9	(exp psychotherapy/ or behavioral activation system/ or bibliotherapy/ or cognitive therapy/ or exp counseling/ or group intervention/ or mindfulness/ or exp problem solving/ or psychoeducation/ or exp self-help techniques/ or support groups/) use psyh
10	((behavio* or abreact* or act* out* or age regression or assertive or autogenic or experiential) adj2 (activation or analys* or cathar* or condition* or intervention* or modification* or therap* or training or treatment*)).tw.
11	((cognitive adj2 (behavior* or therap*)) or (CBT* or CBASP or biofeedback or contingency management or covert conditioning or covert sensiti?ation or defusion or MBCT* or neurofeedback or problem focus* or problem solving or rational emotive or REBT or schema or solution focus*) or ((third wave or 3rd wave) adj2 (intervention* or therap* or treatment*))).tw.
12	(counsel* or ((art or creative or compassion* or conversation* or dialectic* or emotion* or group* or insight or narrative or non-directive or nondirective or non-specific or nonspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centred or person-centered or personal construct or persuasion or Rogerian or talking or time-limited) adj2 (intervention* or therap* or training or treatment*))).tw.
13	(psychotherap* or (psycho* adj (aid* or help* or intervention* or support* or therap* or training or treatment*)) or (balint group or group program* or mindfulness* or mind training or role play* or support group*)).tw.
14	(self-help or bibliotherap* or meditat* or self-analy* or self-esteem or self-control or self-imag* or self-validat* or stress manag* or (computer* adj2 (intervention* or program* or therap* or treatment*)) or CCBT).tw.
15	or/7-14
16	drug therapy/ or drug therapy.fs.
17	psychopharmacotherapy/ use oemezd,emcr,psyh
18	antidepressant agent/ use oemezd,emcr
19	Antidepressive Agents/ use ppez
20	antidepressant drugs/ use psyh
21	serotonin uptake inhibitor/ use oemezd,emcr
22	Serotonin Uptake Inhibitors/ use ppez
23	serotonin reuptake inhibitors/ use psyh
24	serotonin noradrenalin reuptake inhibitor/ use oemezd,emcr
25	"Serotonin and Noradrenaline Reuptake Inhibitors"/ use ppez

#	Searches
26	serotonin norepinephrine reuptake inhibitors/ use psyh
27	tricyclic antidepressant agent/ use oemezd,emcr
28	Antidepressive Agents, Tricyclic/ use ppez
29	tricyclic antidepressant drugs/ use psyh
30	monoamine oxidase inhibitor/ use oemezd,emcr
31	monoamine oxidase inhibitors/ use ppez,psyh
32	tetracyclic antidepressive agent/ use oemezd,emcr
33	amfebutamone/ or amineptine/ or amitriptyline/ or bupropion/ or clomipramine/ or chlorimipramine/ or citalopram/ or desipramine/ or duloxetine/ or Duloxetine Hydrochloride/ or escitalopram/ or fluvoxamine/ or fluoxetine/ or imipramine/ or lofepramine/ or mianserin/ or mirtazapine/ or moclobemide/ or nefazadone/ or nortriptyline/ or paroxetine/ or phenelzine/ or sertraline/ or venlafaxine/ or Venlafaxine Hydrochloride/
34	(antidepress* or amfebutamone or amineptin* or amitr?ptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mianserin or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or phenelzin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or TeCA* or tetracyclic or tricyclic or ((monoamine or serotonin) adj2 inhibitor*)).tw.
35	or/16-34
36	(anticonvulsive agent/ or anticonvulsant therapy/) use oemezd,emcr
37	Anticonvulsants/ use ppez
38	anticonvulsive drugs/ use psyh
39	lamotrigine/ or (lamotrigine or anticonvul* or anti-convul*).tw.
40	or/38-39
41	neuroleptic agent/ use oemezd,emcr
42	Antipsychotic Agents/ use ppez
43	neuroleptic drugs/ use psyh
44	amisulpride/ or aripiprazole/ or olanzapine/ or quetiapine/ or Quetiapine Fumarate/ or risperidone/ or ziprasidone/
45	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone).tw.
46	or/41-45
47	anxiolytic agent/ use oemezd,emcr
48	Anti-Anxiety Agents/ use ppez
49	tranquilizing drugs/ use psyh
50	buspirone/
51	(anxiolytic* or antianxiet* or anti-anxiet* or tranquili* or buspirone).tw.
52	or/47-51
53	central stimulant agent/ use oemezd,emcr
54	Central Nervous System Stimulants/ use ppez
55	CNS stimulating drugs/ use psyh
56	methylphenidate/ or (methylphenidate or ritalin).tw.
57	or/53-56
58	lithium/ or lithium.tw.
59	omega 3 fatty acid/ use oemezd,emcr
60	Fatty Acids, Omega-3/ use ppez
61	fatty acids/ use psyh
62	(omega adj ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)).tw.
63	thyroid hormone/ use oemezd,emcr
64	Thyroid Hormones/ use ppez
65	exp thyroid hormones/ use psyh
66	(thyroid hormone* or calcitonin or dextrothyroxine or diiodotyrosine or monoiodotyrosine or thyronines or thyroxine).tw.
67	or/58-66
68	acupuncture/ or acupuncture.tw.
69	electroconvulsive therapy/ use oemezd,emcr,ppez
70	electroconvulsive shock therapy/ use psyh
71	(ECT or ((electroconvuls* or electro-convuls*) adj2 (therap* or treatment*)) or electroshock* or (shock adj (therap* or treatment*))).tw.
72	exp exercise/
73	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Swimming/ or Walking/) use ppez
74	(exp kinesiotherapy/ or exp physical activity/ or fitness/ or exp sport/) use oemezd,emcr
75	(exp physical fitness/ or exp sports/) use psyh
76	yoga/
77	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking).tw.
78	or/68-77
79	peer group/ or mentoring/
80	peer relations/ use psyh
81	friendship/
82	Friends/ use ppez
83	(befriend* or friend* or mentor* or peer group* or peer support or (communit* adj (navigat* or support*))).tw.

#	Searches
84	or/79-83
85	or/15,35,40,46,52,57,67,78,84
86	6 and 85
87	Letter/ use ppez
88	letter.pt. or letter/ use oemezd,emcr
89	note.pt.
90	editorial.pt.
91	Editorial/ use ppez
92	News/ use ppez
93	exp Historical Article/ use ppez
94	Anecdotes as Topic/ use ppez
95	Comment/ use ppez
96	Case Report/
97	case study/ use oemezd,emcr
98	(letter or comment*).ti.
99	or/87-98
100	randomized controlled trial/
101	random*.ti,ab.
102	100 or 101
103	99 not 102
104	(animals/ not humans/) use ppez
105	(animal/ not human/) use oemezd,emcr
106	nonhuman/ use oemezd,emcr
107	exp animals/ use psyh
108	"primates (nonhuman)"/ use psyh
109	exp Animals, Laboratory/ use ppez
110	exp Animal Experimentation/ use ppez
111	exp animal experiment/ use oemezd,emcr
112	exp experimental animal/ use oemezd,emcr
113	exp Models, Animal/ use ppez
114	animal model/ use oemezd,emcr
115	animal models/ use psyh
116	animal research/ use psyh
117	exp Rodentia/ use ppez
118	exp rodent/ use oemezd,emcr
119	exp rodents/ use psyh
120	(rat or rats or mouse or mice).ti.
121	or/103-120
122	86 not 121
123	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
124	123 use ppez
125	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
126	125 use ppez
127	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
128	127 use oemezd,emcr
129	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
130	129 use psyh
131	124 or 126
132	128 or 130 or 131
133	Meta-Analysis/
134	exp Meta-Analysis as Topic/
135	systematic review/
136	meta-analysis/
137	(meta analy* or metanaly* or metaanaly*).ti,ab.
138	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
139	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
140	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
141	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
142	(search* adj4 literature).ab.
143	(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.
144	cochrane.jw.
145	((pool* or combined) adj2 (data or trials or studies or results)).ab.
146	(or/133-135,137,139-144) use ppez
147	(or/135-138,140-145) use oemezd,emcr

#	Searches
148	(or/133,137,139-144) use psyh
149	or/146-148
150	network meta-analysis/
151	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
152	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
153	or/150-152
154	or/132,149,153
155	122 and 154
156	limit 155 to english language
157	limit 156 to yr="2016 -Current"

The Cochrane Library, issue 5 of 12, May 2019

Searched: 21/05/2019

Search updated: 05/06/2020

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melancholo* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or ill-health)) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	MeSH descriptor: [Psychotherapy] explode all trees
#11	MeSH descriptor: [Bibliotherapy] this term only
#12	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
#13	MeSH descriptor: [Counseling] explode all trees
#14	MeSH descriptor: [Problem Solving] this term only
#15	MeSH descriptor: [Self Care] this term only
#16	MeSH descriptor: [Self Efficacy] this term only
#17	MeSH descriptor: [Self-Help Groups] this term only
#18	((behaviour* or behavior* or abreact* or "act* out*" or "age regression" or assertive or autogenic or experiential) next/2 (activation or analys* or cathar* or condition* or intervention* or modification* or therap* or training or treatment*)):ti,ab
#19	((cognitive next/2 (behavio* or therap*)) or (CBT* or CBASP or biofeedback or "contingency management" or "covert conditioning" or "covert sensitisation" or "covert sensiitization" or defusion or MBCT* or neurofeedback or "problem focus*" or "problem solving" or "rational emotive" or REBT or schema or "solution focus*") or (("third wave" or "3rd wave") next (intervention* or therap* or treatment*))):ti,ab
#20	(counsel* or ((art or creative or compassion* or conversation* or dialectic* or emotion* or group* or insight or narrative or non-directive or nondirective or non-specific or nonspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centred or person-centered or "personal construct*" or persuasion or Rogerian or talking or time-limited) next (intervention* or therap* or training or treatment*))):ti,ab
#21	(psychotherap* or (psycho* next (aid* or help* or intervention* or support* or therap* or training or treatment*)) or ("balint group*" or "group program*" or mindfulness* or "mind training" or "role play*" or "support group*")):ti,ab
#22	(self-help or bibliotherap* or meditat* or self-analy* or self-esteem or self-control or self-imag* or self-validat* or "stress manag*" or (computer* next/2 (intervention* or program* or therap* or treatment*)) or CCBT):ti,ab
#23	MeSH descriptor: [Drug Therapy] this term only
#24	MeSH descriptor: [Antidepressive Agents] this term only
#25	MeSH descriptor: [Serotonin Uptake Inhibitors] this term only
#26	MeSH descriptor: [Serotonin and Noradrenaline Reuptake Inhibitors] this term only
#27	MeSH descriptor: [Antidepressive Agents, Tricyclic] this term only
#28	MeSH descriptor: [Monoamine Oxidase Inhibitors] this term only
#29	MeSH descriptor: [Bupropion] this term only
#30	MeSH descriptor: [Amitriptyline] this term only
#31	MeSH descriptor: [Bupropion] this term only
#32	MeSH descriptor: [Clomipramine] this term only
#33	MeSH descriptor: [Clomipramine] this term only
#34	MeSH descriptor: [Citalopram] this term only
#35	MeSH descriptor: [Desipramine] this term only
#36	MeSH descriptor: [Duloxetine Hydrochloride] this term only
#37	MeSH descriptor: [Citalopram] this term only

ID	Search
#38	MeSH descriptor: [Fluvoxamine] this term only
#39	MeSH descriptor: [Fluoxetine] this term only
#40	MeSH descriptor: [Imipramine] this term only
#41	MeSH descriptor: [Lofepramine] this term only
#42	MeSH descriptor: [Mianserin] this term only
#43	MeSH descriptor: [Mirtazapine] this term only
#44	MeSH descriptor: [Moclobemide] this term only
#45	MeSH descriptor: [Nortriptyline] this term only
#46	MeSH descriptor: [Paroxetine] this term only
#47	MeSH descriptor: [Phenelzine] explode all trees
#48	MeSH descriptor: [Sertraline] this term only
#49	MeSH descriptor: [Venlafaxine Hydrochloride] this term only
#50	(antidepress* or amfebutamone or amineptin* or amitriptylin* or amitryptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mianserin or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or phenelzin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or TeCA* or tetracyclic or tricyclic or ((monoamine or serotonin) next/2 inhibitor*)):ti,ab
#51	MeSH descriptor: [Anticonvulsants] this term only
#52	MeSH descriptor: [Lamotrigine] this term only
#53	(lamotrigine or anticonvul* or anti-convul*):ti,ab
#54	MeSH descriptor: [Antipsychotic Agents] this term only
#55	MeSH descriptor: [Amisulpride] this term only
#56	MeSH descriptor: [Aripiprazole] this term only
#57	MeSH descriptor: [Olanzapine] this term only
#58	MeSH descriptor: [Quetiapine Fumarate] this term only
#59	MeSH descriptor: [Risperidone] this term only
#60	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone):ti,ab
#61	MeSH descriptor: [Anti-Anxiety Agents] this term only
#62	MeSH descriptor: [Buspirone] this term only
#63	(anxiolytic* or antianxiet* or anti-anxiet* or tranquilis* or tranquiliz* or buspirone):ti,ab
#64	MeSH descriptor: [Central Nervous System Stimulants] this term only
#65	MeSH descriptor: [Methylphenidate] this term only
#66	(methylphenidate or ritalin):ti,ab
#67	MeSH descriptor: [Lithium] this term only
#68	lithium:ti,ab
#69	MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
#70	(omega next/2 ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)):ti,ab
#71	MeSH descriptor: [Thyroid Hormones] explode all trees
#72	("thyroid hormone*" or calcitonin or dextrothyroxine or diiodotyrosine or monoiodotyrosine or thyronines or thyroxine):ti,ab
#73	MeSH descriptor: [Acupuncture] this term only
#74	acupuncture:ti,ab
#75	MeSH descriptor: [Electroconvulsive Therapy] this term only
#76	(ECT or ((electroconvuls* or electro-convuls*) next/2 (therap* or treatment*)) or electroshock* or (shock next (therap* or treatment*))):ti,ab
#77	MeSH descriptor: [Exercise Therapy] explode all trees
#78	MeSH descriptor: [Physical Exertion] this term only
#79	MeSH descriptor: [Physical Fitness] explode all trees
#80	MeSH descriptor: [Bicycling] this term only
#81	MeSH descriptor: [Running] explode all trees
#82	MeSH descriptor: [Swimming] this term only
#83	MeSH descriptor: [Walking] this term only
#84	MeSH descriptor: [Yoga] this term only
#85	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking):ti,ab
#86	MeSH descriptor: [Peer Group] this term only
#87	MeSH descriptor: [Mentoring] this term only
#88	MeSH descriptor: [Friends] this term only
#89	(befriend* or friend* or mentor* or "peer group*" or "peer support" or (communit* next (navigat* or support*))):ti,ab
#90	{or #10-#89}
#91	#9 and #90 with Cochrane Library publication date Between Jan 2016 and May 2019, in Cochrane Reviews, Cochrane Protocols, Trials

Health Economics search

Database(s): Embase 1974 to 2019 Week 08, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 26, 2019, PsycINFO 1806 to February Week 1 2019

Searched: 27/02/2019

Search updated: 02/03/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysphoria/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or "mixed depression and dementia"/ or premenstrual dysphoric disorder/ or reactive depression/ or recurrent brief depression/ or seasonal affective disorder/ or treatment resistant depression/) use oemezd
2	((Depression/ or exp Depressive Disorder/ or Adjustment Disorders/ or Affective Disorders, Psychotic/ or Factitious Disorders/ or Premenstrual Dysphoric Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/ or premenstrual dysphoric disorder/ or seasonal affective disorder/) use psyh
4	(depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder* or ((affective or mood) adj disorder*)).tw.
5	or/1-4
6	Letter/ use ppez
7	letter.pt. or letter/ use oemezd
8	note.pt.
9	editorial.pt.
10	Editorial/ use ppez
11	News/ use ppez
12	exp Historical Article/ use ppez
13	Anecdotes as Topic/ use ppez
14	Comment/ use ppez
15	Case Report/
16	case study/ use oemezd
17	(letter or comment*).ti.
18	or/6-17
19	randomized controlled trial/
20	random*.ti,ab.
21	19 or 20
22	18 not 21
23	(animals/ not humans/) use ppez
24	(animal/ not human/) use oemezd
25	nonhuman/ use oemezd
26	exp animals/ use psyh
27	"primates (nonhuman)"/ use psyh
28	exp Animals, Laboratory/ use ppez
29	exp Animal Experimentation/ use ppez
30	exp animal experiment/ use oemezd
31	exp experimental animal/ use oemezd
32	exp Models, Animal/ use ppez
33	animal model/ use oemezd
34	animal models/ use psyh
35	animal research/ use psyh
36	exp Rodentia/ use ppez
37	exp rodent/ use oemezd
38	exp rodents/ use psyh
39	(rat or rats or mouse or mice).ti.
40	or/22-39
41	5 not 40
42	Economics/
43	Value of life/
44	exp "Costs and Cost Analysis"/
45	exp Economics, Hospital/
46	exp Economics, Medical/
47	Economics, Nursing/
48	Economics, Pharmaceutical/
49	exp "Fees and Charges"/
50	exp Budgets/
51	(or/42-50) use ppez
52	health economics/
53	exp economic evaluation/
54	exp health care cost/
55	exp fee/
56	budget/

#	Searches
57	funding/
58	(or/52-57) use oemezd
59	exp economics/
60	exp "costs and cost analysis"/
61	cost containment/
62	money/
63	resource allocation/
64	(or/59-63) use psyh
65	budget*.ti,ab.
66	cost*.ti.
67	(economic* or pharmaco?economic*).ti.
68	(price* or pricing*).ti,ab.
69	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
70	(financ* or fee or fees).ti,ab.
71	(value adj2 (money or monetary)).ti,ab.
72	or/65-70
73	51 or 58 or 64 or 72
74	Quality-Adjusted Life Years/ use ppez
75	Sickness Impact Profile/
76	quality adjusted life year/ use oemezd
77	"quality of life index"/ use oemezd
78	(quality adjusted or quality adjusted life year*).tw.
79	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
80	(illness state* or health state*).tw.
81	(hui or hui2 or hui3).tw.
82	(multiattibute* or multi attribute*).tw.
83	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
84	utilities.tw.
85	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
86	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
87	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
88	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
89	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
90	Quality of Life/ and ec.fs.
91	Quality of Life/ and (health adj3 status).tw.
92	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
93	(quality of life or qol).tw. and cost benefit analysis/ use oemezd
94	(quality of life or qol).tw. and "costs and cost analysis"/ use psyh
95	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
96	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
97	cost benefit analysis/ use oemezd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
98	"costs and cost analysis"/ use psyh and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
99	*quality of life/ and (quality of life or qol).ti.
100	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
101	quality of life/ and health-related quality of life.tw.
102	Models, Economic/ use ppez
103	economic model/ use oemezd
104	or/74-101
105	73 or 104
106	41 and 105
107	limit 106 to english language
108	limit 107 to yr="2016 -Current"

Database(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA)

Searched: 26/02/2019

#	Searches
#1	MESH DESCRIPTOR: depressive disorder EXPLODE ALL TREES
#2	((depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder* or affective disorder* or mood disorder*))

#	Searches
#3	#1 or #2 IN HTA FROM 2016 TO 2019

Database(s): CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature) 1937-current, EBSCO Host

Searched: 26/02/2019

Search updated: 02/03/2021

#	Query	Limiters/Expanders
S31	S4 AND S30	Limiters - Publication Year: 2016-2019; Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S30	S10 OR S29	Search modes - Boolean/Phrase
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S28	(MH "Quality of Life") AND TX (health-related quality of life)	Search modes - Boolean/Phrase
S27	(MH "Quality of Life") AND TI (quality of life or qol)	Search modes - Boolean/Phrase
S26	AB ((qol or hrqol or quality of life) AND ((qol or hrqol* or quality of life) N2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)))	Search modes - Boolean/Phrase
S25	(MH "Cost Benefit Analysis") AND TX ((quality of life or qol) or (cost-effectiveness ratio* and (perspective* or life expectanc*))	Search modes - Boolean/Phrase
S24	(MH "Quality of Life") TX (health N3 status)	Search modes - Boolean/Phrase
S23	(MH "Quality of Life") AND TX ((quality of life or qol) N (score*1 or measure*1))	Search modes - Boolean/Phrase
S22	TX (time trade off*1 or time tradeoff*1 or tto or timetradeoff*1)	Search modes - Boolean/Phrase
S21	TX (sf36 or sf 36 or sf thirty six or sf thirtysix)	Search modes - Boolean/Phrase
S20	TX (euro* N3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*))	Search modes - Boolean/Phrase
S19	TX (eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol)	Search modes - Boolean/Phrase
S18	TI utilities	Search modes - Boolean/Phrase
S17	TX (utilit* N3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*))	Search modes - Boolean/Phrase
S16	TX (multiattibute* or multi attribute*)	Search modes - Boolean/Phrase
S15	TX (hui or hui2 or hui3)	Search modes - Boolean/Phrase
S14	TX (illness state* or health state*)	Search modes - Boolean/Phrase
S13	TX (quality adjusted or quality adjusted life year*or qaly* or qal or qald* or qale* or qtime* or qwb* or daly)	Search modes - Boolean/Phrase
S12	(MH "Sickness Impact Profile")	Search modes - Boolean/Phrase
S11	(MH "Quality-Adjusted Life Years")	Search modes - Boolean/Phrase
S10	S5 OR S6 OR S7 OR S8 OR S9	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S9	TX (value N2 (money or monetary))	Search modes - Boolean/Phrase
S8	TX (cost* N2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*))	Search modes - Boolean/Phrase
S7	TI cost* or economic* or pharmaco?economic*	Search modes - Boolean/Phrase
S6	TX budget* or fee or fees or finance* or price* or pricing	Search modes - Boolean/Phrase
S5	(MH "Fees and Charges+") OR (MH "Costs and Cost Analysis+") OR (MH "Economics") OR (MH "Economic Value of Life") OR (MH "Economics, Pharmaceutical") OR (MH "Economic Aspects of Illness") OR (MH "Resource Allocation+")	Search modes - Boolean/Phrase
S4	S1 OR S2 OR S3	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S3	TX (depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder)	Search modes - Boolean/Phrase
S2	(MH "Adjustment Disorders+") OR (MH "Factitious Disorders") OR (MH "Affective Disorders, Psychotic")	Search modes - Boolean/Phrase
S1	(MH "Depression+") OR (MH "Premenstrual Dysphoric Disorder") OR (MH "Seasonal Affective Disorder")	Search modes - Boolean/Phrase

Additional EMDR search

Database(s): Embase 1980 to 2021 Week 43, Emcare 1995 to present, Ovid MEDLINE(R) ALL 1946 to November 03, 2021, APA PsycInfo 1806 to November Week 1 2021

Date of Search: 04/11/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use emez,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use medall
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melanchol* or ((affective or mood) adj disorder*)).tw.
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	(eye movement desensiti?ation or EMDR).tw.
8	6 and 7
9	Meta-Analysis/
10	exp Meta-Analysis as Topic/
11	systematic review/
12	meta-analysis/
13	(meta analy* or metanaly* or metaanaly*).ti,ab.
14	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
15	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
16	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
17	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
18	(search* adj4 literature).ab.
19	(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.
20	cochrane.jw.
21	((pool* or combined) adj2 (data or trials or studies or results)).ab.
22	(or/9-11,13,15-20) use medall
23	(or/11-14,16-21) use emez,emcr
24	(or/9,13,15-20) use psyh
25	or/22-24
26	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
27	26 use medall
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
29	28 use medall
30	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
31	30 use emez,emcr
32	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
33	32 use psyh
34	27 or 29
35	31 or 33 or 34
36	network meta-analysis/
37	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
38	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
39	or/36-38
40	25 or 35 or 39
41	8 and 40
42	limit 41 to english language

The Cochrane Library, issue 10 of 12, October 2021

Date of search: 04/11/2021

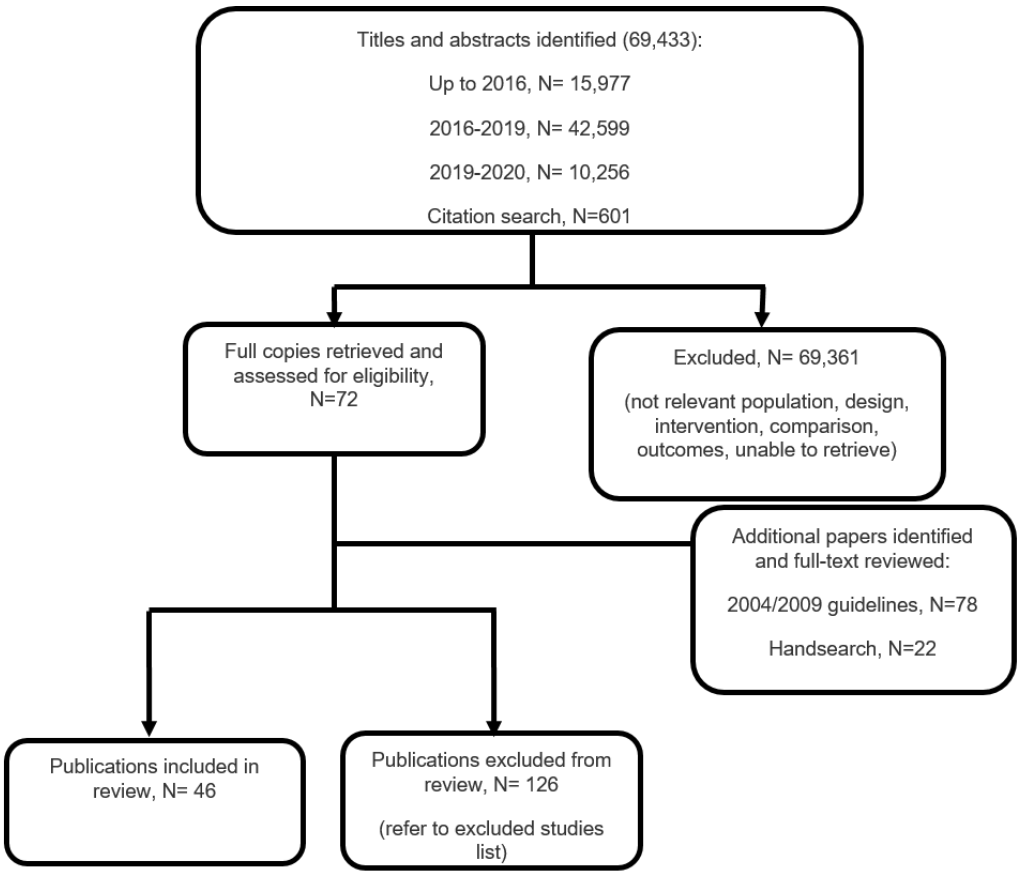
ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only

ID	Search
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or "ill health")) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	("eye movement desensitisation" or "eye movement desensitization" or EMDR):ti,ab
#11	#9 and #10

Appendix C – Clinical evidence study selection

Study selection for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Please refer to the clinical evidence tables in supplement E – Clinical evidence tables for review question 2.6 Chronic depression

Appendix E – Forest plots

Forest plots for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Comparison 1: CBT (individual) versus pill placebo for chronic depression (MDD ≥ 2 years)

Figure 2: Depression symptomatology change score

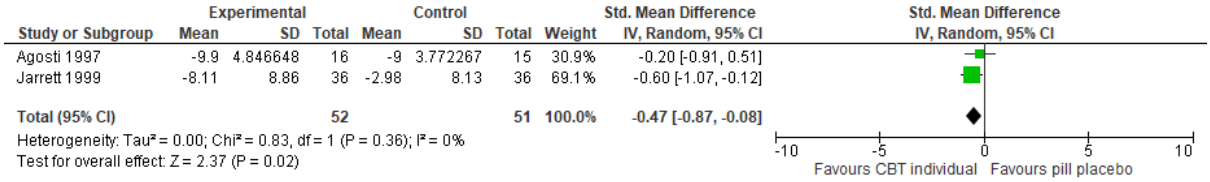


Figure 3: Remission

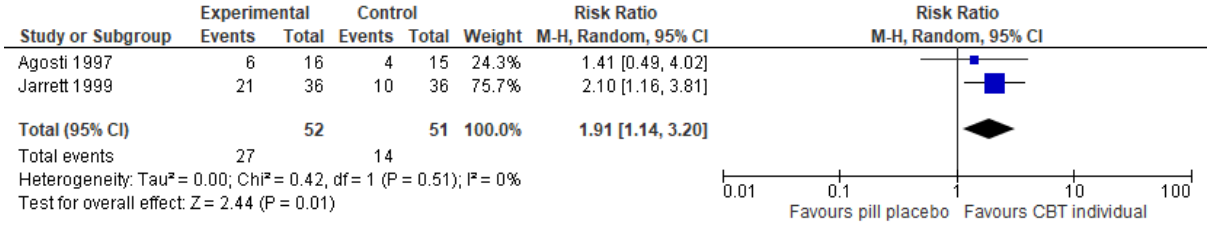
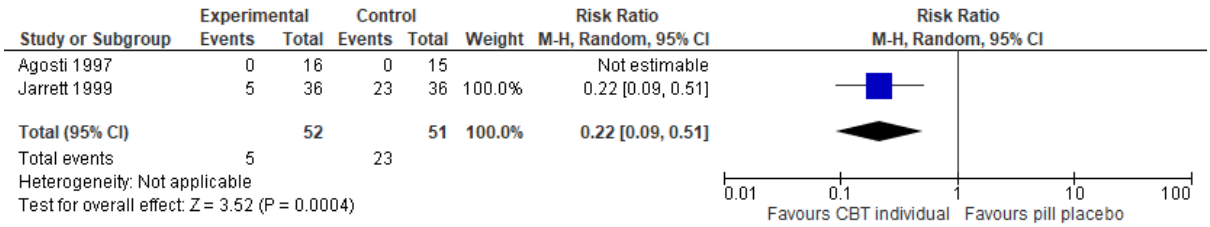


Figure 4: Discontinuation due to any reason



Comparison 2: CBT (individual) versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Figure 5: Depression symptomatology change score

