National Institute for Health and Care Excellence

FINAL

Depression in adults

[C] Preventing relapse

NICE guideline NG222

Evidence review underpinning recommendations 1.8.1 to 1.8.12 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.

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Contents

Prevention of relapse

Review question

For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Introduction

Depression is often a recurring or relapsing disorder, with at least 50% of people going on to have a second episode of depression, and after the second and third episodes the risk of relapse rises to 70% and 90% respectively.

Relapse is typically defined as an individual re-experiencing an episode of depression within 6 months of improvement or remission of symptoms, whereas recurrence is used to describe a new episode that follows a more developed recovery lasting at least 4 to 6 months. However, for simplicity, in this report 'relapse' is used to refer to both relapse and recurrence.

There is robust evidence that the risk of relapse increases progressively with each prior episode of major depression, and further predictors of relapse include the severity of initial depression, residual symptoms of depression after initial treatment, and a history of coexisting psychiatric disorders. There is also some evidence that later episodes may be more severe. However, the risk of relapse decreases as the period of recovery increases.

The risks of relapse raise questions about the need for continuing treatment beyond recovery from the acute episode of depression, and how long treatment should be continued to avoid relapse. There is evidence, for example, that for patients who are still at appreciable risk of relapse after 4 to 6 months of treatment with antidepressants, maintenance treatment may halve their risk, at last up to 2 years of continued use. Furthermore, there is some evidence that psychological treatments do not have an increased risk for relapse/recurrence following their discontinuation when compared with antidepressants, raising the possibility that some psychological interventions may confer ongoing prophylactic benefits in terms of individuals learning new coping skills and strategies that extend beyond the period of treatment. However, there is considerable variation in practice, suggesting that many patients do not receive optimum treatment.

The committee agreed that relapse prevention may be different for some subgroups of people with depression, and as outlined in the review protocol (see Appendix A) studies on relapse prevention for those with chronic depression, depression with coexisting personality disorder, or psychotic depression were not included in this review. However, relapse prevention for these groups is covered in the relevant evidence reviews as follows: chronic depression (Evidence report E); depression with coexisting personality disorder (Evidence report F); psychotic depression (Evidence report G).

The aim of this review is to determine, in adults whose depression has responded to treatment, which interventions reduce the rate of relapse.

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 whose depression has responded to treatment according to DSM, ICD or similar criteria, or depressive symptoms as indicated by depression scale score, who are randomised to relapse prevention intervention whilst in full or partial remission. If some, but not all, of a study's participants are eligible for the review, for instance, mixed anxiety and depression diagnoses, 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 (IPT) • Psychodynamic psychotherapies • Psychoeducational interventions • Self-help with or without support • Art therapy • Music therapy • Eye movement desensitization and reprocessing (for depression, not PTSD) **Pharmacological interventions:** • SSRIs (including paroxetine, sertraline, fluoxetine, escitalopram, citalopram, fluvoxamine) • TCAs (including amitriptyline, dothiepin, imipramine, nortriptyline) • SNRIs (including duloxetine, venlafaxine, desvenlafaxine) • Mirtazapine • Antipsychotics (including olanzapine, risperidone, quetiapine) • Lithium **Physical interventions:** • Acupuncture • Exercise • Yoga • ECT • Light therapy (for depression, not SAD) **Psychosocial interventions**: • Peer support • Mindfulness, meditation or relaxation
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo

Outcome	Critical: • Relapse 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; IPT: interpersonal therapy; PTSD: post-traumatic stress disorder; SAD: seadonal affective disorder; SNRIs: serotonin noradrenaline reuptake inhibitor SSRIs: selective serotonin reuptake inhibitor; TCA: tricyclic 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

70 randomised controlled trials (RCTs) were included in this review (Alexopoulos 2000; Bauer 2000; Biesheuvel-Leliefeld 2017; Bockting 2005/2015 [1 study reported across 2 papers]; Bockting 2018; Bondolfi 2010; Brakemeier 2014; Brunner 2014; Coppen 1978; de Jonge 2019; Dobson 2008; Doogan 1992; Elices 2017; Farb 2018; Fava 1994/1996/1998c [1 study reported across 3 papers]; Fava 1998a/2004 [1 study reported across 2 papers]; Franchini 1997/2000a [1 study reported across 2 papers]; Franchini 1998; Frank 1990; Frank 2007; Gilaberte 2001; Glen 1984; Godfrin 2010; Gorwood 2007; Greil 1996; Hochstrasser 2001; Holländare 2011/2013 [1 study reported across 2 papers]; Hujibers 2015; Huijbers 2016a; Jarrett 2001; Jarrett 2013; Kamijima 2006; Kellner 2016/McCall 2018 [1 study reported across 2 papers]; Klein 2018a; Klerman 1974; Klysner 2002; Kocsis 2007; Kornstein 2006; Kuyken 2008; Kuyken 2015a/2015b [1 study reported across 2 papers]; Lepine 2004; Liebowitz 2010; Ma 2004; Martiny 2015; Meadows 2014; Montgomery 1988; Montgomery 1993a; Montgomery 1993b; Montgomery 2004; Old Age Depression Interest Group 1993; Perahia 2006; Perahia 2009; Prien 1984; Rapaport 2004; Rapaport 2006; Rickels 2010; Robert 1995; Rosenthal 2013; Schmidt 2000; Segal 2020; Shallcross 2015/2018 [1 study reported across 2 papers]; Simon 2004; Stangier 2013; Stein 1980; Teasdale 2000; Terra 1998; Wilkinson 2002; Wilkinson 2009; Williams 2014; Wilson 2003).

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 to Table 35.

Table 2: Summary of included studies. Comparison 1. Cognitive and cognitive behavioural therapies versus no treatment

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Jarrett 2001 RCT US	N=84 Mean age (years): 42.7 Gender (% female): 73 Acute treatment: Cognitive therapy	Cognitive therapy Intensity: 10x 60-90-min sessions	No treatment	Remission: HAMD≤9 and no MDD Relapse: Met DSM-IV criteria for MDD (i.e. LIFE PSR score of 5 or 6 for 2 weeks)	Treatment length (weeks): 35 Outcomes: • Relapse at: ○ 35 weeks post-randomisation ○ 104 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; LIFE: longitudinal follow-up examination; MDD: major depressive disorder; PSR: psychiatric status rating scale; RCT: randomised controlled trial

Table 3: Summary of included studies. Comparison 2. Cognitive and cognitive behavioural therapies versus TAU

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Fava 1994/1996/1998c RCT Italy	N=43 Mean age (years): 46.1 Gender (% female): 68 Acute treatment: Antidepressants	Cognitive therapy (10x 40-min fortnightly sessions)	TAU	Remission: Partial remission (rating of at least 3 on the 7-point scales of Paykel's Clinical Interview for Depression) Relapse: RDC-defined episode of major	Treatment length (weeks): 20 Outcomes: • Relapse at: ○ 124 weeks post-randomisation ○ 228 weeks post-randomisation ○ 332 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				depressio n	

RCT: randomised controlled trial; RDC: research diagnostic criteria; TAU: treatment as usual

Table 4: Summary of included studies. Comparison 3. Cognitive and cognitive behavioural therapies + TAU versus TAU

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Bockting 2005/2015 RCT Netherlands	N=187 Mean age (years): 44.7 Gender (% female): 73 Acute treatment: NR	Cognitive group therapy (8x weekly 2-hour sessions) + TAU	TAU	Remission: in remission (according to DSM–IV criteria) for longer than 10 weeks and no longer than 2 years; HAMD score <10 Relapse: met DSM–IV criteria for major depression	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 13 weeks post-randomisation ○ 26 weeks post-randomisation ○ 39 weeks post-randomisation ○ 52 weeks post-randomisation ○ 78 weeks post-randomisation ○ 104 weeks post-randomisation ○ 520 weeks post-randomisation
Bondolfi 2010 RCT Switzerland	N=60 Mean age (years): NR (Median= for intervention	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour sessions; + 4 booster	TAU	Remission: MADRS score ≤ 13 Relapse: Met DSM-IV criteria for major	Treatment length (weeks): 8 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	46, for control 49) Gender (% female): 72 Acute treatment: Antidepressants	sessions during follow-up) + TAU		depressive episode	• Relapse at 60 weeks post-randomisation
de Jonge 2019 RCT Netherlands	N=214 Mean age (years): 43.4 Gender (% female): 68 Acute treatment: CBT	Cognitive therapy (8x weekly sessions) + TAU	TAU	Remission: No MDE (DSM-IV) and HAMD score <14 Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at 65 weeks post-randomisation
Godfrin 2010 RCT Belgium	N=106 Mean age (years): 45.7 Gender (% female): 81 Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2.75-hour sessions) + TAU	TAU	Remission: No MDE (DSM-IV-R) and HAMD score<14 Relapse: Met DSM-IV-R criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 56 weeks post-randomisation • Quality of life impairment at: ○ 8 weeks post-randomisation ○ 34 weeks post-randomisation ○ 60 weeks post-randomisation
Ma 2004 RCT UK	N=75 Mean age (years): 44.5	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour	TAU	Remission: HAMD score <10 Relapse: Met DSM-	Treatment length (weeks): 8 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Gender (% female): 76 Acute treatment: Antidepressants	sessions) + TAU		IV criteria for MDE	• Relapse at 60 weeks post-randomisation
Meadows 2014 RCT Australia	N=204 Mean age (years): 48.4 Gender (% female): 81 Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour sessions) + TAU	TAU	Remission: No MDD (DSM-IV) Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 60 weeks post-randomisation ○ 113 weeks post-randomisation
Teasdale 2000 RCT UK & Canada	N=145 Mean age (years): 43.3 Gender (% female): 76 Acute treatment: Antidepressants	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour sessions) + TAU	TAU	Remission: HAMD score <10 Relapse: Met DSM-III-R criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at 60 weeks post-randomisation
Williams 2014 RCT UK	N=164 Mean age (years): 43.8 Gender (% female): 70 Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour sessions) + TAU	TAU	Remission: participant did not report that at least 1 week during the previous 8 they experienced either a core symptom of depression (depressed mood, anhedonia) or	Treatment length (weeks): 8 Outcomes: • Relapse at 60 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				suicidal feelings and at least one other symptom of depression, which together were not attributable to bereavement, substances, or medical condition, but were impairing functioning Relapse: Met DSM-IV-TR criteria for MDD	

CBT: cognitive behavioural therapy; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial; TAU: treatment as usual

Table 5: Summary of included studies. Comparison 4. Cognitive and cognitive behavioural therapies + TAU versus attention placebo + TAU

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Shallcross 2015/2018 RCT US	N=92 Mean age (years): 34.9 Gender (% female): 77 Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2.5-hour sessions) + TAU	Attention placebo + TAU	Remission: BDI–II score = 4-30 Relapse: Met DSM-IV criteria for MDD	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 60 weeks post-randomisation ○ 121 weeks post-

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
					randomisation • Quality of life change score at: ○ 8 weeks post-randomisation ○ 34 weeks post-randomisation ○ 60 weeks post-randomisation ○ 121 weeks post-randomisation
Williams 2014 RCT UK	N=218 Mean age (years): 43.9 Gender (% female): 72 Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2-hour sessions) + TAU	Attention placebo + TAU	Remission: participant did not report that at least 1 week during the previous 8 they experienced either a core symptom of depression (depressed mood, anhedonia) or suicidal feelings and at least one other symptom of depression, which together were not attributable to bereavem	Treatment length (weeks): 8 Outcomes: • Relapse at 60 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				ent, substances, or medical condition, but were impairing functioning Relapse: Met DSM-IV-TR criteria for MDD	

BDI: Beck depression inventory; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; TAU: treatment as usual

Table 6: Summary of included studies. Comparison 5. Cognitive and cognitive behavioural therapies versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Jarrett 2013 RCT US	N=155 Mean age (years): 43.3 Gender (% female): 68 Acute treatment: Cognitive therapy	Cognitive therapy (10x fortnightly to monthly 1-hour sessions)	Pill placebo	Remission: HAMD≤12 and no DSM-IV MDE Relapse: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks)	Treatment length (weeks): 35 Outcomes: • Relapse at: ○ 35 weeks post-randomisation ○ 87 weeks post-randomisation ○ 139 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; LIFE: longitudinal follow-up examination; MDE: major depressive episode; PSR: psychiatric status rating scale; RCT: randomised controlled trial

Table 7: Summary of included studies. Comparison 6. Cognitive and cognitive behavioural therapies (+/- TAU) versus psychoeducation (+/- TAU)

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Elices 2017 RCT Spain	N=75 Mean age (years): 52.6 Gender (% female): 79 Acute treatment: NR	Dialectical behavioural therapy (DBT) group (10x weekly 2-hour sessions)	Psychoeducation group (5x fortnightly 90-min sessions)	Remission: DSM-IV complete or partial remission and HAMD score < 17 Relapse: Met DSM-IV-TR criteria for MDE	Treatment length (weeks): 10 Outcomes: • Relapse at 62 weeks post-randomisation
Stangier 2013 RCT Germany	N=180 Mean age (years): 48.6 Gender (% female): 72 Acute treatment: NR	CBT individual (16x 50-min sessions) + TAU	Psychoeducation individual sessions (16x 20-min sessions) + TAU	Remission: DSM-IV remission and HAMD score ≤9 Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 35 Outcomes: • Relapse at 87 weeks post-randomisation

CBT: cognitive behavioural therapy; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial

Table 8: Summary of included studies. Comparison 7. Mindfulness-based cognitive therapy (MBCT) group (+ TAU) versus cognitive therapy group (+ TAU)

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Farb 2018 RCT Canada	N=166 Mean age (years): NR Gender (% female): NR Acute treatment: NR	Mindfulness-based cognitive therapy (MBCT) group (: 8x weekly 2-hour sessions + retreat day) + TAU	Cognitive therapy group (8x weekly 2-hour sessions) + TAU	Remission: No DSM-IV MDD Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 8 Outcomes : • Relapse at 104 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; MDD: major depressive disorder; MDE: major depressive episode; NR: not reported; RCT: randomised controlled trial

Table 9: Summary of included studies. Comparison 8. Cognitive and cognitive behavioural therapies versus antidepressants

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Bockting 2018 RCT Netherlands	N=185 Mean age (years): 47.4 Gender (% female): 63 Acute treatment: Antidepressants	Cognitive therapy (8x weekly group or individual sessions)	Any antidepressant (dose NR)	Remission: No DSM-IV-TR MDD and HAMD≤10 Relapse: Met DSM-IV-TR criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 28 weeks post-randomisation ○ 43 weeks post-randomisation ○ 57 weeks post-randomisation ○ 100 weeks post-randomisation
Jarrett 2013 RCT US	N=172 Mean age (years): 42.4 Gender (% female): 70 Acute treatment: Cognitive therapy	Cognitive therapy (10x fortnightly to monthly 1-hour sessions)	Fluoxetine (10-40mg/day)	Remission: HAMD≤12 and no DSM-IV MDE Relapse: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks)	Treatment length (weeks): 35 Outcomes: • Relapse at: ○ 35 weeks post-randomisation ○ 87 weeks post-randomisation ○ 139 weeks post-randomisation
Kuyken 2008 RCT UK	N=123 Mean age (years): 49.2 Gender (% female): 76 Acute treatment:	Mindfulness-based cognitive therapy (MBCT) group (8 x weekly 2-hour sessions; +4 follow-up sessions over a year)	Any antidepressant (dose NR)	Remission: Full or partial remission (DSM-IV) Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at 65 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Antidepressants				
Kuyken 2015a/2015b RCT UK	N=424 Mean age (years): 49.5 Gender (% female): 77 Acute treatment: Antidepressants	Mindfulness-based cognitive therapy (MBCT) group (8 x weekly 2.25-hour sessions; +4 follow-up sessions over year)	Any antidepressant (dose NR)	Remission: Full or partial remission (DSM-IV) Relapse: Met DSM-IV criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 22 weeks post-randomisation ○ 43 weeks post-randomisation ○ 65 weeks post-randomisation ○ 87 weeks post-randomisation • Quality of life at: ○ 12 weeks post-randomisation ○ 39 weeks post-randomisation ○ 52 weeks post-randomisation ○ 78 weeks post-randomisation ○ 104 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; LIFE: longitudinal follow-up examination; MDD: major depressive disorder; MDE: major depressive episode; NR: not reported; PSR: psychiatric status rating scale; RCT: randomised controlled trial

Table 10: Summary of included studies. Comparison 9. Cognitive and cognitive behavioural therapies + antidepressants versus antidepressants

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Bockting 2018 RCT Netherlands	N=204 Mean age (years): 47.1 Gender (% female): 67 Acute treatment: Antidepressants	Cognitive therapy (8x weekly group or individual sessions) + any antidepressant (dose NR)	Any antidepressant (dose NR)	Remission: No DSM-IV-TR MDD and HAMD≤10 Relapse: Met DSM-IV-TR criteria for MDE	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 28 weeks post-randomisation ○ 43 weeks post-randomisation ○ 57 weeks post-randomisation ○ 100 weeks post-randomisation
Brakemeier 2014 RCT Germany	N=35 Mean age (years): 62.5 Gender (% female): 80 Acute treatment: ECT	CBT group (15x weekly CBT sessions) + any antidepressant (dose NR; continued for 26 weeks)	Any antidepressant (dose NR)	Remission: HAMD improvement from baseline ≥50% and HAMD score<16 post-acute treatment Relapse: Hospitalized for symptomatic worsening and/or HAMD scores increased by ≥ 18 points or increased from baseline ≥ 10 points	Treatment length (weeks): 26 Outcomes: • Relapse at: ○ 26 weeks post-randomisation ○ 52 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Fava 1998a/2004 RCT Italy	N=45 Mean age (years): 46.9 Gender (% female): 60 Acute treatment: Antidepressants	Cognitive therapy individual (10x fortnightly 30-min sessions) + any antidepressant (dose NR)	Any antidepressant (dose NR)	Remission: Residual symptoms (rating of at least 3 on the 7-point scales of Paykel's Clinical Interview for Depression) Relapse: Met RDC for MDE	Treatment length (weeks): 20 Outcomes: • Relapse at: ○ 104 weeks post-randomisation ○ 310 weeks post-randomisation
Huijbers 2015 RCT Netherlands	N=68 Mean age (years): 51.8 Gender (% female): 72 Acute treatment: Antidepressants	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2.5-hour sessions) + any antidepressant (dose NR)	Any antidepressant (dose NR)	Remission: No MDD (DSM-IV) Relapse: Met DSM-IV criteria for MDD	Treatment length (weeks): 8 Outcomes: • Relapse at 65 weeks post-randomisation • Quality of life at: ○ 12 weeks post-randomisation ○ 65 weeks post-randomisation
Wilkinson 2009 RCT UK	N=45 Mean age (years): 74.0 Gender (% female): 62 Acute treatment: Antidepressant	CBT group (8x 90-min sessions) + any antidepressant (equivalent to fluoxetine 20 mg or amitriptyline 150 mg)	Any antidepressant (equivalent to fluoxetine 20 mg or amitriptyline 150 mg)	Remission: MADRS score<10 Relapse: MADRS ≥10	Treatment length (weeks): 10 Outcomes: • Relapse at: ○ 26 weeks post-randomisation ○ 52 weeks post-randomisation

AD: antidepressant; CBT: cognitive behavioural therapy; DSM: diagnostic and statistical manual of mental disorders; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg

depression rating scale; MDD: major depressive disorder; MDE: major depressive episode; RCT: randomised controlled trial

Table 11: Summary of included studies. Comparison 10. Cognitive and cognitive behavioural therapies + antidepressants versus ECT + antidepressants

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Brakemeier 2014 RCT Germany	N=42 Mean age (years): 60.5 Gender (% female): 74 Acute treatment: ECT	CBT group (15x weekly sessions) + any antidepressant (dose NR; continued for 26 weeks)	ECT (11 sessions) + any antidepressant (dose NR)	Remission: HAMD improvement from baseline ≥50% and HAMD score<16 post-acute treatment Relapse: Hospitalized for symptomatic worsening and/or HAMD scores increased by ≥ 18 points or increased from baseline ≥ 10 points	Treatment length (weeks): 26 Outcomes: • Relapse at: ○ 26 weeks post-randomisation ○ 52 weeks post-randomisation

AD: antidepressant; CBT: cognitive behavioural therapy; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; RCT: randomised controlled trial

Table 12: Summary of included studies. Comparison 11. Mindfulness-based cognitive therapy (MBCT) group + continuation antidepressants versus MBCT group (discontinuationantidepressants)

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Huijbers 2016a RCT Netherlands	N=249 Mean age (years): 50.3 Gender (% female): 67 Acute treatment:	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2.5-hour sessions) + continuation antidepressant (adequate	Mindfulness-based cognitive therapy (MBCT) group (8x weekly 2.5-hour sessions; discontinuation	Remission: No MDD (DSM-IV) Relapse: Met DSM-IV criteria for MDD	Treatment length (weeks): 8 Outcomes: • Relapse at 65 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Antidepressants	dose of antidepressant maintained or reinstated)	antidepressants)		

AD: antidepressant; DSM: diagnostic and statistical manual of mental disorders; MDD: major depressive disorder; RCT: randomised controlled trial

Table 13: Summary of included studies. Comparison 12. Interpersonal therapy (IPT) versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=49 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	IPT (36x monthly sessions)	Pill placebo (dose NR)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and Raskin severity score ≥7	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation

HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria

Table 14: Summary of included studies. Comparison 13. Interpersonal therapy (IPT) versus antidepressant

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=54 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	IPT (36x monthly sessions)	Imipramine (mean dose 200mg/day)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				Raskin severity score ≥7	

HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria

Table 15: Summary of included studies. Comparison 14. Interpersonal therapy (IPT) + antidepressant versus antidepressant

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=53 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	IPT (36x monthly sessions) + imipramine (mean dose 200mg/day)	Imipramine (mean dose 200mg/day)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and Raskin severity score ≥7	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation

HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria

Table 16: Summary of included studies. Comparison 15. Interpersonal therapy (IPT) + antidepressant versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=48 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	IPT (36x monthly sessions) + imipramine (mean dose 200mg/day)	Pill placebo (dose NR)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and	Treatment length (weeks): 156 Outcomes Relapse at: ○ 156 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				Raskin severity score ≥7	

HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria

Table 17: Summary of included studies. Comparison 16. Interpersonal therapy (IPT) + pill placebo versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=49 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	IPT (36x monthly sessions) + pill placebo (dose NR)	Pill placebo (dose NR)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and Raskin severity score ≥7	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation

HAMD: Hamilton depression scale; IPT: interpersonal therapy; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria

Table 18: Summary of included studies. Comparison 17. Self-help + TAU versus TAU

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Biesheuvel-Leliefeld 2017 RCT Netherlands	N=248 Mean age (years): 48.7 Gender (% female): 70 Acute treatment: NR	Cognitive bibliotherapy (8 modules; minimal guidance, weekly call of no longer than 15 mins) + TAU	TAU	Remission: No MDD (DSM-IV) Relapse: Met DSM-IV criteria for MDD	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 52 weeks post-randomisation • Quality of life mental health component at:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
					○ 26 weeks post-randomisation ○ 52 weeks post-randomisation • Quality of life physical health component at: ○ 26 weeks post-randomisation ○ 52 weeks post-randomisation
Klein 2018a RCT Netherlands	N=264 Mean age (years): 46 Gender (% female): 75 Acute treatment: NR	Computerised preventive cognitive therapy (PCT; 8 online modules, recommended to work on 1 module per week) + TAU	TAU	Remission: No MDE (DSM-IV) and HAMD score ≤ 10 Relapse: Met DSM-IV criteria for MDD	Treatment length (weeks): 8 Outcomes: • Relapse at: ○ 14 weeks post-randomisation ○ 28 weeks post-randomisation ○ 43 weeks post-randomisation ○ 57 weeks post-randomisation ○ 71 weeks post-randomisation ○ 85 weeks post-randomisation ○ 100 weeks post-

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
					randomisation
Segal 2020 RCT Canada	N=460 Mean age (years): 48.3 Gender (% female): 76 Acute treatment: NR	Computerised mindfulness-based cognitive therapy (MBCT; 8 online sessions) + TAU	TAU	Remission: PHQ-9 score=5-9 Relapse: PHQ-9 score ≥15	Treatment length (weeks): 13 Outcomes: • Relapse at: ○ 12 weeks post-randomisation ○ 65 weeks post-randomisation • Quality of life mental health component at: ○ 12 weeks post-randomisation ○ 52 weeks post-randomisation • Quality of life physical health component at: ○ 12 weeks post-randomisation ○ 52 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; MDD: major depressive disorder; NR: not reported; PHQ: patient health questionnaire; RCT: randomised controlled trial; TAU: treatment as usual

Table 19: Summary of included studies. Comparison 18. Self-help with support + TAU versus attention placebo + TAU

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Holländare 2011/2013	N=84	Computerised CBT (CCBT) with support	Attention placebo + TAU	Remission: MADRS	Treatment length (weeks): 10

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
RCT Sweden	Mean age (years): 45.3 Gender (% female): 85 Acute treatment: Psychotherapy and/or antidepressant	(9 basic mandatory modules and 7 advanced optional modules (approximately 2.5 hours of total therapist time／participant) + TAU		score=7-19 Relapse: Met DSM-IV criteria for MDD	Outcomes: • Relapse at: ○ 36 weeks post-randomisation ○ 114 weeks post-randomisation • Quality of life change score at: ○ 10 weeks post-randomisation ○ 36 weeks post-randomisation ○ 62 weeks post-randomisation ○ 114 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; RCT: randomised controlled trial; TAU: treatment as usual

Table 20: Summary of included studies. Comparison 19. SSRIs versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Dobson 2008 RCT US	N=49 Mean age (years): 38.9 Gender (% female): 78 Acute treatment: Paroxetine	Paroxetine (maximum 50mg/day)	Pill placebo	Remission: No MDD (DSM-IV) Relapse: HAMD score of at least 14, or PSRs ≥5, for 2 successive weeks	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Doogan 1992 RCT UK, Ireland, Austria, France, Germany, Switzerland and Finland	N=300 Mean age (years): 51 Gender (% female): 69 Acute treatment: Sertraline	Sertraline (50-200mg/day)	Pill placebo	Remission: Achieved 'satisfactory' response Relapse: CGI-S score=4-7	Treatment length (weeks): 44 Outcomes: • Relapse at 44 weeks post-randomisation
Gilaberte 2001 RCT Spain	N=140 Mean age (years): 44.1 Gender (% female): 79 Acute treatment: Fluoxetine	Fluoxetine (20mg/day)	Pill placebo	Remission: No MDD (DSM-III-R), HAMD≤8 and CGI-S score ≤2 Relapse: Met DSM-III-R criteria for MDD, and had HAMD score ≥18 and/or a CGI score ≥ 4 for at least 2 weeks	Treatment length (weeks): 48 Outcomes: • Relapse at 48 weeks post-randomisation
Gorwood 2007 RCT Czech Republic, France, Germany, The Netherlands, Poland, Slovakia and Spain	N=305 Mean age (years): 73 Gender (% female): 79 Acute treatment: Escitalopram	Escitalopram (fixed dose of 10 or 20 mg/day)	Pill placebo	Remission: MADRS≤ 12 Relapse: MADRS total score≥ 22 or an unsatisfactory treatment effect (lack of efficacy) as judged by the investigator	Treatment length (weeks): 24 Outcomes: • Relapse at 24 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Hochstrasser 2001 RCT Austria, Belgium, Finland, France, Italy, The Netherlands, Norway, Switzerland, and UK	N=269 Mean age (years): 43.1 Gender (% female): 71 Acute treatment: Citalopram	Citalopram (20, 40 or 60mg/day)	Pill placebo	Remission: MADRS≤ 11 Relapse: MADRS total score≥ 22	Treatment length (weeks): 48-77 Outcomes: • Relapse at 48-77 weeks post-randomisation
Jarrett 2013 RCT US	N=155 Mean age (years): 42.5 Gender (% female): 64 Acute treatment: Cognitive therapy	Fluoxetine (10-40mg/day)	Pill placebo	Remission: No MDD (DSM-IV) and HAMD≤12 Relapse: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks)	Treatment length (weeks): 35 Outcomes: • Relapse at: ○ 35 weeks post-randomisation ○ 87 weeks post-randomisation ○ 139 weeks post-randomisation
Kamijima 2006 RCT Japan	N=235 Mean age (years): 39.6 Gender (% female): 63 Acute treatment: Sertraline	Sertraline (50-100mg/day)	Pill placebo	Remission: HAMD score <14 and CGI-I<4 Relapse: Either (i) HAM-D score ≥18 points or greater and a CGI-I (compared to baseline of the open-label phase) of 'no	Treatment length (weeks): 16 Outcomes: • Relapse at 16 weeks post-randomisation • Quality of life change score at 16 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				change' or worse, at 2 consecutive visits or (ii) being unable to continue treatment because of insufficient efficacy	
Klysner 2002 RCT Denmark	N=121 Mean age (years): 74.5 Gender (% female): 77 Acute treatment: Citalopram	Citalopram (20mg [10%], 30mg [42%], or 40mg [48%], final fixed dose of citalopram continued)	Pill placebo	Remission: MADRS≤ 11 Relapse: MADRS total score≥ 22	Treatment length (weeks): 48 Outcomes: • Relapse at 48 weeks post-randomisation
Kornstein 2006 RCT US	N=139 Mean age (years): 42.8 Gender (% female): 79 Acute treatment: Escitalopram	Escitalopram (10-20mg/day, fixed dose same as final dose at end of flexible-dose open-label treatment)	Pill placebo	Remission: MADRS≤ 12 Relapse: MADRS total score≥ 22, or withdrawal from the study due to insufficient treatment response based on the judgement of the principal investigator	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation
Lepine 2004 RCT	N=288 Mean age (years): 46.9	Sertraline (2 fixed-dose arms, 50mg/day or 100 mg/day)	Pill placebo	Remission: No MDD (DSM-IV)	Treatment length (weeks): 78

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
France	Gender (% female): 70 Acute treatment: Antidepressant (except sertraline)			Relapse: Met DSM-IV criteria for MDD or the appearance of symptoms which, in the opinion of the clinician, required the administration of another antidepressant treatment	Outcomes: • Relapse at 78 weeks post-randomisation
Montgomery 1988 RCT France	N=220 Mean age (years): NR Gender (% female): NR Acute treatment: Fluoxetine	Fluoxetine (40mg/day)	Pill placebo	Remission: HAMD<12 Relapse: HAMD score>18	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation
Montgomery 1993a RCT UK	N=135 Mean age (years): 47.1 Gender (% female): 79 Acute treatment: Paroxetine	Paroxetine (20-30mg/day)	Pill placebo	Remission: HAMD≤8 Relapse: Withdrawal from study and ≥1 of the following: CGI-S score ≥4; deterioration of the CGI by ≥2 points since previous visit; met DSM-III-R criteria for MDD; in the	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				opinion of the investigators the patient needed antidepressant treatment; depressive symptomatology was present for more than 7 days	
Montgomery 1993b RCT Europe	N=147 Mean age (years): NR Gender (% female): NR Acute treatment: Citalopram	Citalopram (2 fixed-dose arms, 20mg/day or 40 mg/day)	Pill placebo	Remission: MADRS≤ 12 Relapse: MADRS total score≥ 22	Treatment length (weeks): 24 Outcomes: • Relapse at 24 weeks post-randomisation
Rapaport 2004 RCT US	N=274 Mean age (years): 42.5 Gender (% female): 61 Acute treatment: Escitalopram	Escitalopram (10-20mg/day)	Pill placebo	Remission: MADRS≤ 12 Relapse: MADRS total score≥ 22, or discontinued treatment because of an insufficient therapeutic response	Treatment length (weeks): 36 Outcomes: • Relapse at 36 weeks post-randomisation
Robert 1995 RCT France	N=226 Mean age (years): Median: 49.5	Citalopram (fixed dose of 20, 40 or 60mg/day)	Pill placebo	Remission: MADRS≤ 12	Treatment length (weeks): 24 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	(intervention); 46.5 (control) Gender (% female): 72 Acute treatment: Citalopram			Relapse: MADRS total score≥ 25 and clinical judgement of the investigator	• Relapse at 24 weeks post-randomisation
Schmidt 2000 RCT US	N=311 Mean age (years): 41.8 Gender (% female): 68 Acute treatment: Fluoxetine	Fluoxetine (20mg/day)	Pill placebo	Remission: No MDD (DSM-IV) and HAMD≤9 and CGI–S score≤2 Relapse: Met DSM-IV criteria for MDE and an increase in CGI-S of 2 or more for 2 consecutive visits	Treatment length (weeks): 25 Outcomes: • Relapse at 25 weeks post-randomisation
Terra 1998 RCT France	N=204 Mean age (years): 44.7 Gender (% female): 74 Acute treatment: Fluvoxamine	Fluvoxamine (100mg/day)	Pill placebo	Remission: MADRS< 10 and CGI-S score ≤2 Relapse: Reappearance of depressive symptoms in the opinion of the investigator (at least 5 symptoms outlined in the DSM-III-R criteria for MDD) at 2 consecutive	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				assessments (8 days apart) or attempted or completed suicide	
Wilson 2003 RCT UK	N=113 Mean age (years): 76.7 Gender (% female): 71 Acute treatment: Sertraline	Sertraline (50-100mg/day)	Pill placebo	Remission: HAMD≤10 and ≥50% improvement in HAMD from baseline Relapse: Met DSM-III-R criteria for MDD and HAMD score ≥13	Treatment length (weeks): 100 Outcomes: • Relapse at 100 weeks post-randomisation