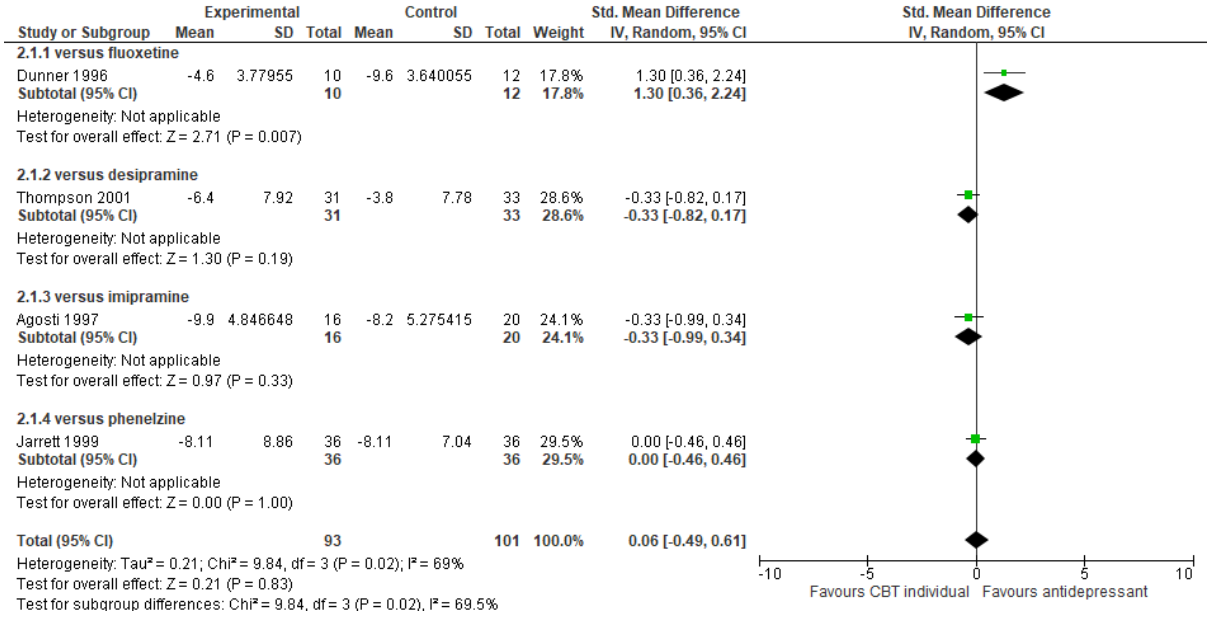


Figure 6: Remission

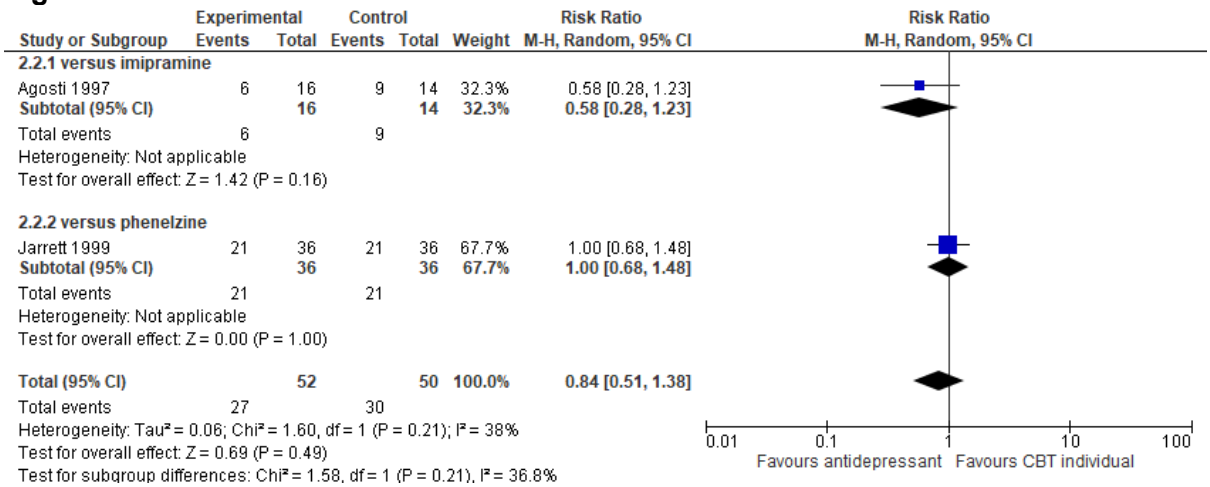
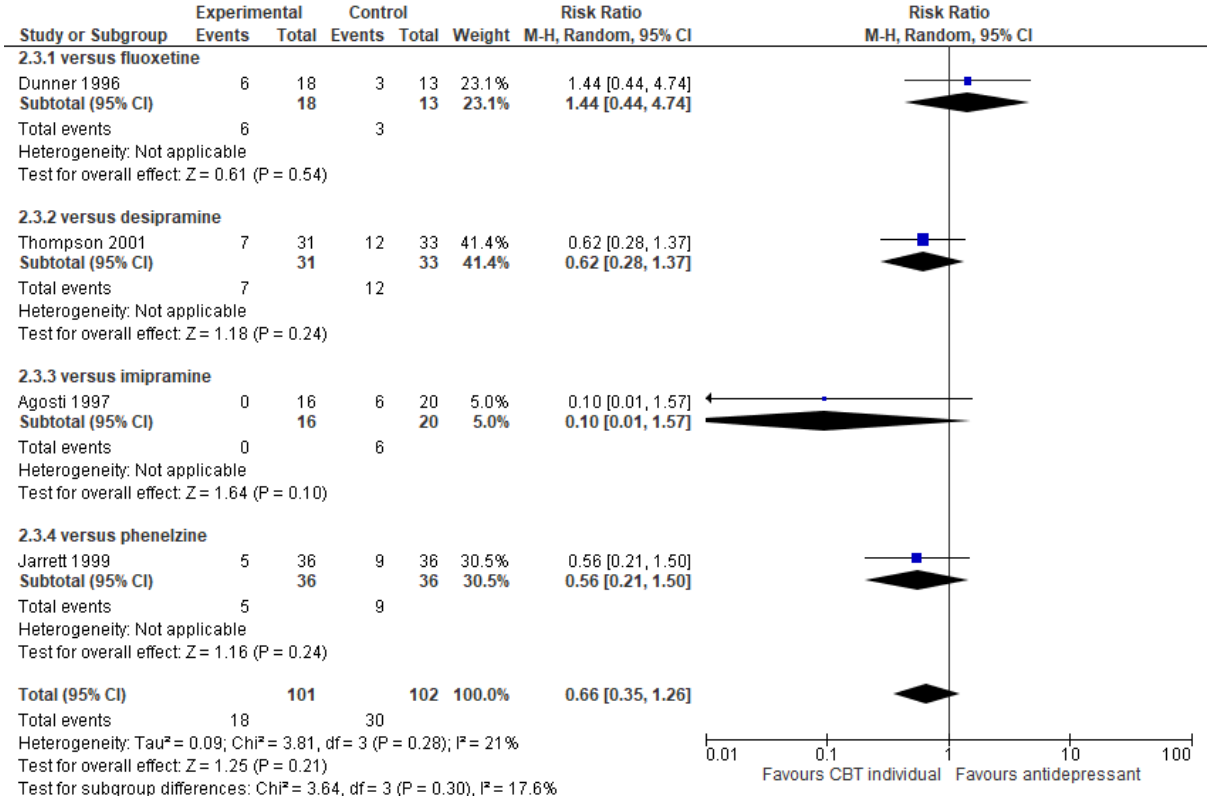


Figure 7: Discontinuation due to any reason



Comparison 3: CBT (individual) versus IPT for chronic depression (MDD ≥ 2 years)

Figure 8: Depression symptomatology change score

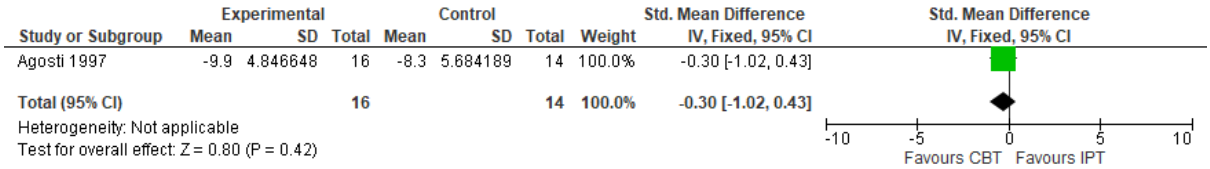


Figure 9: Remission

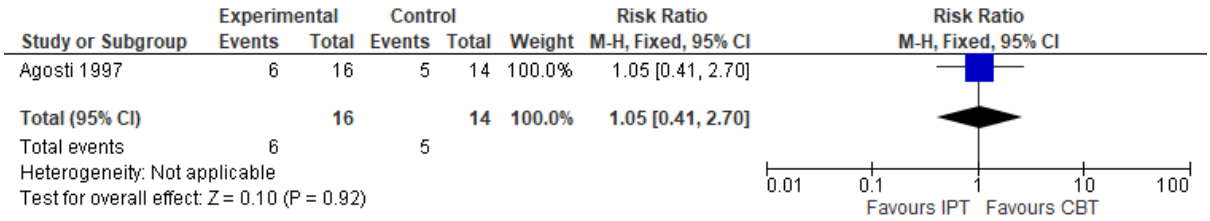
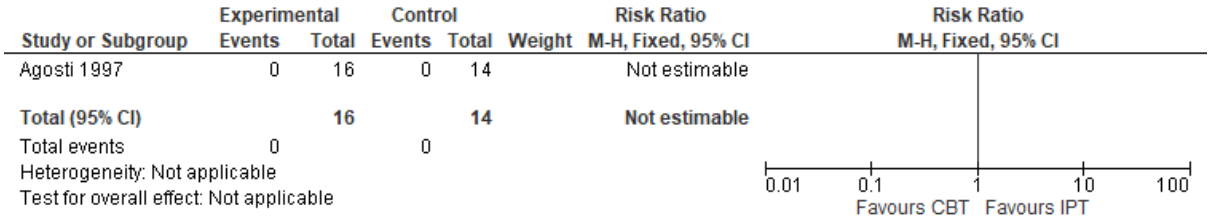


Figure 10: Discontinuation due to any reason



Comparison 4: Cognitive-behavioural analysis system for psychotherapy (CBASP) versus assessment-only for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Figure 11: Depression symptomatology change score

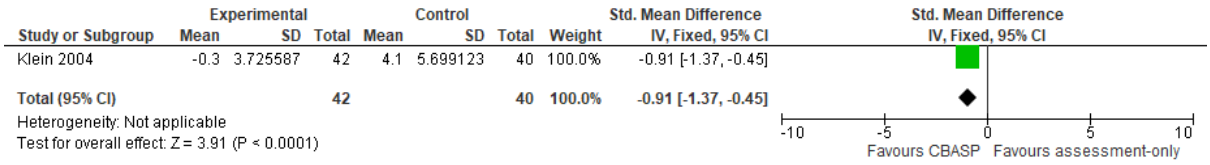


Figure 12: Relapse

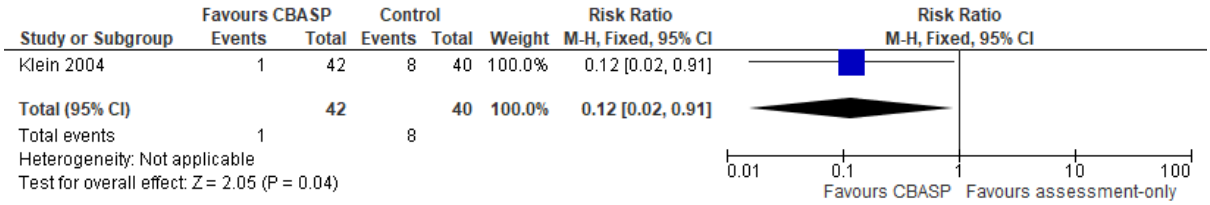


Figure 13: Discontinuation due to any reason

Comparison 5: CBT individual + desipramine versus desipramine for chronic depression (MDD ≥2 years)

Figure 14: Depression symptomatology change score

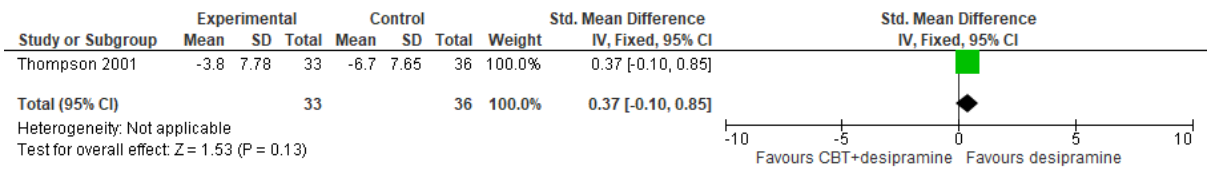
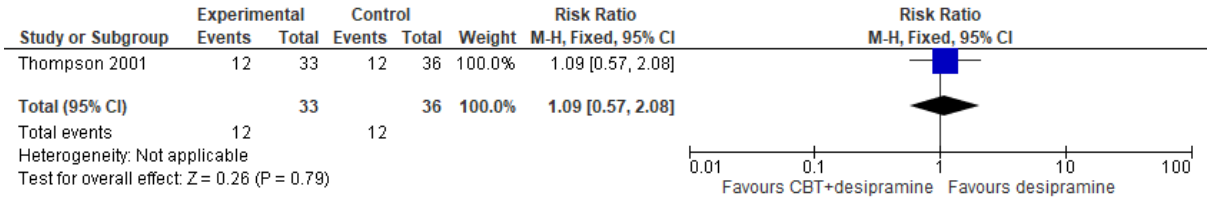


Figure 15: Discontinuation for any reason



Comparison 6: Mindfulness-based cognitive therapy (MBCT) group + medication versus medication for dysthymia or double depression

Figure 16: Depression symptomatology change score

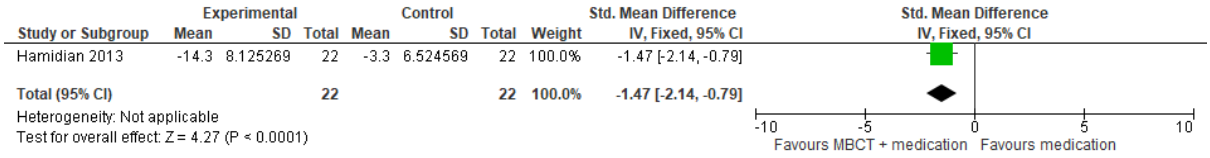
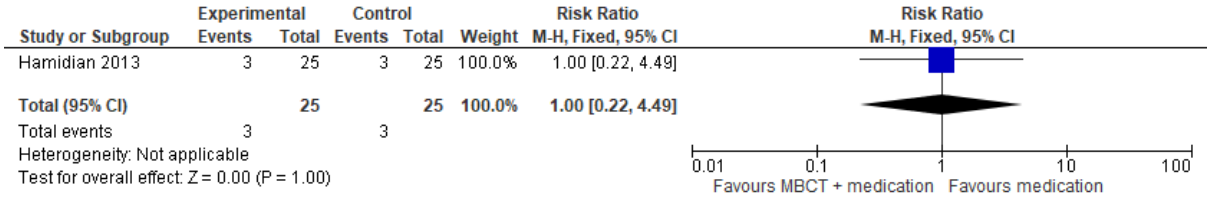


Figure 17: Discontinuation due to any reason



Comparison 7: CBT individual + fluoxetine versus fluoxetine for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Figure 18: Depression symptomatology change score

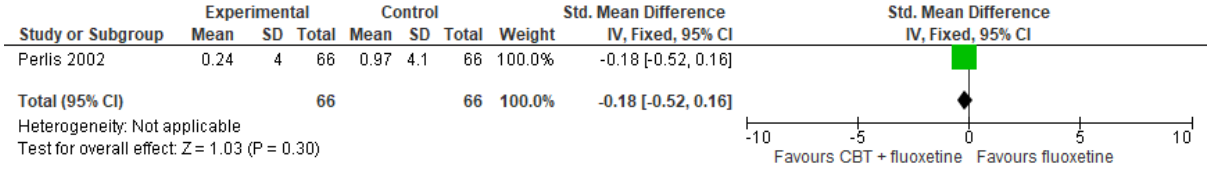


Figure 19: Relapse

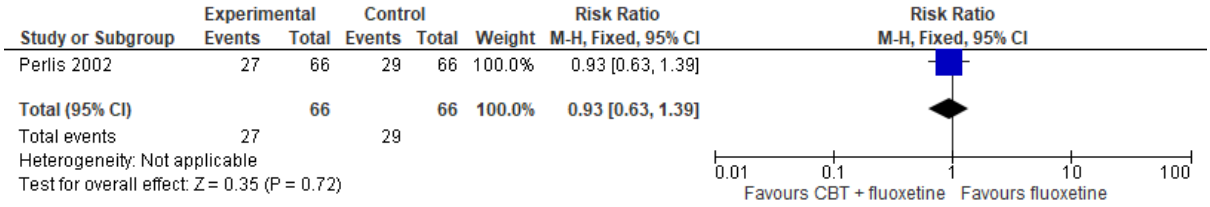


Figure 20: Discontinuation due to side effects

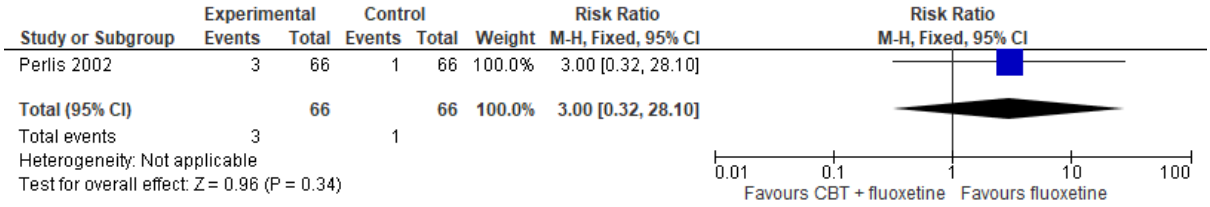
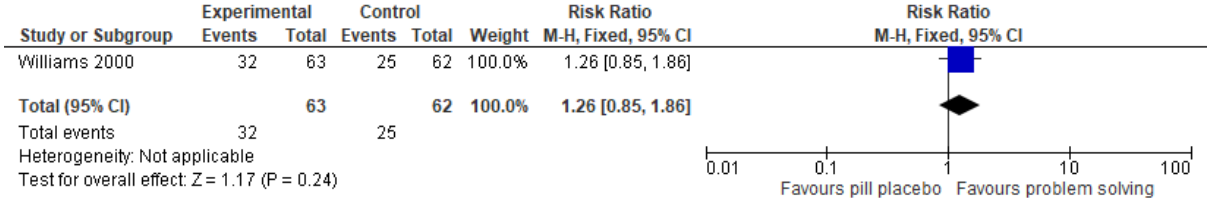


Figure 21: Discontinuation due to any reason

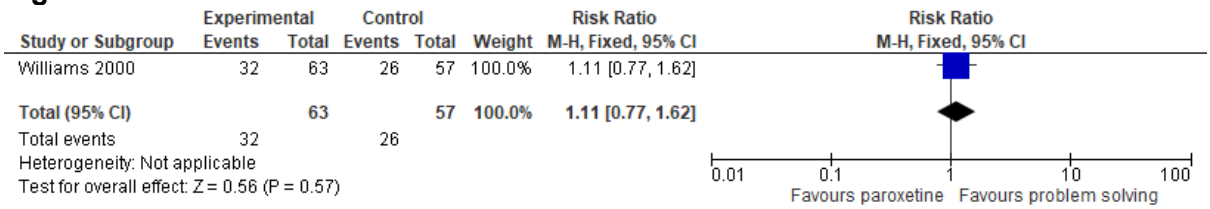
Comparison 8: Problem solving versus pill placebo for dysthymia

Figure 22: Remission



Comparison 9: Problem solving versus paroxetine for dysthymia

Figure 23: Remission



Comparison 10: IPT versus pill placebo for chronic depression (MDD ≥ 2 years)

Figure 24: Depression symptomatology change score

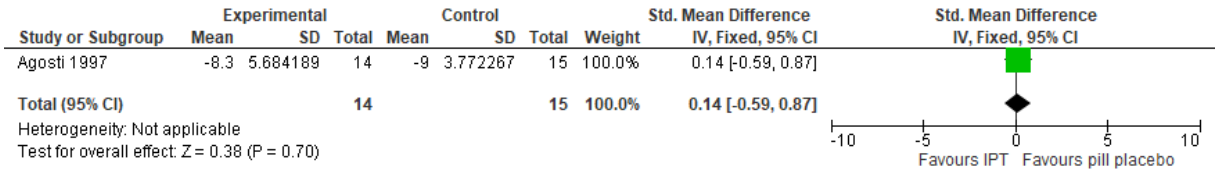


Figure 25: Remission

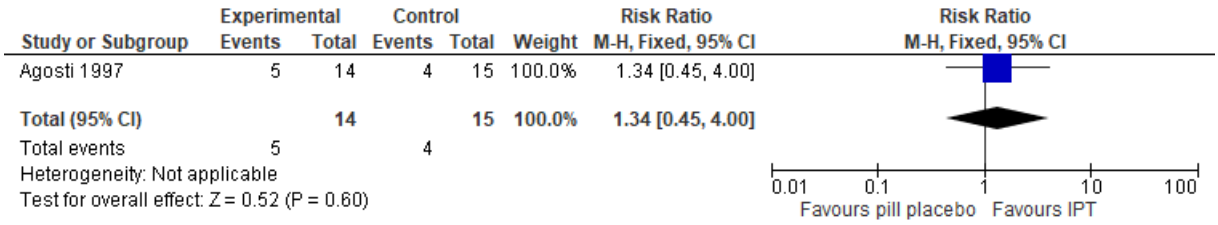
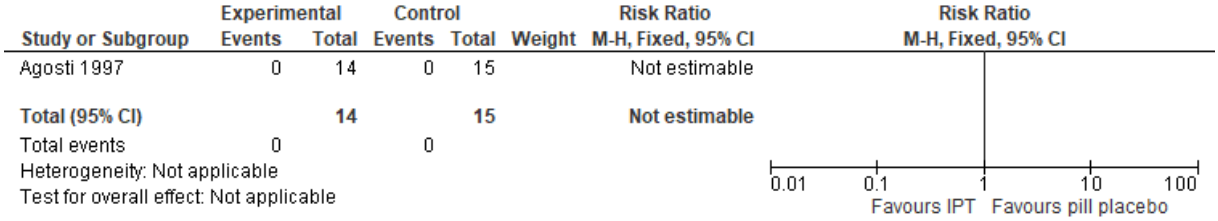


Figure 26: Discontinuation due to any reason



Comparison 11: IPT versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Figure 27: Depression symptomatology change score

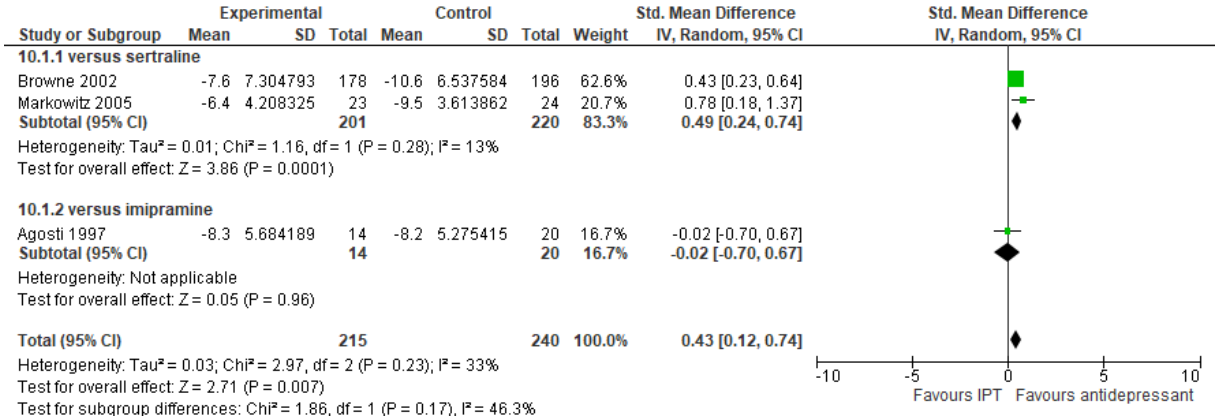


Figure 28: Remission

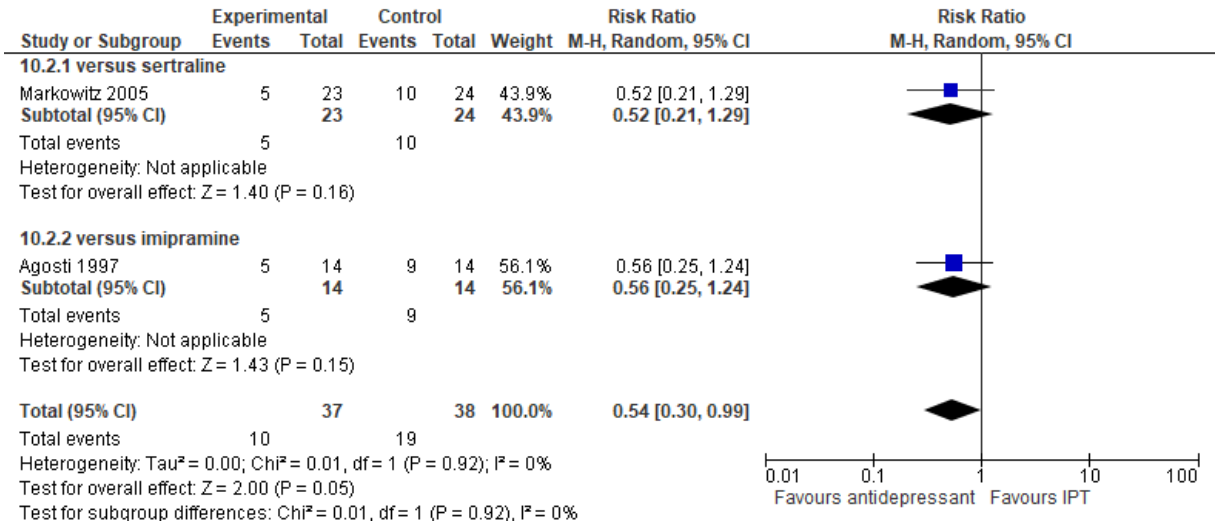


Figure 29: Response

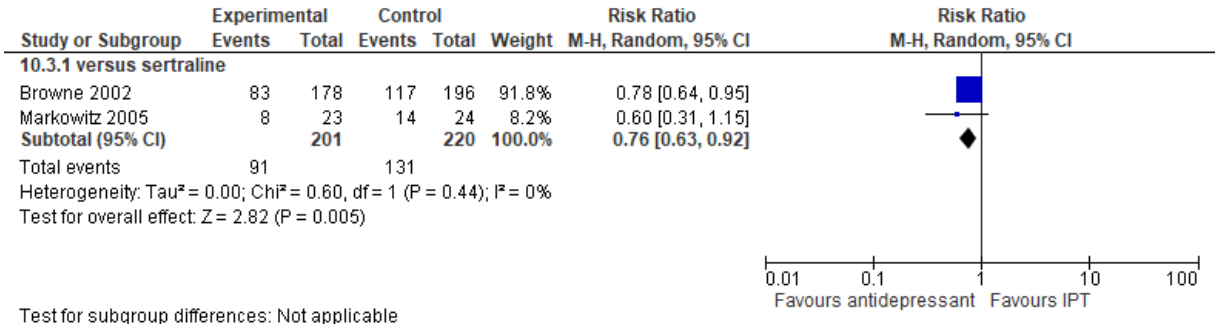
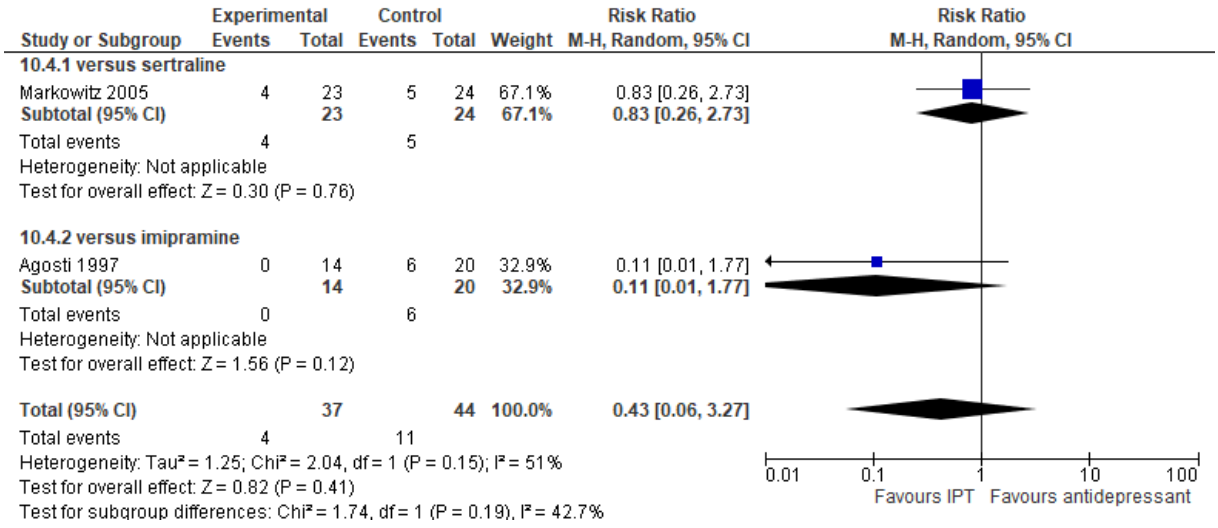


Figure 30: Discontinuation due to any reason



Comparison 12: IPT versus counselling for dysthymia

Figure 31: Depression symptomatology change score

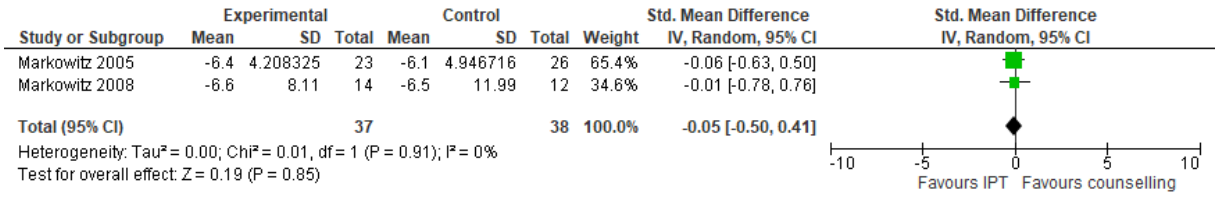


Figure 32: Remission

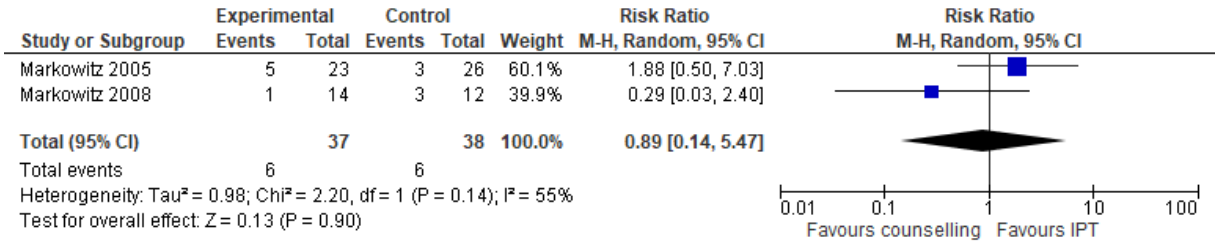


Figure 33: Response

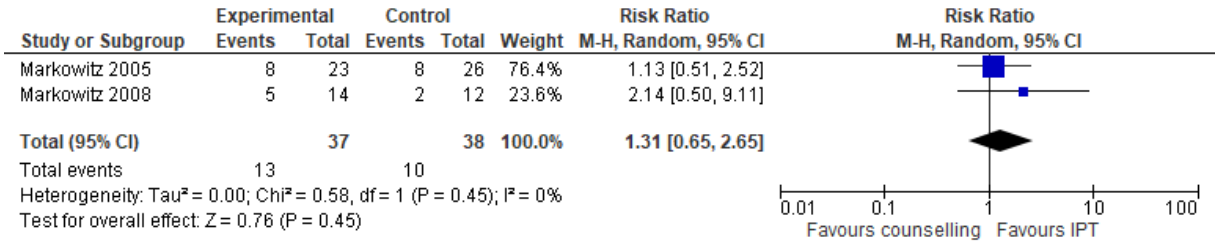
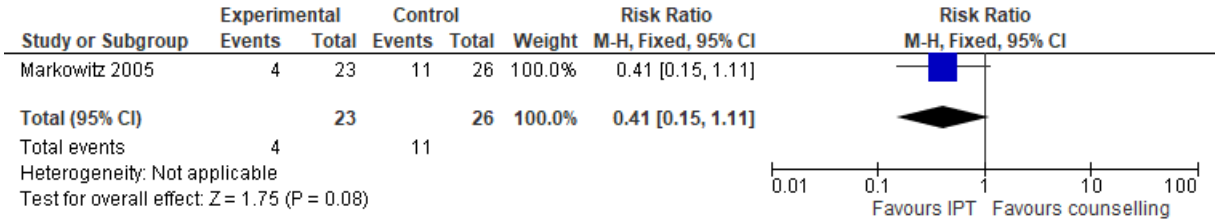
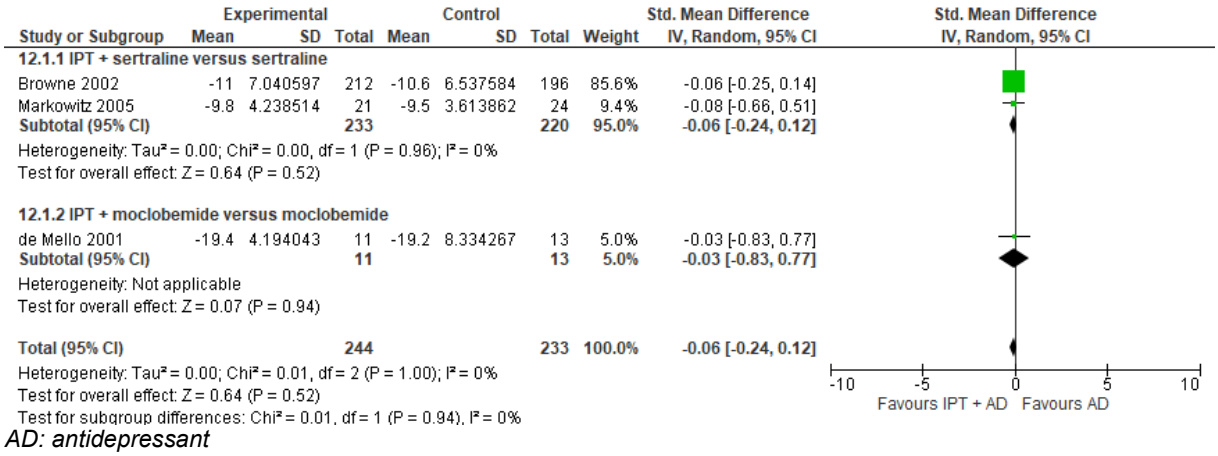


Figure 34: Discontinuation due to any reason



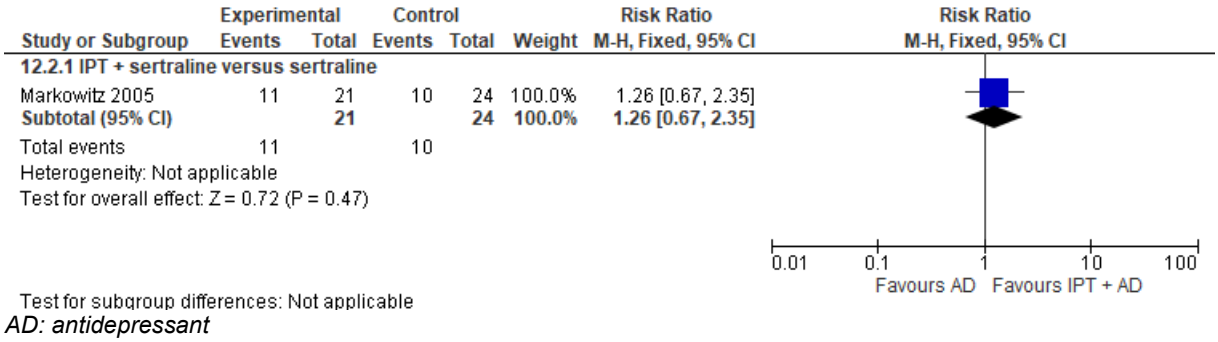
Comparison 13: IPT + antidepressant versus antidepressant-only for dysthymia or double depression