CGI-I: clinical global impressions scale – improvement; CGI-S: clinical global impressions scale – severity; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; LIFE: longitudinal follow-up examination; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; MDE: major depressive episode; PSR: Psychiatric status ratings; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 21: Summary of included studies. Comparison 20. SSRI versus TCA

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Martiny 2015 RCT Denmark	N=46 Mean age (years): 55.3 Gender (% female): 61 Acute treatment: ECT	Escitalopram (10mg, 20mg or 30mg/day)	Nortriptyline (100mg/day)	Remission: HAMD score <10 Relapse: HAMD score ≥ 16, present for 14 days	Treatment length (weeks): 25 Outcomes: • Relapse at 25 weeks post-randomisation

ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Table 22: Summary of included studies. Comparison 21. TCAs versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Alexopoulos 2000 RCT US	N=43 Mean age (years): 73.3 Gender (% female): 63 Acute treatment: Nortriptyline	Nortriptyline (plasma levels 60-150ng/mL)	Pill placebo	Remission: No depression (RDC) and HAMD score ≤10 and Cornell Scale score ≤6 for 3 consecutive weeks Relapse: Met RDC and DSM-IV criteria for MDD and HAMD score≥17	Treatment length (weeks): 104 Outcomes: • Relapse at 104 weeks post-randomisation
Coppen 1978 RCT UK	N=32 Mean age (years): 53.5 Gender (% female): 87 Acute treatment: Amitriptyline	Amitriptyline (150mg/day)	Pill placebo	Remission: HAMD<7 Relapse: An increase in morbidity sufficiently severe to warrant admission to hospital	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation
Klerman 1974 RCT US	N=100 Mean age (years): NR Gender (% female): 100 Acute treatment: Amitriptyline	Amitriptyline (100-200mg/day)	Pill placebo	Remission: ≥ 50% improvement in Raskin Depression Scale score Relapse: NR	Treatment length (weeks): 35 Outcomes: • Relapse at 35 weeks post-randomisation
Old Age Depression Interest Group 1993 RCT	N=69 Mean age (years): 75.7	Dothiepin (75mg/day)	Pill placebo	Remission: MADRS< 11 Relapse: Clinical	Treatment length (weeks): 104 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
UK	Gender (% female): 73 Acute treatment: NR			judgement or MADRS score >10	• Relapse at 104 weeks post-randomisation
Prien 1984 RCT US	N=73 Mean age (years): NR Gender (% female): NR Acute treatment: Imipramine + lithium	Imipramine (75-150mg/day)	Pill placebo	Remission: RSDM scale score<7 and GAS score>60 Relapse: Met RDC for MDD and GAS rating ≤ 60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcomes: • Relapse at 104 weeks post-randomisation
Stein 1980 RCT US	N=55 Mean age (years): 42.3 Gender (% female): 65 Acute treatment: Amitriptyline	Amitriptyline (100-150mg/day)	Pill placebo	Remission: Raskin Depression Scale total was reduced by ≥ 50% and both the patient and physician rated the patient as at least moderately improved Relapse: NR	Treatment length (weeks): 26 Outcomes: • Relapse at 26 weeks post-randomisation

DSM: diagnostic and statistical manual of mental disorders; GAS: global assessment scale; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; TCA: tricyclic antidepressant

Table 23: Summary of included studies. Comparison 22. TCA versus no treatment

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Klerman 1974 RCT US	N=100 Mean age (years): NR Gender (% female): 100 Acute treatment: Amitriptyline	Amitriptyline (100-200mg/day)	No treatment	Remission: ≥ 50% improvement in Raskin Depression Scale score Relapse: NR	Treatment length (weeks): 35 Outcomes: • Relapse at 35 weeks post-randomisation

NR: not reported; RCT: randomised controlled trial; TCA: tricyclic antidepressant

Table 24: Summary of included studies. Comparison 23. TCA + lithium versus lithium

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Prien 1984 RCT US	N=75 Mean age (years): NR Gender (% female): NR Acute treatment: Imipramine + lithium	Imipramine (75-150mg/day) + lithium (target serum level 0.6-0.9 mEq/L)	Lithium (target serum level 0.6-0.9 mEq/L)	Remission: RSDM scale score<7 and GAS score>60 Relapse: Met RDC for MDD and GAS rating ≤ 60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcomes: • Relapse at 104 weeks post-randomisation

GAS: global assessment scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; TCA: tricyclic antidepressant

Table 25: Summary of included studies. Comparison 24. TCA + IPT versus IPT

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=51 Mean age (years): NR	Imipramine (mean dose 200mg/day) + IPT (36x monthly sessions)	IPT (36x monthly sessions)	Remission: HAMD score of ≤7 and a Raskin score ≤5	Treatment length (weeks): 156 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Gender (% female): NR Acute treatment: IPT + imipramine			Relapse: Met RDC for MDD, HAMD score ≥15, and Raskin severity score ≥7	• Relapse at 156 weeks post-randomisation

IPT: interpersonal therapy; HAMD: Hamilton depression scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; TCA: tricyclic antidepressant

Table 26: Summary of included studies. Comparison 25. TCA + IPT versus pill placebo + IPT

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Frank 1990 RCT US	N=51 Mean age (years): NR Gender (% female): NR Acute treatment: IPT + imipramine	Imipramine (mean dose 200mg/day) + IPT (36x monthly sessions)	Pill placebo (dose NR) + IPT (36x monthly sessions)	Remission: HAMD score of ≤7 and a Raskin score ≤5 Relapse: Met RDC for MDD, HAMD score ≥15, and Raskin severity score ≥7	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation

IPT: interpersonal therapy; HAMD: Hamilton depression scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; TCA: tricyclic antidepressant

Table 27: Summary of included studies. Comparison 26. SNRIs versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Kocsis 2007 RCT US	N=336 Mean age (years): 42.3 Gender (% female): 68	Venlafaxine (75-300mg/day)	Pill placebo	Remission: HAMD≤12 and ≥50% improvement in HAMD score from baseline	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Acute treatment: Venlafaxine			Relapse: Met DSM-IV criteria for MDD, or HAMD score>12, or <50% reduction from baseline at 2 consecutive visits	• Functional impairment at 52 weeks post-randomisation • Quality of life at 52 weeks post-randomisation
Montgomery 2004 RCT Europe and US	N=235 Mean age (years): 43.7 Gender (% female): 61 Acute treatment: Venlafaxine	Venlafaxine (100-200mg/day)	Pill placebo	Remission: HAMD≤12 Relapse: Withdrawn for lack of efficacy	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation
Perahia 2006 RCT France, Italy, Spain and US	N=278 Mean age (years): 45.2 Gender (% female): 72 Acute treatment: Duloxetine	Duloxetine(60 mg/day)	Pill placebo	Remission: No MDD (DSM-IV) and HAMD≤9 and CGI–S score≤2 Relapse: Increased CGI–S score ≥2 points and met DSM-IV criteria for MDD at 2 consecutive visits at least 2 weeks apart, or investigator judgement	Treatment length (weeks): 26 Outcomes: • Relapse at 26 weeks post-randomisation
Perahia 2009 RCT	N=288	Duloxetine (60-120mg/day)	Pill placebo	Remission: No MDD (DSM-IV) and	Treatment length (weeks): 52

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
France, Germany, Italy, Russia, Sweden, US	Mean age (years): 47.5 Gender (% female): 72 Acute treatment: Duloxetine			HAMD≤9 and CGI–S score≤2 Relapse: Any of the following: (i) CGI-S score ≥4 and met DSM-IV criteria for MDD for at least 2 weeks; (2) 3 consecutive visits with CGI-S score ≥4 but not meeting the DSM-IV criteria for MDD or 10 total re-emergence visits; (3) discontinued the study due to lack of efficacy	Outcomes: • Relapse at 52 weeks post-randomisation • Functional impairment change score at 52 weeks post-randomisation • Quality of life mental component change score at 52 weeks post-randomisation • Quality of life physical component change score at 52 weeks post-randomisation
Rickels 2010 RCT Europe, US, and Taiwan	N=375 Mean age (years): 42.8 Gender (% female): 67 Acute treatment: Desvenlafaxine	Desvenlafaxine (200 or 400 mg/day)	Pill placebo	Remission: HAMD≤11 Relapse: HAMD score ≥16 or CGI-I score ≥6 or withdrawal from the study because of an unsatisfactory response to treatment as	Treatment length (weeks): 26 Outcomes: • Relapse at 26 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				determined by the investigator	
Rosenthal 2013 RCT North America, South America, South Africa, and Europe	N=548 Mean age (years): 46.0 Gender (% female): 71 Acute treatment: Desvenlafaxine	Desvenlafaxine (50mg/day)	Pill placebo	Remission: HAMD≤11 and CGI-I score ≤2 Relapse: ≥1 of the following: HAMD score ≥16; discontinuation for unsatisfactory response (including the need for additional/ alternate treatment for depression, investigator decision to remove the patient from the study for efficacy reasons, or failure to return if the investigator deemed it was related to efficacy), hospitalization for depression, suicide attempt, or suicide	Treatment length (weeks): 26 Outcomes: • Relapse at 26 weeks post-randomisation
Simon 2004 RCT	N=318	Venlafaxine (75-225 mg/day)	Pill placebo	Remission: HAMD≤10 and CGI-	Treatment length (weeks): 26

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
US	Mean age (years): 42.1 Gender (% female): 64 Acute treatment: Venlafaxine			S score ≤3 Relapse: Met DSM-IV criteria for MDD and CGI-S score ≥4, 2 consecutive CGI-S scores ≥4, or a final CGI-S score ≥4 for any patient who withdrew from the study for any reason	Outcomes: • Relapse at 26 weeks post-randomisation

CGI-S: clinical global impression scale-severity; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake Inhibitor

Table 28: Summary of included studies. Comparison 27. Antipsychotic versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Liebowitz 2010 RCT Bulgaria, Finland, France, Germany, Romania, Russia, the Slovak Republic, UK, Canada, South Africa, US	N=776 Mean age (years): 44.6 Gender (% female): 66 Acute treatment: Quetiapine	Quetiapine (50mg [23%], 150mg [44%] or 300mg [33%])	Pill placebo	Remission: MADRS< 18 at 2 consecutive visits and CGI-S score≤4 Relapse: ≥1 of the following: (i) initiation of pharmacological treatment by the investigator to treat	Treatment length (weeks): 52 Outcomes: • Relapse at 52 weeks post-randomisation • Sleeping difficulties change score at 52 weeks post-randomisation • Functional impairment change score at 52 weeks

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				depression or self-medication with prohibited medications for ≥1 week; (ii) hospitalization for depressive symptoms; (iii) MADRS score ≥18 at 2 consecutive assessments 1 week apart, or at the final assessment if patient discontinued; (iv) CGI-S score ≥5; (v) suicide attempt or discontinuation from the study due to imminent risk of suicide	post-randomisation

CGI-S: clinical global impression scale-severity; MADRS: Montgomery-Asberg depression rating scale; RCT: randomised controlled trial

Table 29: Summary of included studies. Comparison 28. Antipsychotics + antidepressant versus antidepressant

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Brunner 2014 RCT	N=444 Mean age (years): 44.5	Olanzapine + fluoxetine (12/25, 6/50, 12/50, or 18/50 mg/day)	Fluoxetine (fixed dose consistent with last olanzapine +	Remission: MADRS score ≥50% improvem	Treatment length (weeks): 27 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Argentina, India, Mexico, Puerto Rico, Russia, South Africa, Turkey, and US	Gender (% female): 67 Acute treatment: Olanzapine + fluoxetine		fluoxetine dose, 25 or 50mg/day)	ent from baseline and CGI-S score ≤3 Relapse: 50% increase in the MADRS score from randomization with concomitant CGI-S score increase to ≥4; hospitalization for depression or suicidality; or discontinuation due to lack of efficacy or worsening of depression or suicidality	• Relapse at 27 weeks post-randomisation
Rapaport 2006 RCT US, Canada, France and the UK	N=243 Mean age (years): 48.1 Gender (% female): 64 Acute treatment: Risperidone + citalopram	Risperidone (0.25-2mg/day) + citalopram (20-60mg/day)	Pill placebo + citalopram (20-60mg/day)	Remission: HAMD≤7 or CGI-S score≤2 Relapse: CGI change (CGI-C) score of 6 (much worse) or 7 (very much worse), or HAMD score ≥16, or discontinuation	Treatment length (weeks): 24 Outcomes: • Relapse at 24 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				owing to lack of therapeutic effect, or deliberate self-injury or suicidal intent	

CGI-S: clinical global impression scale-severity; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; RCT: randomised controlled trial

Table 30: Summary of included studies. Comparison 29. Lithium versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Prien 1984 RCT US	N=72 Mean age (years): NR Gender (% female): NR Acute treatment: Imipramine + lithium	Lithium (target serum level 0.6-0.9 mEq/L)	Pill placebo	Remission: RSDM depression score<7 and GAS score>60 Relapse: Met RDC for MDD and GAS rating ≤60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcomes: • Relapse at 104 weeks post-randomisation

CGI-S: clinical global impression scale-severity; GAS: global assessment scale; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; RCT: randomised controlled trial

Table 31: Summary of included studies. Comparison 30. Lithium + antidepressant versus pill placebo + antidepressant

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Bauer 2000 RCT Germany	N=30 Mean age (years): 47.4 Gender (% female): 59	Lithium (target 12-hour post-dose serum lithium levels of 0.5–1.0 mmol/liter) + any	Pill placebo + any ntidepressant	Remission: HAMD ≤10 on 2 consecutive visits within a 7-day period,	Treatment length (weeks): 16 Outcomes:

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
	Acute treatment: Lithium + any AD	antidepressant		and CGI-S score ≤3 and CGI-I score=2 or 3, and judged by 2 independent senior or supervising psychiatrists as asymptomatic Relapse: Met DSM-III-R criteria for MDE, HAMD score ≥15, or CGI-S score ≥4	• Relapse at 16 weeks post-randomisation
Wilkinson 2002 RCT UK	N=49 Mean age (years): 75.8 Gender (% female): 65 Acute treatment: Antidepressants	Lithium (200-600mg/day) + any antidepressant	Pill placebo + any antidepressant	Remission: MADRS score <13 and MMSE score >23 Relapse: required an increase or change in antidepressants or admission for ECT in the opinion of the responsible psychiatrist, or MADRS score ≥13	Treatment length (weeks): 104 Outcomes: • Relapse at 104 weeks post-randomisation

AD: antidepressant; CGI-I: clinical global impression scale-improvement; CGI-S: clinical global impression scale-severity; DSM: diagnostic and statistical manual of mental disorders; HAMD: Hamilton depression scale; MADRS:

Montgomery-Asberg depression rating scale; MDE: major depressive episode; MMSE: mini-mental state examination; RCT: randomised controlled trial

Table 32: Summary of included studies. Comparison 31. Lithium versus TCAs

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Glen 1984 RCT UK	N=107 Mean age (years): Median=amitriptyline 51; lithium 53 Gender (% female): 80 Acute treatment: 6% ECT; 51% drugs only; 42% ECT + drugs	Lithium (target plasma concentrations: 0-6-1.2 equivalents/litre)	Amitriptyline (60-230 mg/ml)	Remission: NR ('recovery') Relapse: An affective episode of sufficient severity to require treatment other than night sedation with benzodiazepine	Treatment length (weeks): 156 Outcomes: • Relapse at 156 weeks post-randomisation
Greil 1996 RCT Germany	N=81 Mean age (years): 51.5 Gender (% female): 72 Acute treatment: Psychotropic medication	Lithium (serum levels, 12 hours after drug intake, had to be adjusted to 0.6 to 0.8 mmol/l)	Amitriptyline (75-100mg)	Remission: GAS score >70 for at least 2 weeks Relapse: Met RDC for MDD	Treatment length (weeks): 130 Outcome: • Relapse at 130 weeks post-randomisation
Prien 1984 RCT US	N=77 Mean age (years): NR Gender (% female): NR Acute treatment: Imipramine + lithium	Lithium (target serum level 0.6-0.9 mEq/L)	Imipramine (75-150mg/day)	Remission: RSDM depression score<7 and GAS score>60 Relapse: met RDC for MDD and GAS rating ≤60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcome: • Relapse at 104 weeks post-randomisation

ECT: electroconvulsive therapy; GAS: global assessment scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; TCA: tricyclic antidepressants

Table 33: Summary of included studies. Comparison 32. Lithium + TCA versus pill placebo

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Prien 1984 RCT US	N=71 Mean age (years): NR Gender (% female): NR Acute treatment: Lithium + imipramine	Lithium (target serum level 0.6-0.9 mEq/L) + imipramine (75-150mg/day)	Pill placebo	Remission: RSDM depression score<7 and GAS score>60 Relapse: met RDC for MDD and GAS rating ≤60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcome: • Relapse at 104 weeks post-randomisation

GAS: global assessment scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; TCA: tricyclic antidepressants

Table 34: Summary of included studies. Comparison 33. Lithium + TCA versus TCA

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Prien 1984 RCT US	N=76 Mean age (years): NR Gender (% female): NR Acute treatment: Lithium + imipramine	Lithium (target serum level 0.6-0.9 mEq/L) + imipramine (75-150mg/day)	Imipramine (75-150mg/day)	Remission: RSDM depression score<7 and GAS score>60 Relapse: met RDC for MDD and GAS rating ≤60 or terminated due to adverse reaction	Treatment length (weeks): 104 Outcome: • Relapse at 104 weeks post-randomisation

GAS: global assessment scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; RDC: research diagnostic criteria; RSDM: Raskin severity of depression and mania scale; TCA: tricyclic antidepressants

Table 35: Summary of included studies. Comparison 34. ECT + pharmacological intervention versus pharmacological intervention

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
Brakemeier 2014 RCT Germany	N=43 Mean age (years): 60.4 Gender (% female): 67 Acute treatment: ECT	ECT (15x weekly sessions) + any antidepressant (dose NR; continued for 26 weeks)	Any antidepressant (dose NR; continued for 26 weeks)	Remission: HAMD improvement from baseline ≥50% and HAMD score<16 post-acute treatment Relapse: Hospitalized for symptomatic worsening and/or HAMD increased by ≥ 18 points or increased from baseline ≥ 10 points	Treatment length (weeks): 26 Outcome: • Relapse at: ○ 26 weeks post-randomisation ○ 52 weeks post-randomisation
Kellner 2016/McCall 2018 RCT US	N=128 Mean age (years): 70.5 Gender (% female): 62 Acute treatment: ECT + venlafaxine	ECT (4 ECT sessions in 1 month and then variable frequency in weeks 5-24 depending on HAMD scores, 0-2 ECT treatments a week) + venlafaxine (225mg/day) + lithium (started at 300 mg/day with target blood level 0.4–0.6mEq/L for most patients, never to exceed 1.0 mEq/L)	Venlafaxine (225mg/day) + lithium (started at 300 mg/day with target blood level 0.4–0.6mEq/L for most patients, never to exceed 1.0 mEq/L)	Remission: HAMD score <11 on 2 consecutive ratings, and HAMD score did not increase by >3 points on the 2nd consecutive rating or it remained <7 Relapse: 2 consecutive HAMD scores ≥21, required psychiatri	Treatment length (weeks): 24 Outcomes: • Relapse at 24 weeks post-randomisation • Quality of life mental component score at 24 weeks post-randomisation • Quality of life physical component score at 24 weeks post-randomisation

Study	Population	Intervention	Comparison	Definition of remission and relapse	Comments
				c hospitalization, or became suicidal	

AD: antidepressant; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; RCT: randomised controlled trial

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. See the literature search strategy in appendix B and economic study selection flow chart in appendix G. Details on the hierarchy of inclusion criteria for economic studies are provided in supplement 1 (methods supplement). For this review question, only economic studies conducted in the UK were included.

The systematic search of the economic literature identified 2 studies that assessed the cost effectiveness of interventions aiming at preventing relapse for adults whose depression has responded to treatment in the UK (Kuyken 2008 & Kuyken 2015a/2015b).

Economic evidence tables are provided in appendix H. Economic evidence profiles are shown in appendix I.

Excluded studies

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

Summary of studies included in the economic evidence review

The two economic studies included in the review (Kuyken 2008 and Kuyken 2015a/2015b) were conducted alongside RCTs (Kuyken 2008, N=123; Kuyken 2015a/2015b, N=424). Both studies assessed the cost effectiveness of mindfulness-based cognitive therapy (MBCT) with support to taper or discontinue antidepressant treatment versus maintenance antidepressant treatment plus medication adherence monitoring. The study population in both studies was adults with at least 3 previous major depressive episodes, who were either in full or partial remission from their most recent depressive episode and on a therapeutic dose of maintenance antidepressants. The perspective of both analyses was the NHS and PSS; a broader societal perspective that included productivity losses and service user expenses was considered in a sensitivity analysis. Healthcare costs included intervention costs (provision of MBCT, medication, including support to taper or adhere to medication, hospital services (inpatient, outpatient, emergency department) and community health and social services (e.g., primary care by GPs, nurses and other healthcare professionals such as community psychiatrists and psychologists, social work, complementary therapies). National unit costs were used. Both studies used the percentage of people relapsing as measure of outcome; in

addition, Kuyken 2015a/2015b used QALYs based on EQ-5D (UK tariff) as a secondary outcome. The duration of the analyses ranged from 15 months (Kuyken 2008) to 2 years (Kuyken 2015a/2015b).

Kuyken 2008 reported that MBCT was more costly and more effective than maintenance antidepressant treatment, with an ICER of £363/additional relapse/recurrence prevented under a NHS and PSS perspective (figure converted from 2006 international dollars and uplifted to 2020 British pounds). As QALYs were not used as an outcome measure, the results of this study are not directly interpretable regarding the cost effectiveness of MBCT, as they require a judgement as to whether the extra benefit (prevention of one extra relapse) is worth the additional cost of £363. The study is thus only partially applicable to the NICE decision-making context and is characterised by minor limitations.

In the other study (Kuyken 2015a/2015b) MBCT was also more costly than maintenance antidepressant treatment and prevented a higher number of relapses, resulting in an ICER of £5,573 per relapse/recurrence averted under a NHS and PSS perspective (2020 prices). MBCT produced a lower number of QALYs compared with maintenance antidepressant treatment; therefore, based on the QALY outcome, MBCT does not appear to be cost-effective compared with maintenance antidepressant treatment as it is more costly and less effective. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Economic model

A decision-analytic model was developed to assess the relative cost effectiveness of interventions aiming at preventing relapse in adults whose depression has responded to treatment. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. This section provides a summary of the methods employed and the results of the economic analysis.

Overview of economic modelling methods

A Markov model with a time horizon of 10 years was constructed to evaluate the relative cost effectiveness of a number of pharmacological, psychological and combined interventions for adults whose depression has responded to treatment, who are treated primarily in primary care. The economic analysis considered two different broad populations according to their risk of relapse as determined by the number of previous depressive episodes: adults with depression at medium risk of relapse (1-2 previous depressive episodes) and those at high risk of relapse (3+ previous depressive episodes). In those at medium risk of relapse, future depressive episodes were assumed to be less severe; in those at high risk of relapse, future depressive episodes were assumed to be more severe. These assumptions were based on committee's expert advice, and aimed to cover a range of adults whose depression has responded to acute treatment presenting in routine clinical practice. The economic analysis considered separately populations whose depression has responded to pharmacological treatment from those whose depression has responded to psychological treatment. The time horizon (10 years) was selected to allow assessment of longer-term costs and benefits associated with relapse prevention treatment without introducing high complexity in the model structure. Based on the available evidence, the following analyses were carried out:

- Cost effectiveness of maintenance antidepressant treatment versus GP care with antidepressant drug tapering (reflected in pill placebo trial arms) in people at medium risk of relapse whose depression has responded to pharmacological treatment; 3 analyses were undertaken, specific to people whose depression has responded to treatment with SSRIs, SNRIs, and TCAs.

- Cost effectiveness of maintenance treatment with individual CT/CBT, antidepressants (fluoxetine), GP care or no treatment in people at medium risk of relapse whose depression has responded to psychological treatment.
- Cost effectiveness of maintenance treatment with antidepressants, MBCT plus antidepressant tapering, MBCT combined with antidepressants, group CT/CBT combined with antidepressants, individual CT/CBT plus antidepressant tapering, individual CT/CBT combined with antidepressants, or GP care with antidepressant tapering, in people at high risk of relapse whose depression has responded to pharmacological treatment. Other low intensity interventions (cCBT with support, cCBT without support, individual psychoeducation) combined with antidepressants were considered in a secondary analysis.
- Cost effectiveness of maintenance treatment with individual CT/CBT, antidepressant (fluoxetine), GP care or no treatment in people at high risk of relapse whose depression has responded to psychological treatment. MBCT, group CT/CBT, cCBT with support, cCBT without support and individual psychoeducation were considered as additional options in secondary analysis.

The model structure considered the events of relapse (depressive episode), remission, and death. The probability of remission following a depressive episode was dependent on the time people spent in the depressive episode and was reduced as the time spent in the depressive episode increased. The probability of relapse for people in remission was dependent on the time people spent in remission and was reduced as the time spent in remission increased. Moreover, the risk of relapse depended on the number of previous episodes people had had in the past and increased with every new depressive episode experienced. People receiving antidepressant treatment were at risk of developing common side effects from treatment. People in a depressive episode were assumed to be at increased mortality risk due to depression.

Efficacy data were derived from the guideline systematic review and were synthesised using network meta-analysis (NMA). Baseline parameters (baseline risk of relapse) and the probability of recovery were estimated assuming a Weibull distribution, using data from a review of naturalistic studies. The measure of outcome of the economic analysis was the number of QALYs gained. Utility data were derived from a systematic review of the literature and were generated using EQ-5D measurements and the UK population tariff. The perspective of the analysis was that of health and personal social services. Resource use was based on published literature, national statistics and, where evidence was lacking, the committee's expert opinion. National UK unit costs were used. The cost year was 2020. Model input parameters were synthesised in a probabilistic analysis. This approach allowed consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. A number of one-way deterministic sensitivity analyses were also carried out.

Results have been reported separately for each cohort examined in the economic model. For each treatment option, the Net Monetary Benefit (NMB) has been estimated and incremental analysis has been conducted using the NICE lower cost-effectiveness threshold of £20,000/QALY. The mean (95%CI) rankings by cost-effectiveness have been reported for each treatment, where a rank of 1 suggests that a treatment is the most cost-effective amongst evaluated treatment options. The probability of each intervention being cost-effective at the NICE lower cost-effectiveness threshold has also been calculated. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds, and the probability that this treatment is the most cost-effective among those assessed.

Overview of economic modelling results and conclusions

In people at medium risk of relapse whose depression has responded to pharmacological treatment (SSRIs, SNRIs or TCAs), maintenance pharmacological treatment appears to be

cost-effective compared with GP care plus antidepressant drug tapering. However, after removing potential exaggeration of maintenance antidepressant treatment effects associated with the development of withdrawal syndrome, GP care plus antidepressant drug tapering appears to be the most cost-effective maintenance treatment option. GP care plus antidepressant drug tapering also becomes the most cost-effective maintenance treatment option when the risk of side effects from antidepressants is increased.

In people at medium risk of relapse whose depression has responded to psychological treatment, GP care appears to be the most cost-effective intervention, followed by no treatment. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions, then it appears to become the most cost-effective maintenance treatment option, provided that its relapse preventive effect is retained over two years.

In people at high risk of relapse whose depression has responded to pharmacological treatment, antidepressant treatment appears to be the most cost-effective maintenance treatment option. High intensity psychological interventions, such as individual CT/CBT, group CT/CBT and MBCT, either alone (following antidepressant drug tapering) or combined with maintenance antidepressant treatment appear to be more cost-effective than GP care and antidepressant drug tapering, but less cost-effective than maintenance antidepressant treatment alone, due to their high intervention costs. Somewhat less applicable and overall more limited evidence suggests that low intensity psychological interventions (cCBT with or without support and individual psychoeducation) combined with maintenance antidepressant treatment may be more cost-effective than maintenance antidepressant treatment alone. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (with 1 therapist and 12 participants per group), then their combinations with maintenance antidepressant treatment become more cost-effective than antidepressant treatment alone, while MBCT with antidepressant drug tapering becomes the most cost-effective treatment option as long as its effect is retained over two years. Increasing the risk of side effects of antidepressants results in options that include antidepressant drug tapering becoming more cost-effective than options that include maintenance antidepressant treatment.

In people at high risk of relapse whose depression has responded to psychological treatment, GP care alone (without any antidepressant treatment) appears to be marginally more cost-effective than maintenance antidepressant treatment or individual CT/CBT. Additional evidence, which is somewhat less applicable and overall more limited, suggests that low intensity psychological interventions (cCBT with support and individual psychoeducation) may be more cost-effective than GP care. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (with 1 therapist and 12 participants per group), then they become more cost-effective than GP care, with individual CT/CBT becoming the most cost-effective option, even if its effect is expected to last 1 year.

In general, assuming lower severity of depression in case of relapse, lower utility gains from relapse prevention, lower risks of relapse (as reflected in lower number of previous episodes) and lower costs of relapse favours less costly interventions such as GP care and antidepressant treatment. Assuming higher severity of depression in case of relapse, higher risks of relapse (as reflected in higher number of previous episodes) and higher costs of treating relapse favours more effective but also costlier interventions such as individual or group psychological interventions alone or combined with maintenance antidepressant treatment. Assuming lower resource intensity in the delivery of individual and group psychological interventions, provided that their relapse preventive effect is retained, greatly improves their cost-effectiveness. Lower intensity psychological interventions such as cCBT with or without support and individual psychoeducation, alone or combined with maintenance antidepressant treatment, as relevant, are not considerably affected by alternative scenarios,

as they combine low costs with high effectiveness, although the latter is based on more limited and somewhat less applicable evidence.

Conclusions from the guideline economic analysis refer mainly to people with depression who are predominantly treated in primary care; however, they may be relevant to people in secondary care as well, especially given that clinical evidence was derived almost exclusively from studies conducted in secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

Evidence statements

Clinical evidence statements

Comparison 1: Cognitive and cognitive behavioural therapies versus no treatment

Critical outcomes

Relapse

- Low to moderate quality evidence from 1 RCT (N=84) shows a clinically important and statistically significant benefit of cognitive therapy relative to treatment as usual on the rate of relapse at 35 weeks post-randomisation, although this benefit is not maintained at 104 weeks post-randomisation.

Important outcomes

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

Comparison 2: Cognitive and cognitive behavioural therapies versus TAU

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=43) shows a clinically important benefit of cognitive therapy relative to treatment as usual on the rate of relapse at 124, 228 and 332 weeks post-randomisation, however the effect is only statistically significant at 228 weeks post-randomisation.