Figure 35: Depression symptomatology change score



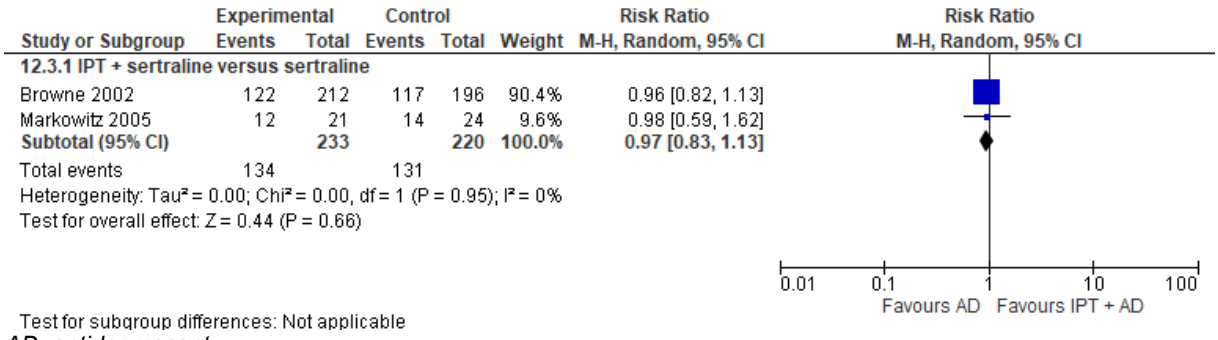
AD: antidepressant

Figure 36: Remission



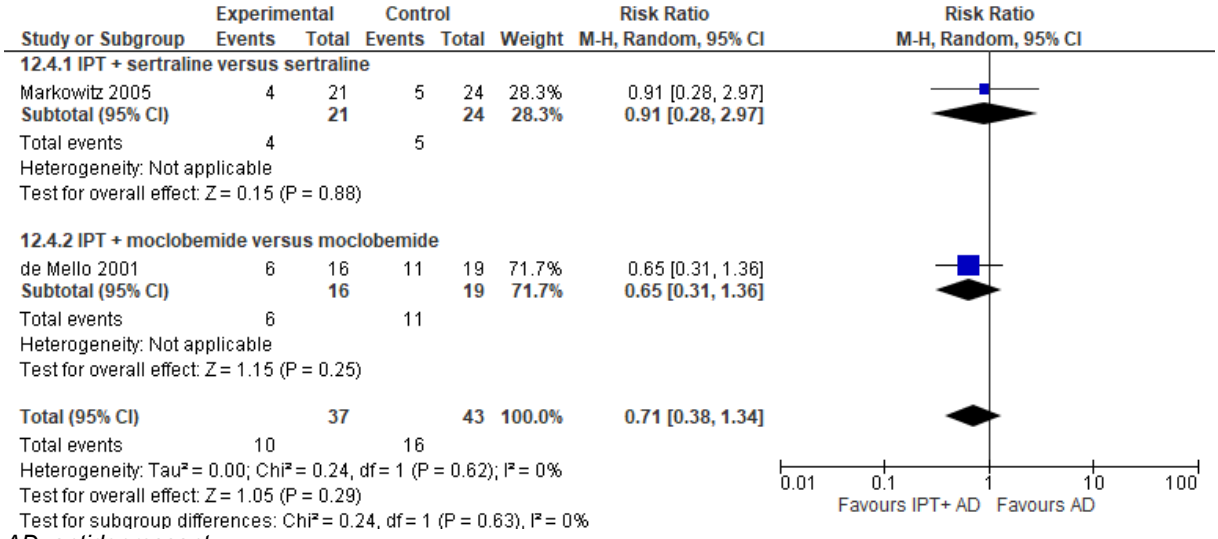
AD: antidepressant

Figure 37: Response



AD: antidepressant

Figure 38: Discontinuation due to any reason



AD: antidepressant

Comparison 14: Counselling versus sertraline for dysthymia

Figure 39: Depression symptomatology change score

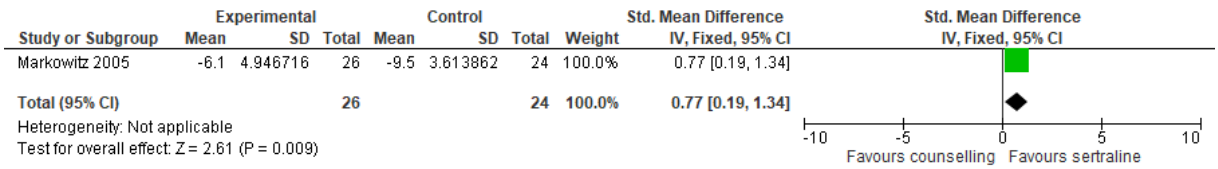


Figure 40: Remission

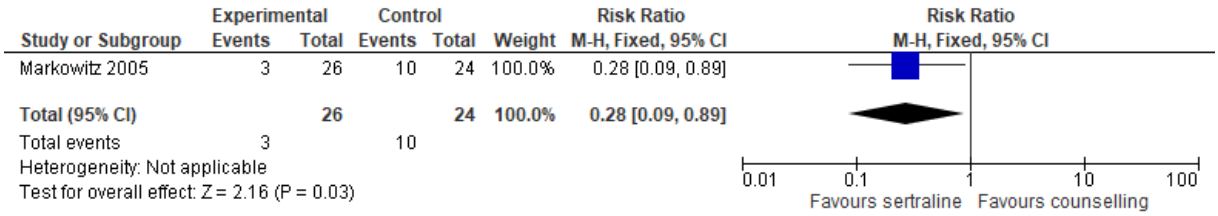
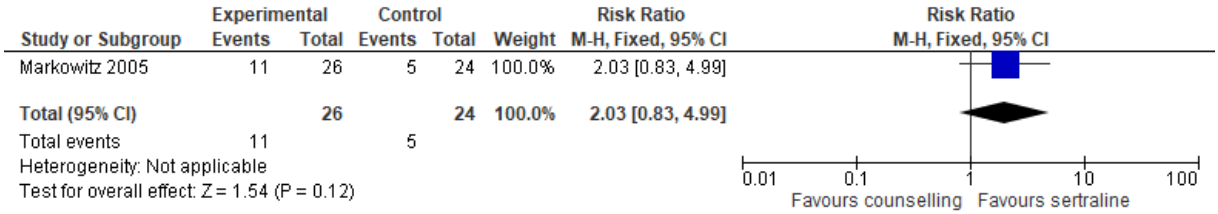


Figure 41: Response

Figure 42: Discontinuation due to any reason



Comparison 15: SSRIs versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Figure 43: Depression symptomatology change score

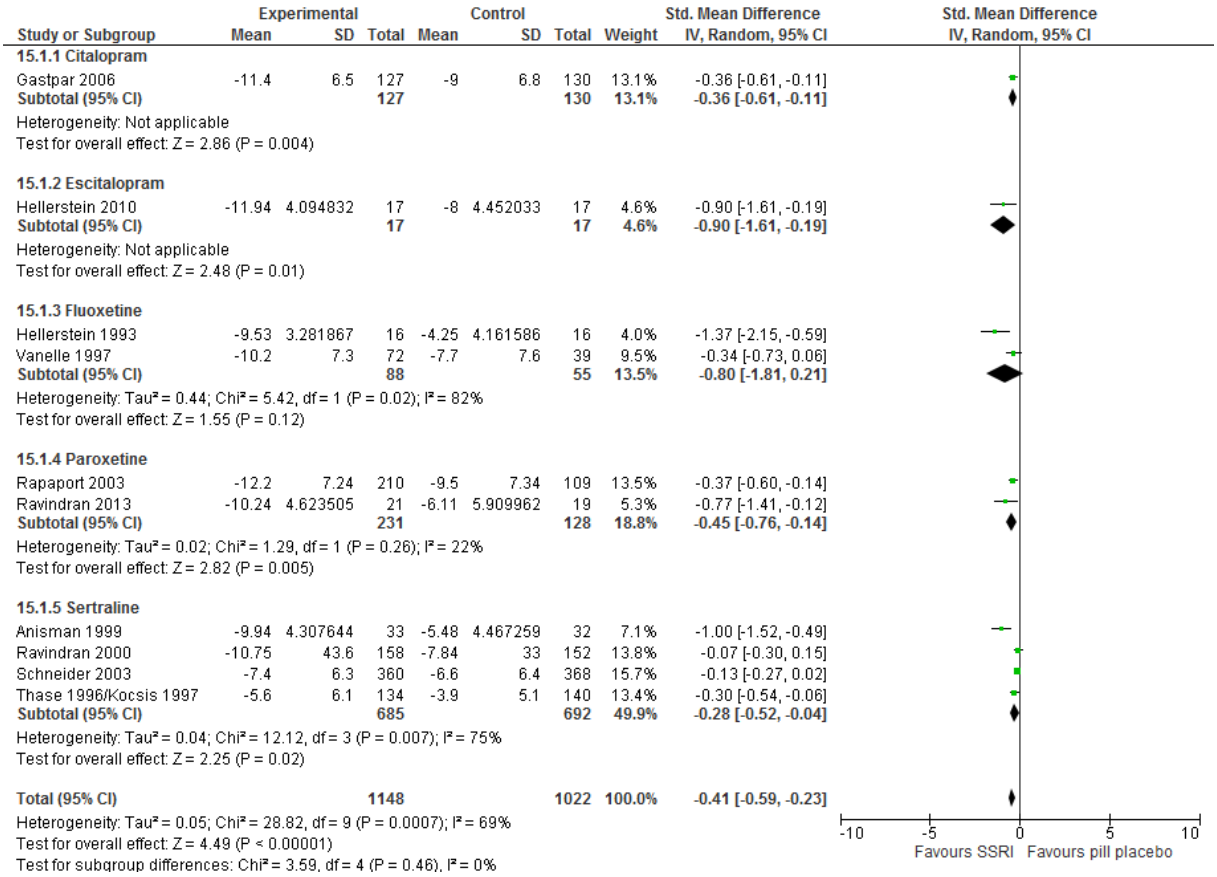


Figure 44: Remission

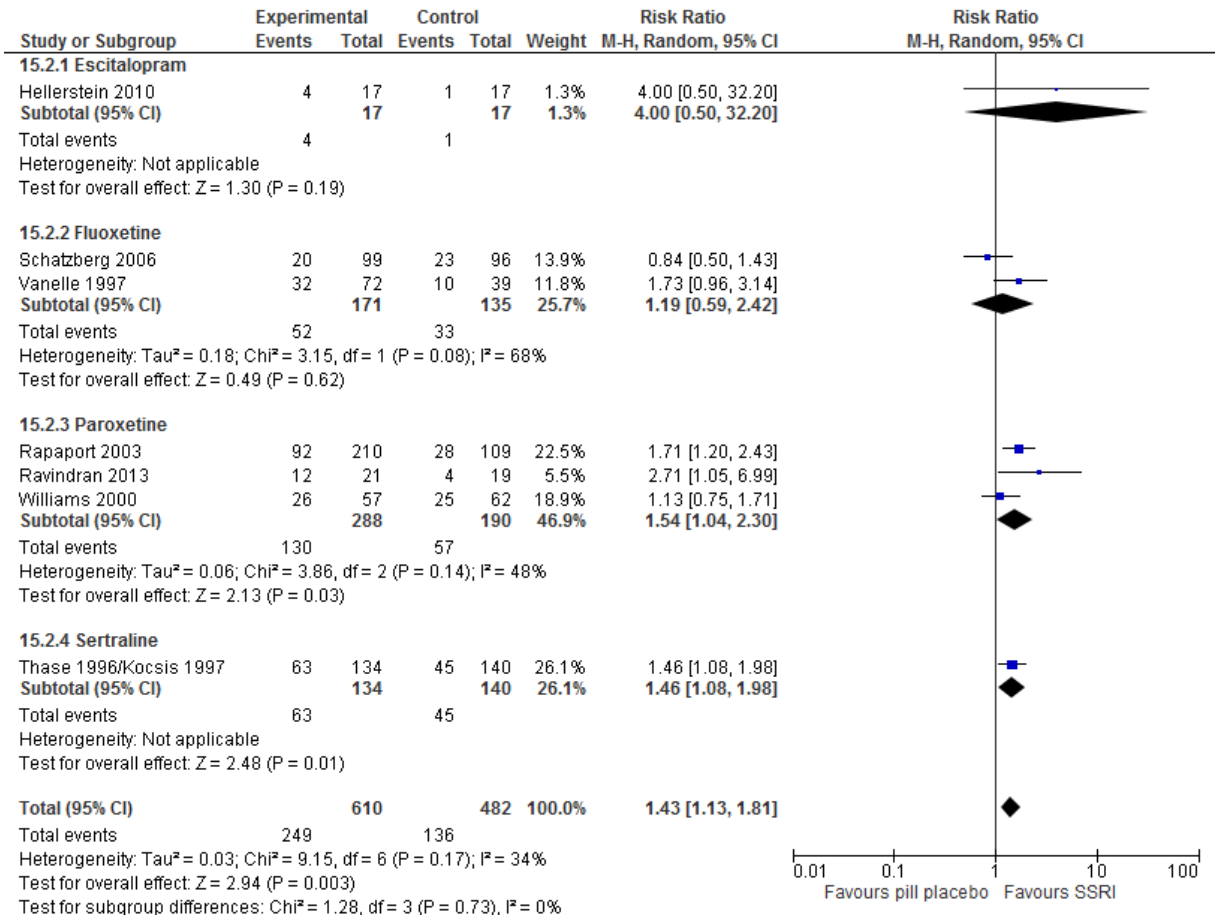


Figure 45: Response

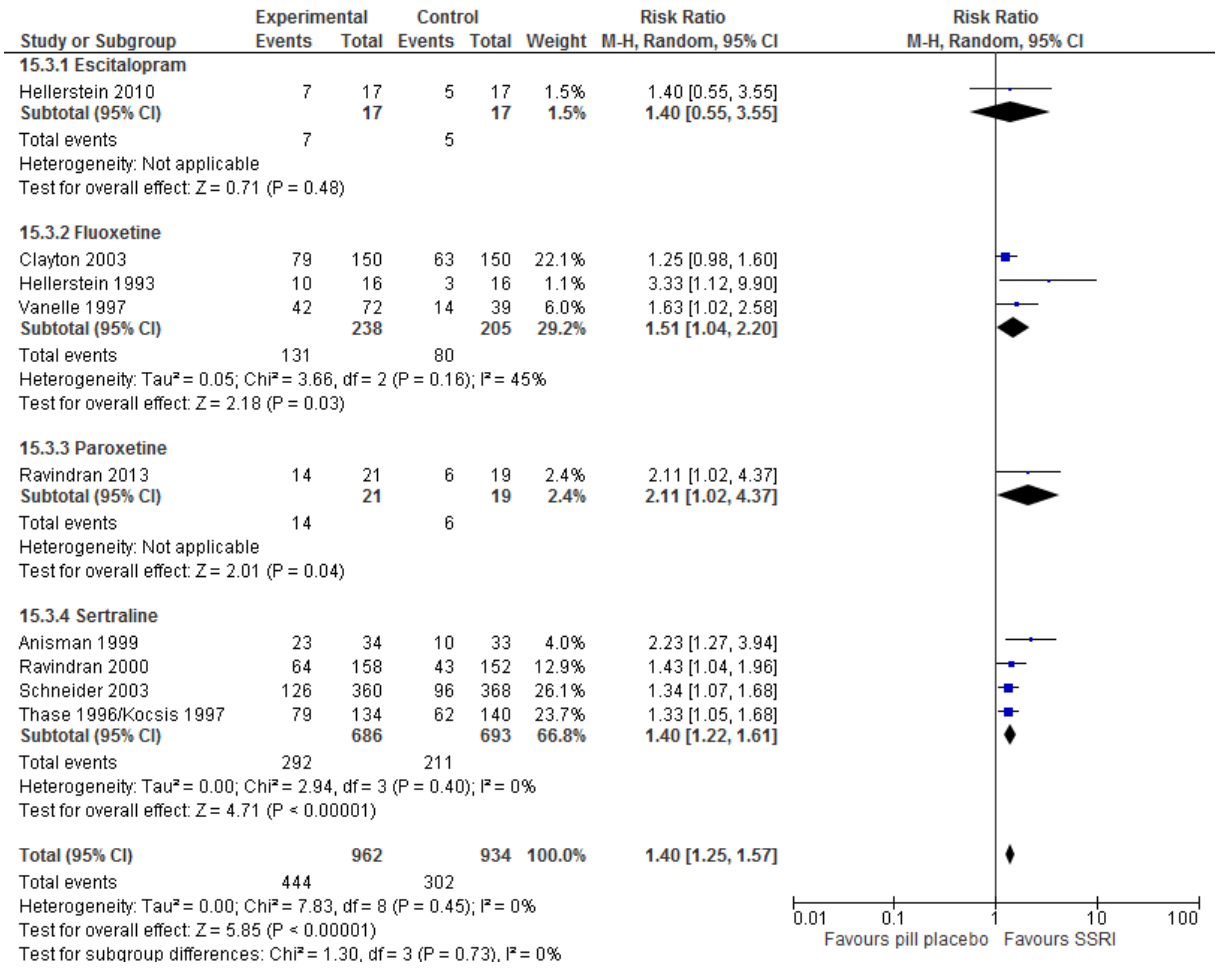


Figure 46: Discontinuation due to side effects

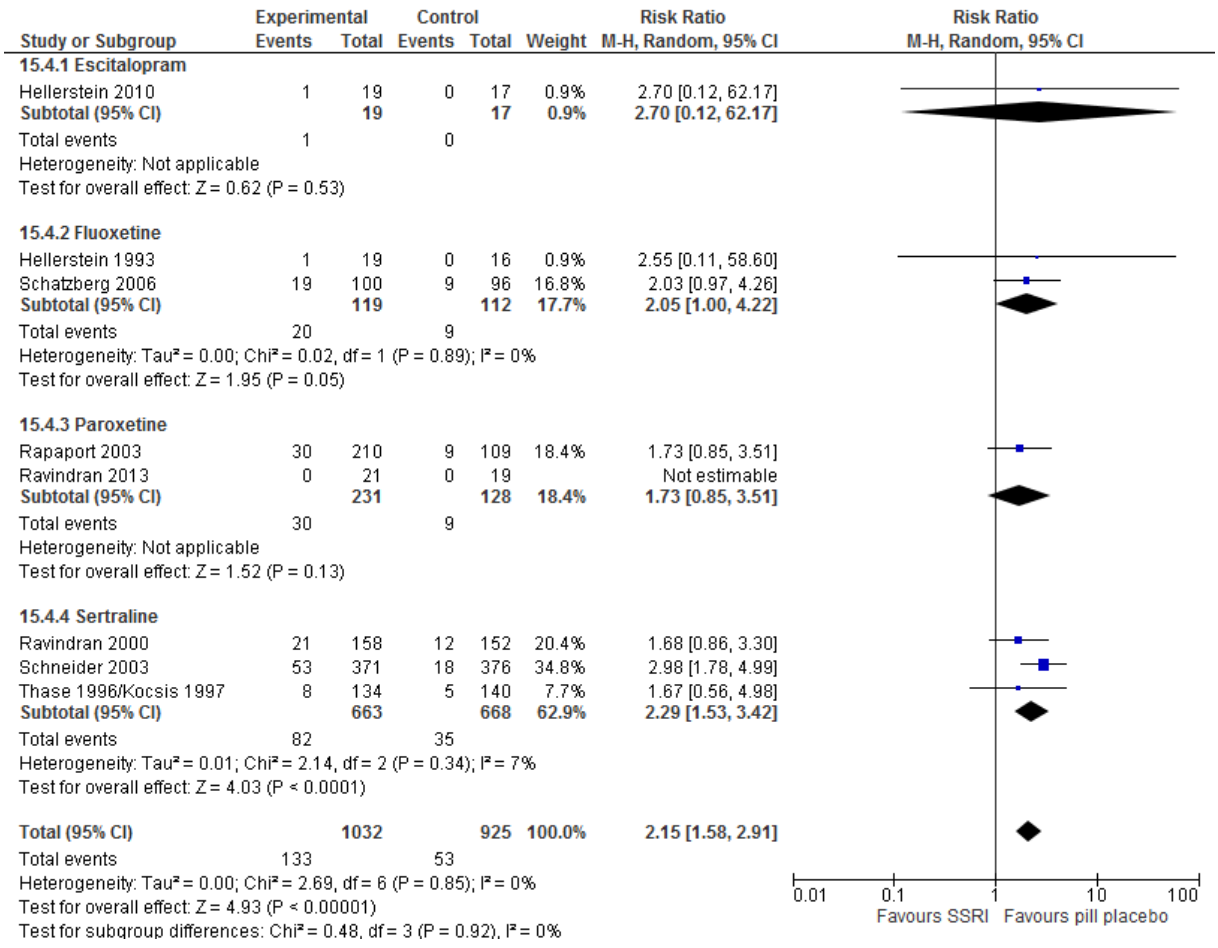


Figure 47: Discontinuation due to any reason

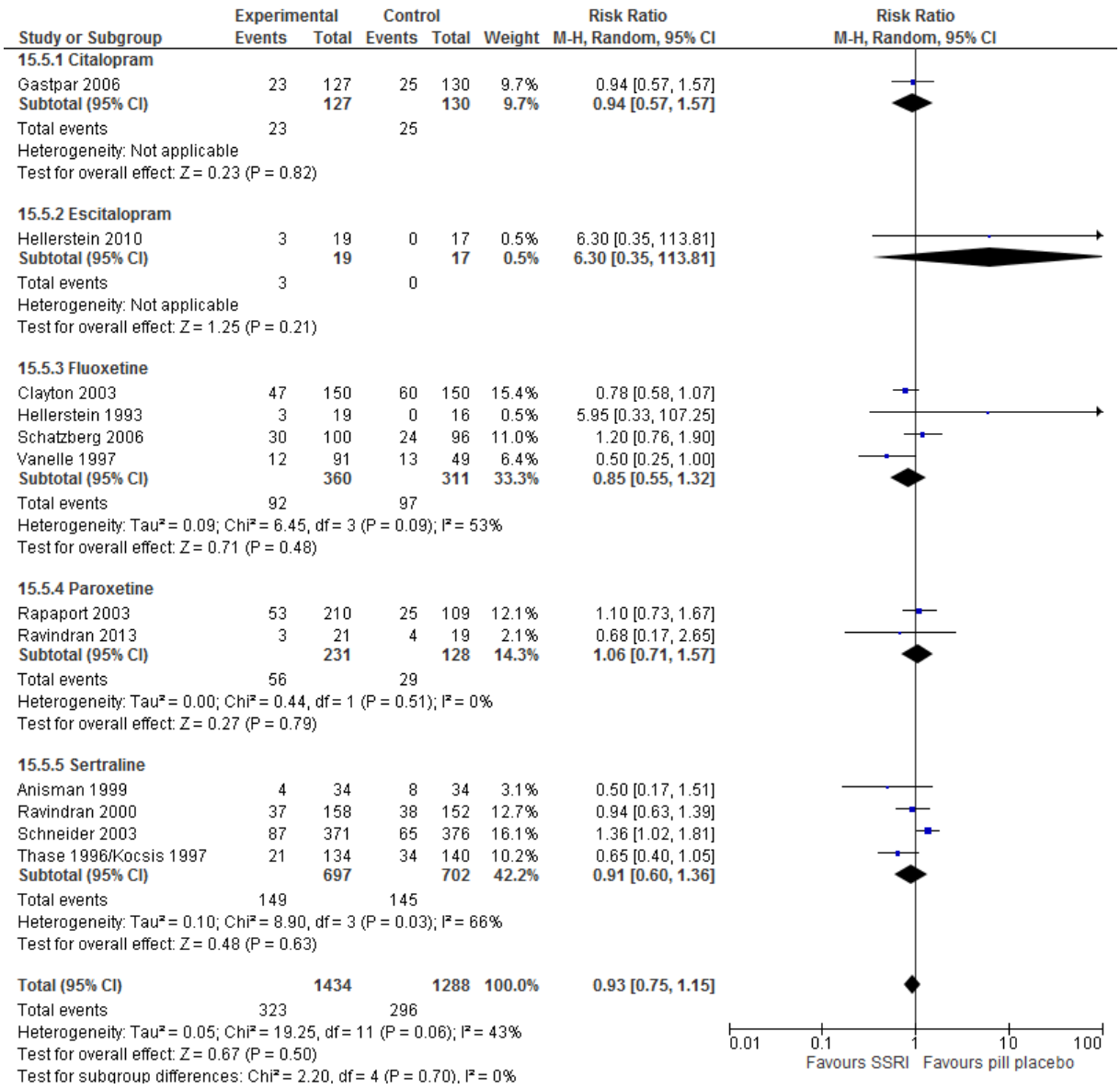


Figure 48: Quality of life

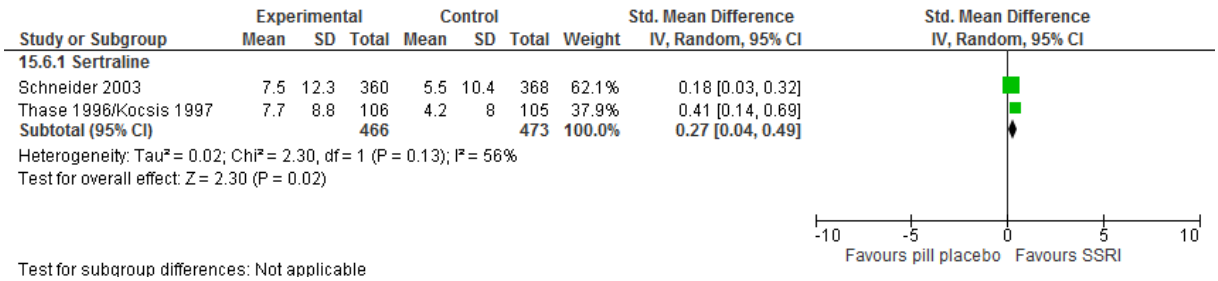


Figure 49: Global functioning

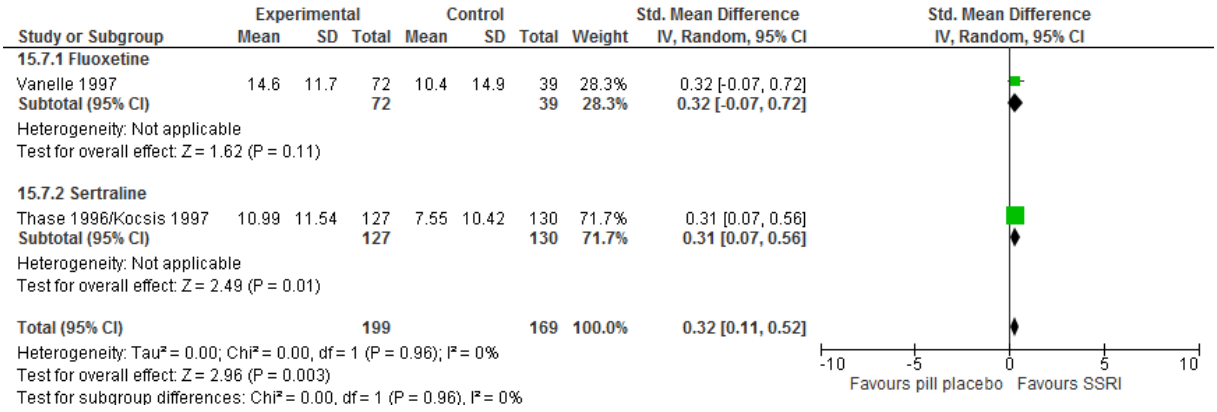
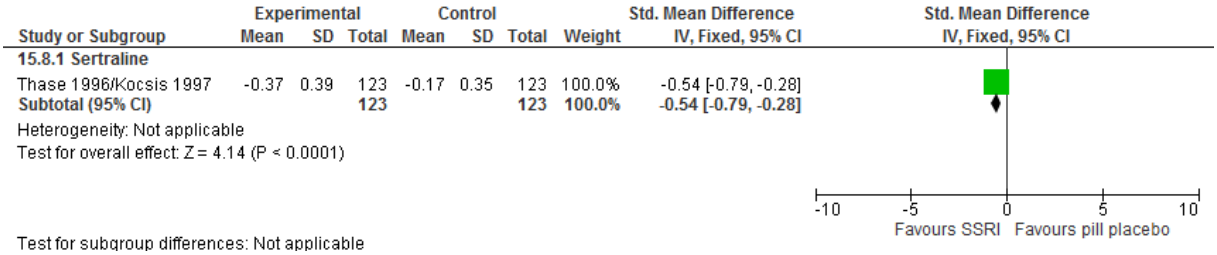


Figure 50: Functional impairment



Comparison 16: Sertraline versus imipramine for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Figure 51: Depression symptomatology change score

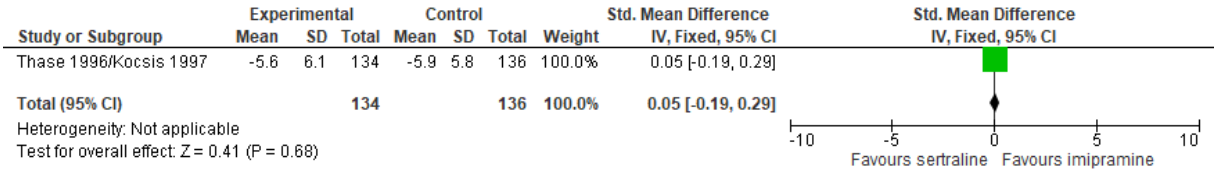


Figure 52: Remission

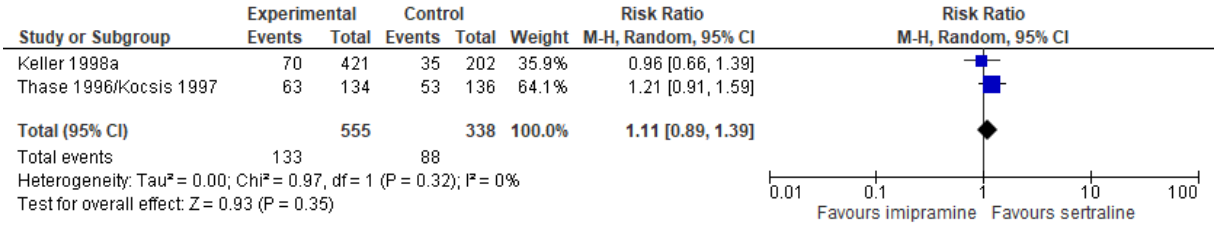


Figure 53: Response

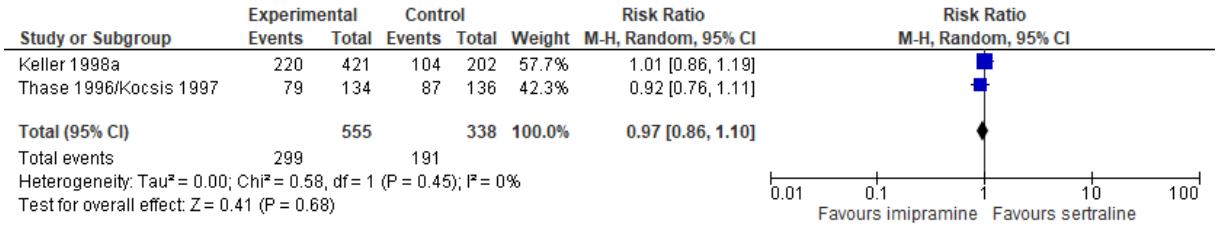


Figure 54: Discontinuation due to side effects

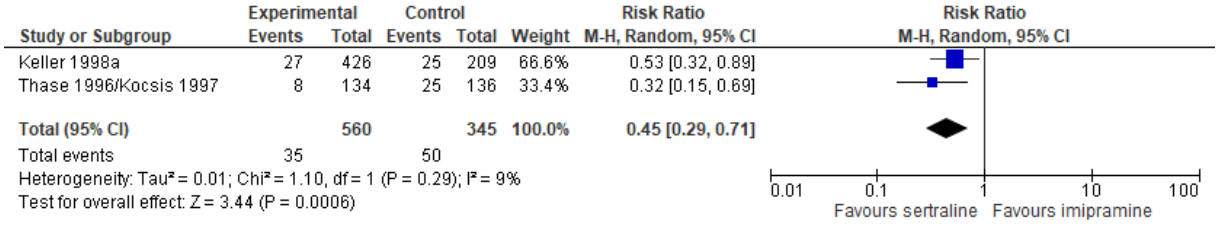


Figure 55: Discontinuation due to any reason

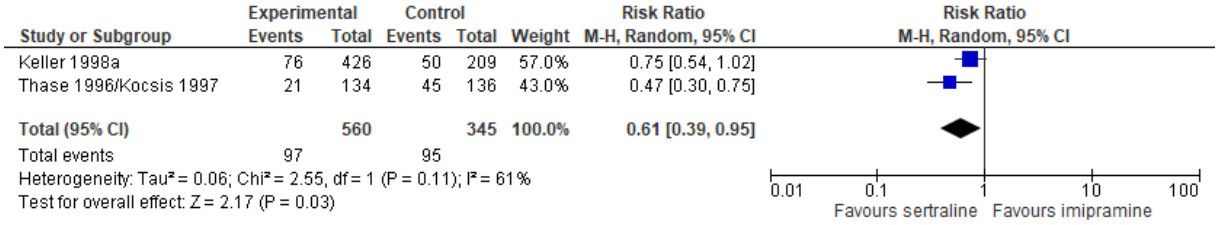


Figure 56: Quality of life

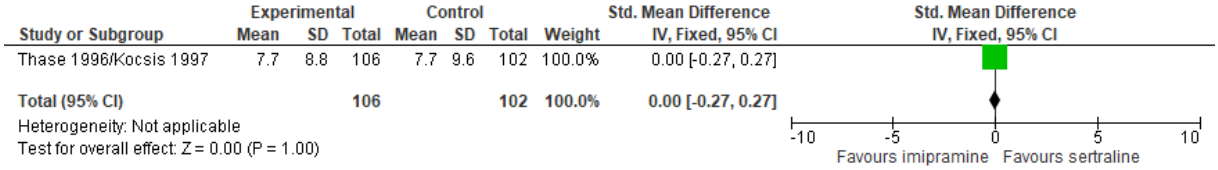


Figure 57: Global functioning

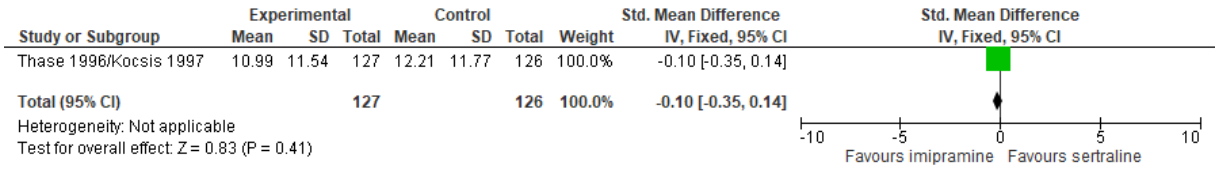
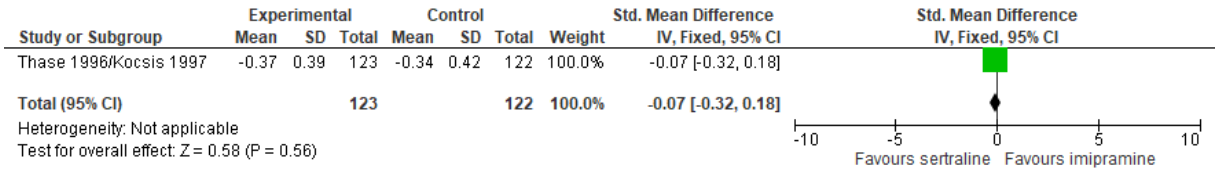