Important outcomes

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

Comparison 3: Cognitive and cognitive behavioural therapies + TAU versus TAU

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=187) shows a clinically important but not statistically significant benefit of cognitive group therapy in addition to TAU relative to TAU-only on the rate of relapse at 13 and 26 weeks post-randomisation, although the effect at 39 weeks post-randomisation is neither clinically important nor statistically significant.
- Moderate quality evidence from 8 RCTs (N=1154) shows a clinically important and statistically significant benefit of CBT (individual and group) in addition to TAU, relative to TAU-only, on the rate of relapse at 52-65 weeks post-randomisation.

- Low to very low quality evidence from 1-2 RCTs (N=187-390) shows neither clinically important nor statistically significant effects of a cognitive behavioural group intervention in addition to TAU relative to TAU-only on the rate of relapse at 78, 104-113, or 520 weeks post-randomisation.

Important outcomes

Quality of life

- Low to moderate quality evidence from 1 RCT (N=75) shows a clinically important and statistically significant benefit of a mindfulness-based cognitive therapy (MBCT) group intervention in addition to TAU, relative to TAU-only, on quality of life impairment at 8, 34 and 60 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 4: Cognitive and cognitive behavioural therapies + TAU versus attention placebo + TAU

Critical outcomes

Relapse

- Moderate to very low quality evidence from 1-2 RCTs (N=92-310) shows neither a clinically important nor statistically significant effect of a mindfulness-based cognitive therapy (MBCT) group intervention (in addition to TAU), relative to attention placebo (in addition to TAU), on the rate of relapse at 60 or 121 weeks post-randomisation.

Important outcomes

Quality of life

- Very low quality evidence from 1 RCT (N=92) shows no clinically important effects of a mindfulness-based cognitive therapy (MBCT) group intervention (in addition to TAU) relative to attention placebo (in addition to TAU) on quality of life change scores at 8, 34, 60 or 121 weeks post-randomisation, in fact there is a statistically significant benefit of attention placebo relative to MBCT group on quality of life change at 8 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 5: Cognitive and cognitive behavioural therapies versus pill placebo

Critical outcomes

Relapse

- Moderate quality evidence from 1 RCT (N=155) shows a clinically important and statistically significant benefit of cognitive therapy relative to pill placebo on the rate of relapse at 35 weeks post-randomisation, however this effect is not maintained at 87 or 139 weeks post-randomisation.

Important outcomes

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

Comparison 6: Cognitive and cognitive behavioural therapies (+/- TAU) versus psychoeducation (+/- TAU)

Critical outcomes

Relapse

- Very low quality evidence from 2 RCTs (N=255) shows a clinically important, but not statistically significant, benefit of a cognitive behavioural intervention relative to psychoeducation on the rate of relapse at 62-87 weeks post-randomisation.

Important outcomes

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

Comparison 7. Mindfulness-based cognitive therapy (MBCT) group (+ TAU) versus cognitive therapy group (+ TAU)

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=166) shows neither a clinically important nor statistically significant difference between a mindfulness-based cognitive therapy (MBCT) group intervention and a cognitive therapy group intervention (both in addition to TAU) on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 8. Cognitive and cognitive behavioural therapies versus antidepressants

Critical outcomes

Relapse

- High to very low quality evidence from 1-3 RCTs (N=172-781) shows neither a clinically important nor statistically significant effect of a cognitive behavioural intervention relative to antidepressants on the rate of relapse at 22-35, 43, 57-65, 87-100, or 139 weeks post-randomisation.

Important outcomes

Quality of life

- Moderate quality evidence from 1 RCT (N=292-347) shows neither clinically important nor statistically significant effects of a mindfulness-based cognitive therapy (MBCT) group intervention relative to antidepressants on quality of life at 12, 39, 52, 78 or 104 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 9. Cognitive and cognitive behavioural therapies + antidepressants versus antidepressants

Critical outcomes

Relapse

- Very low to moderate quality evidence from 1-4 RCTs (N=204-352) shows a clinically important but not statistically significant benefit of a cognitive behavioural intervention in addition to antidepressants, relative to antidepressants-only, on the rate of relapse at 26-28 weeks and 100-104 weeks post-randomisation, however effects at 43 and 52-65 weeks post-randomisation are neither clinically important nor statistically significant.
- Low quality evidence from 1 RCT (N=45) shows a clinically important and statistically significant benefit of cognitive therapy in addition to antidepressants, relative to antidepressants-only, on the rate of relapse at 310 weeks post-randomisation.

Important outcomes

Quality of life

- Very low quality evidence from 1 RCT (N=50-54) shows neither clinically important nor statistically significant effects of a mindfulness-based cognitive therapy (MBCT) group intervention in addition to antidepressants, relative to antidepressants-only, on quality of life at 12 and 65 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 10. Cognitive and cognitive behavioural therapies + antidepressants versus ECT + antidepressants

Critical outcomes

Relapse

- Moderate quality evidence from 1 RCT (N=42) shows a clinically important and statistically significant benefit of a CBT group intervention (in addition to antidepressants), relative to ECT (in addition to antidepressants), on the rate of relapse at 26 and 52 weeks post-randomisation.

Important outcomes

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

Comparison 11. Mindfulness-based cognitive therapy (MBCT) group + continuation AD versus MBCT group (discontinuation AD)

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=249) shows a clinically important and statistically significant benefit of a combined mindfulness-based cognitive therapy (MBCT) group and continuation antidepressant intervention, relative to MBCT group-only (with antidepressants discontinued), on the rate of relapse at 65 weeks post-randomisation.

Important outcomes

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

Comparison 12. Interpersonal therapy (IPT) versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=49) shows a clinically important but not statistically significant benefit of IPT, relative to pill placebo, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 13. Interpersonal therapy (IPT) versus antidepressant

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=54) shows a clinically important but not statistically significant benefit of imipramine, relative to IPT, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 14: Interpersonal therapy (IPT) + antidepressant versus antidepressant

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=53) shows a clinically important but not statistically significant benefit of a combined IPT and imipramine intervention, relative to imipramine-only, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 15: Interpersonal therapy (IPT) + antidepressant versus pill placebo

Critical outcomes

Relapse

- Low quality evidence from 1 RCT (N=48) shows a clinically important and statistically significant benefit of a combined IPT and imipramine intervention, relative to pill placebo, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 16: Interpersonal therapy (IPT) + pill placebo versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=49) suggests neither a clinically important nor statistically significant effect of a combined IPT and pill placebo intervention, relative to pill placebo-only, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 17: Self-help + TAU versus TAU

Critical outcomes

Relapse

- Moderate quality evidence from 1 RCT (N=264) shows a clinically important and statistically significant benefit of a computerised cognitive therapy intervention in addition to treatment as usual, relative to treatment as usual-only, on the rate of relapse at 28 and 43 weeks post-randomisation.
- Moderate quality evidence from 1 RCT (N=264) shows a statistically significant but not clinically important benefit of a computerised cognitive therapy intervention in addition to treatment as usual, relative to treatment as usual-only, on the rate of relapse at 100 weeks post-randomisation.
- Moderate to very low quality evidence from 1-3 RCTs (N=264-972) shows neither clinically important nor statistically significant effects of a self-help intervention in addition to treatment as usual, relative to treatment as usual-only, on the rate of relapse at 12-14, 52-65, 71 or 85 weeks post-randomisation.

Important outcomes

Quality of life

- Moderate to very low quality evidence from 1-2 RCTs (N=248-708) shows neither clinically important nor statistically significant effects of a self-help intervention in addition to treatment as usual, relative to treatment as usual-only, on overall quality of life score at 26 or 52 weeks post-randomisation, or on quality of life mental or physical component scores at 12-26 or 52-65 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 18: Self-help with support + TAU versus attention placebo + TAU

Critical outcomes

Relapse

- Low to moderate quality evidence from 1 RCT (N=84) shows a clinically important and statistically significant benefit of a computerised CBT with support intervention (in addition to TAU), relative to attention placebo (in addition to TAU), on the rate of relapse at 36 and 114 weeks post-randomisation.

Important outcomes

Quality of life

- Low quality evidence from 1 RCT (N=67-77) shows a clinically important and statistically significant benefit of a computerised CBT with support intervention (in addition to TAU) relative to attention placebo (in addition to TAU) on improving the quality of life score at 114 weeks post-randomisation, however effects at 10, 36 and 62 weeks post-randomisation are neither clinically important nor statistically significant.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 19: SSRIs versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 4-7 RCTs (N=825-1653) shows a clinically important and statistically significant benefit of a SSRI relative to pill placebo on the rate of relapse at 16-36, 44-48 and 52-87 weeks post-randomisation, although very low quality evidence from 2 RCTs (N=268) suggests this effect is not significant at 100-139 weeks post-randomisation.

Important outcomes

Quality of life

- Low quality evidence from 1 RCT (N=235) shows a clinically important and statistically significant benefit of sertraline relative to pill placebo on improving quality of life scores at 16 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Comparison 20: SSRI versus TCA

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=46) shows a clinically important benefit of nortriptyline relative to escitalopram on the rate of relapse at 25 weeks post-randomisation, however this effect is not statistically significant.

Important outcomes

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

Comparison 21: TCAs versuspill placebo

Critical outcomes

Relapse

- Low quality evidence from 2 RCTs (N=155) shows a clinically important and statistically significant benefit of amitriptyline relative to pill placebo on the rate of relapse at 26-35 weeks post-randomisation, however low to very low quality evidence from 1-3 RCTs (N=32-185) shows a clinically important but not statistically significant benefit of a TCA on the rate of relapse at 52 or 104 weeks post-randomisation.

Important outcomes

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

Comparison 22: TCA versus no treatment

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=100) shows a clinically important but not statistically significant benefit of amitriptyline relative to no treatment on the rate of relapse at 35 weeks post-randomisation.

Important outcomes

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

Comparison 23: TCA + lithium versus lithium

Critical outcomes

Relapse

- Low quality evidence from 1 RCT (N=75) shows a clinically important but not statistically significant benefit of lithium, relative to continuation combined imipramine and lithium, on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 24: TCA + IPT versus IPT

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=51) shows a clinically important but not statistically significant benefit of a continuation combined imipramine and IPT intervention, relative to IPT-only, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 25: TCA + IPT versus pill placebo + IPT

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=51) shows a clinically important and statistically significant benefit of a continuation combined imipramine and IPT intervention, relative to combined pill placebo and IPT, on the rate of relapse at 156 weeks post-randomisation.

Important outcomes

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

Comparison 26: SNRIs versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 3-4 RCTs (N=859-1493) shows a clinically important and statistically significant benefit of a SNRI, relative to pill placebo, on the rate of relapse at 26 and 52 weeks post-randomisation.

Important outcomes

Quality of life

- Low to very low quality evidence from single-RCT analyses (N=258-287) shows a statistically significant but not clinically important benefit of a SNRI relative to pill placebo on quality of life, as measured by overall score and mental component change score at 52 weeks post-randomisation, while effects on physical component change score is neither clinically important nor statistically significant.

Personal, social and occupational functioning

- Low to very low quality evidence from single-RCT analyses (N=258-287) shows a statistically significant but not clinically important benefit of a SNRI relative to pill placebo on functional impairment (at endpoint or change from baseline) at 52 weeks post-randomisation.

Comparison 27: Antipsychotic versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=776) shows neither a clinically important nor statistically significant effect of continuation quetiapine, relative to pill placebo, on the rate of relapse at 52 weeks post-randomisation.

Important outcomes

Quality of life

No evidence was identified for quality of life outcomes for this comparison.

Personal, social and occupational functioning

- Very low quality evidence from 1 RCT (N=771) shows a statistically significant but not clinically important benefit of continuation quetiapine, relative to pill placebo, on improvement in functional impairment at 52 weeks post-randomisation.
- Very low quality evidence from 1 RCT (N=771) shows a statistically significant but not clinically important benefit of continuation quetiapine, relative to pill placebo, on improvement in sleeping difficulties at 52 weeks post-randomisation.

Comparison 28: Antipsychotics + antidepressant versus antidepressant

Critical outcomes

Relapse

- Very low quality evidence from 2 RCTs (N=687) shows neither a clinically important nor statistically significant effect of continuation combined antipsychotic and antidepressant treatment, relative to antidepressants-alone or in addition to pill placebo, on the rate of relapse at 24-27 weeks post-randomisation.

Important outcomes

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

Comparison 29: Lithium versus pill placebo

Critical outcomes

Relapse

- Low quality evidence from 1 RCT (N=72) shows a clinically important and statistically significant benefit of lithium, relative to pill placebo, on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 30: Lithium + antidepressant versus pill placebo + antidepressant

Critical outcomes

Relapse

- Low quality evidence from 1 RCT (N=29) shows evidence for a clinically important but not statistically significant benefit of a combined lithium and antidepressant treatment, relative to pill placebo and antidepressant, on the rate of relapse at 16 weeks post-randomisation.
- Low quality evidence from 1 RCT (N=49) shows evidence for a clinically important and statistically significant benefit of a combined lithium and antidepressant treatment, relative to pill placebo and antidepressant, on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 31: Lithium versus TCAs

Critical outcomes

Relapse

- Low quality evidence from 3 RCTs (N=265) shows neither a clinically important nor statistically significant effect of lithium, relative to a TCA, on the rate of relapse at 104-156 weeks post-randomisation.

Important outcomes

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

Comparison 32: Lithium + TCA versus pill placebo

Critical outcomes

Relapse

- Very low quality evidence from 1 RCT (N=71) shows neither a clinically important nor statistically significant benefit of continuation combined lithium and imipramine treatment, relative to pill placebo, on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 33: Lithium + TCA versus TCA

Critical outcomes

Relapse

- Low quality evidence from 1 RCT (N=76) shows a clinically important but not statistically significant benefit of imipramine, relative to continuation combined lithium and imipramine, on the rate of relapse at 104 weeks post-randomisation.

Important outcomes

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

Comparison 34: ECT + pharmacological intervention versus pharmacological intervention

Critical outcomes

Relapse

- Low to very low quality evidence from 1-2 RCTs (N=43-171) shows neither a clinically important nor statistically significant effect of a combined ECT and antidepressant/lithium intervention, relative to antidepressant/lithium intervention-only, on the rate of relapse at 24-26 or 52 weeks post-randomisation.

Important outcomes

Quality of life

- Low quality evidence from 1 RCT (N=120) shows a clinically important and statistically significant benefit of a combined ECT and venlafaxine and lithium intervention, relative to venlafaxine and lithium only, on improving quality of life (mental and physical component scores) at 24 weeks post-randomisation.

Personal, social and occupational functioning

No evidence was identified for functioning outcomes for this comparison.