Figure 58: Functional impairment



Comparison 17: Fluoxetine versus venlafaxine for chronic depression (MDD ≥2 years)

Figure 59: Remission

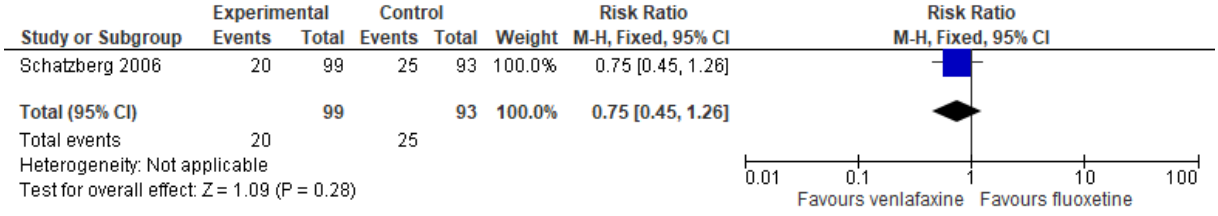
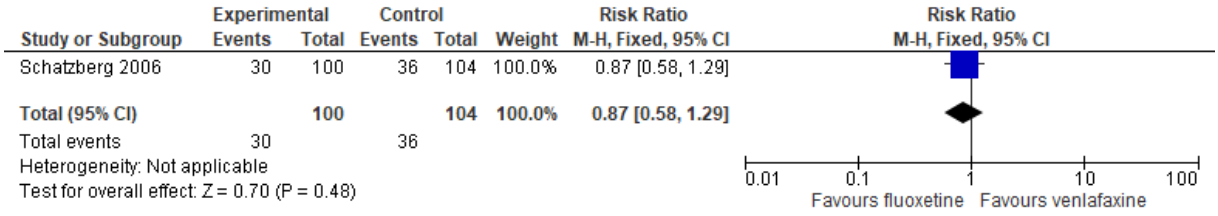


Figure 60: Discontinuation due to side effects

Figure 61: Discontinuation due to any reason



Comparison 18: SSRI versus amisulpride for dysthymia or double depression

Figure 62: Depression symptomatology change score

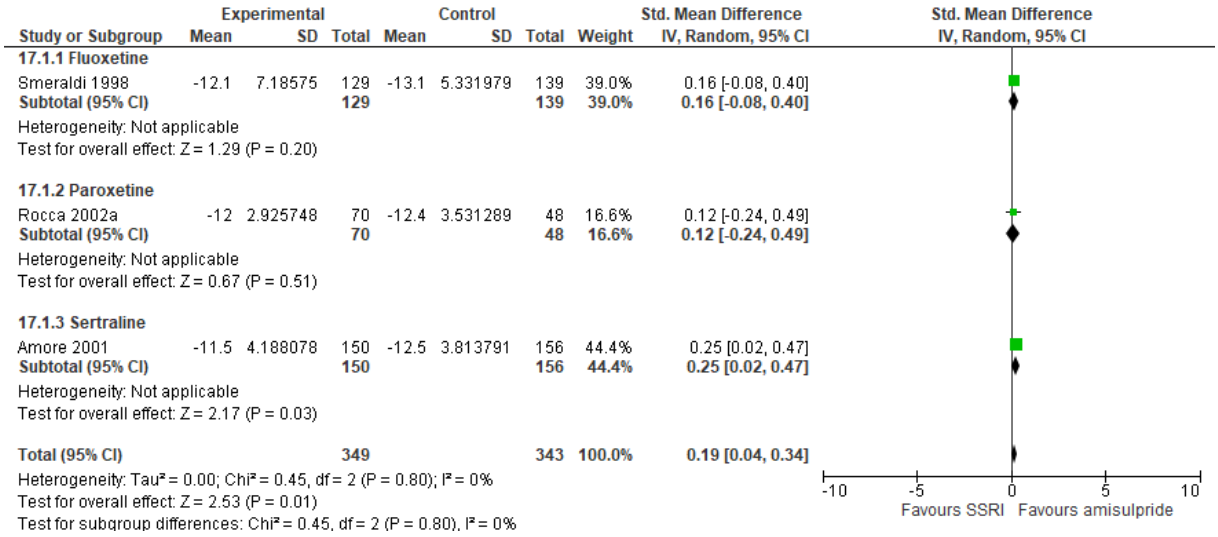


Figure 63: Remission

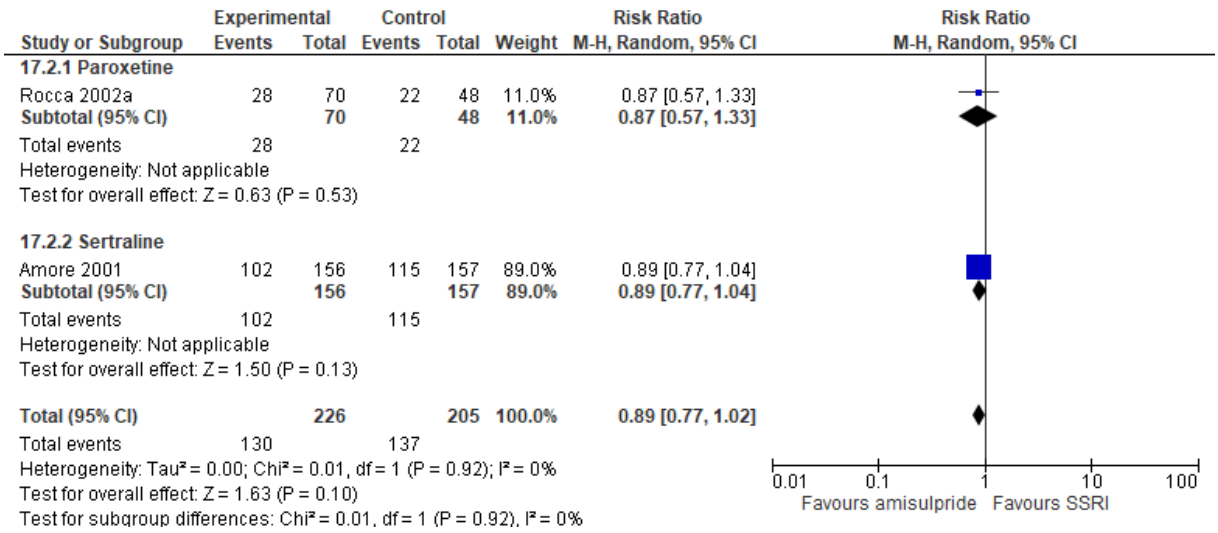


Figure 64: Response

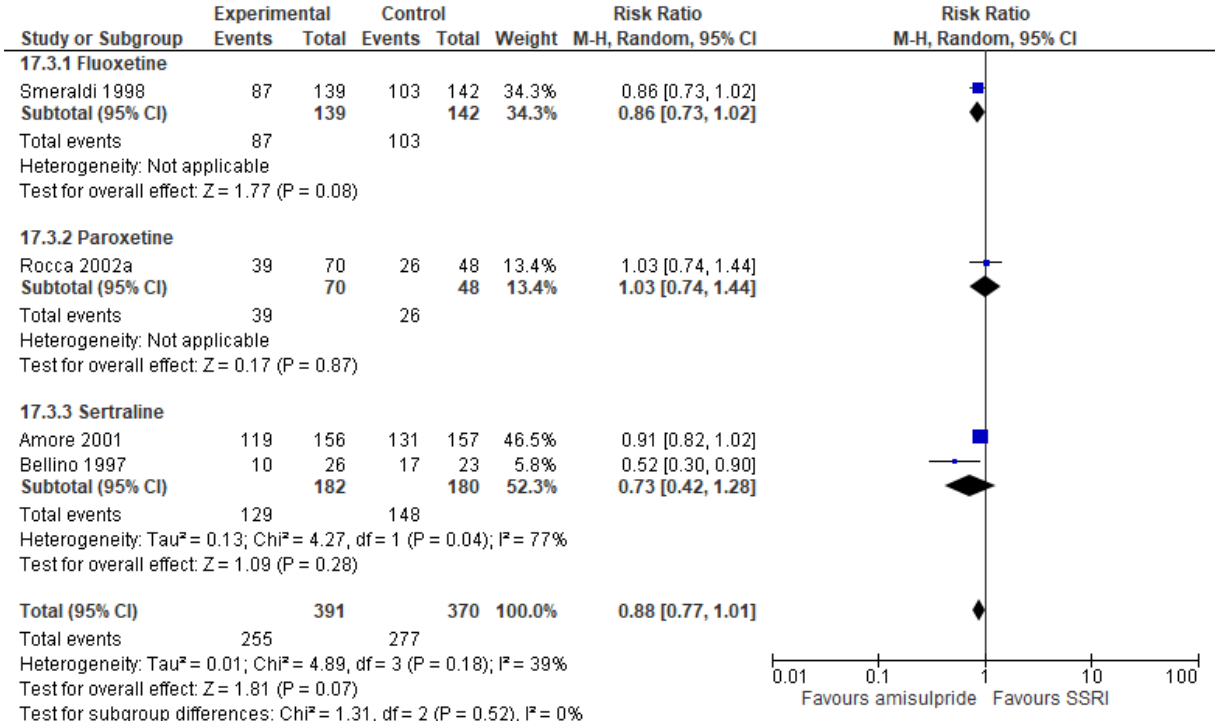


Figure 65: Discontinuation due to side effects

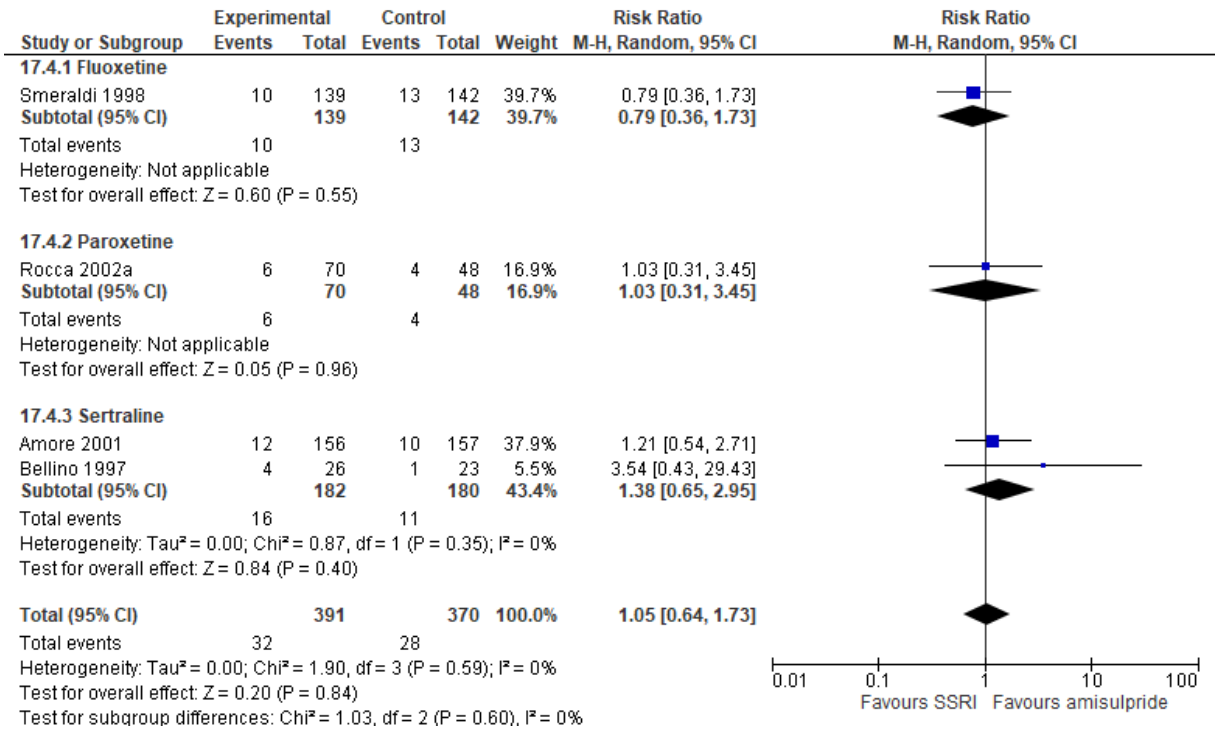


Figure 66: Discontinuation due to any reason

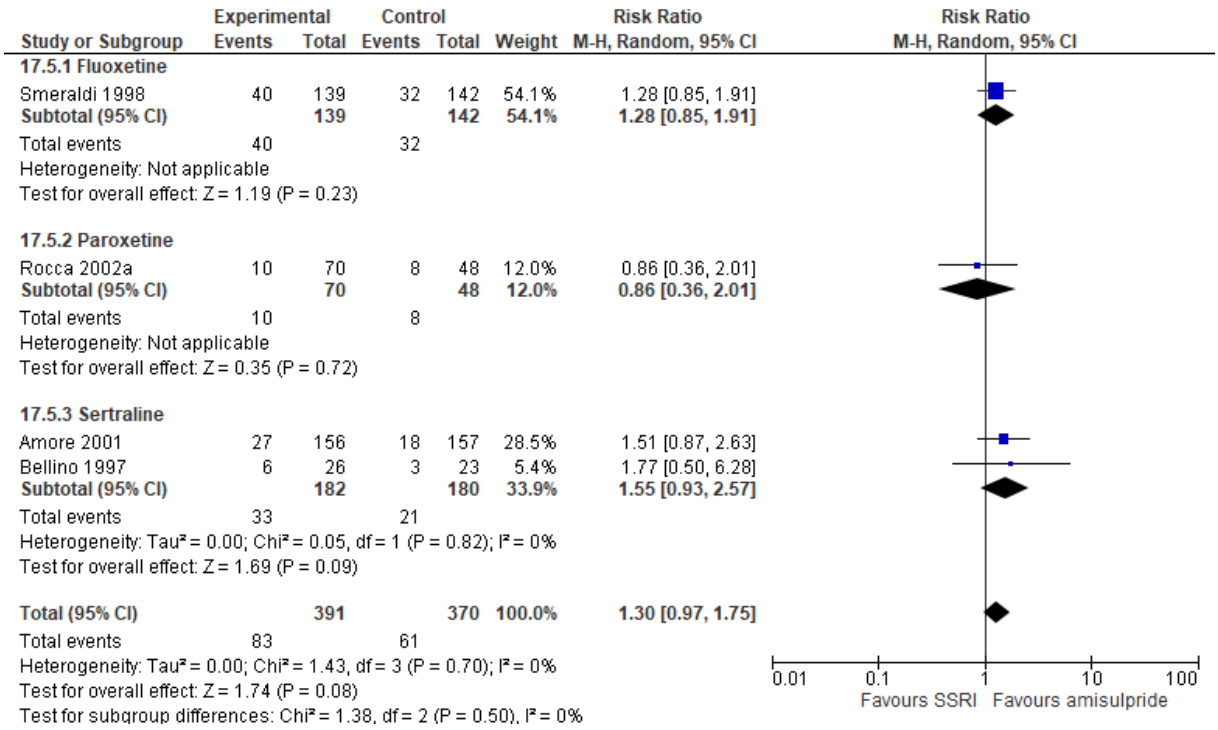
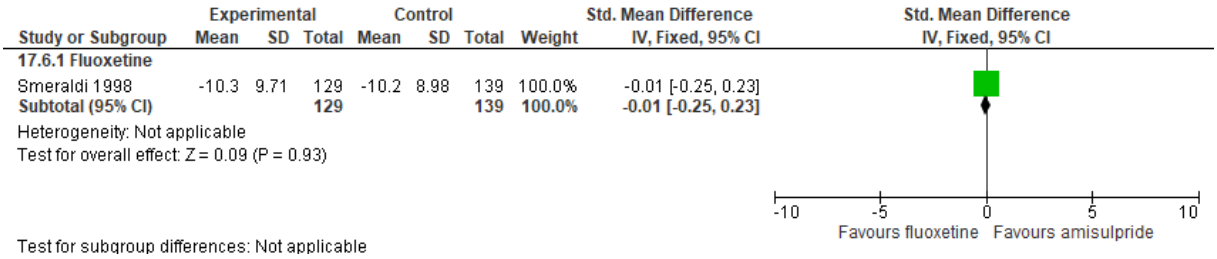


Figure 67: Functional impairment



Comparison 19: Sertraline + IPT versus IPT-only for dysthymia

Figure 68: Depression symptomatology change score

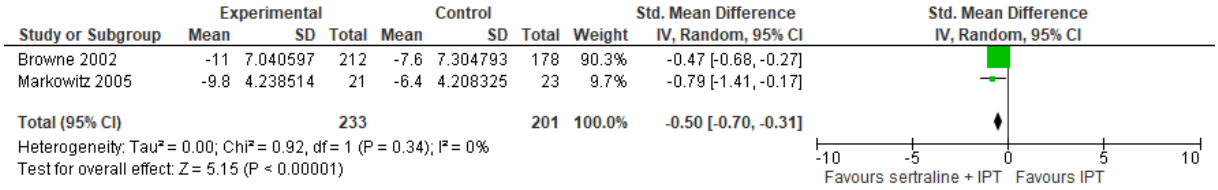


Figure 69: Remission

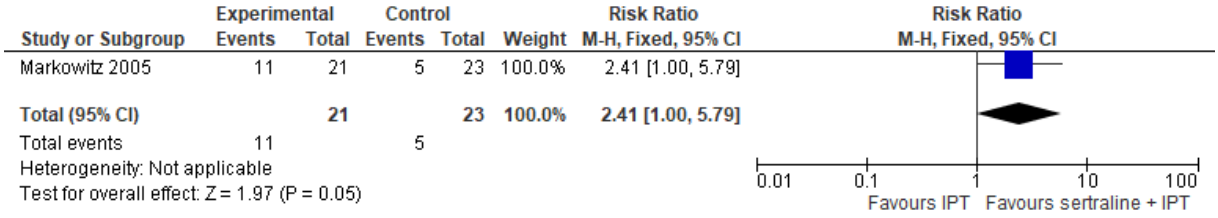


Figure 70: Response

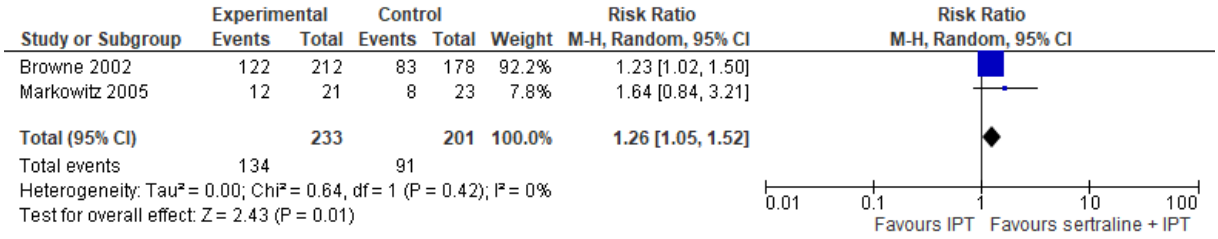
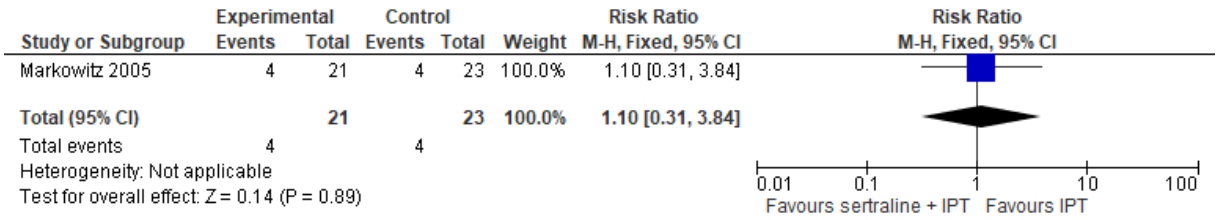


Figure 71: Discontinuation due to any reason



Comparison 20: TCAs versus pill placebo for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Figure 72: Depression symptomatology change score

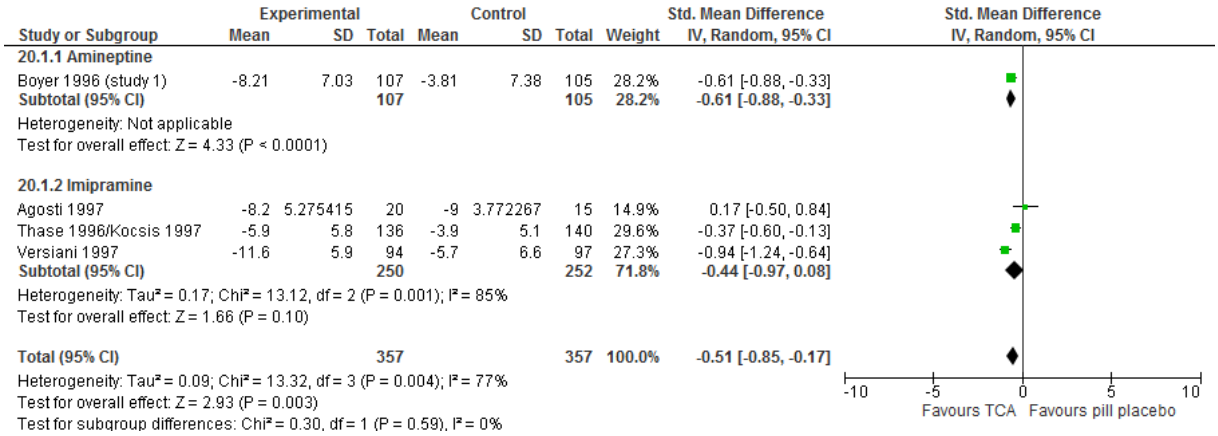


Figure 73: Remission

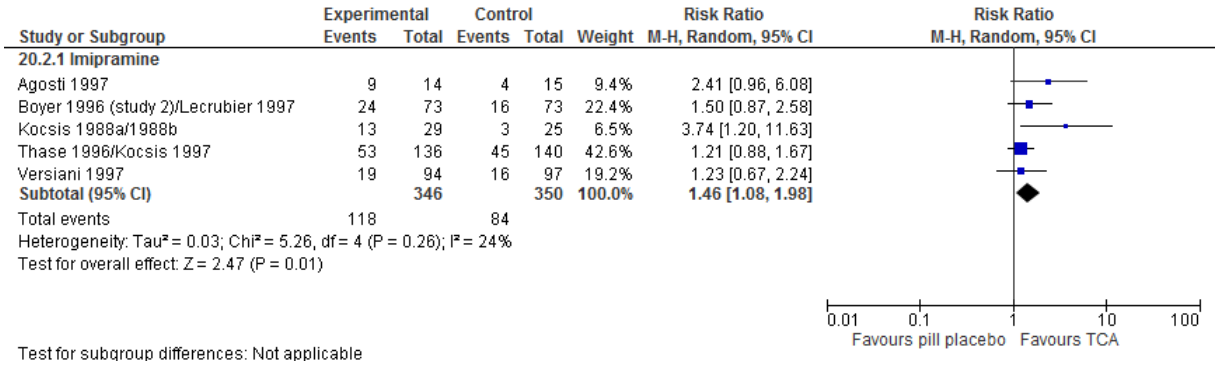


Figure 74: Response

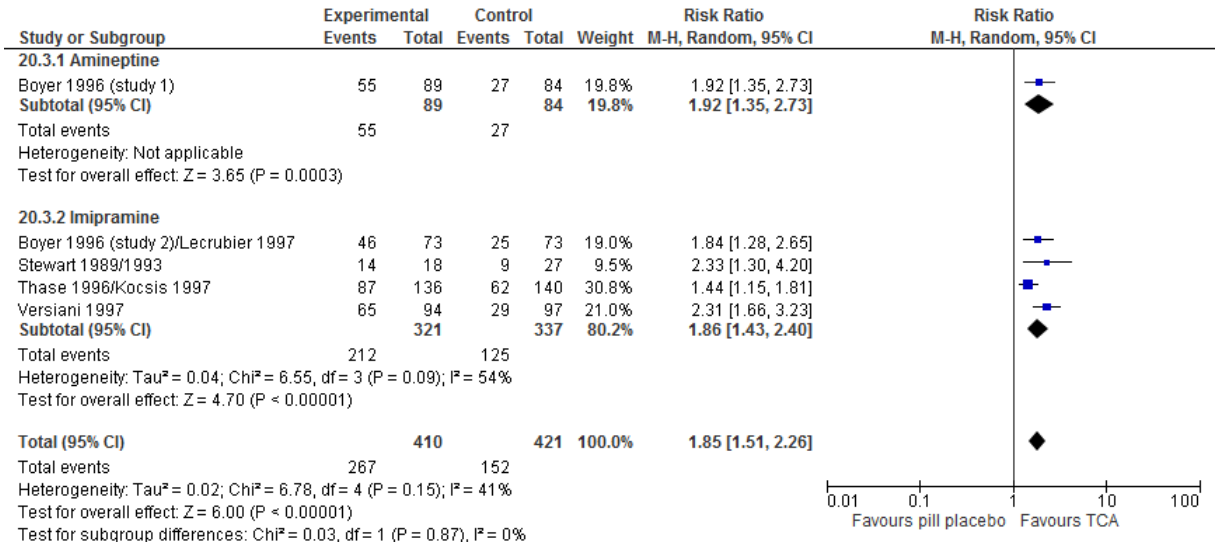


Figure 75: Discontinuation due to side effects

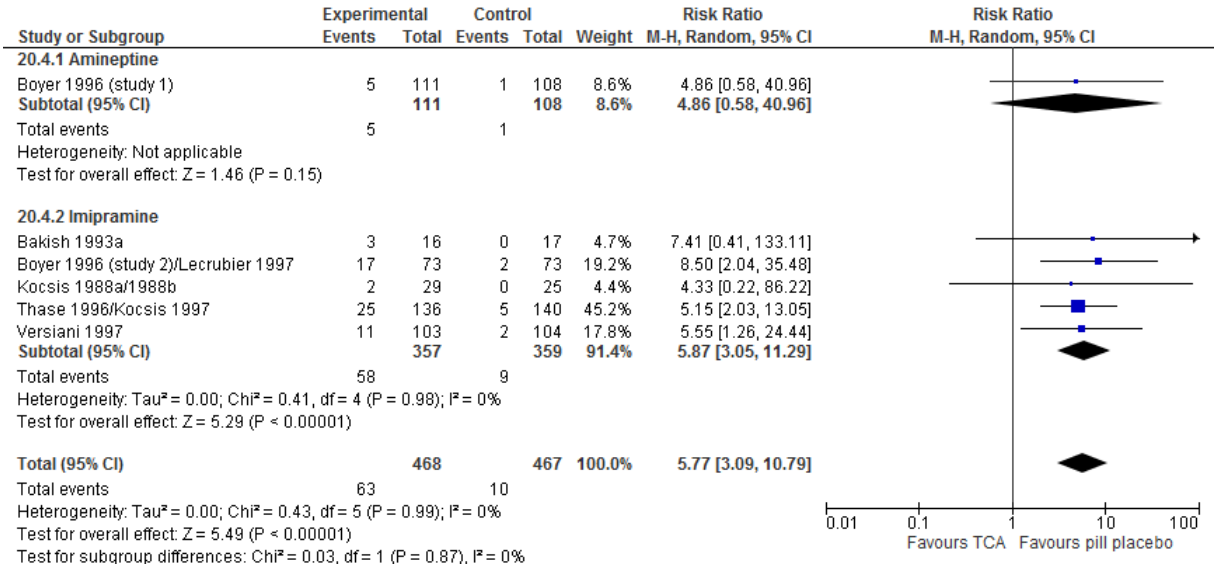


Figure 76: Discontinuation due to any reason

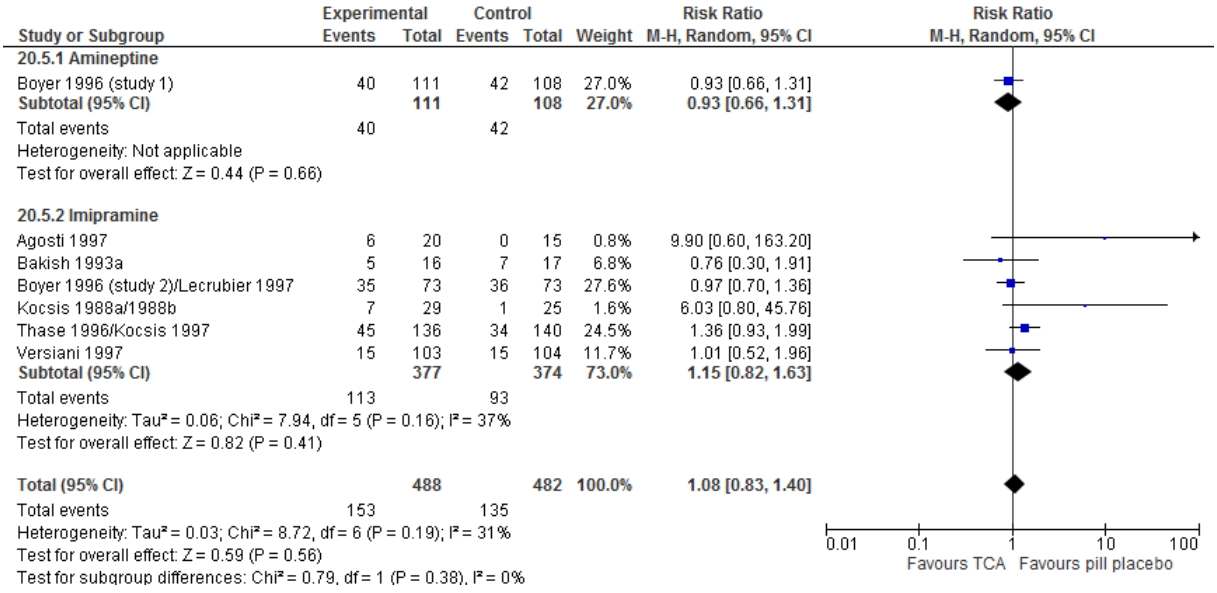


Figure 77: Quality of life

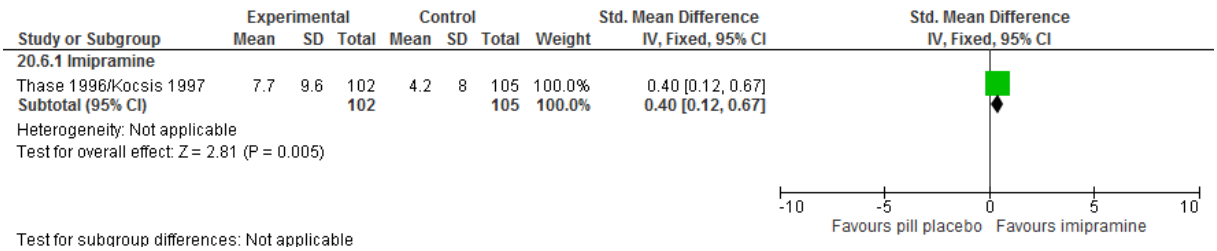


Figure 78: Global functioning

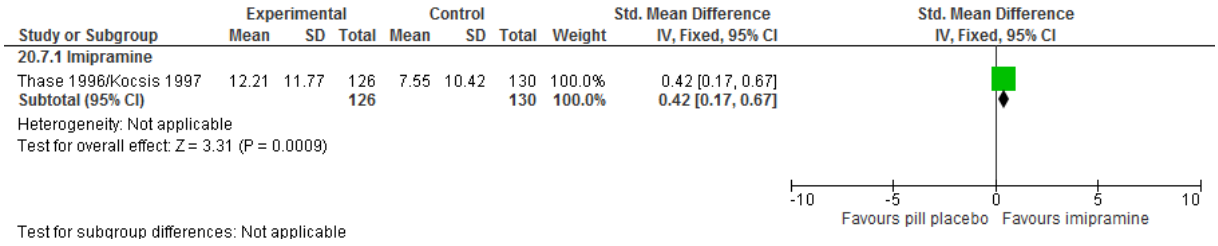


Figure 79: Functional impairment change score

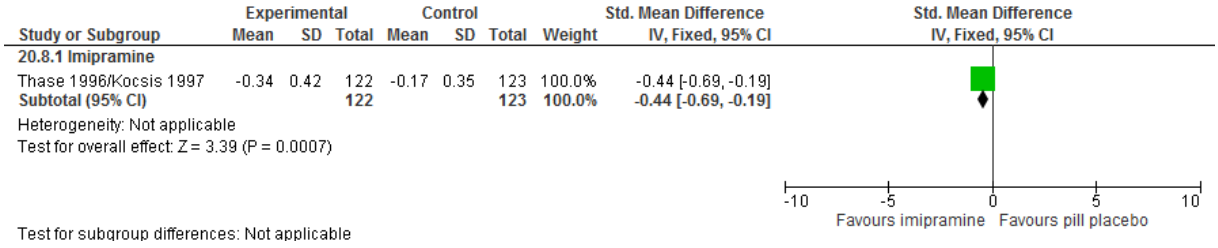
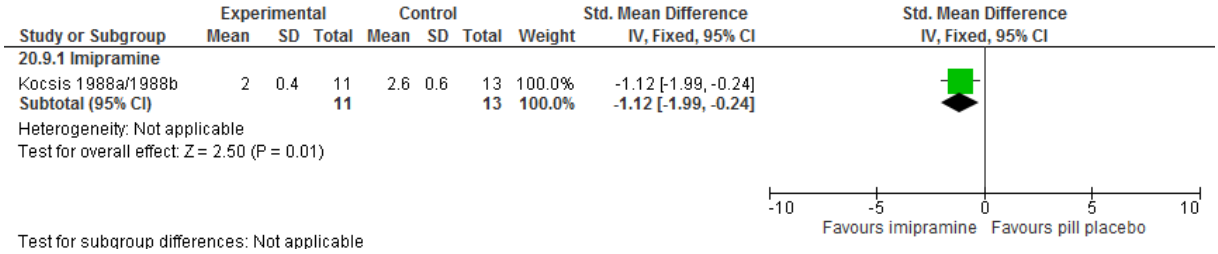


Figure 80: Functional impairment endpoint



Comparison 21: TCA versus amisulpride for dysthymia or double depression

Figure 81: Depression symptomatology change score

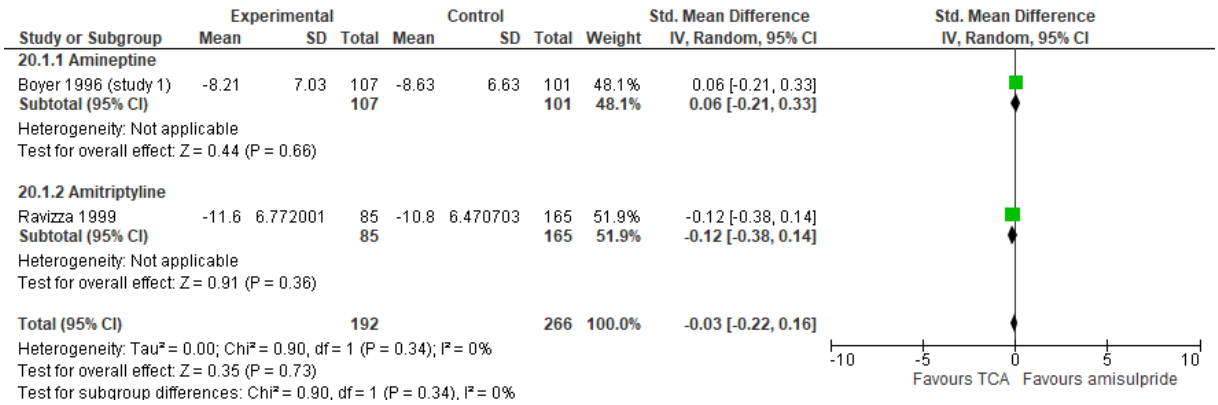


Figure 82: Remission

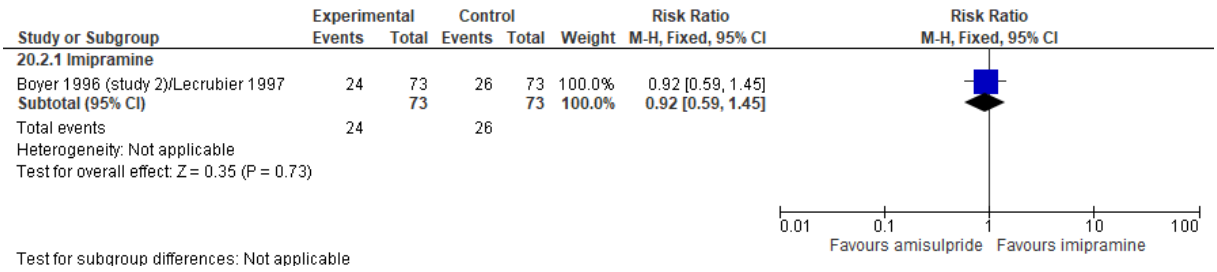


Figure 83: Response

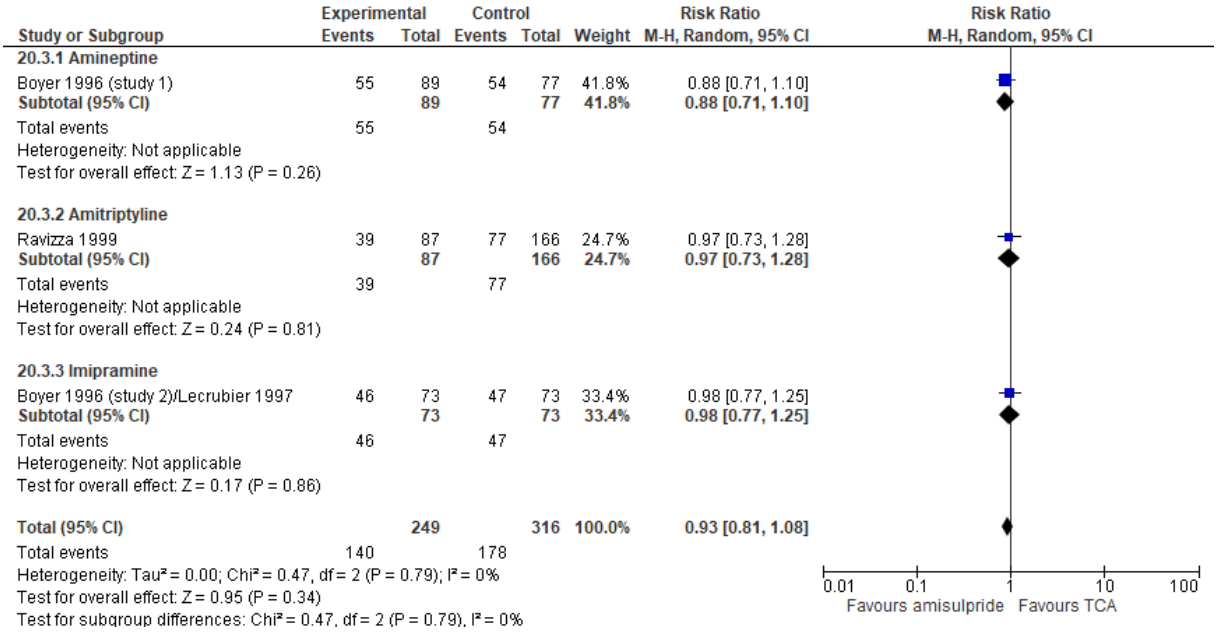


Figure 84: Discontinuation due to side effects

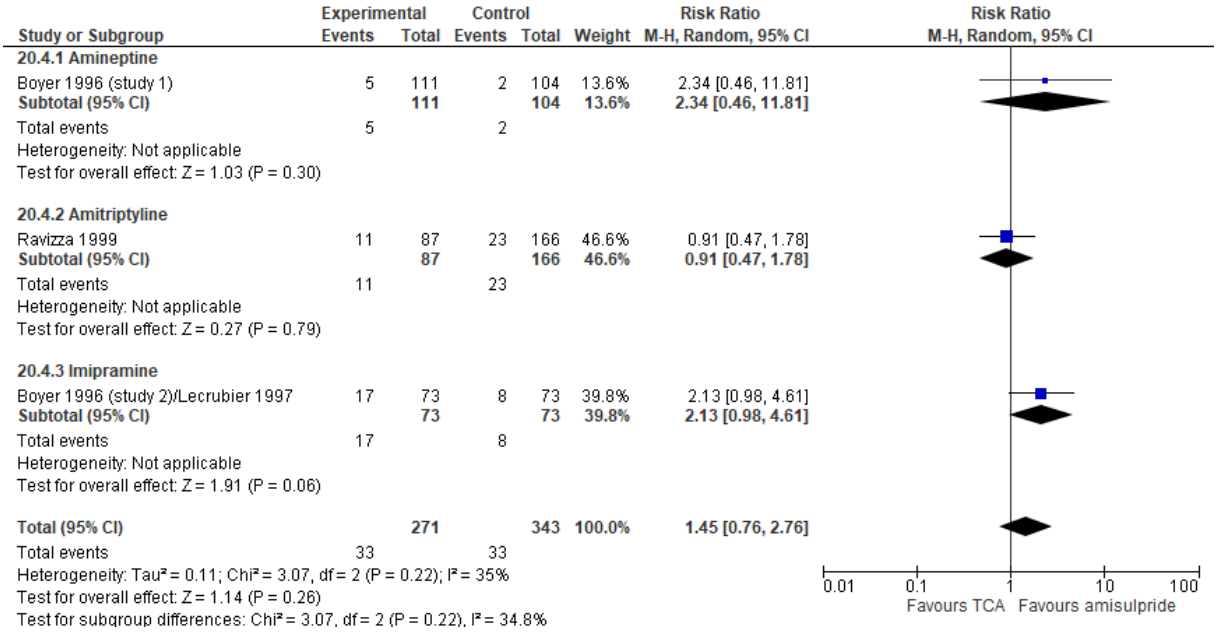


Figure 85: Discontinuation due to any reason

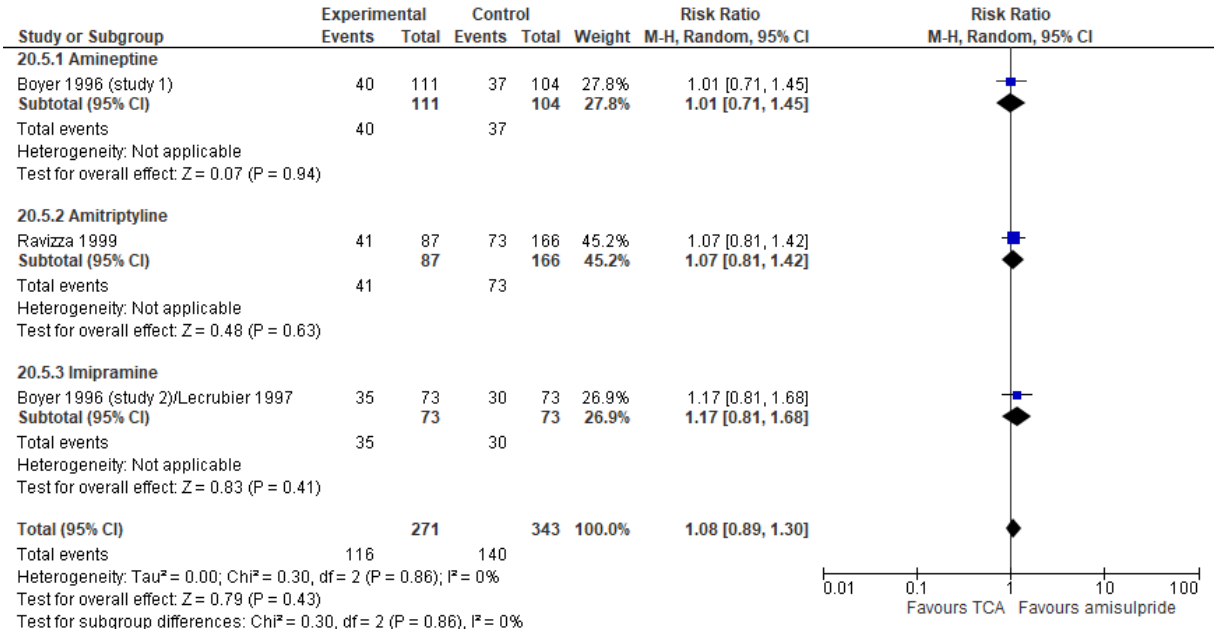
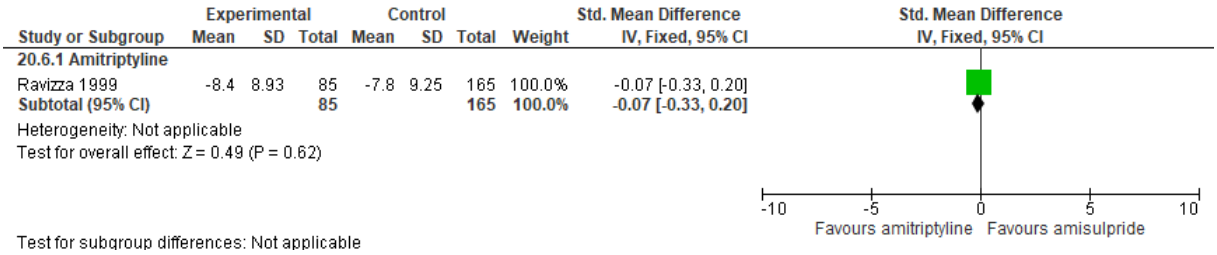


Figure 86: Functional impairment



Comparison 22: TCAs versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia, or double depression)

Figure 87: Relapse

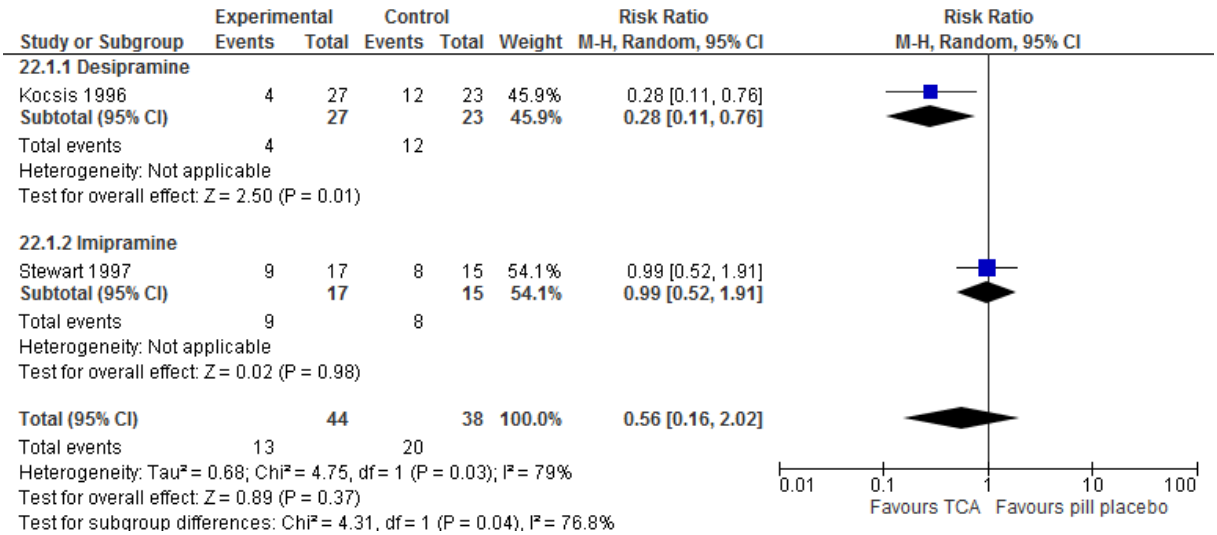
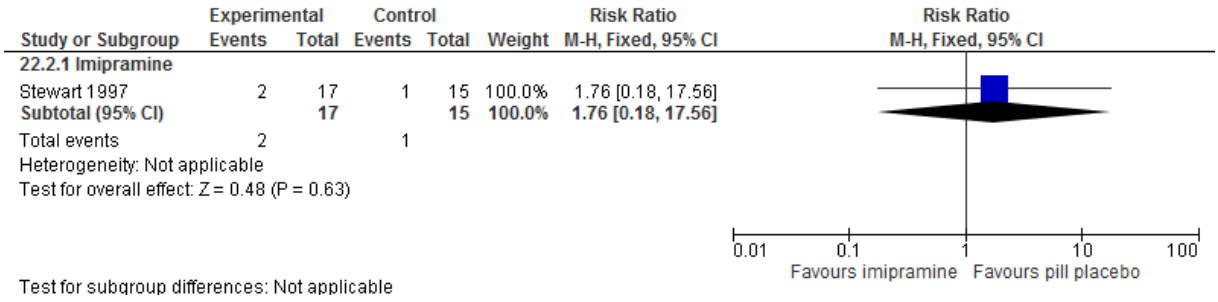


Figure 88: Discontinuation due to any reason



Comparison 23: Phenelzine versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Figure 89: Depression symptomatology change score

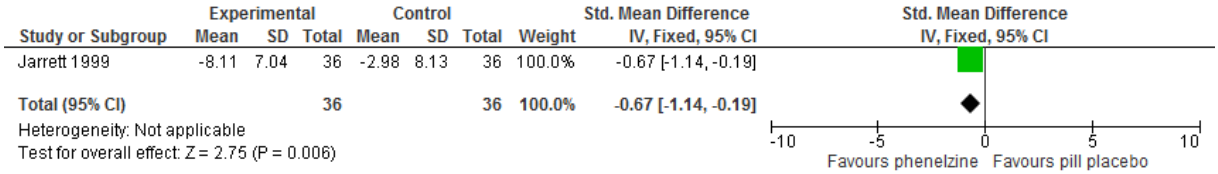


Figure 90: Remission

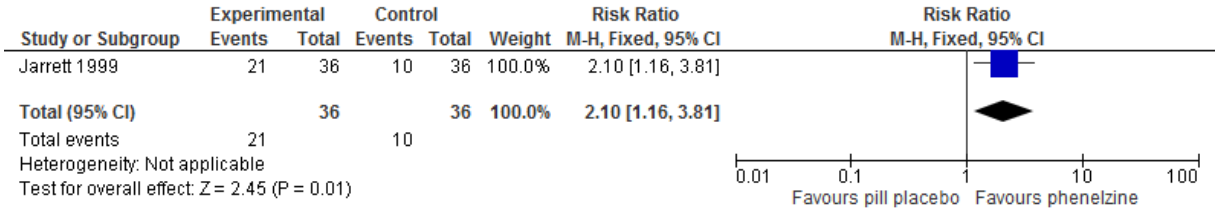


Figure 91: Response

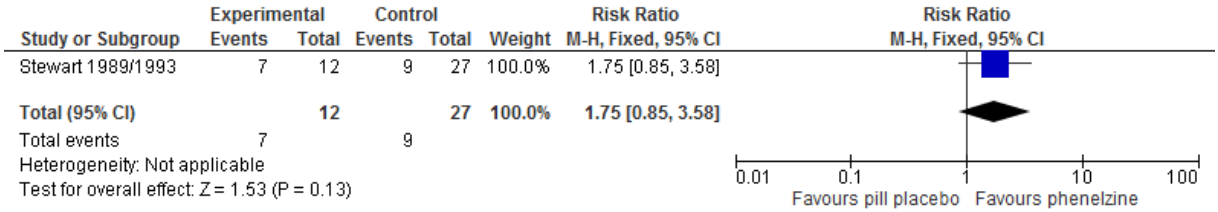
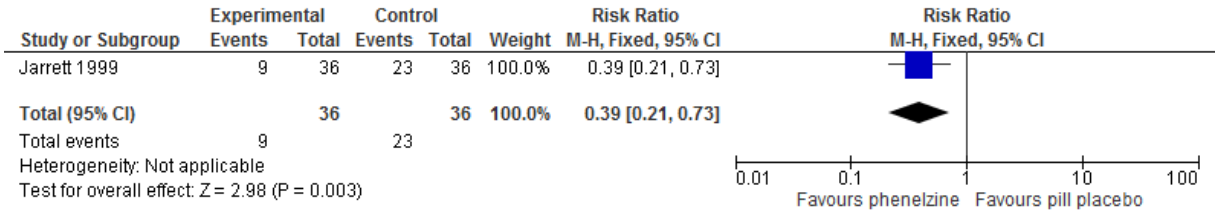


Figure 92: Discontinuation due to any reason



Comparison 24: Phenelzine versus imipramine for dysthymia

Figure 93: Depression symptomatology endpoint

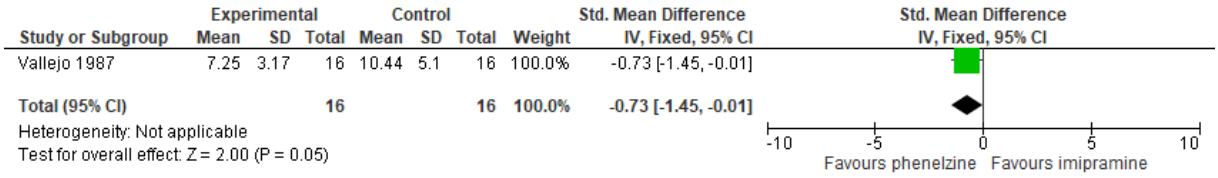


Figure 94: Response

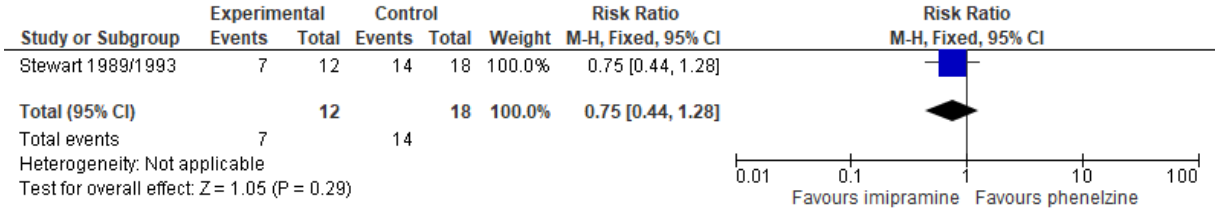


Figure 95: Discontinuation due to side effects

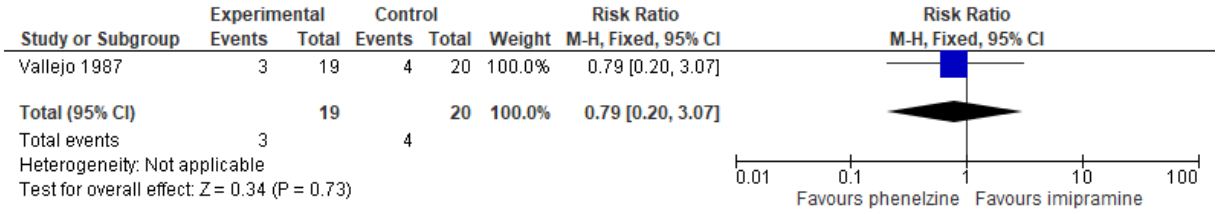
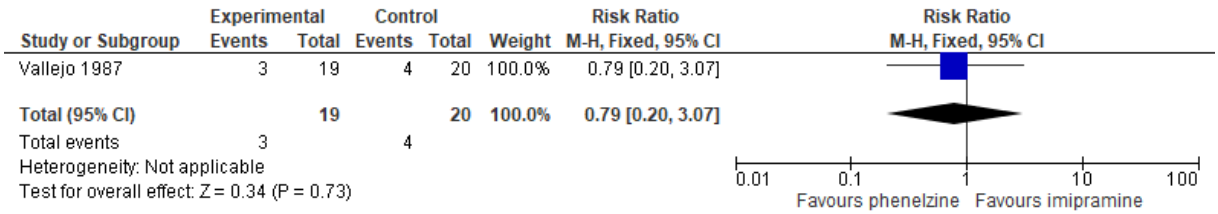


Figure 96: Discontinuation due to any reason



Comparison 25: Phenelzine versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Figure 97: Relapse

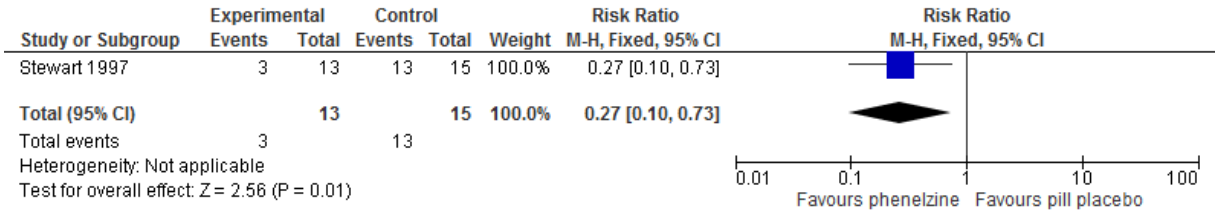
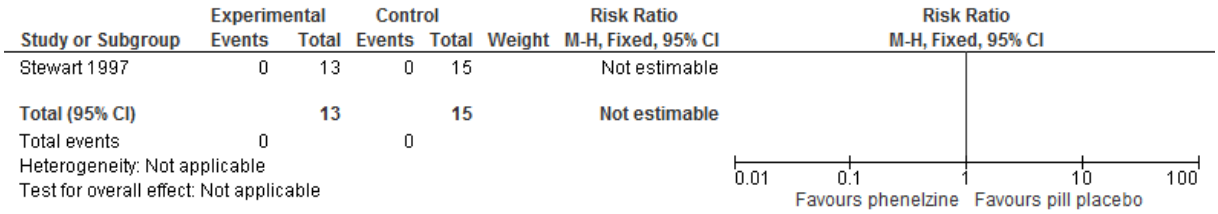


Figure 98: Discontinuation due to any reason



Comparison 26: SNRIs versus pill placebo for chronic depression (MDD ≥2 years, dysthymia)