Economic evidence statements

- Evidence from 1 single UK study conducted alongside a RCT (N =424) suggests that MBCT is not cost-effective compared with maintenance antidepressant treatment in people who have had at least 3 previous depressive episodes and are in full or partial remission from their most recent episode following acute pharmacological treatment. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations. Evidence from another single UK study conducted alongside a RCT on the same population (N=123) is inconclusive regarding the cost effectiveness of MBCT compared with maintenance antidepressant treatment, as the outcome measure was not the QALY and interpretation of the results depends on the willingness to pay in order to avoid an additional relapse/recurrence of depression. Therefore the study, although it was conducted in the UK, is only partially applicable to the NICE decision-making context. The study is characterised by minor limitations.
- Evidence from the guideline economic analysis suggests that in people at medium risk of relapse whose depression has responded to pharmacological treatment, maintenance pharmacological treatment with the same drug they had received to treat their depressive episode is likely to be cost-effective compared with GP care and antidepressant tapering. However, after removing potential exaggeration of maintenance antidepressant treatment effects associated with the development of withdrawal syndrome, GP care with antidepressant drug tapering appears to be more cost-effective than maintenance antidepressant treatment. Moreover, when increasing the risk of side effects of antidepressants, GP care with antidepressant drug tapering also becomes more cost-effective than maintenance antidepressant treatment. The analysis is directly applicable to the NICE decision-making context and is characterised by minor limitations.
- Evidence from the guideline economic analysis suggests that in people at medium risk of relapse whose depression has responded to psychological treatment, maintenance individual CT/CBT comprising 10 hourly sessions is unlikely to be cost-effective, and GP care should be preferred instead. However, if the preventive effect of individual CT/CBT can be achieved with 4 hourly sessions, then maintenance individual CT/CBT is likely to be cost-effective provided that its relapse preventive effect lasts two years. The analysis is directly applicable to the NICE decision-making context and is characterised by minor limitations.
- Evidence from the guideline economic analysis suggests that in people at high risk of relapse whose depression has responded to pharmacological treatment, maintenance antidepressant treatment is likely to be the most cost-effective maintenance treatment option while GP care and antidepressant drug tapering is likely to be the least cost-effective option. High intensity psychological interventions, such as individual CT/CBT, group CT/CBT and MBCT, either alone (following antidepressant drug tapering) or combined with maintenance antidepressant treatment appear to be more cost-effective than GP care and antidepressant drug tapering, but less cost-effective than maintenance antidepressant treatment alone, due to their high intervention costs. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources

(with 1 therapist and 12 participants per group), then their combinations with maintenance antidepressant treatment become more cost-effective than antidepressant treatment alone, while MBCT with antidepressant drug tapering becomes the most cost-effective treatment option as long as its effect is retained over two years. Moreover, somewhat less applicable (to this population) and overall more limited evidence suggests that low intensity psychological interventions (cCBT with or without support and individual psychoeducation) combined with maintenance antidepressant treatment may also be more cost-effective than maintenance antidepressant treatment alone. If the risk of side effects from antidepressants is increased, then treatment options that include antidepressant drug tapering become more cost-effective than treatment options that included maintenance antidepressant treatment. The analysis is directly applicable to the NICE decision-making context and is characterised by minor limitations.

- Evidence from the guideline economic analysis suggests that in people at high risk of relapse whose depression has responded to psychological treatment, GP is marginally more cost-effective than both maintenance antidepressant treatment and individual CT/CBT. Additional evidence, which is somewhat less applicable to this population, suggests that low intensity psychological interventions (cCBT with support, based on more limited evidence, and individual psychoeducation) may be more cost-effective than GP care and that other psychological interventions (MBCT, group CT/CBT, cCBT without support) are likely to be less cost-effective than GP care but more cost-effective than no treatment. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (with 1 therapist and 12 participants per group), then they become more cost-effective than GP care, with individual CT/CBT becoming the most cost-effective option, even if its effect is expected to last 1 year.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the aim of this review was to identify interventions that reduced the rate of relapse, the critical outcome of interest to the committee was relapse.

As relapse in people with depression can have an important effect on quality of life and functioning, these 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 so would be less useful for making decisions.

The quality of the evidence

The quality of the evidence was assessed using GRADE. The committee noted generally that the evidence for psychological interventions was much longer-term than for pharmacological interventions, with some psychological trials providing follow-up data to 3 or 4 years, with no pharmacological interventions being followed up for longer than 2 years.

The evidence for psychological interventions to reduce risk of relapse ranged from high to very low quality, with a significant proportion of the evidence rated as moderate quality, and was generally from trials with fairly small numbers of participants and therefore frequently downgraded on the basis of imprecision. Lack of blinding of participants and intervention administrators introduced potential bias for the psychological interventions, however, many of the studies used blinded outcome assessment.

The evidence for pharmacological interventions was generally of low to very low quality, but came from trials with large numbers of participants. For most of the pharmacological trials

participants and intervention administrators were blinded, however, outcome assessors were non-blind, or blinding was unclear, in the majority of the studies.

The committee noted the lack of data from the primary care population and agreed to recommend further research to establish what the rate of relapse is in people with depression who present, and are treated, in primary and secondary care.

The committee also recognised that there was limited data comparing psychological interventions for relapse against each other and against antidepressants. They therefore recommended further research in this area.

Benefits and harms

The committee were aware that relapse prevention therapy usually involves continuation of treatment to help people stay well after their depression has remitted, but agreed that the decision to continue treatment and the nature of that treatment should be discussed and agreed jointly based on the individual's clinical needs and preferences.

The committee discussed that in people whose depression had remitted with antidepressant medication, and where this was being considered for relapse prevention, it was important to discuss the potential risks of long-term medication treatment, or conversely for people who did not wish to carry on with antidepressant medication in the longer term, the antidepressants should be stopped with appropriate tapering as necessary. The committee therefore made recommendations covering both of these situations. Based on their knowledge of the literature and their experience, the committee highlighted a number of risk factors that may increase the likelihood of relapse including a history of frequent or recent episodes of depression, severe depression, depression that has not responded completely to treatment with residual symptoms of depression, where there are unhelpful coping styles such as avoidance or rumination, or where there are physical health or social or environmental factors contributing to the depression. In particular, the committee noted that these social factors contributing to depression should be identified and addressed if possible. The committee noted that relapse prevention was likely to be more cost-effective in people at a higher risk of relapse.

The committee discussed that there are a number of possible scenarios – people whose depression has remitted on antidepressant medication and who wish to continue on medication; people whose depression has remitted on antidepressant medication and who do not wish to continue on medication, and people who have remitted on a psychological therapy or on a combination of medication and a psychological therapy. The committee therefore agreed they would need to frame their recommendations to take into account the therapy the person had already received, and to discuss with the person whether they wished to continue, change or augment their existing therapy to help prevent relapse.

For people whose depression remitted with antidepressant medication but who are considered at a higher risk of relapse, the committee agreed that continuing antidepressant medication should be offered as an option for relapse prevention. There was good evidence that SSRIs, SNRIs and TCAs were effective relapse prevention treatments, compared to pill placebo or no treatment, with follow-up of up to 2 years. However, the committee noted that it is important that antidepressants are maintained at an effective dose if side effects allow. The committee discussed that there may be some limitations with the data for continued antidepressants compared to pill placebo however, as abrupt antidepressant discontinuation and immediate switch to pill placebo increases risk of relapse and may induce withdrawal symptoms that register as increased depression scores, and so over-inflate the comparison of relapse rates achieved with continued antidepressants.

The committee were aware that some people whose depression has remitted with antidepressants and who are at a higher risk of relapse may wish to engage with a psychological intervention, either alone (so that they can stop their antidepressant

medication) or in combination with the antidepressant treatment. The majority of the evidence for psychological interventions for relapse prevention adopted a cognitive behavioural approach and studies showed a reduced rate of relapse with group CBT or MBCT compared to a number of comparators (no treatment, pill placebo, treatment as usual, attention placebo, psychoeducation), and benefits of CBT in combination with antidepressants compared to antidepressants alone, and compared to ECT plus antidepressants. There was also some evidence that these benefits were sustained in the longer term. Based on this evidence, the committee agreed to make particular reference to these interventions in their recommendations for psychological therapy for relapse prevention. The committee considered it important that for people starting group CBT or MBCT for relapse prevention the therapy should have an explicit focus on the development of relapse prevention skills, and they therefore agreed to include this in their recommendation.

For people whose depression remitted with a psychological intervention but who are considered at a higher risk of relapse, the committee agreed that a discussion should be had about continuing with psychological treatment. For people who wish to continue with a psychological intervention, the committee agreed that usually a brief intervention with adaptations that specifically target relapse prevention skills should be included, but as there was no evidence for these brief intervention the committee also made a research recommendation. The committee discussed that relapse prevention should include components such as a review of what vulnerabilities have been identified for the patient in terms of situations or behaviours that increase risk for depression; what actions and strategies and insights in therapy have been useful during the course of therapy (what has worked/helped), and marrying the active elements to possible future points of vulnerability, and making plans for continued practice/development and what to do for warning signs or stressful situations in the future.

For people whose depression remitted with a combination of antidepressant treatment and psychological therapy, the committee agreed that the considerations outlined above about continuing with antidepressants or psychological interventions should be discussed, and a shared decision should be made about continuing with either or both of these treatments based on the person's clinical needs and preferences.

The committee considered the clinical benefits of their recommendations would be a reduced risk of relapse, with potential harms including relapse if treatments proved to be ineffective, or people having side effects that may impact negatively upon quality of life or decrease engagement with their treatment, potentially in itself inducing a relapse.

The committee noted that, in both psychological and pharmacological trials, there appeared to be diminishing returns in terms of efficacy over the longer-term. The committee also discussed the issue of people remaining on antidepressant medication in the long-term, potentially with debilitating adverse effects. For these reasons they recommended regular follow-up for people continuing with antidepressant medication with no more than 6 months between reviews. Psychological therapies for relapse prevention usually followed a defined length of course. However, the committee advised that people should be followed up at the end of this treatment, and that the need for any further follow-up should be assessed at this time in order to reassess the risk of relapse over a longer time period.

Quality of life and functioning outcomes

The committee 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 some benefit associated with SSRIs, MBCT group, and computerised CBT with support, on quality of life. Given the sparsity of this evidence, and that it is broadly consistent with the findings observed for the critical

outcomes, the committee did not consider it necessary to make any changes to recommendations based on effects observed for quality of life and functioning outcomes.

Cost effectiveness and resource use

The guideline economic analysis showed that, in people at medium risk of relapse whose depression has responded to pharmacological treatment, maintenance pharmacological treatment is cost-effective compared with GP and antidepressant drug tapering. However, the committee was aware that the NMA that informed this analysis included trials on people who were already receiving antidepressant treatment, which compared maintenance antidepressant drug treatment versus antidepressant drug tapering occurring over a short period or abruptly. The committee advised that antidepressants are associated with withdrawal symptoms if they are discontinued abruptly, thus inflating the relative effect of maintenance antidepressant treatment versus abrupt discontinuation. This means that the overall treatment effect of maintenance antidepressant treatment versus antidepressant tapering is likely to have been exaggerated in the NMA and, consequently, in the economic analysis. The committee noted the results of sensitivity analysis that obtained the relative effect of drugs versus GP care and pill placebo from trials on people who were not already on antidepressants (and, therefore, the development of withdrawal syndrome was not relevant so that potential exaggeration of the relative effect was removed). Results of this sensitivity analysis suggested that GP care plus antidepressant drug tapering may be more cost-effective than maintenance antidepressant treatment. However, the committee acknowledged that the relative treatment effect came from a different population (people whose depression has responded to psychological treatment) and thus might not be directly applicable to the population of interest (people whose depression has responded to pharmacological treatment). The committee also noted that increasing the risk of antidepressant side effects that led to a reduction in HRQoL and additional GP contacts resulted in GP care plus antidepressant drug tapering becoming more cost-effective than maintenance antidepressant treatment.

In people at medium risk of relapse whose depression has responded to psychological treatment, the guideline economic analysis suggested that maintenance individual CT/CBT (comprising 10 hourly sessions) was unlikely to be cost-effective, and GP care or no treatment should be preferred instead. However, if the preventive effect of individual CT/CBT can be achieved with 4 hourly sessions (the committee noted that there was evidence from CBT as a maintenance intervention to support this) so that the intervention cost is greatly reduced, then maintenance individual CT/CBT is likely to be cost-effective provided that its relapse preventive effect lasts two years; otherwise GP care remains the most cost-effective treatment option in this population.

In people at high risk of relapse whose depression has responded to pharmacological treatment, maintenance antidepressant treatment appears to be the most cost-effective maintenance treatment option albeit with a rather low probability of being cost-effective (0.39). High intensity psychological interventions, such as individual CT/CBT, group CT/CBT and MBCT, either alone (following antidepressant drug tapering) or combined with maintenance antidepressant treatment, appear to be more cost-effective than GP care and antidepressant drug tapering, but less cost-effective than maintenance antidepressant treatment alone, due to their high intervention costs. However, if the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (with 1 therapist and 12 participants per group), then their combinations with maintenance antidepressant treatment become more cost-effective than antidepressant treatment alone, while MBCT with antidepressant drug tapering becomes the most cost-effective treatment option as long as its effect is retained over two years; otherwise group CT/CBT combined with maintenance antidepressant treatment becomes the most cost-effective option. The committee also noted that increasing the risk of antidepressant side effects that led to a reduction in HRQoL and additional GP contacts resulted in treatment options that included antidepressant drug

tapering becoming more cost-effective than treatment options that included maintenance antidepressant treatment. There was also some more limited and/or somewhat less applicable evidence to this population according to which low intensity interventions (cCBT, individual psychoeducation) combined with maintenance antidepressant treatment are cost-effective treatment options.

The committee noted that evidence from a RCT conducted in the UK suggested that MBCT was not cost-effective compared with maintenance antidepressant treatment in people at high risk of relapse (at least 3 previous depressive episodes) who were in full or partial remission from their most recent depressive episode following acute drug treatment. In this study, MBCT reduced the risk of relapse relative to maintenance antidepressant treatment, so it was more effective in this aspect, but also resulted in a lower number of QALYs, which was a rather unexpected finding, as a reduced risk of relapse is expected to be associated with longer periods of remission and, subsequently, a higher HRQoL. In contrast, the guideline economic model, which attached a higher utility value in the health state of remission than in the health state of relapse, found a better effect of MBCT compared with maintenance antidepressant treatment regarding relapse prevention, and, consequently, a higher gain in QALYs.

In another RCT conducted in the UK on the same population, evidence was inconclusive regarding the cost effectiveness of MBCT compared with maintenance antidepressant treatment, as the outcome measure was not the QALY and interpretation of the results required judgements on the value of preventing an additional relapse/recurrence of depression. Nevertheless, in this analysis MBCT was more effective in preventing relapses than maintenance antidepressant treatment, which is consistent with the findings of the guideline economic analysis.

In people at high risk of relapse whose depression has responded to psychological treatment, maintenance individual CT/CBT (comprising 10 individual hourly sessions) and maintenance antidepressant treatment were marginally less cost-effective than GP care. However, maintenance individual CT/CBT consisting of 4 hourly sessions was shown to be more cost-effective than GP care, provided that it can achieve the same effect as therapy comprising 10 individual sessions. MBCT and group CT/CBT also appeared to be cost-effective options versus no treatment for this population in the guideline secondary economic analysis, although less cost-effective than 4 individual hourly sessions of CT/CBT. The committee considered 10 sessions of psychological therapy to be unrealistically high as maintenance treatment, and expressed the view that 4 sessions are adequate to maintain a relapse preventive effect, hence, 4 sessions were tested in a sensitivity analysis. There was also some more limited and/or less applicable evidence to this population according to which low intensity interventions (cCBT, individual psychoeducation) are cost-effective treatment options.

The committee noted that results across analyses were characterised by considerable uncertainty, indicated by the wide 95% CI around the mean rankings of interventions in each analysis.

The guideline economic modelling considered predominantly people treated in primary care; however, the committee noted that the vast majority of clinical evidence was derived from secondary care settings, due to lack of relevant evidence derived from primary care settings. The committee agreed that this may suggest that the populations in the trials had a higher level of severity of depression (and might potentially be at a higher risk of relapse) compared with people treated in primary care, or may simply reflect clinical practice patterns at the time and in the countries in which the RCTs were conducted. The committee considered it reasonable and essential to extrapolate the secondary care evidence to the primary care population when formulating recommendations due to a lack of more relevant evidence. In doing so, the committee expressed the view that the relative effects of treatments derived

from studies conducted in secondary care settings should not be considerably different from relative treatment effects in primary care.

The committee noted that the definition of 'medium' and 'high' risk of relapse in the economic analysis was based exclusively on the number of previous depressive episodes experienced by the study population (1-2 previous episodes and 3+ previous episodes, respectively) and was made for practical reasons, in order to populate the economic model. However, it was acknowledged that the risk of future relapse is determined by a combination of several other factors, including the frequency of previous depressive episodes and how recently these were experienced; the presence of residual symptoms and unhelpful coping styles such as avoidance and rumination; the severity of previous episodes and the presence of functional impairment and risk-to-self during the episodes; the effectiveness of previous interventions for treatment and relapse prevention; the presence of other chronic physical health or mental health problems and the presence of personal, social and environmental factors. Therefore, the population at a 'higher' risk of relapse in clinical practice may include people with 1-2 previous episodes (considered as being at 'medium' risk in the economic analysis) if other factors that increase the risk of relapse are present.