Figure 99: Depression symptomatology change score

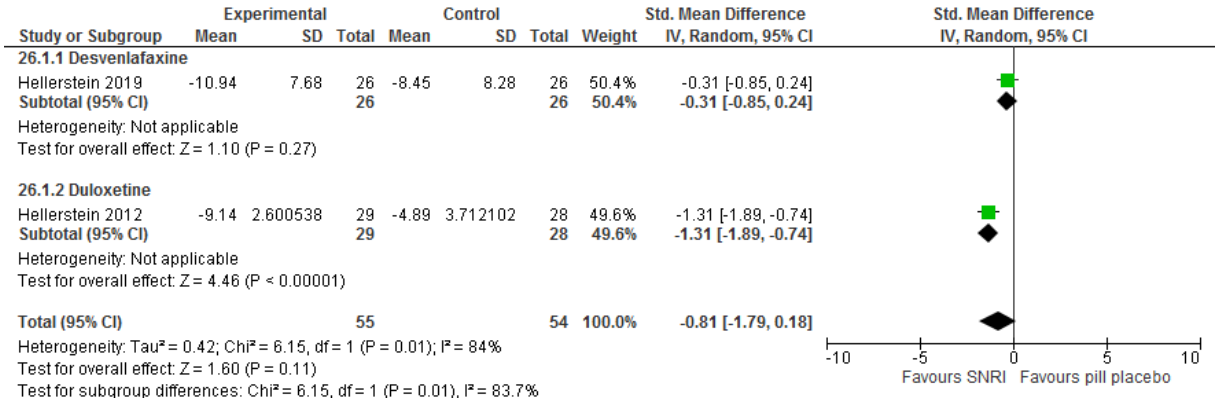


Figure 100: Remission

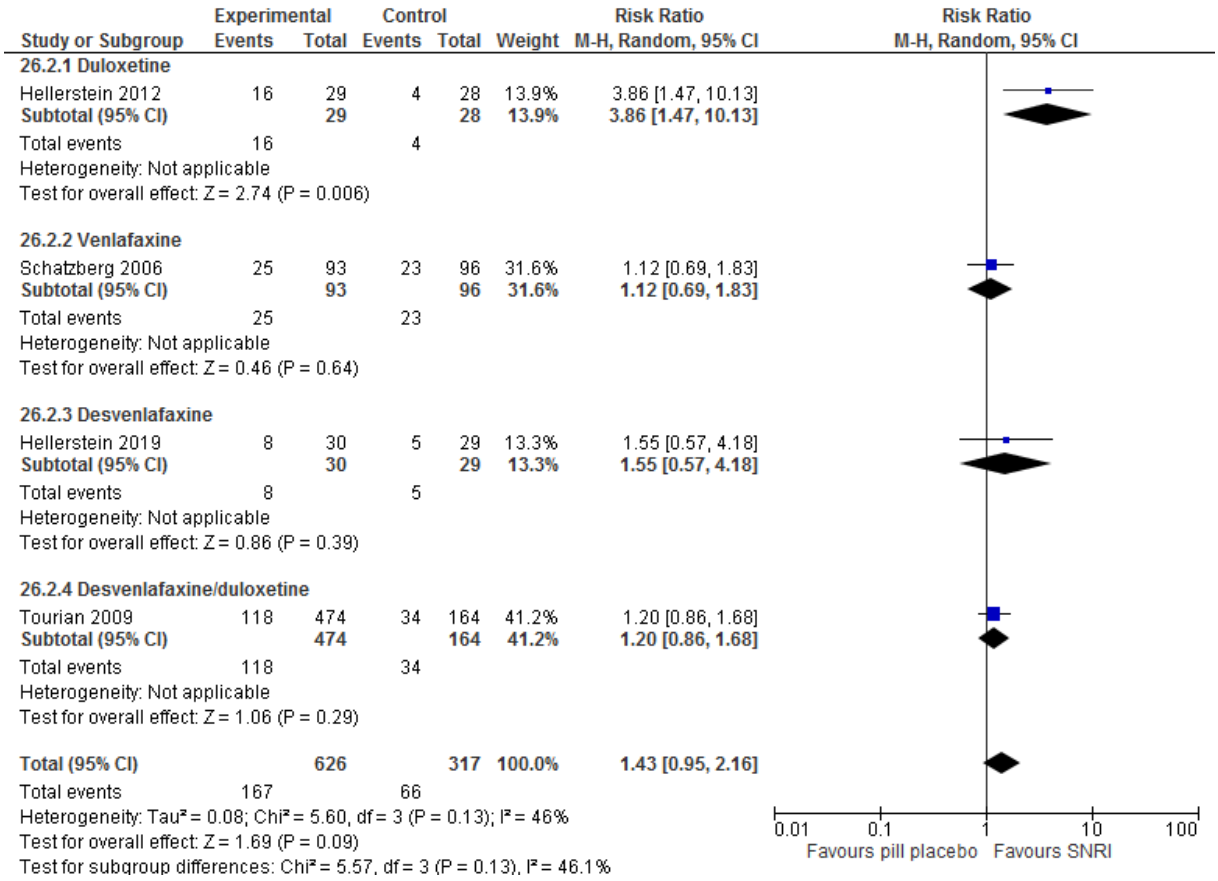


Figure 101: Response

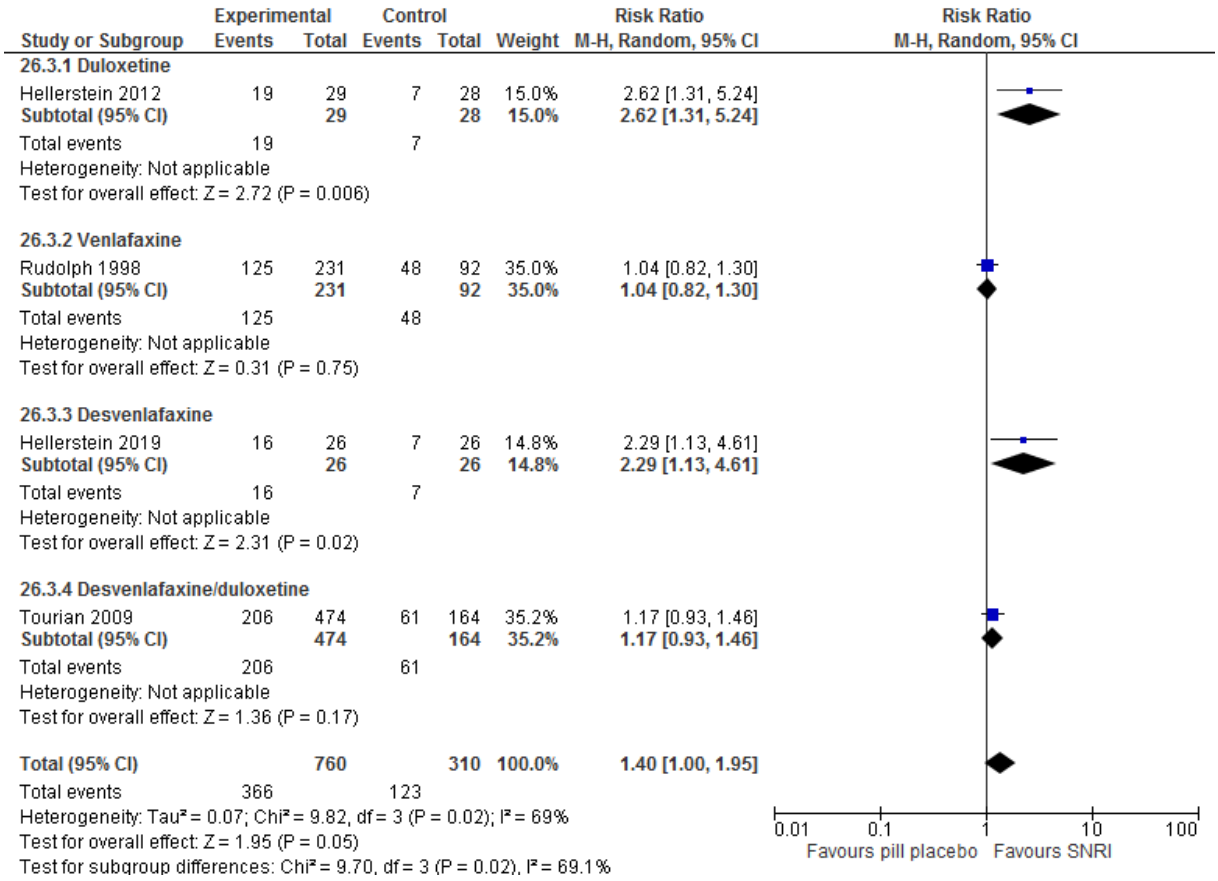


Figure 102: Discontinuation due to side effects

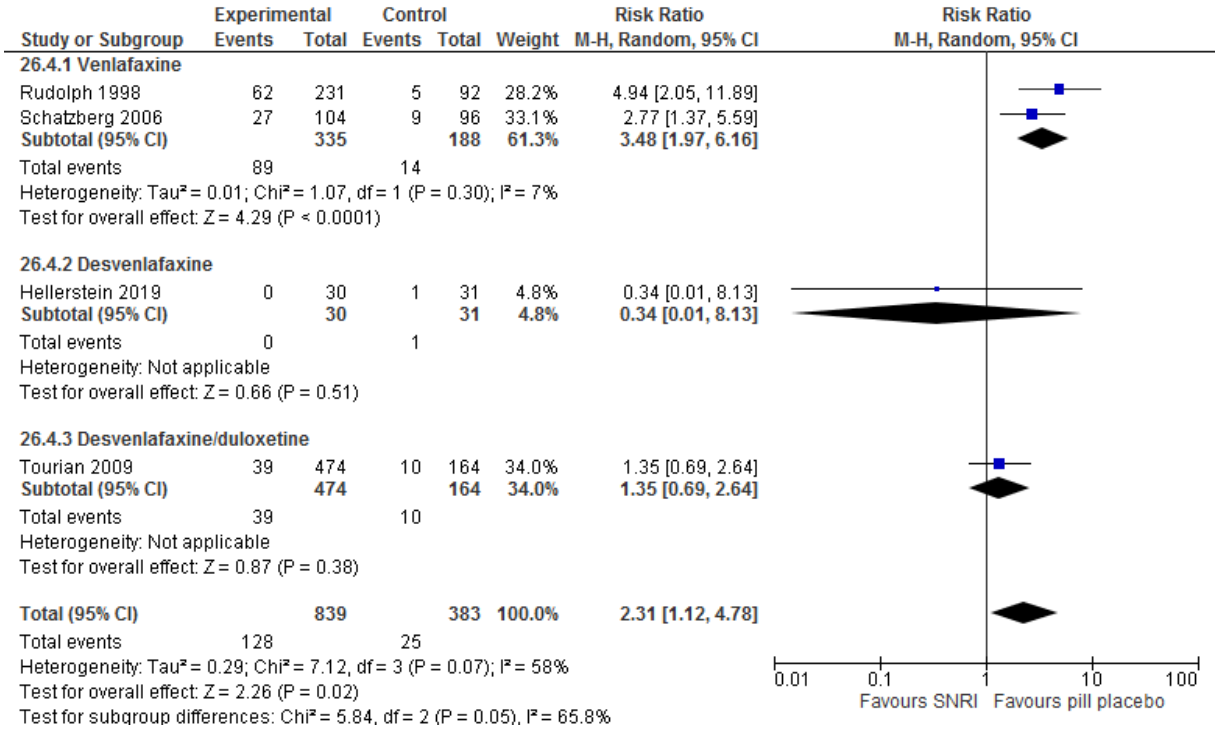


Figure 103: Discontinuation due to any reason

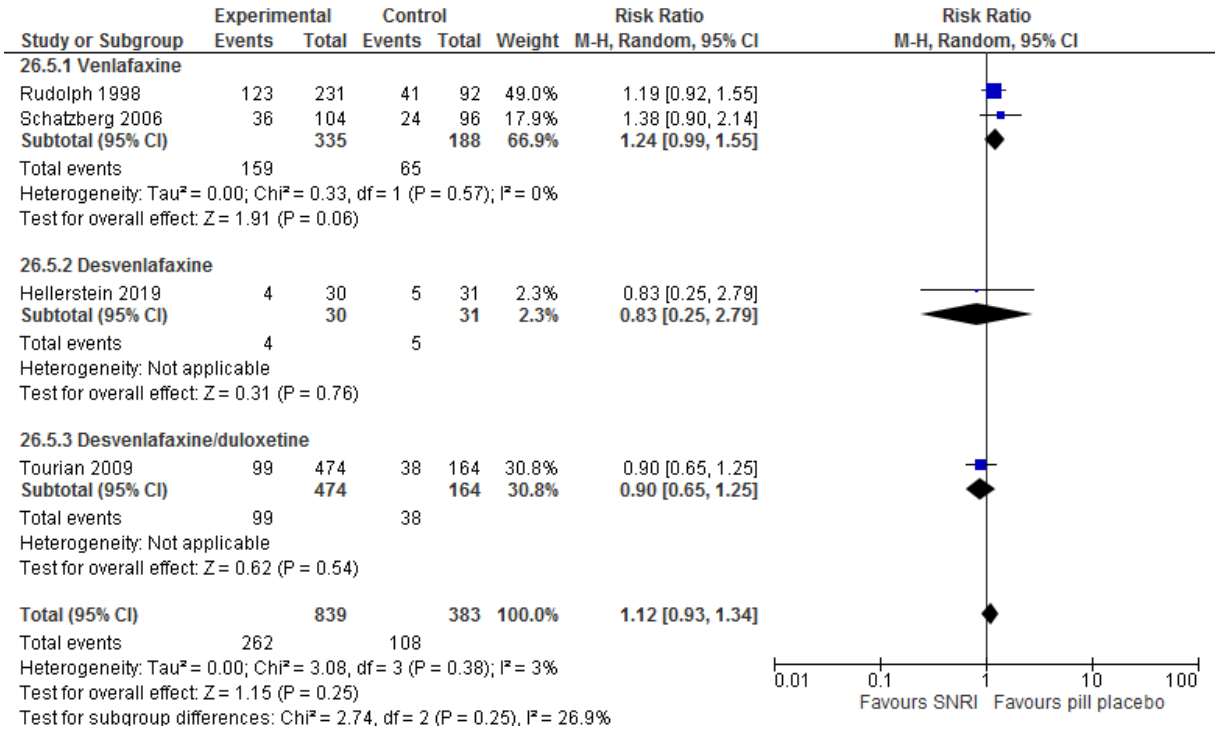
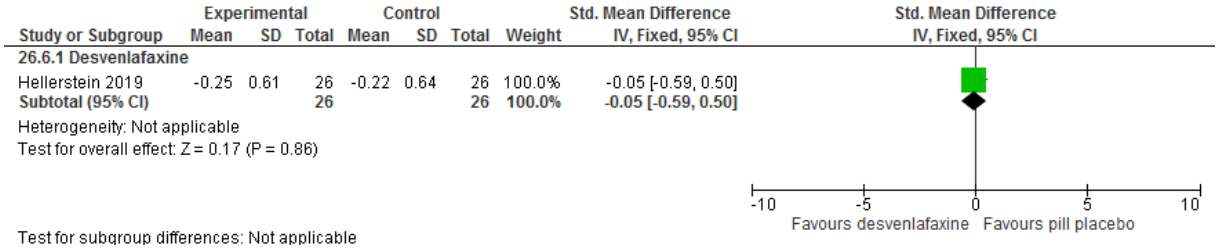


Figure 104: Functional impairment



Comparison 27: Moclobemide versus pill placebo for dysthymia or double depression

Figure 105: Depression symptomatology change score

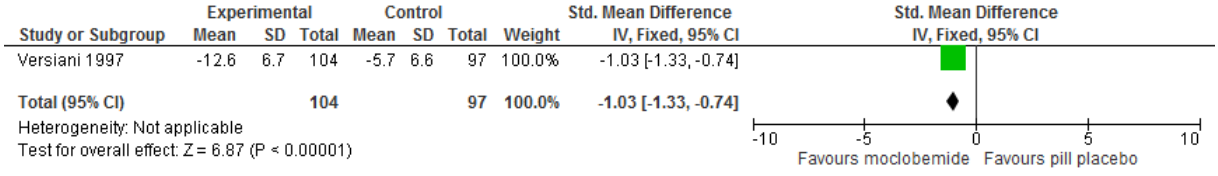


Figure 106: Remission

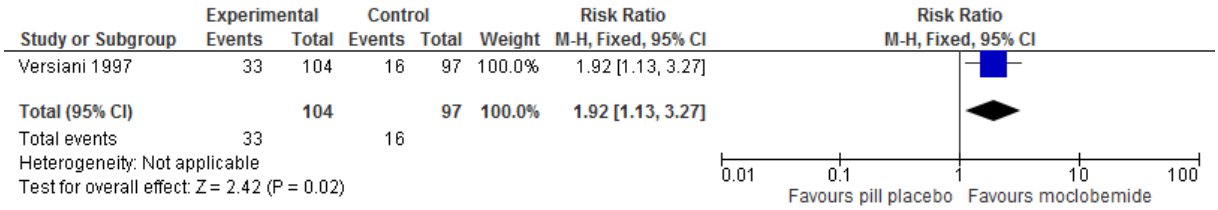


Figure 107: Response

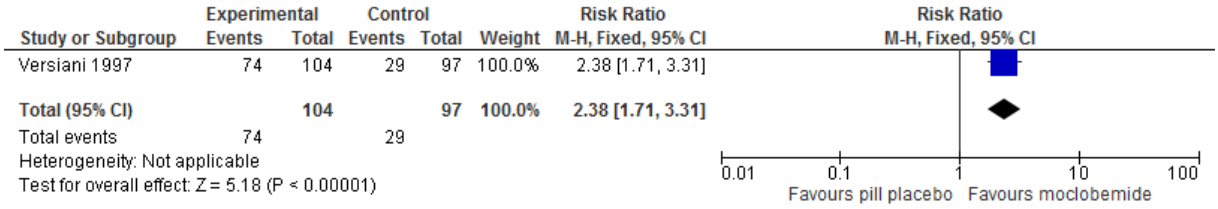


Figure 108: Discontinuation due to side effects

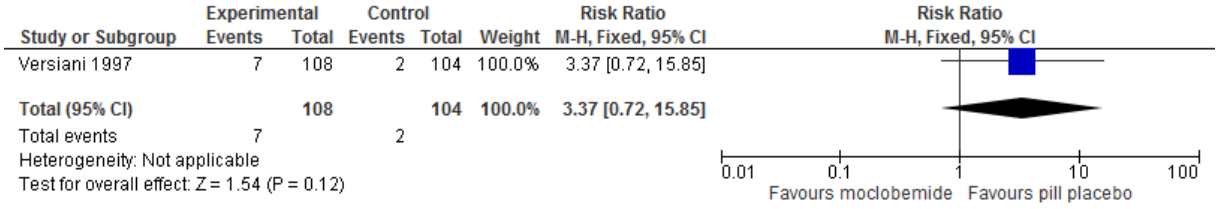
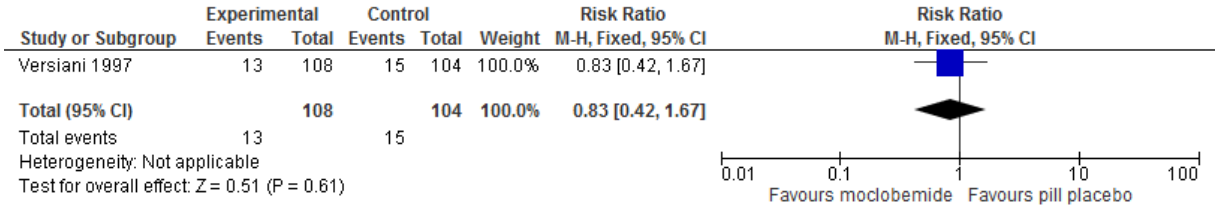


Figure 109: Discontinuation due to any reason



Comparison 28: Moclobemide versus fluoxetine for double depression

Figure 110: Response

Figure 111: Discontinuation due to side effects

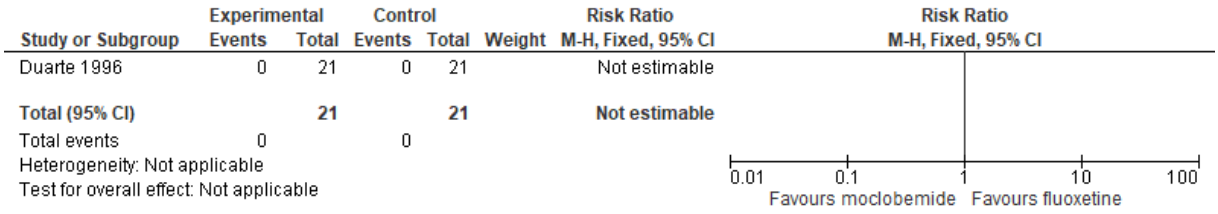
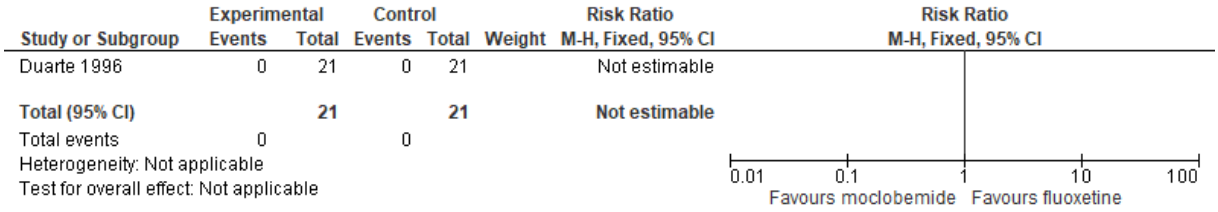


Figure 112: Discontinuation due to any reason



Comparison 29: Moclobemide versus imipramine for dysthymia or double depression

Figure 113: Depression symptomatology change score

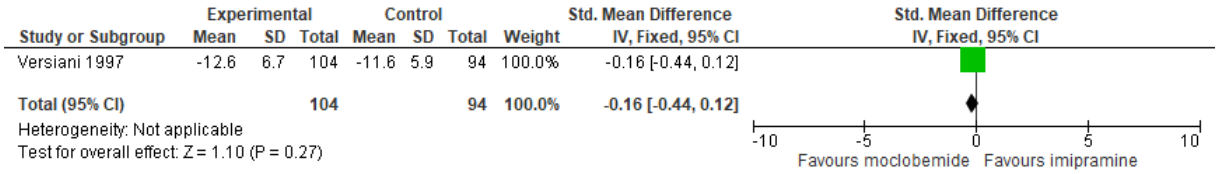


Figure 114: Remission

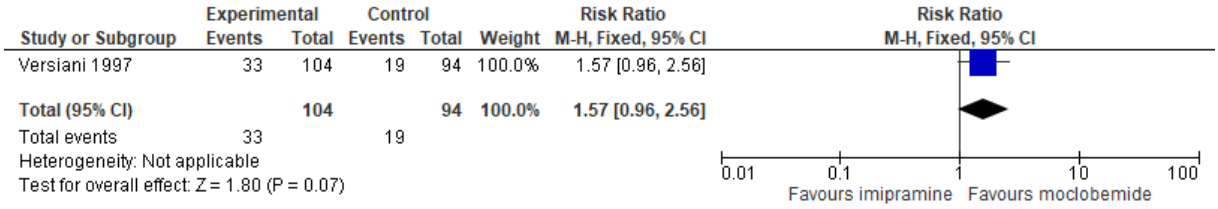


Figure 115: Response

Figure 116: Discontinuation due to side effects

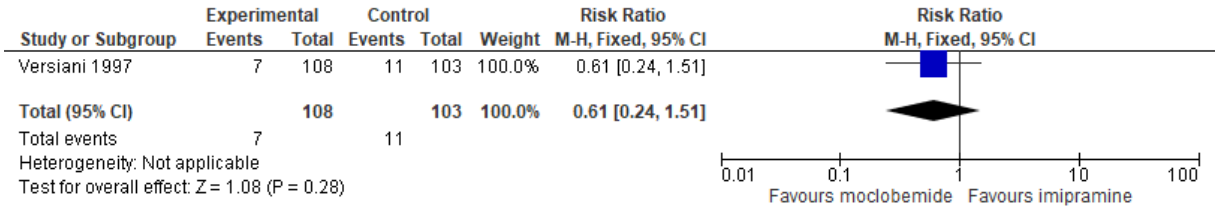
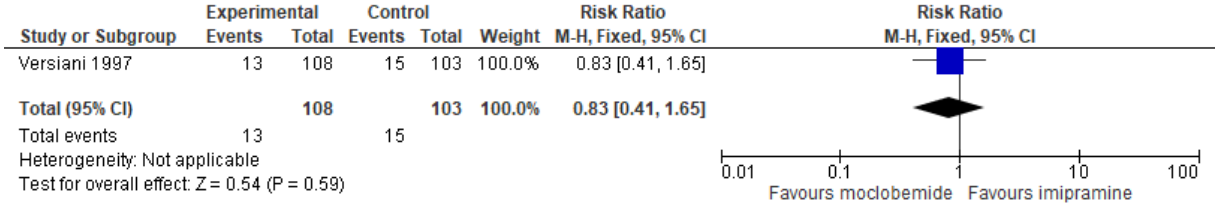


Figure 117: Discontinuation due to any reason



Comparison 30: Nefazodone versus pill placebo for relapse prevention in chronic depression

Figure 118: Relapse

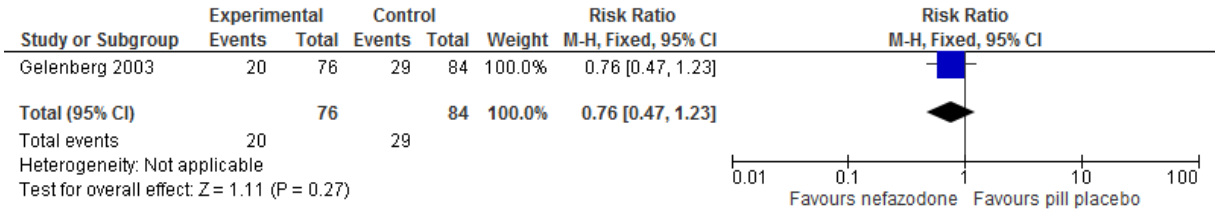


Figure 119: Discontinuation due to side effects

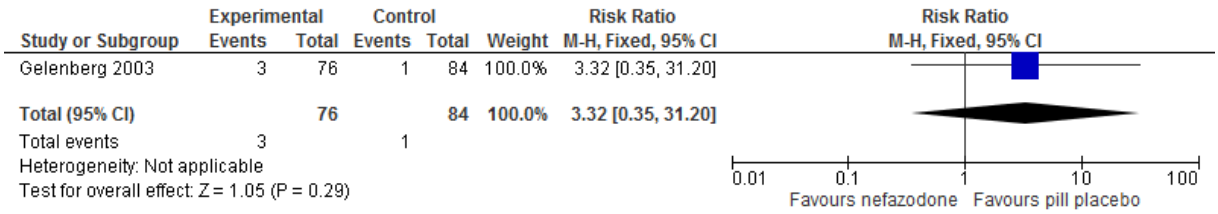
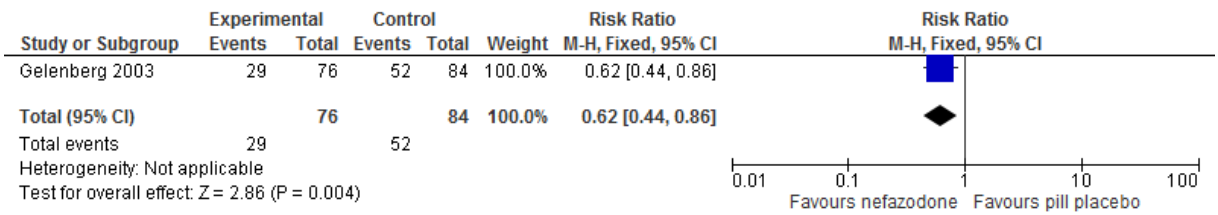


Figure 120: Discontinuation due to any reason



Comparison 31: Amisulpride versus pill placebo for dysthymia or double depression

Figure 121: Depression symptomatology change score

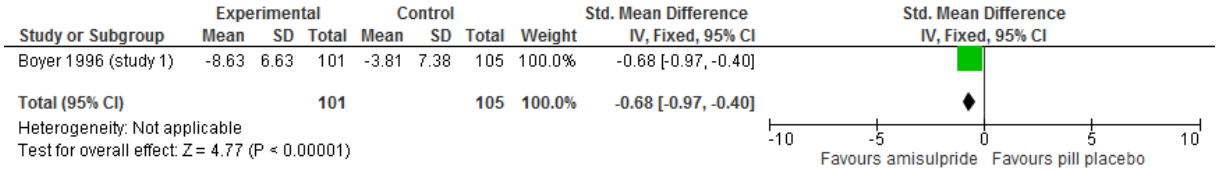


Figure 122: Remission

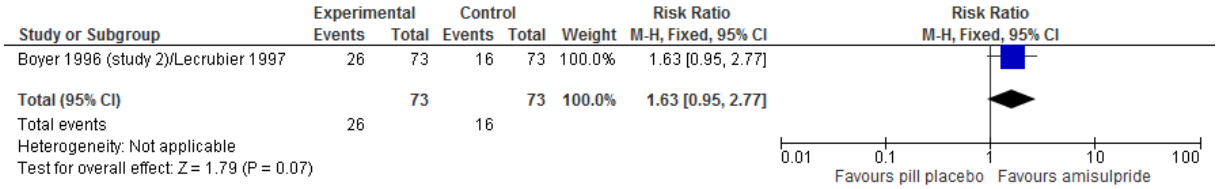


Figure 123: Response

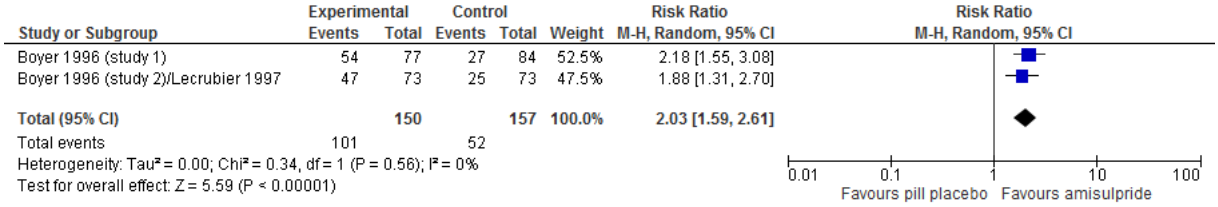


Figure 124: Discontinuation due to side effects

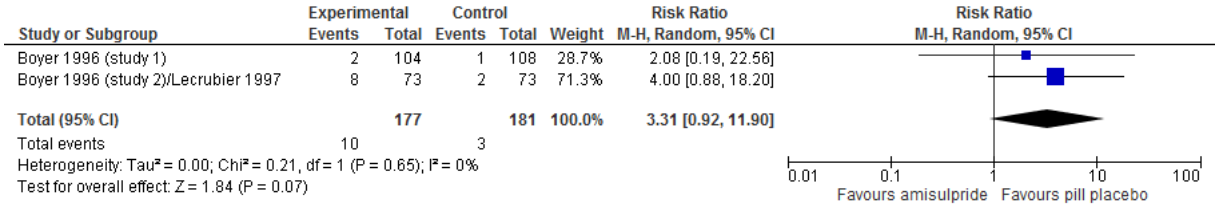
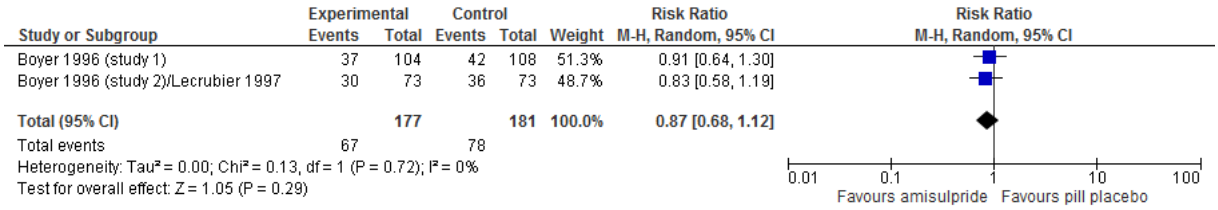


Figure 125: Discontinuation due to any reason



Comparison 32: Yoga + TAU versus TAU for chronic depression (MDD ≥ 2 years)

Figure 126: Depression symptomatology endpoint

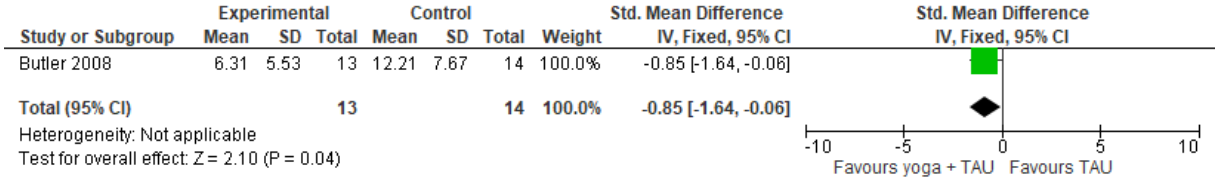
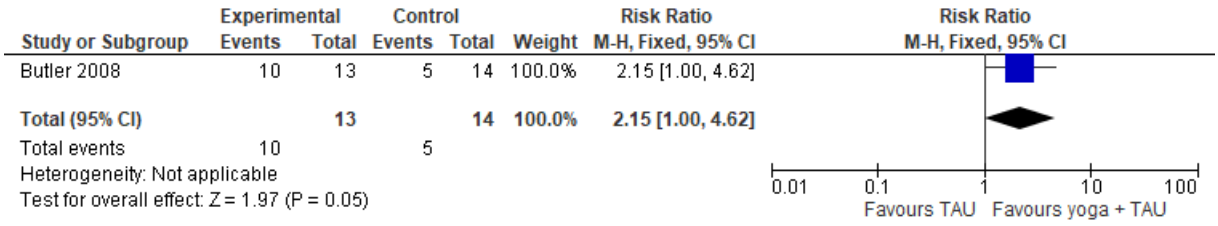


Figure 127: Remission



Appendix F – GRADE tables

GRADE tables for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Table 35: Clinical evidence profile for Comparison 1: CBT (individual) versus pill placebo for chronic depression (MDD ≥ 2 years)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual (over 15 sessions)	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up 10-16 weeks; measured with HAMD change score; Better indicated by lower values)												
2 (Agosti 1997, Jarrett 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	52	51	-	SMD 0.47 lower (0.87 to 0.08 lower)	VERY LOW	CRITICAL
Remission (follow-up 10-16 weeks; assessed with: Number of participants scoring ≤9/<7 on HAM-D												
2 (Agosti 1997, Jarrett 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	27/52 (51.9%)	14/51 (27.5%)	RR 1.91 (1.14 to 3.2)	250 more per 1000 (from 38 more to 604 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 10-16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
2 (Agosti 1997, Jarrett 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	5/52 (9.6%)	23/51 (45.1%)	RR 0.22 (0.09 to 0.51)	352 fewer per 1000 (from 221 fewer to 410 fewer)	VERY LOW	CRITICAL

CBT: cognitive behavioural therapy; CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio; SMD: standardised mean difference

[1] *Risk of bias is unclear or high across multiple domains*

[2] *95% CI crosses one clinical decision threshold*

[3] *Study medication supplied by pharmaceutical company*

Table 36: Clinical evidence profile for Comparison 2: CBT (individual) versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual (over 15 sessions)	Antidepressant	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up 10-16 weeks; measured with HAM-D change score; (Better indicated by lower values)												
4 (Agosti 1997, Dunner 1996, Jarrett 1999, Thompson 2001)	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	93	101	-	SMD 0.06 higher (0.49 lower to 0.61 higher)	VERY LOW	CRITICAL
Remission (follow-up 10-16 weeks; assessed with: Number of participants scoring ≤9/<7 on HAM-D)												
2 (Agosti 1997, Jarrett 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[4]	27/52 (51.9%)	30/50 (60%)	RR 0.84 (0.51 to 1.38)	96 fewer per 1000 (from 294 fewer to 228 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 10-16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
4 (Agosti 1997, Dunner 1996, Jarrett 1999, Thompson 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[4]	18/101 (17.8%)	30/102 (29.4%)	RR 0.66 (0.35 to 1.26)	100 fewer per 1000 (from 191 fewer to 76 more)	VERY LOW	CRITICAL

AD: antidepressants; CBT: cognitive behavioural therapy; CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio; SMD: standardised mean difference

[1] *Risk of bias is unclear or high across multiple domains*

[2] *I^2>50%*

[3] *95% CI crosses one clinical decision threshold*

[4] *Study medication supplied by pharmaceutical company*

[5] *95% CI crosses two clinical decision thresholds*

Table 37: Clinical evidence profile for Comparison 3: CBT (individual) versus IPT for chronic depression (MDD ≥ 2years)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT individual (over 15 sessions)**	**IPT**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology (follow-up mean 16 weeks; measured with HAM-D change score; Better indicated by lower values)												
1 (Agosti 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	14	-	SMD 0.3 lower (1.02 lower to 0.43 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: Number of participants scoring ≤8 on HAM-D)												
1 (Agosti 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/16 (37.5%)	5/14 (35.7 %)	RR 1.05 (0.41 to 2.7)	18 more per 1000 (from 211 fewer to 607 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Agosti 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	0/16 (0%)	0/14 (0%)	not pooled	not pooled	VERY LOW	CRITICAL

CBT: cognitive behavioural therapy; CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; IPT: Interpersonal psychotherapy; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains

[2] 95% CI crosses one clinical decision threshold

[3] 95% CI crosses two clinical decision thresholds

[4] OIS not met (events<300)

Table 38: Clinical evidence profile for Comparison 4: Cognitive-behavioural analysis system for psychotherapy (CBASP) versus assessment-only for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBASP (maintenance treatment)**	**Assessment-only**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology (follow-up mean 52 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1 (Klein 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	42	40	-	SMD 0.91 lower (1.37 to 0.45 lower)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBASP (maintenance treatment)	Assessment-only	Relative (95% CI)	Absolute	Quality	Importance
Relapse (follow-up mean 52 weeks; assessed with: Number of participants scoring ≥16 on HAM-D on 2 consecutive visits and meeting DSM-IV criteria for a diagnosis of MDD)												
1 (Klein 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	1/42 (2.4%)	8/40 (20%)	RR 0.12 (0.02 to 0.91)	176 fewer per 1000 (from 18 fewer to 196 fewer)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 52 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Klein 2004)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	10/42 (23.8%)	11/40 (27.5%)	RR 0.87 (0.41 to 1.81)	36 fewer per 1000 (from 162 fewer to 223 more)	VERY LOW	CRITICAL

CBASP: cognitive behavioural analysis system of psychotherapy; CI: confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAMD-D: Hamilton Rating Scale for Depression; MDD: major depressive disorder; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] *Risk of bias is unclear or high across multiple domains*

[2] *95% CI crosses one clinical decision threshold*

[3] *Funding from pharmaceutical company*

[4] *95% CI crosses two clinical decision thresholds*

Table 39: Clinical evidence profile for Comparison 5: CBT individual + desipramine versus desipramine for chronic depression (MDD ≥2 years)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual (over 15 sessions) + desipramine	Desipramine	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up mean 16 weeks; measured with HAM-D change score; Better indicated by lower values)												
1 (Thompson 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	33	36	-	SMD 0.37 higher (0.1 lower to 0.85 higher)	VERY LOW	
Discontinuation due to any reason (follow-mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual (over 15 sessions) + desipramine	Desipramine	Relative (95% CI)	Absolute		
1 (Thompson 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	12/33 (36.4%)	12/36 (33.3%)	RR 1.09 (0.57 to 2.08)	30 more per 1000 (from 143 fewer to 360 more)	VERY LOW	CRITICAL

CBT: cognitive behavioural therapy; CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio; SMD: standardised mean difference
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses one clinical decision threshold
[3] Study medication supplied by pharmaceutical company
[4] 95% CI crosses two clinical decision thresholds

Table 40: Clinical evidence profile for Comparison 6: Mindfulness-based cognitive therapy (MBCT) group + medication versus medication for dysthymia or double depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MBCT + TAU	TAU	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 8 weeks; measured with: BDI-II change score; Better indicated by lower values)												
1 (Hamidian 2013)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	22	-	SMD 1.47 lower (2.14 to 0.79 lower)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Hamidian 2013)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/25 (12%)	3/25 (12%)	RR 1 (0.22 to 4.49)	0 fewer per 1000 (from 94 fewer to 419 more)	VERY LOW	CRITICAL

BDI: beck depression inventory; CI: confidence interval; MBCT: mindfulness-based cognitive therapy; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference; TAU: treatment as usual
[1] Risk of bias is unclear or high across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses two clinical decision thresholds

Table 41: Clinical evidence profile for Comparison 7: CBT individual + fluoxetine versus fluoxetine for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT individual (over 15 sessions) + fluoxetine**	**Fluoxetine**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Depression symptomatology (follow-mean 28 weeks; measured with HAM-D change score; Better indicated by lower values)												
1 (Perlis 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	66	66	-	SMD 0.18 lower (0.52 lower to 0.16 higher)	VERY LOW	CRITICAL
Relapse (follow-mean 28 weeks; assessed with: Number of participants scoring ≥15 on HAM-D on 2 consecutive visits or DSM-III-R MDD)												
1 (Perlis 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	27/66 (40.9%)	29/66 (43.9%)	RR 0.93 (0.63 to 1.39)	31 fewer per 1000 (from 163 fewer to 171 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-mean 28 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Perlis 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	3/66 (4.5%)	1/66 (1.5%)	RR 3 (0.32 to 28.1)	30 more per 1000 (from 10 fewer to 411 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-mean 28 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Perlis 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	23/66 (34.8%)	24/66 (36.4%)	RR 0.96 (0.61 to 1.52)	15 fewer per 1000 (from 142 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual (over 15 sessions) + fluoxetine	Fluoxetine	Relative (95% CI)	Absolute		
										to 189 more)		

CBT: cognitive behavioural therapy; CI: confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAMD-D: Hamilton Rating Scale for Depression; MDD: major depressive disorder; RR: risk ratio; SMD: standardised mean difference
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses one clinical decision threshold
[3] Study partially funded by pharmaceutical company
[4] 95% CI crosses two clinical decision thresholds

Table 42: Clinical evidence profile for Comparison 8: Problem solving versus pill placebo for dysthymia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Problem solving	Pill placebo	Relative (95% CI)	Absolute		
Remission (follow-up 10 weeks; assessed with: Number of participants scoring <7 on HAM-D)												
1 (Williams 2000)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32/63 (50.8%)	25/62 (40.3%)	RR 1.26 (0.85 to 1.86)	105 more per 1000 (from 60 fewer to 347 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses one clinical decision threshold
[3] Study medication supplied by pharmaceutical company and authors have some financial interests in pharmaceutical companies

Table 43: Clinical evidence profile for Comparison 9: Problem solving versus paroxetine for dysthymia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Problem solving	Paroxetine	Relative (95% CI)	Absolute		
Remission (follow-up 10 weeks; assessed with Number of participants scoring <7 on HAM-D)												
1 (Williams 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	32/63 (50.8%)	26/57 (45.6%)	RR 1.11 (0.77 to 1.62)	50 more per 1000 (from 105 fewer to 283 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses two clinical decision thresholds
[3] Study medication supplied by pharmaceutical company and authors have some financial interests in pharmaceutical companies

Table 44: Clinical evidence profile for Comparison 10: IPT versus pill placebo for chronic depression (MDD ≥ 2 years)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 16 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1 (Agosti 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14	15	-	SMD 0.14 higher (0.59 lower to 0.87 higher)	VERY LOW	CRTICAL
Remission (follow-up mean 16 weeks; assessed with: Number of participants scoring <7 on HAM-D)												
1 (Agosti 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/14 (35.7 %)	4/15 (26.7%)	RR 1.34 (0.45 to 4)	91 more per 1000 (from 147 fewer to 800 more)	VERY LOW	CRTICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Agosti 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/14 (0%)	0/15 (0%)	not pooled	not pooled	VERY LOW	CRITICAL

CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; IPT: Interpersonal psychotherapy; MDD: major depressive disorder; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses two clinical decision thresholds
[3] OIS not met (events<300)

Table 45: Clinical evidence profile for Comparison 11: IPT versus antidepressants for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Antidepressant	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up 16-26 weeks; measured with: MADRS/HAMD change score; Better indicated by lower values)												
3 (Agosti 1997, Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	215	240	-	SMD 0.43 higher (0.12 to 0.74 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: score <7 on HAM-D and >50% improvement on HAM-D and GAF score>70/<7 HAM-D only)												
2 (Agosti 1997, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	10/37 (27%)	19/38 (50%)	RR 0.54 (0.3 to 0.99)	230 fewer per 1000 (from 5 fewer to 350 fewer)	VERY LOW	CRITICAL
Response (follow-up 16-26 weeks; assessed with: ≥40% improvement on MADRS/≥50% improvement on HAM-D)												
2 (Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	91/201 (45.3 %)	131/220 (59.5 %)	RR 0.76 (0.63 to 0.92)	143 fewer per 1000 (from 48 fewer to 220 fewer)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
2 (Agosti 1997, Markowitz 2005)	randomised trials	very serious[1]	serious[6]	no serious indirectness	very serious[3]	reporting bias[2]	4/37 (10.8 %)	11/44 (25%)	RR 0.43 (0.06 to 3.27)	142 fewer per 1000 (from 235 fewer to 567 more)	VERY LOW	CRITICAL

AD: antidepressants; CI: confidence interval; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; IPT: Interpersonal psychotherapy; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference
[1] Risk of bias is unclear or high across multiple domains
[2] Funding from pharmaceutical company
[3] 95% CI crosses two clinical decision thresholds
[4] OIS not met (events<300)

Table 46: Clinical evidence profile for Comparison 12: IPT versus counselling for dysthymia

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	BSP	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up mean 16 weeks; measured with: HAM-D change score; Better indicated by lower values)												
2 (Markowitz 2005, Markowitz 2008)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	37	38	-	SMD 0.05 lower (0.5 lower to 0.41 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: Number of participants scoring <7 on HAM-D and >50% improvement on HAM-D and GAF score>70)												
2 (Markowitz 2005, Markowitz 2008)	randomised trials	very serious [1]	serious[4]	no serious indirectness	very serious[5]	reporting bias[3]	6/37 (16.2%)	6/38 (15.8%)	RR 0.89 (0.14 to 5.47)	17 fewer per 1000 (from 136 fewer to 706 more)	VERY LOW	CRITICAL
Response (follow-up mean 16 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D)												
2 (Markowitz 2005, Markowitz 2008)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	13/37 (35.1%)	10/38 (26.3%)	RR 1.31 (0.65 to 2.65)	82 more per 1000 (from 92 fewer to 434 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Markowitz 2005)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	4/23 (17.4%)	11/26 (42.3%)	RR 0.41	250 fewer per 1000 (from 360 fewer to 47 more)	VERY LOW	CRITICAL

BSP: brief supportive psychotherapy; CI: confidence interval; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; IPT: interpersonal psychotherapy; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains

[2] 95% CI crosses one clinical decision threshold

[3] Funding from pharmaceutical company

[4] I-squared>50%

[5] 95% CI crosses one clinical decision threshold

Table 47: Clinical evidence profile for Comparison 13: IPT + antidepressant versus antidepressant-only for dysthymia or double depression

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT + Antidepressant	Antidepressant	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up 5-26 weeks; measured with: HAM-D/MADRS change score; Better indicated by lower values)												
3 (de Mello 2001, Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	244	233	-	SMD 0.06 lower (0.24 lower to 0.12 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: Participants scoring <7 on HAM-D and >50% improvement on HAM-D and GAF score>70)												
1 (Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	11/21 (52.4 %)	10/24 (41.7 %)	RR 1.26 (0.67 to 2.35)	108 more per 1000 (from 138 fewer to 562 more)	VERY LOW	CRITICAL
Response (follow-up 16-26 weeks; assessed with: Participants showing ≥50% improvement on HAM-D/≥40% improvement on MADRS)												
2 (Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	134/233 (57.5 %)	131/220 (59.5 %)	RR 0.97 (0.83 to 1.13)	18 fewer per 1000 (from 101 fewer to 77 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 5-16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
2 (de Mello 2001, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	10/37 (27%)	16/43 (37.2 %)	RR 0.71 (0.38 to 1.34)	108 fewer per 1000 (from 231 fewer to 127 more)	VERY LOW	CRITICAL

AD: antidepressants; CI: confidence interval; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; IPT: interpersonal psychotherapy; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains

[2] Funding from pharmaceutical company

[3] 95% CI crosses two clinical decision thresholds

[4] OIS not met (events<300)

[5] 95% CI crosses one clinical decision threshold

Table 48: Clinical evidence profile for Comparison 14: Counselling versus sertraline for dysthymia

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Counselling	Sertraline	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up mean 16 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1 (Markowitz 2005)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	26	24	-	SMD 0.77 higher (0.19 to 1.34 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: Number of participants scoring <7 on HAM-D and >50% improvement on HAM-D AND GAF score>70)												
1 (Markowitz 2005)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	3/26 (11.5 %)	10/24 (41.7%)	RR 0.28 (0.09 to 0.89)	300 fewer per 1000 (from 46 fewer to 379 fewer)	VERY LOW	CRITICAL
Response (follow-up mean 16 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D)												
1 (Markowitz 2005)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	8/26 (30.8 %)	14/24 (58.3%)	RR 0.53 (0.27 to 1.03)	274 fewer per 1000 (from 426 fewer to 17 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Markowitz 2005)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	11/26 (42.3 %)	5/24 (20.8%)	RR 2.03 (0.83 to 4.99)	215 more per 1000 (from 35 fewer to 831 more)	VERY LOW	CRITICAL

CI: confidence interval; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains

[2] OIS not met (N<400)

[3] Funding from pharmaceutical company

[4] OIS not met (events<300)

[5] 95% CI crosses one clinical decision threshold

Table 49: Clinical evidence profile for Comparison 15: SSRIs versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up 6-13 weeks; measured with: HAM-D/MADRS change score; Better indicated by lower values)												
10 (Anisman 1999, Gastpar 2006, Hellerstein 1993, Hellerstein 2010, Rapaport 2003 Ravindran 2000, Ravindran 2013, Schneider 2003, Thase 1996/Kocsis 1997, Vanelle 1997)	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	1148	1022	-	SMD 0.41 lower (0.59 to 0.23 lower)	VERY LOW	CRITICAL
Remission (follow-up 8-13 weeks; assessed with: Number of participants scoring ≤4/ <7/≤8 on HAM-D/≤4 on HAM-D and HAM-D item # 1 [depressed mood] score=0)												
7 (Hellerstein 2010, Rapaport 2003, Ravindran 2013, Schartzberg 2006, Thase 1996/Kocsis 1997, Vanelle 1997,Williams 2000)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	249/610 (40.8%)	136/482 (28.2%)	RR 1.43 (1.13 to 1.81)	121 more per 1000 (from 37 more to 229 more)	VERY LOW	CRITICAL
Response (follow-up 8-13 weeks; assessed with: Number of participants with ≥50% improvement on HAM-D and HAM-D score≤10/≥50% improvement on HAM-D and/or much/very much improved on CGI-I/≥50% improvement on MADRS)												
9 (Anisman 1999, Clayton 2003, Hellerstein 1993, Hellerstein 2010, Ravindran 2000, Ravindran 2013, Schneider 2003, Thase 1996/Kocsis 1997, Vanelle 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	444/962 (46.2%)	302/934 (32.3%)	RR 1.4 (1.25 to 1.57)	129 more per 1000 (from 81 more to 184 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants discontinuing due to side effects)												
8 (Hellerstein 1993, Hellerstein 2010, Rapaport 2003, Ravindran 2000, Ravindran 2013, Schatzberg 2006,	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[7]	reporting bias[4]	133/1032 (12.9%)	53/925 (5.7%)	RR 2.15 (1.58 to 2.91)	66 more per 1000 (from 33 more to 109 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRIs**	**Pill placebo**	**Relative (95% CI)**	**Absolute**		
Schneider 2003, Thase 1996/Kocsis 1997)												
Discontinuation due to any reason (follow-up 6-13 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
12 (Anisman 1999, Clayton 2003, Gastpar 2006, Hellerstein 1993, Hellerstein 2010, Rapaport 2003, Ravindran 2000, Ravindran 2013, Schatzberg 2006, Schneider 2003, Thase 1996/Kocsis 1997, Vanelle 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	323/1434 (22.5%)	296/1288 (23%)	RR 0.93 (0.75 to 1.15)	16 fewer per 1000 (from 57 fewer to 34 more)	VERY LOW	CRITICAL
Quality of life (follow-up 8-12 weeks; measured with: Q-LES-Q change score; Better indicated by lower values)												
2 (Schneider 2003, Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[4]	466	473	-	SMD 0.27 higher (0.04 to 0.49 higher)	VERY LOW	CRITICAL
Global functioning (follow-up 12-13 weeks; measured with: GAF change score; Better indicated by lower values)												
2 (Thase 1996/Kocsis 1997, Vanelle 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	199	169	-	SMD 0.32 higher (0.11 to 0.52 higher)	VERY LOW	CRITICAL
Functional impairment (follow-up mean 12 weeks; measured with: SAS change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	123	123	-	SMD 0.54 lower (0.79 to 0.28 lower)	VERY LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression-improvement; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; RR: risk ratio; SAS: social adjustment scale; SMD: standardised mean difference; SSRIs: selective serotonin reuptake inhibitors

[1] Risk of bias is unclear or high across multiple domains

[2] I^2>50%
[3] 95% CI crosses one clinical decision threshold
[4] Study funded or partially funded by pharmaceutical company
[5] I^2 >80%
[6] 95% CI crosses two clinical decision thresholds
[7] OIS not met (events<300)

Table 50: Clinical evidence profile for Comparison 16: Sertraline versus imipramine for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Imipramine	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up mean 12 weeks; measured with HAM-D change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	134	136	-	SMD 0.05 higher (0.19 lower to 0.29 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 12 weeks; assessed with: Number of participants scoring ≤7 on HAM-D and much/very much improved on CGI-I/≤4 on HAM-D)												
2 (Keller 1998a, Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	133/555 (24%)	88/338 (26%)	RR 1.11 (0.89 to 1.39)	29 more per 1000 (from 29 fewer to 102 more)	VERY LOW	CRITICAL
Response (follow-up mean 12 weeks; assessed with: Number of participants with ≥50% improvement on HAM-D and HAM-D≤15 and CGI-I score 1-2 [much/very much improved] & CGI-S≤3 [mildly ill])/CGI-I score 1-2 (much/very much improved)												
2 (Keller 1998a, Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	299/555 (53.9%)	191/338 (56.5%)	RR 0.97 (0.86 to 1.1)	17 fewer per 1000 (from 79 fewer to 57 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants discontinuing due to side effects)												
2 (Keller 1998a, Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	35/560 (6.3%)	50/345 (14.5%)	RR 0.45 (0.29 to 0.71)	80 fewer per 1000 (from 42 fewer to 103 fewer)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sertraline	Imipramine	Relative (95% CI)	Absolute		
2 (Keller 1998a, Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	serious[6]	no serious indirectness	serious[4]	reporting bias[3]	97/560 (17.3%)	95/345 (27.5%)	RR 0.61 (0.39 to 0.95)	107 fewer per 1000 (from 14 fewer to 168 fewer)	VERY LOW	CRITICAL
Quality of life (follow-up mean 12 weeks; measured with: Q--LES-Q change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	106	102	-	SMD 0 higher (0.27 lower to 0.27 higher)	VERY LOW	IMPORTANT
Global functioning (follow-up mean 12 weeks; assessed with: GAF change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	127	126	-	SMD 0.1 lower (0.35 lower to 0.14 higher)	VERY LOW	IMPORTANT
Functional impairment (follow-up mean 12 weeks; measured with: SAS change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	123	122	-	SMD 0.07 lower (0.32 lower to 0.18 higher)	VERY LOW	IMPORTANT

CI: confidence interval; CGI: Clinical Global Impression; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; OIS: optimal information size; RR: risk ratio; SAS: social adjustment scale; SMD: standardised mean difference; QLES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire

[1] Risk of bias is unclear or high across multiple domains

[2] OIS not met (N<400)

[3] Study funded or partially funded by pharmaceutical company

[4] 95% CI crosses one clinical decision threshold

[5] OIS not met (events<300)

[6] I^2>50%

Table 51: Clinical evidence profile for Comparison 17: Fluoxetine versus venlafaxine for chronic depression (MDD ≥2 years)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoxetine	Venlafaxine	Relative (95% CI)	Absolute	Quality	Importance
Remission (follow-up mean 8 weeks; assessed with: Number of participants scoring ≤7 on HAM-D)												
1 (Schatzberg 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	20/99 (20.2%)	25/93 (26.9%)	RR 0.75 (0.45 to 1.26)	67 fewer per 1000 (from 148 fewer to 70 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Schatzberg 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	19/100 (19%)	27/104 (26%)	RR 0.73 (0.44 to 1.23)	70 fewer per 1000 (from 145 fewer to 60 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Schatzberg 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	30/100 (30%)	36/104 (34.6%)	RR 0.87 (0.58 to 1.29)	45 fewer per 1000 (from 145 fewer to 100 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses two clinical decision thresholds
[3] Study funded by pharmaceutical company
[4] 95% CI crosses one clinical decision threshold

Table 52: Clinical evidence profile for Comparison 18: SSRI versus amisulpride for dysthymia or double depression

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Amisulpride	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up 8-13 weeks; measured with: HAM-D/MADRS change score; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRIs	Amisulpride	Relative (95% CI)	Absolute		
3 (Amore 2001, Rocca 2002a, Smeraldi 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	349	343	-	SMD 0.19 higher (0.04 to 0.34 higher)	LOW	CRITICAL
Remission (follow-up 8-12 weeks; assessed with: Number of participants scoring <7/≤7 on HAM-D)												
2 (Amore 2001, Rocca 2002a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	130/226 (57.5 %)	137/205 (66.8%)	RR 0.89 (0.77 to 1.02)	74 fewer per 1000 (from 154 fewer to 13 more)	VERY LOW	CRITICAL
Response (follow-up 8-26 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D/MADRS)												
4 (Amore 2001, Bellino 1997, Rocca 2002a, Smeraldi 1998)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	255/391 (65.2 %)	277/370 (74.9%)	RR 0.88 (0.77 to 1.01)	90 fewer per 1000 (from 172 fewer to 7 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-26 weeks; assessed with: Number of participants discontinuing due to side effects)												
4 (Amore 2001, Bellino 1997, Rocca 2002a, Smeraldi 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	32/391 (8.2 %)	28/370 (7.6%)	RR 1.05 (0.64 to 1.73)	4 more per 1000 (from 27 fewer to 55 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (any SSRI versus amisulpride) (follow-up 8-26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
4 (Amore 2001, Bellino 1997, Rocca 2002a, Smeraldi 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	83/391 (21.2 %)	61/370 (16.5%)	RR 1.3 (0.97 to 1.75)	49 more per 1000 (from 5 fewer to 124 more)	LOW	CRITICAL
Functional impairment (follow-up mean 13 weeks; measured with: SDS change score; Better indicated with lower values)												
1 (Smeraldi 1998)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129	139	-	SMD 0.01 lower (0.25 lower to 0.23 higher)	MODERATE	IMPORTANT

CI: confidence interval; HAMD-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; RR: risk ratio; SDS: Sheehan disability scale; SMD: standardised mean difference; SSRIs: selective serotonin reuptake inhibitors
[1] Risk of bias is unclear or high across multiple domains
[2] OIS not met (N<400)
[3] OIS not met (events<300)
[4] 95% CI crosses two clinical decision thresholds
[5] I^2>50%
[6] 95% CI crosses one clinical decision threshold

Table 53: Clinical evidence profile for Comparison 19: Sertraline + IPT versus IPT-only for dysthymia

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sertraline + IPT**	**IPT-only**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Depression symptomatology (follow-up 16-26 weeks; measured with: HAM-D change score/MADRS change score; Better indicated by lower values)												
2 (Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	233	201	-	SMD 0.5 lower (0.7 to 0.31 lower)	VERY LOW	CRITICAL
Remission (follow-up mean 16 weeks; assessed with: Number of participants scoring <7 on HAM-D and >50% improvement on HAM-D and GAF score>70)												
1 (Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	11/21 (52.4%)	5/23 (21.7 %)	RR 2.41 (1 to 5.79)	307 more per 1000 (from 0 more to 1000 more)	VERY LOW	CRITICAL
Response (follow-up 16-26 weeks; assessed with: Number of participants showing ≥40% improvement on MADRS/≥50% improvement on HAM-D)												
2 (Browne 2002, Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	134/233 (57.5%)	91/201 (45.3 %)	RR 1.26 (1.05 to 1.52)	118 more per 1000 (from 23 more to 235 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 16 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Markowitz 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	4/21 (19%)	4/23 (17.4 %)	RR 1.1 (0.31 to 3.84)	17 more per 1000 (from 120 fewer to 494 more)	VERY LOW	CRITICAL

CI: confidence interval; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; IPT: interpersonal psychotherapy; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference; SSRIs: selective serotonin reuptake inhibitors
[1] Risk of bias is unclear or high across multiple domains
[2] Study partially funded by pharmaceutical company
[3] OIS not met (events<300)
[4] 95% CI crosses two clinical decision thresholds

Table 54: Clinical evidence profile for Comparison 20: TCAs versus pill placebo for chronic depression (MDD ≥ 2years, dysthymia or double depression)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (Follow-up 8-16 weeks; measured with: HAM-D/MADRS change score; Better indicated by lower values)												
4 (Agosti 1997, Boyer 1996 study 1, Thase 1996/Kocsis 1997, Versiani 1997)	randomised trials	very serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	357	357	-	SMD 0.51 lower (0.85 to 0.17 lower)	VERY LOW	CRITICAL
Remission (Follow-up 6-26 weeks; assessed with: Number of participants scoring ≤4/<7 on HAM-D/≤6 on HAM-D and ≥10-point improvement on GAF and no longer meeting DSM-III-R criteria for dysthymia/<8 on MADRS)												
5 (Agosti 1997, Boyer 1996 study 2/Lecrubier 1997, Kocsis 1988a/Kocsis 1988b, Stewart 1989/1993, Thase 1996/Kocsis 1997, Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	118/346 (34.1%)	84/350 (24%)	RR 1.46 (1.08 to 1.98)	110 more per 1000 (from 19 more to 235 more)	VERY LOW	CRITICAL
Response (Follow-up 6-26 weeks; assessed with: Number of participants with a CGI-I score 1-2 [much/very much improved]/≥50% improvement on HAM-D)												
5 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Stewart 1989/1993, Thase 1996/Kocsis 1997, Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	267/410 (65.1%)	152/421 (36.1%)	RR 1.85 (1.51 to 2.26)	307 more per 1000 (from 184 more to 455 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 7-26 weeks; assessed with: Number of participants discontinuing due to side effects)												
6 (Bakish 1993a, Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Kocsis 1988a/Kocsis 1988b, Thase 1996/Kocsis 1997, Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	63/468 (13.5%)	10/467 (2.1%)	RR 5.77 (3.09 to 10.79)	102 more per 1000 (from 45 more to 210 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 7-26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Pill placebo	Relative (95% CI)	Absolute		
7 (Agosti 1997, Bakish 1993a, Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Kocsis 1988a/Kocsis 1988b, Thase 1996/Kocsis 1997, Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	153/488 (31.4%)	135/482 (28%)	RR 1.08 (0.83 to 1.4)	22 more per 1000 (from 48 fewer to 112 more)	VERY LOW	CRITICAL
Quality of life (follow-up mean 12 weeks; measured with: Q-LES-Q change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	102	105	-	SMD 0.4 higher (0.12 to 0.67 higher)	VERY LOW	IMPORTANT
Global functioning (follow-up mean 12 weeks; measured with: GAF change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	126	130	-	SMD 0.42 higher (0.17 to 0.67 higher)	VERY LOW	IMPORTANT
Functional impairment change score (follow-up mean 12 weeks; measured with: SAS change score; Better indicated by lower values)												
1 (Thase 1996/Kocsis 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	122	123	-	SMD 0.44 lower (0.69 to 0.19 lower)	VERY LOW	IMPORTANT
Functional impairment endpoint (follow-up mean 6 weeks; measured with: SAS endpoint; Better indicated by lower values)												
1 (Kocsis 1988a/Kocsis 1988b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	11	13	-	SMD 1.12 lower (1.99 to 0.24 lower)	VERY LOW	IMPORTANT

CI: confidence interval; CGI-I: clinical global impression-improvement; DSM: Diagnostic and Statistical Manual of Mental Disorders; GAF: global assessment of functioning; HAMD-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire; RR: risk ratio; SAS: social adjustment scale; SMD: standardised mean difference; TCAs: tricyclic antidepressants

[1] Risk of bias is unclear or high across multiple domains

[2] I^2>50%
[3] 95% CI crosses one clinical decision threshold
[4] Study partially funded by pharmaceutical company
[5] I^2>80%
[6] OIS not met (events<300)
[7] 95% CI crosses two clinical decision thresholds

Table 55: Clinical evidence profile for Comparison 21: TCA versus amisulpride for dysthymia or double depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Amisulpride	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up 13-26 weeks; measured with: MADRS change score; Better indicated by lower values)												
2 (Boyer 1996 study 1, Ravizza 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	192	266	-	SMD 0.03 lower (0.22 lower to 0.16 higher)	LOW	CRITICAL
Remission (follow-up mean 26 weeks; assessed with: Number of participants scoring <8 on MADRS)												
1 (Boyer 1996 Study 2/Lecrubier 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/73 (32.9%)	26/73 (35.6%)	RR 0.92 (0.59 to 1.45)	28 fewer per 1000 (from 146 fewer to 160 more)	VERY LOW	CRITICAL
Response (follow-up 13-26 weeks; assessed with: Number of participants showing a MADRS ≥50% improvement/CGI-I score 1-2 [much/very much improved])												
3 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Ravizza 1999)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	140/249 (56.2%)	178/316 (56.3%)	RR 0.93 (0.81 to 1.08)	39 fewer per 1000 (from 107 fewer to 45 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 13-26 weeks; assessed with: Number of participants discontinuing due to side effects)												
3 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Ravizza 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	33/271 (12.2%)	33/343 (9.6%)	RR 1.45 (0.76 to 2.76)	43 more per 1000 (from 23 fewer to 169 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 13-26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
3 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997, Ravizza 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	116/271 (42.8%)	140/343 (40.8%)	RR 1.08 (0.89 to 1.3)	33 more per 1000 (from 45	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Amisulpride	Relative (95% CI)	Absolute		
										fewer to 122 more)		
Functional impairment (follow-up mean 26 weeks; measured with: SDS change score; Better indicated by lower values)												
1 (Ravizza 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85	165	-	SMD 0.07 lower (0.33 lower to 0.2 higher)	MODERATE	IMPORTANT

CI: confidence interval; CGI-I: clinical global impression-improvement; GAF: global assessment of functioning; MADRS: Montgomery-Asberg Depression Rating Scale; RR: risk ratio; SDS: Sheehan disability scale; SMD: standardised mean difference; TCAs: tricyclic antidepressants
[1] Risk of bias is unclear or high across multiple domains
[2] OIS not met (N<400)
[3] 95% CI crosses two clinical decision thresholds
[4] 95% CI crosses one clinical decision threshold

Table 56: Clinical evidence profile for Comparison 22: TCAs versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia, or double depression)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCAs	Pill placebo	Relative (95% CI)	Absolute		
Relapse follow-up mean 26 weeks; assessed with: Number of participants scoring ≥3 on CGI-I on 2 consecutive weeks/>12 on HAM-D and GAS scores below 60 on three successive ratings or at least one rating meeting these criteria and an urgent need for alternative treatment for a depressive syndrome)												
2 (Kocsis 1996, Stewart 1997)	randomised trials	very serious[1]	serious[2]	no serious indirectness	very serious[3]	reporting bias[4]	13/44 (29.5%)	20/38 (52.6%)	RR 0.56 (0.16 to 2.02)	232 fewer per 1000 (from 442 fewer to 537 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Stewart 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/17 (11.8%)	1/15 (6.7%)	RR 1.76 (0.18 to 17.56)	51 more per 1000 (from 55 fewer to 1000 more)	VERY LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression-improvement; GAS: goal attainment scaling; HAMD-D: Hamilton Rating Scale for Depression; RR: risk ratio; TCAs: tricyclic antidepressants
[1] Risk of bias is unclear or high across multiple domains

[2] I^2>50%
[3] 95% CI crosses two clinical decision thresholds
[4] Medication supplied by pharmaceutical company

Table 57: Clinical evidence profile for Comparison 23: Phenelzine versus pill placebo for chronic depression (MDD ≥2 years or dysthymia)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 10 weeks; measured with: HAMD change score; Better indicated by lower values)												
1 (Jarrett 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	36	36	-	SMD 0.67 lower (1.14 to 0.19 lower)	VERY LOW	CRITICAL
Remission (follow-up mean 10 weeks; assessed with: Number of participants scoring ≤9 on HAM-D)												
1 (Jarrett 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	21/36 (58.3%)	10/36 (27.8%)	RR 2.1 (1.16 to 3.81)	306 more per 1000 (from 44 more to 781 more)	VERY LOW	CRITICAL
Response (follow-up mean 6 weeks; assessed with: Number of participants with CGI-I score 1-2 [much/very much improved])												
1 (Stewart 1989/1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/12 (58.3%)	9/27 (33.3%)	RR 1.75 (0.85 to 3.58)	250 more per 1000 (from 50 fewer to 860 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 10 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Jarrett 1999)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	9/36 (25%)	23/36 (63.9%)	RR 0.39 (0.21 to 0.73)	390 fewer per 1000 (from 172 fewer to 505 fewer)	LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression-improvement; GAS: goal attainment scaling; HAMD-D: Hamilton Rating Scale for Depression; MAOIs: monoamine oxidase inhibitors; RR: risk ratio; SMD: standardised mean difference
[1] *Risk of bias is unclear or high across multiple domains*
[2] *95% CI crosses one clinical decision threshold*
[3] *Study medication supplied by pharmaceutical company*

Table 58: Clinical evidence profile for Comparison 24: Phenelzine versus imipramine for dysthymia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Imipramine	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 6 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1 (Vallejo 1987)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	16	-	SMD 0.73 lower (1.45 to 0.01 lower)	VERY LOW	CRITICAL
Response (follow-up mean 6 weeks; assessed with: Number of participants rated as much or very much improved on CGI-I)												
1 (Stewart 1989/1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/12 (58.3%)	14/18 (77.8%)	RR 0.75 (0.44 to 1.28)	194 fewer per 1000 (from 436 fewer to 218 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Vallejo 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/19 (15.8%)	4/20 (20%)	RR 0.79 (0.2 to 3.07)	42 fewer per 1000 (from 160 fewer to 414 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Vallejo 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/19 (15.8%)	4/20 (20%)	RR 0.79 (0.2 to 3.07)	42 fewer per 1000 (from 160 fewer to 414 more)	VERY LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression-improvement; HAMD-D: Hamilton Rating Scale for Depression; MAOIs: monoamine oxidase inhibitors; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference; TCAs: tricyclic antidepressants

[1] *Risk of bias is unclear or high across multiple domains*

[2] *OIS not met (N<400)*

[3] *95% CI crosses two clinical decision thresholds*

Table 59: Clinical evidence profile for Comparison 25: Phenelzine versus pill placebo for relapse prevention in chronic depression (MDD ≥ 2 years, dysthymia or double depression)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	Pill placebo	Relative (95% CI)	Absolute		
Relapse (follow-up mean 26 weeks; assessed with: Number of participants scoring ≥3 on CGI-I on 2 consecutive weeks)												
1 (Stewart 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/13 (23.1%)	13/15 (86.7%)	RR 0.27 (0.1 to 0.73)	633 fewer per 1000 (from 234 fewer to 780 fewer)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Stewart 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/13 (0%)	0/15 (0%)	not pooled	not pooled	VERY LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression-improvement; MAOIs: monoamine oxidase inhibitors; OIS: optimal information size: RR: risk ratio;
[1] Risk of bias is unclear or high across multiple domains
[2] OIS not met (events<300)

Table 60: Clinical evidence profile for Comparison 26: SNRIs versus pill placebo for chronic depression (MDD ≥2 years, dysthymia)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SNRIs	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 10 weeks; measured with: HAM-D change score; Better indicated by lower values)												
2 (Hellerstein 2012, Hellerstein 2019)	randomised trials	very serious[1]	very serious[7]	no serious indirectness	very serious[6]	reporting bias[3]	55	54	-	SMD 0.81 lower (1.79 lower to 0.18 higher)	VERY LOW	CRITICAL
Remission (follow-up 8-10 weeks; assessed with: Number of participants scoring ≤7/≤4 on HAM-D and HAM-D item # 1 [depressed mood] score=0)												
4 (Hellerstein 2012, Hellerstein 2019, Schatzberg 2006, Tourian 2009)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	167/626	66/317	RR 1.43 (0.95 to 2.16)	90 more per 1000 (from 10 fewer to 242 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SNRIs	Pill placebo	Relative (95% CI)	Absolute		
Response (follow-up 8-10 weeks; assessed with: Number of participants with ≥50% improvement on HAM-D & much/very much improved on CGI-I [score 1-2])												
4 (Hellerstein 2012, Hellerstein 2019, Rudolph 1998, Tourian 2009)	randomised trials	very serious[1]	serious[4]	no serious indirectness	serious[5]	reporting bias[3]	366/760	123/310	RR 1.4 (1.00 to 1.95)	159 more per 1000 (from 0 more to 377 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 6-8 weeks; assessed with: Number of participants discontinuing due to side effects)												
4 (Hellerstein 2019, Rudolph 1998, Schatzberg 2006, Tourian 2009)	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[5]	reporting bias[3]	128/839	25/383	RR 2.31 (1.12 to 4.78)	86 more per 1000 (from 8 more to 247 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 6-8 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
4 (Hellerstein 2019, Rudolph 1998, Schatzberg 2006, Tourian 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	262/839	108/383	RR 1.12 (0.93 to 1.34)	34 more per 1000 (from 20 fewer to 96 more)	VERY LOW	CRITICAL
Functional impairment (follow-up mean 12 weeks; measured with: SAS change score; Better indicated by lower values)												
1 (Hellerstein 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[3]	26	26	-	SMD 0.05 lower (0.59 lower to 0.5 higher)	VERY LOW	IMPORTANT