The committee reviewed the results of the guideline economic analysis and noted that in people at medium risk of relapse, defined as having had 1-2 previous depressive episodes, relapse preventive interventions might not be as cost-effective as in people at higher risk of relapse compared with GP care (and drug tapering, if relevant). However, as expected, the cost effectiveness of relapse preventive interventions improves as the risk for future relapses increases, as there is more scope for gains in HRQoL if relapses are prevented. A range of relapse preventive interventions were cost-effective compared with GP care and/or no treatment in people whose depression had responded to treatment and who were at high risk of relapse, defined as having had at least 3 previous depressive episodes. The committee noted the uncertainty around the results of the analysis, reflected in wide 95% CI around mean rankings, and decided to recommend a range of interventions for each population.

Therefore the committee decided to recommend interventions that were cost-effective relative to GP care and/or no treatment, as identified in the guideline economic analysis, for people at a 'higher' risk of relapse, which should be estimated after considering all the factors affecting the risk of relapse, and not based solely on the number of previous depressive episodes. The committee did not make recommendations specifically for people at 'low' or even 'medium' risk of relapse, as relapse preventive interventions are less likely to be cost-effective in this population and, for maintenance antidepressant treatment, harms (side effects) could potentially outweigh benefits (as there is limited scope for prevention of new depressive episodes in a population with a low baseline risk of relapse).

For people who had already responded to psychological therapy, the committee considered 10 further sessions of the same psychological therapy as maintenance treatment to be unrealistically high, as this number reflected a full course of treatment. Nevertheless, the committee agreed that it is clinically sensible to offer further sessions of the same intervention and expressed the view that this group of people would benefit from receiving a shorter number of sessions with a focus on a relapse prevention component, to further build their therapeutic relationship and consolidation. The committee agreed that offering 4 additional sessions of the psychological intervention that had led to remission, with a focus on a relapse prevention component, should usually be adequate for this population and represents a cost-effective use of resources according to the guideline economic analysis. The committee made recommendations on the minimum or usual number of sessions of psychological interventions to be offered, as they agreed that more sessions might be needed according to individual needs and/or programme manuals.

Other factors the committee took into account

The committee discussed the importance of explaining that a relapse was a possibility. The lay members on the committee explained that it can be quite empowering to understand that depression can be a recurrent condition, and that a relapse does not indicate any kind of failure on the part of the person with depression, nor on the initial treatment or work undertaken with a therapist. Therefore, the committee agreed that it would be helpful to recommend that the risk of relapse is discussed at an appropriate time and to highlight the importance of people seeking help as soon as possible if the symptoms of depression return, or worsen in the case of residual symptoms.

The committee discussed that the previous 2009 version of the guideline had included a research recommendation relating to the use of maintenance ECT for relapse prevention and that although the PRIDE study of continuation ECT in depression in older people (Kellner 2016) had been included in this review, the evidence did not support recommendations on the use of ECT for relapse prevention in general, and the committee therefore carried forward the research recommendation, as they agreed that more research into the use of maintenance ECT was necessary,

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.1 to 1.8.12 and research recommendations in the NICE guideline.

References

Alexopoulos 2000

Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, Sirey JA, Hull J. (2000) Executive dysfunction and long-term outcomes of geriatric depression. Archives of General Psychiatry 57(3): 285-290.

Bauer 2000

Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Muller-Oerlinghausen B (2000) Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. American Journal of Psychiatry 157(9): 1429-1435.

Biesheuvel-Leliefeld 2017

Biesheuvel-Leliefeld KEM, Dijkstra-Kersten SMA, Van Schaik DJF, Van Marwijk HWJ, Smit F, Van Der Horst HE, Bockting CLH (2017) Effectiveness of supported self-help in recurrent depression: a randomized controlled trial in primary care. Psychotherapy and Psychosomatics 86(4): 220-230.

Bockting 2005/Bockting 2015

Bockting CL, Schene AH, Spinhoven P, Koeter MW, Wouters LF, Huyser J, Kamphuis JH (2005) Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. Journal of Consulting and Clinical Psychology 73(4): 647.

Bockting CL, Smid NH, Koeter MW, Spinhoven P, Beck AT, Schene AH (2015) Enduring effects of preventive cognitive therapy in adults remitted from recurrent depression: a 10 year follow-up of a randomized controlled trial. Journal of Affective Disorders 185: 188-194.

Bockting 2018

Bockting CL, Klein NS, Elgersma HJ, van Rijsbergen GD, Slofstra C, Ormel J, Buskens E, Dekker J, de Jong PJ, Nolen WA, Schene AH (2018) Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. The Lancet Psychiatry 5(5): 401-410.

Bondolfi 2010

Bondolfi G, Jermann F, Van der Linden M, Gex-Fabry M, Bizzini L, Rouget BW, Myers-Arrazola L, Gonzalez C, Segal Z, Aubry JM, Bertschy G (2010) Depression relapse prophylaxis with mindfulness-based cognitive therapy: replication and extension in the Swiss health care system. Journal of Affective Disorders 122(3): 224-231.

Brakemeier 2014

Brakemeier EL, Merkl A, Wilbertz G, Quante A, Regen F, Bührsch N, van Hall F, Kischkel E, Danker-Hopfe H, Anghelescu I, Heuser I (2014) Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. Biological Psychiatry 76(3): 194-202.

Brunner 2014

Brunner E, Tohen M, Osuntokun O, Landry J, Thase ME (2014) Efficacy and safety of olanzapine/fluoxetine combination vs fluoxetine monotherapy following successful combination therapy of treatment-resistant major depressive disorder. Neuropsychopharmacology 39(11): 2549.

Coppen 1978

Coppen A, Ghose K, Montgomery S, Rama R, V, Bailey J, Jorgensen A (1978) Continuation therapy with amitriptyline in depression. British Journal of Psychiatry 133: 28-33.

de Jonge 2019

de Jonge M, Bockting CL, Kikkert MJ, van Dijk MK, van Schaik DJ, Peen J, Hollon SD, Dekker JJ (2019) Preventive cognitive therapy versus care as usual in cognitive behavioral therapy responders: a randomized controlled trial. Journal of Consulting and Clinical Psychology 87(6): 521.

Dobson 2008

Dobson KS, Hollon SD, Dimidjian S, Schmaling KB, Kohlenberg RJ, Gallop RJ, Rizvi SL, Gollan JK, Dunner DL, Jacobson NS (2008) Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. Journal of Consulting and Clinical Psychology 76(3): 468-477.

Doogan 1992

Doogan DP, Caillard V (1992) Sertraline in the prevention of depression. British Journal of Psychiatry 160: 217-222.

Elices 2017

Elices M, Soler J, Feliu-Soler A, Carmona C, Tiana T, Pascual JC, García-Palacios A, Álvarez E (2017) Combining emotion regulation and mindfulness skills for preventing depression relapse: a randomized-controlled study. Borderline Personality Disorder and Emotion Dysregulation 4(1): 1-9.

Farb 2018

Farb N, Anderson A, Ravindran A, Hawley L, Irving J, Mancuso E, Gulamani T, Williams G, Ferguson A, Segal ZV (2018) Prevention of relapse/recurrence in major depressive disorder with either mindfulness-based cognitive therapy or cognitive therapy. Journal of Consulting and Clinical Psychology 86(2): 200.

Fava 1994/1996/1998c

Fava GA, Grandi S, Zielezny M, Canestrari R (1994) Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. American Journal of Psychiatry 9: 1295–1299.

Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R (1996) Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. American Journal of Psychiatry 153: 945-947.

Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA (1998) Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. American Journal of Psychiatry 155: 1443-1445.

Fava 1998a/2004

Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P (1998) Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Archives of General Psychiatry 55: 816-820.

Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S (2004) Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. American Journal of Psychiatry 161: 1872-1876.

Franchini 1997/2000a

Franchini L, Gasperini M, Perez J, Smeraldi E (1997) A double-blind study of long-term treatment with sertraline or fluvoxamine for prevention of highly recurrent unipolar depression. Journal of Clinical Psychiatry 58(3): 104-107.

Franchini L, Gasperini M, Zanardi R, Smeraldi E (2000) Four-year follow-up study of sertraline and fluvoxamine in long-term treatment of unipolar subjects with high recurrence rate. Journal of Affective Disorders 58(3): 233-236.

Franchini 1998

Franchini L, Gasperini M, Perez J, Smeraldi E, Zanardi R (1998) Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. Journal of Clinical Psychiatry 59: 229–232.

Frank 1990

Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ (1990) Three-year outcomes for maintenance therapies in recurrent depression. Archives of General Psychiatry 47(12): 1093-1099.

Frank 2007

Frank E, Kupfer DJ, Buysse DJ, Swartz HA, Pilkonis PA, Houck PR, Rucci P, Novick DM, Grochocinski VJ, Stapf DM (2007) Randomized trial of weekly, twice-monthly, and monthly interpersonal psychotherapy as maintenance treatment for women with recurrent depression. American Journal of Psychiatry 164(5): 761-767.

Gilaberte 2001

Gilaberte I (2001) Fluoxetine in the prevention of depressive recurrences: a double-blind study. Journal of Clinical Psychopharmacology 21(4): 417-24.

Glen 1984

Glen AI, Johnson AL, Shepherd M (1984) Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized, double-blind, controlled trial. Psychological Medicine 14(1): 37-50.

Godfrin 2010

Godfrin KA, Heeringen C (2010) The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: a randomized controlled study. Behaviour Research and Therapy 48(8): 738-746.

Gorwood 2007

Gorwood P, Weiller E, Lemming O, Katona C (2007) Escitalopram prevents relapse in older patients with major depressive disorder. American Journal of Geriatric Psychiatry 15: 581-593.

Greil 1996

Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J (1996) Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. Journal of Affective Disorders 40(3): 179-190.

Hochstrasser 2001

Hochstrasser B, Isaksen PM, Koponen H, Lauritzen L, Mahnert FA, Rouillon F, Wade AG, Andersen M, Pedersen SF, Swart JC, Nil R (2001) Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. British Journal of Psychiatry 178: 304-310.

Holländare 2011/2013

Holländare F, Johnsson S, Randestad M, Tillfors M, Carlbring P, Andersson G, Engström I (2011) Randomized trial of Internet-based relapse prevention for partially remitted depression. Acta Psychiatrica Scandinavica 124(4): 285-294.

Holländare F, Anthony SA, Randestad M, Tillfors M, Carlbring P, Andersson G, Engström I (2013) Two-year outcome of internet-based relapse prevention for partially remitted depression. Behaviour Research and Therapy 51(11): 719-722.

Huijbers 2015

Huijbers MJ, Spinhoven P, Spijker J, Ruhé HG, van Schaik DJ, van Oppen P, Nolen WA, Ormel J, Kuyken W, van der Wilt GJ, Blom MB (2015) Adding mindfulness-based cognitive therapy to maintenance antidepressant medication for prevention of relapse/recurrence in major depressive disorder: randomised controlled trial. Journal of Affective Disorders 187: 54-61.

Huijbers 2016a

Huijbers MJ, Spinhoven P, Spijker J, Ruhe HG, van Schaik DJ, van Oppen P, Nolen WA, Ormel J, Kuyken W, van der Wilt GJ, Blom MB (2016) Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: randomised controlled non-inferiority trial. British Journal of Psychiatry 208(4): 366-373.

Jarrett 2001

Jarrett RB, Kraft D, Doyle J, Foster BM, Eaves GG, Silver PC (2001) Preventing recurrent depression using cognitive therapy with and without a continuation phase. Archives of General Psychiatry 4: 381–388.

Jarrett 2013

Jarrett RB, Minhajuddin A, Gershenfeld H, Friedman ES, Thase ME (2013) Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. JAMA Psychiatry 70(11): 1152-1160.

Kamijima 2006

Kamijima K, Burt T, Cohen G, Arano I, Hamasaki T (2006) A placebo-controlled, randomized withdrawal study of sertraline for major depressive disorder in Japan. International Clinical Psychopharmacology 21(1): 1-9.

Kellner 2016/McCall 2018

Kellner CH, Husain MM, Knapp RG, McCall WV, Petrides G, Rudorfer MV, Young RC, Sampson S, McClintock SM, Mueller M, Prudic J (2016) A novel strategy for continuation ECT in geriatric depression: phase 2 of the PRIDE study. American Journal of Psychiatry 173(11): 1110-1118.

McCall WV, Lisanby SH, Rosenquist PB, Dooley M, Husain MM, Knapp RG, Petrides G, Rudorfer MV, Young RC, McClintock SM, Mueller M (2018) Effects of continuation electroconvulsive therapy on quality of life in elderly depressed patients: a randomized clinical trial. Journal of Psychiatric Research 97: 65-69.

Klein 2018a

Klein NS, Kok GD, Burger H, Van Valen E, Riper H, Cuijpers P, Dekker J, Smit F, Van Der Heiden C, Bockting CL (2018) No sustainable effects of an Internet-based relapse prevention program over 24 months in recurrent depression: primary outcomes of a randomized controlled trial. Psychotherapy and Psychosomatics 87(1): 55-57.

Klerman 1974

Klerman GL, DiMascio A, Weissman MM, Prusoff B, Paykel ES (1974) Treatment of depressions by drugs and psychotherapy. American Journal of Psychiatry 131(2): 186-191.

Klysner 2002

Klysner R, Bent-Hansen J, Hansen HL, Lunde M, Pleidrup E, Poulsen DL, Andersen M, Petersen HE (2002) Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. British Journal of Psychiatry 181: 29-35.

Kocsis 2007

Kocsis JH, Thase ME, Trivedi MH, Shelton RC, Kornstein SG, Nemeroff CB, Friedman ES, Gelenberg AJ, Dunner DL, Hirschfeld RM, Rothschild AJ (2007) Prevention of recurrent episodes of depression with venlafaxine ER in a 1-year maintenance phase from the PREVENT Study. Journal of Clinical Psychiatry 68(7): 1014-1023.

Kornstein 2006

Kornstein S, Bose A, Li D, Saikali K, Gandhi C (2006) Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. Journal of Clinical Psychiatry 67: 1767-1775.

Kuyken 2008

Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD (2008) Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. Journal of Consulting and Clinical Psychology 76(6): 966-978.

Kuyken 2015a/2015b

Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, Lewis G, Watkins E, Brejcha C, Cardy J, Causley A (2015a) Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. Lancet 386: 63-73.

Kuyken W, Hayes R, Barrett B, Byng R, Dalgleish T, Kessler D, Lewis G, Watkins E, Morant N, Taylor RS, Byford S (2015b) The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: Results of a randomised controlled trial (The PREVENT study). Health Technology Assessment 19: 1-123.

Lepine 2004

Lepine J-P, Caillard V, Bisserbe J-C, Troy S, Hotton J-M, Boyer P (2004) A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. American Journal of Psychiatry 161: 836–842.

Liebowitz 2010

Liebowitz M, Lam RW, Lepola U, Datto C, Sweitzer D, Eriksson H (2010) Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. Depression and Anxiety 27(10): 964-976.

Ma 2004

Ma SH, Teasdale JD (2004) Mindfulness-based cognitive therapy for depression: Replication and exploration of differential relapse prevention effects. Journal of Consulting and Clinical Psychology 1: 31–40.

Martiny 2015

Martiny K, Larsen ER, Licht RW, Nielsen CT, Damkier P, Refsgaard E, Lunde M, Straasø B, Christensen EM, Lolk A, Holmskov J (2015) Relapse prevention in major depressive disorder after successful acute electroconvulsive treatment: a 6-month double-blind comparison of three fixed dosages of escitalopram and a fixed dose of nortriptyline–lessons from a failed randomised trial of the Danish University Antidepressant Group (DUAG-7). Pharmacopsychiatry 48(07): 274-278.

Meadows 2014

Meadows GN, Shawyer F, Enticott JC, Graham AL, Judd F, Martin PR, Piterman L, Segal Z (2014) Mindfulness-based cognitive therapy for recurrent depression: a translational research study with 2-year follow-up. Australian & New Zealand Journal of Psychiatry 48(8): 743-755.

Montgomery 1988

Montgomery SA, Dufour H, Brion S, Gailledreau J, Laqueille X, Ferrey G, Moron P, Parant-Lucena N, Singer L, Danion JM (1988) The prophylactic efficacy of fluoxetine in unipolar depression. British Journal of Psychiatry Supplementum(3): 69-76.