CI: confidence interval; CGI-I: clinical global impression-improvement; HAM-D: Hamilton Depression Rating Scale; MAOIs: monoamine oxidase inhibitors; OIS: optimal information size: RR: risk ratio; SNRIs: serotonin and norepinephrine reuptake inhibitors

[1] Risk of bias is unclear or high across multiple domains

[2] OIS not met (N<400)

[3] Study funded by pharmaceutical company

[4] I^2>50%

[5] 95% CI crosses one clinical decision threshold

[6] 95% CI crosses two clinical decision thresholds

[7] I^2 >80%

Table 61: Clinical evidence profile for Comparison 27: Moclobemide versus pill placebo for dysthymia or double depression

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology (follow-up mean 8 weeks; measured with: HAM-D; change score; Better indicated by lower values)												
1 (Versiani 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	97	-	SMD 1.03 lower (1.33 to 0.74 lower)	VERY LOW	CRITICAL
Remission (follow-up mean 8 weeks; assessed with: Number of participants scoring ≤4 on HAM-D)												
1 (Versiani 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	33/104 (31.7%)	16/97 (16.5%)	RR 1.92 (1.13 to 3.27)	152 more per 1000 (from 21 more to 374 more)	VERY LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D)												
1 (Versiani 1997)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	74/104 (71.2%)	29/97 (29.9%)	RR 2.38 (1.71 to 3.31)	413 more per 1000 (from 212 more to 691 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Versiani 1997)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/108 (6.5%)	2/104 (1.9%)	RR 3.37 (0.72 to 15.85)	46 more per 1000 (from 5 fewer to 286 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Versiani 1997)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/108 (12%)	15/104 (14.4%)	RR 0.83 (0.42 to 1.67)	25 fewer per 1000 (from 84 fewer to 97 more)	VERY LOW	CRITICAL

CI: confidence interval; HAM-D: Hamilton Depression Rating Scale; OIS: optimal information size: RIMAs: reversible inhibitors of monoamine oxidase; RR: risk ratio; SMD: standardised mean difference

[1] Risk of bias is unclear or high across multiple domains

[2] OIS not met (N<400)

[3] OIS not met (events<300)

[4] 95% CI crosses two clinical decision thresholds

Table 62: Clinical evidence profile for Comparison 28: Moclobemide versus fluoxetine for double depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Fluoxetine	Relative (95% CI)	Absolute		
Response (follow-up mean 6 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D)												
1 (Duarte 1996)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	15/21 (71.4%)	8/21 (38.1%)	RR 1.88 (1.02 to 3.45)	335 more per 1000 (from 8 more to 933 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Duarte 1996)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	0/21 (0%)	0/21 (0%)	not pooled	not pooled	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Duarte 1996)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	0/21 (0%)	0/21 (0%)	not pooled	not pooled	VERY LOW	CRITICAL

CI: confidence interval; HAM-D: Hamilton Depression Rating Scale; OIS: optimal information size: RIMAs: reversible inhibitors of monoamine oxidase; RR: risk ratio; SSRIs: selective serotonin reuptake inhibitors

[1] *Risk of bias is unclear or high across multiple domains*

[2] *OIS not met (events<300)*

[3] *One of the authors is employed by pharmaceutical company*

Table 63: Clinical evidence profile for Comparison 29: Moclobemide versus imipramine for dysthymia or double depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moclobemide	Imipramine	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 8 weeks; measured with: HAM-D change score; Better indicated by lower values)												
1 (Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104	94	-	SMD 0.16 lower (0.44 lower to 0.12 higher)	VERY LOW	CRITICAL
Remission (follow-up mean 8 weeks; assessed with: Number of participants scoring ≤4 on HAM-D)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Moclobemide**	**Imipramine**	**Relative (95% CI)**	**Absolute**		
1 (Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	33/104 (31.7%)	19/94 (20.2%)	RR 1.57 (0.96 to 2.56)	115 more per 1000 (from 8 fewer to 315 more)	VERY LOW	CRITICAL
Response (follow-up mean 8 weeks; assessed with: Number of participants showing ≥50% improvement on HAM-D)												
1 (Versiani 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	74/104 (71.2%)	65/94 (69.1%)	RR 1.03 (0.86 to 1.23)	21 more per 1000 (from 97 fewer to 159 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Versiani 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/108 (6.5%)	11/103 (10.7%)	RR 0.61 (0.24 to 1.51)	42 fewer per 1000 (from 81 fewer to 54 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Versiani 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	13/108 (12%)	15/103 (14.6%)	RR 0.83 (0.41 to 1.65)	25 fewer per 1000 (from 86 fewer to 95 more)	VERY LOW	CRITICAL

CI: confidence interval; HAM-D: Hamilton Depression Rating Scale; OIS: optimal information size: RIMAs: reversible inhibitors of monoamine oxidase; RR: risk ratio; SMD: standardised mean difference; TCAs: tricyclic antidepressants

[1] Risk of bias is unclear or high across multiple domains

[2] OIS not met (N<400)

[3] 95% CI crosses one clinical decision threshold

[4] OIS not met (events<300)

[5] 95% CI crosses two clinical decision thresholds

Table 64: Clinical evidence profile for Comparison 30: Nefazodone versus pill placebo for relapse prevention in chronic depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nefazodone	Pill Placebo	Relative (95% CI)	Absolute		
Relapse (follow-up mean 52 weeks; assessed with: Number of participants scoring ≥ 16 on HAM-D on 2 consecutive visits and meeting DSM-IV criteria for a diagnosis of MDD)												
1 (Gelenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/76 (26.3%)	29/84 (34.5%)	RR 0.76 (0.47 to 1.23)	83 fewer per 1000 (from 183 fewer to 79 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 52 weeks; assessed with: Number of participants discontinuing due to side effects)												
1 (Gelenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	3/76 (3.9%)	1/84 (1.2%)	RR 3.32 (0.35 to 31.2)	28 more per 1000 (from 8 fewer to 360 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 52 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
1 (Gelenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	29/76 (38.2%)	52/84 (61.9%)	RR 0.62 (0.44 to 0.86)	235 fewer per 1000 (from 87 fewer to 347 fewer)	VERY LOW	CRITICAL

CI: confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D: Hamilton Depression Rating Scale; MDD: major depressive disorder; RR: risk ratio;
[1] Risk of bias is unclear or high across multiple domains
[2] 95% CI crosses one clinical decision threshold
[3] Study funded by pharmaceutical company
[4] 95% CI crosses two clinical decision thresholds

Table 65: Clinical evidence profile for Comparison 31: Amisulpride versus pill placebo for dysthymia or double depression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amisulpride	Pill placebo	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 13 weeks; measured with: MADRS; change score; Better indicated by lower values)												
1 (Boyer 1996 study 1)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	101	105	-	SMD 0.68 lower (0.97 to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amisulpride	Pill placebo	Relative (95% CI)	Absolute		
										0.4 lower)		
Remission (follow-up mean 26 weeks; assessed with: Number of participants scoring <8 on MADRS)												
1 (Boyer 1996 study 2/Lecrubier 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	26/73 (35.6%)	16/73 (21.9 %)	RR 1.62 (0.95 to 2.77)	136 more per 1000 (from 11 fewer to 388 more)	LOW	CRITICAL
Response (follow-up 13-26 weeks; assessed with: Number of participants rated as much or very much improved on CGI-I)												
2 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	101/150 (67.3%)	52/157 (33.1 %)	RR 2.03 (1.59 to 2.61)	341 more per 1000 (from 195 more to 533 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 13-26 weeks; assessed with: Number of participants discontinuing due to side effects)												
2 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/177 (5.6%)	3/181 (1.7%)	RR 3.31 (0.92 to 11.9)	38 more per 1000 (from 1 fewer to 181 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 13-26 weeks; assessed with: Number of participants discontinuing for any reason including side effects)												
2 (Boyer 1996 study 1, Boyer 1996 study 2/Lecrubier 1997)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	67/177 (37.9%)	78/181 (43.1 %)	RR 0.87 (0.68 to 1.12)	56 fewer per 1000 (from 138 fewer to 52 more)	LOW	CRITICAL

CI: confidence interval; CGI-I: clinical global impression scale-improvement; MADRS: Montgomery-Asberg Depression Rating Scale; OIS: optimal information size; RR: risk ratio; SMD: standardised mean difference

[1] *Risk of bias is unclear or high across multiple domains*

[2] *OIS not met (N<400)*

[3] *95% CI crosses one clinical decision threshold*

[4] *OIS not met (events<300)*

Table 66: Clinical evidence profile for Comparison 32: Yoga + TAU versus TAU for chronic depression (MDD ≥ 2 years)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga + TAU	TAU	Relative (95% CI)	Absolute		
Depression symptomatology (follow-up mean 39 weeks; measured with: Hamilton Rating Scale for Depression (HAMD) change score; Better indicated by lower values)												
1 (Butler 2008)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	13	14	-	SMD 0.85 lower (1.64 to 0.06 lower)	VERY LOW	CRITICAL
Remission (follow-up mean 39 weeks; assessed with: Number of participants no longer meeting DSM-IV criteria for MDD diagnosis)												
1 (Butler 2008)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/13 (76.9%)	5/14 (35.7%)	RR 2.15 (1 to 4.62)	411 more per 1000 (from 0 more to 1000 more)	VERY LOW	CRITICAL

CI: confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder; RR: risk ratio; SMD: standardised mean difference; TAU: treatment as usual

[1] Risk of bias is unclear or high across multiple domains

[2] 95% CI crosses one clinical decision threshold

[3] Partially funded by a private foundation

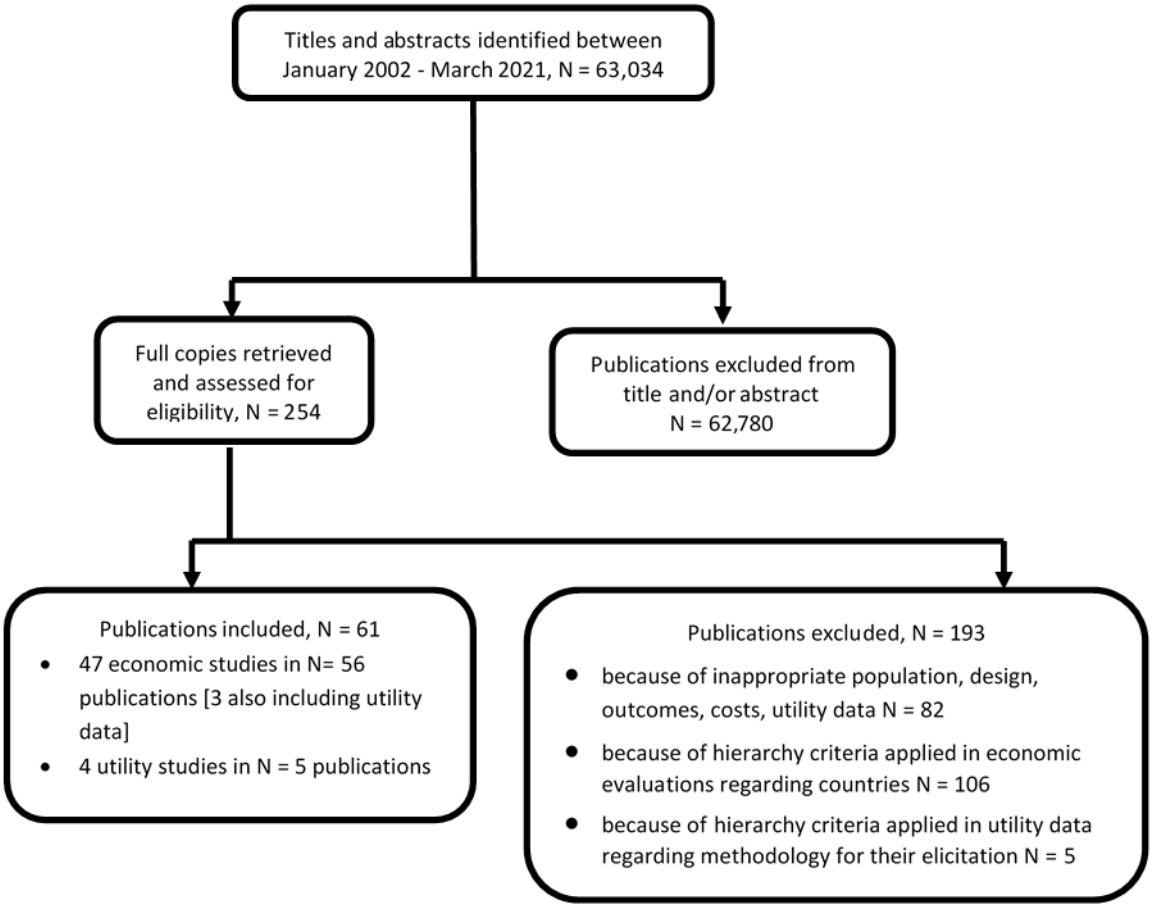
Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

A global health economics search was undertaken for all areas covered in the guideline. Figure 128: Flow diagram of selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data.<Insert graphic title here>

shows the flow diagram of the selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data.

Figure 128: Flow diagram of selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data.<Insert graphic title here>



Appendix H – Economic evidence tables

Economic evidence tables for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Clinical studies

Please refer to the excluded studies in supplement E – Clinical evidence tables for review question 2.6 Chronic depression

Economic studies

Please refer to supplement 3 - Economic evidence included & excluded studies.

Appendix L – Research recommendations

Research recommendations for review question: For adults with chronic depression or persistent subthreshold depression symptoms what are the relative benefits and harms of first-line treatment or relapse prevention with psychological, psychosocial, pharmacological and physical interventions (alone or in combination)?

Research question

Are psychological, pharmacological or a combination of these treatments effective and cost effective for the treatment of older adults with chronic depressive symptoms?

Why this is important

Depression in older people is often not recognised and therefore may go untreated for a significant period of time. The consequences of this are serious as depression, and chronic depressive symptoms in particular, are associated with an increased risk of developing physical health problems in addition to the burden resulting from the depression. Even when depression is recognised, treatment can be sub-optimal and there is uncertainty about the most effective interventions for this age group.

Table 67: Research recommendation rationale

Research question	**Are psychological, pharmacological or a combination of these treatments effective and cost effective for the treatment adults aged over 75 with chronic depressive symptoms?**
Why is this needed	
Importance to 'patients' or the population	Chronic depression in older people is poorly recognised and under-treated, so identifying effective treatments for this age group is important to improve outcomes and quality of life.
Relevance to NICE guidance	The guidelines currently make general recommendations about the treatment of chronic depression but do not make specific evidence-based recommendations for people over 75 years.
Relevance to the NHS	Treating chronic depression in older people would reduce costs to the NHS due to the burden of depression and the increased physical health problems associated with chronic depression.
National priorities	The NHS Five Year Forward plan makes access to effective mental health services a key national priority
Current evidence base	Although there are research studies investigating interventions for depression in older adults, many of these study populations have mean ages between 60 and 70 years and the focus is primarily on people with recent onset depression, not on chronic depression.
Equality	NA
Feasibility	Numbers of older people with chronic depression make large RCTs feasible.

Research question	Are psychological, pharmacological or a combination of these treatments effective and cost effective for the treatment adults aged over 75 with chronic depressive symptoms?
Other comments	NA

NA: not applicable

Table 68: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (75 years or older) with chronic depression
Intervention	• Antidepressants • Psychological therapies • Combinations of antidepressants and psychological therapies
Comparator	• Other active interventions • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	**Critical:** • Depression symptomatology • Remission • Response • Relapse • Discontinuation due to side effects • Discontinuation due to any reason **Important:** • Quality of life • Personal, social, and occupational functioning
Study design	A series of randomised controlled trials
Timeframe	At least 12 months follow-up after the end of treatment
Additional information	NA

NA: not applicable

Research question

What is the effectiveness, acceptability and safety of Monoamine Oxidase Inhibitors (MAOIs) (for example, phenelzine) compared to alternative SSRI/SNRI options in treatment resistant chronic depression with anhedonia?

Why this is important

Chronic depression is common, with evidence indicating that only two-thirds of people will recover even after 12-months of intensive treatment for depression. Whilst most available antidepressants work through monoamine reuptake inhibition and have little evidence of comparative superiority, Monoamine Oxidase Inhibitors (MAOIs) have a unique mode of action through enzyme inhibition resulting in a triple effect enhancing serotonin, noradrenaline and dopamine transmission. This may be particularly relevant where anhedonia is salient in depression (due to links with blunted dopamine transmission), or

where an individual is less likely to tolerate/respond to reuptake inhibitors (e.g. through variants of transporter genes). Recent Network Meta-analysis (NMA) indicates that MAOIs are clinically effective compared to other antidepressants (Suchting, 2021) but is significantly limited by the age of the primary studies (generally conducted between 1965 – 1988 when concepts, populations, trial methods and reporting standards were very different, therefore making this evidence base difficult to robustly synthesise now). MAOIs have fallen out of use, partly related to this outdated evidence and partly through earlier safety concerns that can now be effectively addressed (for example regarding levels of tyramine taken in the diet, which is now comfortably manageable). MAOIs may therefore provide a safe and effective modern treatment alternative for chronic depression but an updated evidence base is needed to robustly support their use. Since they are out of patent, there is little incentive for pharmaceutical companies to provide this evidence base and it may fall to organisations like NICE to promote research in this area, without which recent experience suggests we may lose them.

Table 69: Research recommendation rationale

Research question	**What is the effectiveness, acceptability and safety of Monoamine Oxidase Inhibitors, (MAOIs) (for example phenlezine) compared to alternative SSRI/SNRI options in treatment resistant depression with anhedonia?**
Why is this needed	
Importance to 'patients' or the population	Chronic depression is common and debilitating, often leading to lost careers, relationships, worsening health and increased mortality. Many patients who choose a medical approach, experience little effect from further-line treatments that exert strongest action in a broadly similar way (through inhibition of serotonin and/or noradrenaline reuptake) and there is little to guide further-line treatment choice. Monoamine Oxidase Inhibitors (MAOIs) offer a unique mode of action (increasing brain dopamine as well as serotonin and noradrenaline) and a recent NMA (Suchting, 2021) identified superior efficacy for phenelzine (a MAOI) compared to 12 other antidepressants. However, these NMA findings are limited by an evidence base that is now out of date, mainly relying on studies between 1965 – 1988, where concepts of depression, treatment pathways and comparators were very different. Methods and data reporting standards were also different, making a robust synthesis difficult. Progress in the knowledge base on tyramine and drug interactions (e.g. Gillman 2019) mean these agents can now be prescribed safely in specialist care and offer a valuable treatment alternative for patients with chronic depression. Parts of the evidence base suggest the effect of MAOIs may be particularly strong where anhedonia is salient (e.g. Davidson 1988). This may plausibly be linked to MAOI mechanisms but needs to be established within a contemporary trial, with modern concepts, populations, treatment comparators and reporting standards. Without this updated evidence, including on safety, acceptability and efficacy we risk losing these

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	medications (a world supply shortage of phenelzine within the last 24 months caused some UK patients to discontinue treatment and relapse).
Relevance to NICE guidance	An updated NICE review of evidence in chronic depression found insufficient evidence to make clear recommendations on antidepressant treatment switch and little to guide clinicians in later stage depression beyond a number of possible treatment alternatives, leaving much still to be worked out through individual consultations. Given their unique mode of action (amongst antidepressants) and their triple effect (including enhancement of dopamine transmission) MAOIs offer a distinct treatment alternative in chronic depression, particularly where some degree of treatment resistance and anhedonia is salient. Trial evidence confirming safety, acceptability and effectiveness in a contemporary UK cohort may enable clearer future guidance on the place of MAOIs in the treatment pathway for people suffering chronic depression.
Relevance to the NHS	Chronic depression is a common condition, associated with high disability, high work absence and worse health outcomes across a range of physical co-morbidities. McCrone (2018) calculated mean costs per patient of £25,000/year for this type of depression (equivalent to the cost for schizophrenia), which through high prevalence has a cost to the economy of £3.9bn. Remission rates drop steeply after the first two treatment trials and the mechanisms of most available next-step antidepressants are similar (although some more distinct classes of antidepressants have been developed recently, e.g. through NMDA modulation, they are currently not available in routine NHS practice). MAOIs are currently available to the NHS and have a distinct mode of action, with some recent evidence indicating they are clinically effective compared to other antidepressants (Suchting, 2021) and that they may now be used safely within specialist care (e.g. Gillman, 2019). There are however limitations to the current evidence base, relating to the age of the primary studies. Contemporary evidence on the safety, acceptability and efficacy of MAOIs in a UK population could establish a distinct NHS treatment alternative in chronic depression: reducing medical and psychiatric morbidity; freeing up service capacity; reducing work absence (including of NHS staff); and reducing overall NHS costs. Phenelzine has been chosen for this trial as it had the greatest overall effect in a recent NMA, against 12 other

Research question	What is the effectiveness, acceptability and safety of Monoamine Oxidase Inhibitors, (MAOIs) (for example phenlezine) compared to alternative SSRI/SNRI options in treatment resistant depression with anhedonia?
	antidepressants (Suchting, 2021). At current costs, phenelzine is also relatively cheap compared to alternative MAOIs (particularly tranylcypromine) and is often better tolerated than tranylcypromine. If there are ongoing supply issues with phenelzine, then the other hydrazine derivative MAOI listed in the BNF, isocarboxazid, could be trialled as an alternative to phenelzine given its similar clinical profile (including tolerability).
National priorities	This research recommendation is for people with chronic, moderate-severe and treatment resistant depression. Therefore it would fall within the definition of Severe Mental Illness in the Five Year Forward View/NHS Mental Health Implementation Plan and is a national priority area for improved management strategies.
Current evidence base	Although there is evidence for the effect of MAOIs in depression, this is largely restricted to another era (1960s – 80s); limited by out-dated concepts, populations, methods and reporting criteria, making it difficult to synthesise and interpret robustly. The best attempt at a recent synthesis (Suchting 2021), caveated by these limitations, found that the MAOI, phenelzine, was more effective than 12 comparator antidepressants. Additional evidence (e.g. Davidson 1988), indicates that MAOIs may be more effective in 'melancholic' (anhedonic) depression. Since MAOIs are now off patent the uncertainties in this out-dated evidence base seem unlikely to be addressed by pharmaceutical companies, who have little obvious incentive (in fact perhaps the contrary given newer patented agents). It may therefore fall to organisations like NICE to promote evidence for MAOIs and similar 'orphan' drugs. Without this, recent indications are that we may lose MAOIs either through excessive cost or supply shortage.
Equality	There are no direct issues here. Use of MAOIs does require diets low in tyramine, which may affect some groups more than others, e.g. people with a vegan diet. Some religious or cultural groups may be more affected by this restriction than others, though dietary modifications are usually acceptable even in this case.
Feasibility	Chronic depression is common and there are indications of high levels of anhedonia (a broad range between 30 – 70%). People often want next-step treatment alternatives, including MAOIs, but these are limited particularly in the case of MAOIs as so few doctors (including psychiatrists) currently know how to safely and effectively use

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	them. Given all of this, the offer of supervised treatment with a potentially effective, novel agent (a MAOI) would attract recruitment and could involve the Clinical Research Network. The clinical trial could be blinded with all randomised participants agreeing to accept diet and medication restrictions, though predictable blood pressure changes may be a challenge to maintaining this.
Other comments	Recent world supply issues have shown how vulnerable MAOIs are now. The recent supply shortage of phenelzine caused understandable concern for many patients taking this drug, who were given little choice but to discontinue and seek alternatives, with some resulting relapses. Lack of robust, updated support for MAOI use may in future mean that fewer patients have this treatment opportunity and may also mean that people already in recovery through these medications (including older adults commenced on MAOIs earlier in life, continued effectively as a maintenance treatment over decades) will be forced to come off them as supply dwindles (or is regarded as too expensive), with the risk of relapse.

Table 70: Research recommendation modified PICO table

Criterion	Explanation
Population	People with treatment resistant depression (MGH-SM score 2+) of at least moderate severity (MADRS>19), with identified anhedonia Temporal Experience of Pleasure Scale (TEPS), mean item level TEPS-A <4.
Intervention	Switch to phenelzine titrated to a minimum dose 45mg/day, with dose flexibility to 90mg/day based on effect and tolerability (including BP).
Comparator	Switch to any standard BNF alternative SSRI or SNRI (e.g. venlafaxine, duloxetine)
Outcomes	MADRS change at 12 weeks, with baseline as covariate. Secondary: Change in self-completion depression measures and TEPS (to assess specific effect on anhedonia). Acceptability assessed through treatment continuation rates, standardised side-effect rating scales and thematic analysis of experience. Safety through adverse event reporting (e.g. falls, hospital admissions). Response, remission. Assessment of response prediction thresholds based on dimensional TEPS score.

Criterion	Explanation
Study design	Randomised parallel-group study (following baseline safety checks). Patients and outcomes assessors will be blinded to group allocation. Patients in both arms will agree to dietary and medication restrictions related to MAOI use. Patients with moderate-severe hepatic illness or phaeochromocytoma will be excluded and a wash-out period of 2 weeks will be agreed for both arms from prior medication (any treatment necessitating a longer wash-out period, e.g. Fluoxetine, will be exclusionary). Within trial there will be regular blood pressure monitoring and repeat liver function. Observer ratings will be blinded at 4, 8, 12 weeks, with a blinding index (BI) used to assess the success of this given the challenges through predictable effects of MAOIs (e.g. hypotension). A semi-structured interview with thematic analysis will aim to assess acceptability of the interventions, including acceptability of diet/medication restrictions.
Timeframe	12-week primary outcome (giving time for dose optimisation and full assessment of response, acceptability and safety).
Additional information	Outcomes from this trial will help to establish a contemporary methodology for the investigation of MAOIs, through incorporation of an assessment of the method itself (e.g. through use of Bis).

Research question

How can identifying and focusing on the social determinants of chronic depression, and on the outcomes that matter to patients, enable greater precision for targeting the relevant causal factors and mechanisms that contribute to sustained recovery?

Why this is important

It is increasingly recognised that not only is depression commonly both chronic and recurring but that a causal link with factors such as loss of employment, or relationship breakdown, can contribute significantly to the extent of chronicity, and inability to recover or to relapse after treatment. Suffering from chronic depression, including risks from suicidality, as well as its economic and social costs, has been exacerbated since 2008, and during the pandemic.

Yet our standard treatment-as-usual offers (for example, long term antidepressant medication) do not address these social determinants and may, in fact, be adding to the ongoing burden.

Longer term treatment interventions, therefore, are one approach that could be pursued, but there is only limited evidence of their cost-effectiveness to date. An alternative approach that may enable the development of more personalised methods to establish individual causal pathways would allow better and more precise focusing, timing and sequencing of interventions.

Table 71: Research recommendation rationale

Research question	How can identifying and focusing on the social determinants of chronic depression, and on the outcomes that matter to patients, enable greater precision for targeting the relevant causal factors and mechanisms that contribute to sustained recovery?
Why is this needed	
Importance to 'patients' or the population	Most first-hand accounts of depression tend to emphasise its chronic and recurrent nature, and its links with causal factors such as loss of employment and inability to find another job; breakdown of relationships and ongoing family problems; adverse or traumatic experiences in earlier life that can manifest in vulnerability and increased risk for chronic depression, and so on. Likewise, when people with chronic depression are asked about the outcomes that matters to them they tend to emphasise those outcomes that are directly related to addressing and overcoming these causal factors, so that future resilience and wellbeing are improved through identifying and focusing on more protective factors, whilst reducing and mitigating the known risk factors. One of the main rationales for offering choice of treatments in depression more generally (and the reason that most patients tend to express a preference for psychological rather than medication treatment) is so that patients, ideally, can seek to match how the intervention is meant to work with how they understand their own depression has been caused – and the key factors that are preventing them from recovering. To date this remains an under-researched area, however, with a degree of uncertainty involved.
Relevance to NICE guidance	No evidence on the cost-effectiveness of interventions for adults with chronic depressive symptoms was identified and no further economic analysis was undertaken. Identifying social determinants and developing more personalised treatment pathways (e.g. with the right focus, combination and sequencing of interventions, using the relevant mechanisms for change) has the potential to reduce the burden of suffering and healthcare costs, as well as the significant wider social and economic costs.
Relevance to the NHS	No evidence was available for psychosocial interventions for chronic depressive symptoms, as a study on befriending that had been included by the 2009 guideline did not meet the revised inclusion criteria in the protocol for this update, as this study had defined chronic depression as greater than 1 year instead of 2 years, and did not report the mean duration of depression. However, the committee recognised the potential benefit of

Research question	How can identifying and focusing on the social determinants of chronic depression, and on the outcomes that matter to patients, enable greater precision for targeting the relevant causal factors and mechanisms that contribute to sustained recovery?
	additional social or vocational support, particularly given the lack of long-term data on psychological or pharmacological interventions and the potential for poor prognosis and long-term functional impairment, and on this basis the committee agreed to retain the recommendation from the 2009 guideline and recommend further research.
National priorities	The burden of suffering from chronic depression has increased since 2008 and is likely to increase further as a result of the impact of the pandemic. There are also risks to the wellbeing of the NHS workforce from burnout and chronic depression.
Current evidence base	In the current review there was limited evidence for single interventions, but no evidence for the kind of personalised approach that would incorporate also social and vocational support.
Equality	Chronic depression is strongly associated with social deprivation. Socially marginalised groups who are stigmatised / experience discrimination are also at increased risk for chronic depression.
Feasibility	Involving stakeholders in identifying outcomes and developing common outcome sets has been developed both in the UK and internationally. Mixed methods research is able to draw on an established knowledge base for the social determinants of chronic depression. Causal process tracing, embedded evidence-based case studies, and other methods for testing specific mechanisms are rapidly advancing in the field although to date there is limited evidence to demonstrate specific mechanisms of change.
Other comments	This research would also address some of the priorities that were identified by stakeholders during previous consultation rounds.

Table 72: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults with chronic depression, defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales, for at least 2 years; persistent subthreshold symptoms (dysthymia); double depression (an acute episode of MDD superimposed on dysthymia)

Criterion	Explanation
Intervention	Interventions listed below are examples which may be included either alone or in combination: **Psychological interventions** Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT], third-wave cognitive therapies, Mindfulness-based Cognitive Therapy [MBCT] and Cognitive Behavioural Analysis System of Psychotherapy [CBASP]) Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) Interpersonal psychotherapy (IPT) Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) Psychoeducational interventions (including psychoeducational group programmes) Art therapy Music therapy Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) **Psychosocial interventions:** Peer support (including befriending, mentoring, and community navigators) Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR]) **Social and vocational support:** Keyworker support (e.g. with accessing help to address debt problems, housing issues, alcohol use etc) Skills training and individual job placement (e.g. accessing further training and job interviews) Social prescribing and local community building (e.g. place based and identity based group activities, environmental / creative arts projects) **Pharmacological interventions** Antidepressants: • SSRIs Citalopram Escitalopram Fluvoxamine Fluoxetine Paroxetine

Criterion	Explanation
	Sertraline • TCAs Amineptine Amitriptyline Clomipramine Desipramine Imipramine Lofepramine Nortriptyline • MAOIs Phenelzine • TeCAs Mianserin • SNRIs Duloxetine Venlafaxine • Other antidepressant drugs Bupropion Mirtazepine Moclobemide Nefazodone Antipsychotics: Amisulpride Aripiprazole Olanzapine Quetiapine Risperidone Ziprasidone **Physical interventions** Acupuncture Exercise Yoga ECT Light therapy (for depression, not SAD)
Comparator	Other active intervention (ie: any other / combination of others from the interventions above) • Treatment as usual • Waitlist • No treatment • Placebo

Criterion	Explanation
Outcomes	Priority and importance to be determined individually for all study participants (patients, carers and clinicians), and measured using a core outcome set agreed with stakeholders beforehand to include (for example): • Suicidality and self-harm (for instance, loss of desire to live and thoughts of suicide, suicide attempt, thoughts of self-harm, actual self-harm) • Interpersonal problems (for instance, withdrawal or lack of motivation for relationships, loss of enjoyment and / or increased conflict in ongoing close relationships, family life, social life) • Employment (for instance, % unemployed, sickness absence rates, dependence on social security benefits) • Debt (for instance, % unable to make ends meet or inability to manage financial commitments) • Personal, social and occupational functioning (for instance, inability to get out of bed, difficulty sleeping, loss of energy and motivation, basic self-care, basic housework tasks, work duties) • Quality of life (for instance, increased life satisfaction, meaningful activity, involvement with significant others and sense of belonging; reduced reliance on alcohol, drugs, and reduced levels of worry, feelings of emptiness, deadness) • Self-esteem and resilience (for instance, increased confidence, self-recognition, capacity to challenge stigma and to talk about issues, personal growth and capacity for reflection) • Reduced symptoms identified as critical, as well as overall (change in score from baseline) • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) • Relapse (number of participants who relapsed) • Acceptability/tolerability of intervention • Success of intervention in addressing causal factors • Discontinuation due to side effects (for pharmacological trials) • Discontinuation due to any reason (including side effects) Outcomes will be assessed continuously using an agreed core outcome set (consisting of validated measures where available, as

Criterion	Explanation
	approved by stakeholders) and at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, 25-36 months, and >3 years).
Study design	Mixed methods, inter-disciplinary, involving co-design with stakeholders
Timeframe	3 years plus follow up period (further 3 years)
Additional information	Participants should be recruited to reflect 'real-world' inclusion across protected characteristics and known risk factors for health inequalities and vulnerability to chronic depression. Sub-group data captured where possible for age, sex, ethnicity, socioeconomic status, disability and comorbidities.