Montgomery 1993a

Montgomery SA, Dunbar G (1993) Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. International Clinical Psychopharmacology 8(3): 189-195.

Montgomery 1993b

Montgomery SA, Rasmussen JG, Tanghoj P (1993) A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. International Clinical Psychopharmacology 8(3): 181-188.

Montgomery 2004

Montgomery S, Entsuah R, Hackett D, Kunz N, Rudolph R (2004) Venlafaxine versus placebo in the preventative treatment of recurrent major depression. Journal of Clinical Psychiatry 65: 328-336.

Old Age Depression Interest Group 1993

Old Age Depression Interest Group (1993) How long should the elderly take antidepressants? A double-blind placebo-controlled study of continuation/prophylaxis therapy with dothiepin. British Journal of Psychiatry 162: 175-182.

Perahia 2006

Perahia DG, Gilaberte I, Wang F, Wiltse CG, Huckins SA, Clemens JW, Montgomery SA, Montejo AL, Detke MJ (2006) Duloxetine in the prevention of relapse of major depressive disorder: double-blind placebo-controlled study. British Journal of Psychiatry 188(4): 346-353.

Perahia 2009

Perahia DG, Maina G, Thase ME, Spann ME, Wang F, Walker DJ, Detke MJ (2009) Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. Journal of Clinical Psychiatry 70(5): 706-716.

Prien 1984

Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Archives of General Psychiatry 41(11): 1096-1104.

Rapaport 2004

Rapaport MH, Bose A, Zheng H (2004) Escitalopram continuation treatment prevents relapse of depressive episodes. Journal of Clinical Psychiatry 65(1):44-49.

Rapaport 2006

Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, Turkoz I, Lasser RA, Loescher A, Bouhours P, Dunbar F (2006) Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 31(11): 2505-2513.

Rickels 2010

Rickels K, Montgomery SA, Tourian KA, Guelfi JD, Pitrosky B, Padmanabhan SK, Germain JM, Leurent C, Brisard C (2010) Desvenlafaxine for the prevention of relapse in major

depressive disorder: results of a randomized trial. Journal of Clinical Psychopharmacology 30(1): 18-24.

Robert 1995

Robert PH, Montgomery SA (1995) Citalopram in doses of 20–60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. International clinical psychopharmacology 10:Suppl-35.

Rosenthal 2013

Rosenthal JZ, Boyer P, Vialet C, Hwang E, Tourian KA (2013) Efficacy and safety of desvenlafaxine 50 mg/d for prevention of relapse in major depressive disorder: a randomized controlled trial. Journal of Clinical Psychiatry 74(2): 158-166.

Schmidt 2000

Schmidt ME, Fava M, Robinson JM, Judge R (2000) The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. Journal of Clinical Psychiatry 61(11): 851-857.

Segal 2020

Segal ZV, Dimidjian S, Beck A, Boggs JM, Vanderkruik R, Metcalf CA, Gallop R, Felder JN, Levy J (2020) Outcomes of online mindfulness-based cognitive therapy for patients with residual depressive symptoms: a randomized clinical trial. JAMA Psychiatry 77(6): 563-573.

Shallcross 2015/2018

Shallcross AJ, Gross JJ, Visvanathan PD, Kumar N, Palfrey A, Ford BQ, Dimidjian S, Shirk S, Holm-Denoma J, Goode KM, Cox E (2015) Relapse prevention in major depressive disorder: Mindfulness-based cognitive therapy versus an active control condition. Journal of Consulting and Clinical Psychology 83(5): 964-975.

Shallcross AJ, Willroth EC, Fisher A, Dimidjian S, Gross JJ, Visvanathan PD, Mauss IB (2018) Relapse/recurrence prevention in major depressive disorder: 26-month follow-up of mindfulness-based cognitive therapy versus an active control. Behavior Therapy 49(5): 836-849.

Simon 2004

Simon J, Aguiar L, Kunz N, Lei D (2004) Extended-release venlafaxine in relapse prevention for patients with major depressive disorder, Journal of Psychiatric Research 38: 249-257.

Stangier 2013

Stangier U, Hilling C, Heidenreich T, Risch AK, Barocka A, Schlösser R, Kronfeld K, Ruckes C, Berger H, Röschke J, Weck F (2013) Maintenance cognitive-behavioral therapy and manualized psychoeducation in the treatment of recurrent depression: a multicenter prospective randomized controlled trial. American Journal of Psychiatry 170(6): 624-632.

Stein 1980

Stein MK, Rickels K, Weise CC (1980) Maintenance therapy with amitriptyline: a controlled trial. American Journal of Psychiatry 137(3): 370-371.

Teasdale 2000

Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA (2000) Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. Journal of Consulting and Clinical Psychology 4: 615–623.

Terra 1998

Terra JL, Montgomery SA (1998) Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. International Clinical Psychopharmacology 13(2): 55-62.

Wilkinson 2002

Wilkinson D, Holmes C, Woolford J, Stammers S, North J (2002) Prophylactic therapy with lithium in elderly patients with unipolar major depression. International Journal of Geriatric Psychiatry 17(7): 619-622.

Wilkinson 2009

Wilkinson P, Alder N, Juszczak E, Matthews H, Merritt C, Montgomery H, Howard R, Macdonald A, Jacoby R (2009) A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. International Journal of Geriatric Psychiatry 24(1): 68-75.

Williams 2014

Williams JM, Crane C, Barnhofer T, Brennan K, Duggan DS, Fennell MJ, Hackmann A, Krusche A, Muse K, Von Rohr IR, Shah D (2014) Mindfulness-based cognitive therapy for preventing relapse in recurrent depression: a randomized dismantling trial. Journal of Consulting and Clinical Psychology 82(2): 275.

Wilson 2003

Wilson KCM, Mottram PG, Ashworth L, Abou-Saleh MT (2003) Older community residents with depression: long term treatment with sertraline. Randomised, double-blind, placebo-controlled study. British Journal of Psychiatry 182: 492-497.

Appendices

Appendix A – Review protocol

Review protocol for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Table 36: Review protocol

Field (based on PRISMA-P)	Content
Review question	For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?
Type of review question	Intervention review
Objective of the review	To identify the most effective interventions for preventing relapse of depression in adults who have responded fully or partially to treatment
Population	• Adults whose depression has responded to treatment according to DSM, ICD or similar criteria, or depressive symptoms as indicated by depression scale score, who are randomised to relapse prevention intervention whilst in full or partial remission. If some, but not all, of a study's participants are eligible for the review, for instance, mixed anxiety and depression diagnoses, 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 of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) • 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 where more than 20% of the population have chronic depression • 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
	• Trials where participants are not randomised to a relapse prevention intervention following response to initial treatment e.g. continuation trials
Intervention	Interventions will 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, and mindfulness-based cognitive therapy [MBCT]) • 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) • Self-help with or without support (including cognitive bibliotherapy with or without support, computerised CBT [CCBT] with or without support, computerised psychodynamic therapy with or without support) • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) **Pharmacological interventions** • SSRIs (including paroxetine, sertraline, fluoxetine, escitalopram, citalopram, fluvoxamine) • TCAs (including amitriptyline, dothiepin, imipramine, nortriptyline) • SNRIs (including duloxetine, venlafaxine, desvenlafaxine) • Mirtazapine • Antipsychotics (including olanzapine, risperidone, quetiapine)[1] • Lithium **Physical interventions** • Acupuncture • Exercise • Yoga

Field (based on PRISMA-P)	Content
	• ECT • Light therapy (for depression, not SAD) **Psychosocial interventions** • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR])
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	**Critical outcomes:** • Relapse (the number of participants who relapsed) **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-BREF], 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).

Field (based on PRISMA-P)	Content
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 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** Pairwise comparisons (meta-analyses using random-effects models) will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible. Network meta-analysis (NMA) in a Bayesian framework will also be used to synthesise the data for all eligible interventions (which are connected to the network). The NMA will be restricted to the critical outcome of relapse. A binomial likelihood and cloglog link linear model will be used (Dias et al., 2011) to allow estimation of hazard ratios between all pairs of interventions. Where possible, different NMAs will be considered for different populations according to their risk of relapse (medium or high, defined according to the number of previous episodes) and the type of previous acute treatment they received (pharmacological, psychological or combined).

Field (based on PRISMA-P)	Content
	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 I2>50%, twice if I2 >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)	Where possible, the following subgroup analyses will be considered: • Type of previous acute treatment received • Risk of relapse (number of previous episodes) • Remission status (participants in partial or full remission vs full remission only) • Abrupt vs slow switch to placebo
Data management (software)	Endnote was used to sift through the references identified by the search Data was extracted into a standardized template in Microsoft Excel 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	One good quality systematic review for non-pharmacological interventions for relapse prevention was identified (Clarke et al., 2015) which was used a source of studies for the review of psychological interventions. 1Note that antipsychotics are not licensed for use in depression (with the exception of quetiapine which is licensed for use as an adjunctive treatment of major depressive episodes with major depressive disorder, but not as monotherapy) Dias, S., Welton, N.J., Sutton, A.J., & Ades, A.E. (2011, last updated September 2016). NICE DSU Technical Support Document 2: A Generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials.

Field (based on PRISMA-P)	Content
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
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

Field (based on PRISMA-P)	Content
PROSPERO registration number	CRD42019152079

(C)CBT: (computerised) cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: Diagnostic and statistical manual; ECT: electronconvulsive 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; ICD: International classification of diseases; IIP: inventory of interpersonal problems; IPT: interpersonal therapy; ISI: insomnia severity index; ITT: intention to treat; N: number; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; 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; SAD: seasonal affective disorder; SAS: social adjustment scale; SDS: Sheehan disability scale; SF-12/SF-36: short form 12/36; SMD: standardised mean difference; SNRI: serotonin-noradrenaline reuptake inhibitor; SOFAS: social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic 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 whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Clinical search

Database(s): Embase 1974 to 2019 Week 20, Emcare 1995 to present, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 21, 2019, PsycINFO 1806 to May Week 2 2019

Searched: 21/05/2019

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
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 psychoeducation/ or self help/) 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 mindfulness/ or exp problem solving/ or psychoeducation/ or exp self-help techniques/) use psyh
10	((behavio* or abreact* or act* out* or age regression or assertive or autogenic or experiential) adj2 (activation or catharsis or conditioning or intervention* or modification* or therap* or training or treatment*)).tw.
11	((cognitive adj2 (behavior* or therap*)) or (CBT* 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 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	exp serotonin uptake inhibitor/ use oemezd,emcr
17	exp Serotonin Uptake Inhibitors/ use ppez
18	exp serotonin reuptake inhibitors/ use psyh
19	exp tricyclic antidepressant agent/ use oemezd,emcr
20	exp Antidepressive Agents, Tricyclic/ use ppez
21	exp tricyclic antidepressant drugs/ use psyh
22	exp neuroleptic agent/ use oemezd,emcr
23	exp Antipsychotic Agents/ use ppez
24	exp neuroleptic drugs/ use psyh
25	amitriptyline/ or citalopram/ or dosulepin/ or escitalopram/ or fluoxetine/ or imipramine/ or lithium/ or mirtazapine/ or nortriptyline/ or olanzapine/ or paroxetine/ or quetiapine/ or risperidone/ or sertraline/
26	(amitryptylin* or citalopram or dosulepin* or dothiepin* or escitalopram or fluoxetin* or imipramin* or lithium or mirtazapin* or nortriptylin* or olanzapine* or paroxetin* or quetiapin* or risperidone* or sertralin* or SSRI* or TCA* or antipsychotic* or anti-psychotic* or (serotonin adj2 inhibitor*)).tw.

#	Searches
27	or/16-26
28	acupuncture/
29	acupuncture.tw.
30	28 or 29
31	electroconvulsive therapy/ use oemezd,emcr,ppez
32	electroconvulsive shock therapy/ use psyh
33	(ECT or ((electroconvulsive or electro-convulsive) adj2 (therap* or treatment*)) or electroshock or (shock adj (therapy or treatment))).tw.
34	or/31-33
35	15 or 27 or 30 or 34
36	6 and 35
37	(relapse/ or aftercare/ or recurrent disease/ or maintenance therapy/) use oemezd,emcr
38	(Aftercare/ or exp Recurrence/ or Secondary Prevention/ or Tertiary Prevention/) use ppez
39	(relapse prevention/ or Aftercare/ or Maintenance Therapy/ or Preventive Medicine/ or Prevention/) use psyh
40	(relaps* or recur*).ti.
41	((relaps* adj2 prevent*) or (time adj2 relaps*)).tw.
42	or/37-41
43	((maintain* or continu*or prophyla*) adj2 (drug* or intervention* or medicat* or therap* or treatment*)).tw.
44	(symptom* adj2 (exacerbat* or flar* or prevent* or recrudescen* or recur* or relaps*)).tw.
45	(recovered or remission or remit* or respond* or "recent* episode" or "recent* depress*" or "previous* depress*" or "previous episode*").tw.
46	or/43-45
47	42 and 46
48	36 and 47
49	Letter/ use ppez
50	letter.pt. or letter/ use oemezd
51	note.pt.
52	editorial.pt.
53	Editorial/ use ppez
54	News/ use ppez
55	exp Historical Article/ use ppez
56	Anecdotes as Topic/ use ppez
57	Comment/ use ppez
58	Case Report/
59	case study/ use oemezd
60	(letter or comment*).ti.
61	or/49-60
62	randomized controlled trial/
63	random*.ti,ab.
64	62 or 63
65	61 not 64
66	(animals/ not humans/) use ppez
67	(animal/ not human/) use oemezd
68	nonhuman/ use oemezd
69	exp animals/ use psyh
70	"primates (nonhuman)"/ use psyh
71	exp Animals, Laboratory/ use ppez
72	exp Animal Experimentation/ use ppez
73	exp animal experiment/ use oemezd
74	exp experimental animal/ use oemezd
75	exp Models, Animal/ use ppez
76	animal model/ use oemezd
77	animal models/ use psyh
78	animal research/ use psyh
79	exp Rodentia/ use ppez
80	exp rodent/ use oemezd
81	exp rodents/ use psyh
82	(rat or rats or mouse or mice).ti.
83	or/65-82
84	48 not 83
85	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.
86	85 use ppez
87	(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.
88	87 use ppez
89	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.

#	Searches
90	89 use oemezd
91	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
92	91 use psyh
93	86 or 88
94	90 or 92 or 93
95	Meta-Analysis/
96	exp Meta-Analysis as Topic/
97	systematic review/
98	meta-analysis/
99	(meta analy* or metanaly* or metaanaly*).ti,ab.
100	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
101	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
102	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104	(search* adj4 literature).ab.
105	(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.
106	cochrane.jw.
107	((pool* or combined) adj2 (data or trials or studies or results)).ab.
108	(or/95-97,99,101-106) use ppez
109	(or/97-100,102-107) use oemezd
110	(or/95,99,101-106) use psyh
111	or/108-110
112	network meta-analysis/
113	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
114	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
115	or/112-114
116	or/94,111,115
117	84 and 116
118	limit 117 to english language

The Cochrane Library, issue 5 of 12, May 2019

Searched: 21/05/2019

Search updated: 04/06/2021

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
#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	MeSH descriptor: [Secondary Prevention] this term only
#11	MeSH descriptor: [Aftercare] this term only
#12	MeSH descriptor: [Recurrence] explode all trees
#13	MeSH descriptor: [Tertiary Prevention] this term only
#14	(relaps* or recur*):ti
#15	((relaps* near/2 prevent*) or (time near/2 relaps*)):ti,ab
#16	{or #10-#15}
#17	((maintain* or continu*or prophyla*) near/2 (drug* or intervention* or medicat* or therap* or treatment*)):ti,ab
#18	(symptom* next/2 (exacerbat* or flar* or prevent* or recrudescen* or recur* or relaps*)):ti,ab
#19	(recovered or remission or remit* or respond* or "recent* episode" or "recent* depress*" or "previous* depress*" or "previous episode*"):ti,ab
#20	{or #10-#18}
#21	#16 and #20
#22	#9 and #21 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/

#	Searches
53	exp economic evaluation/
54	exp health care cost/
55	exp fee/
56	budget/
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*))
#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 (multiattribute* 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

#	Query	Limiters/Expanders
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 melancholic* 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

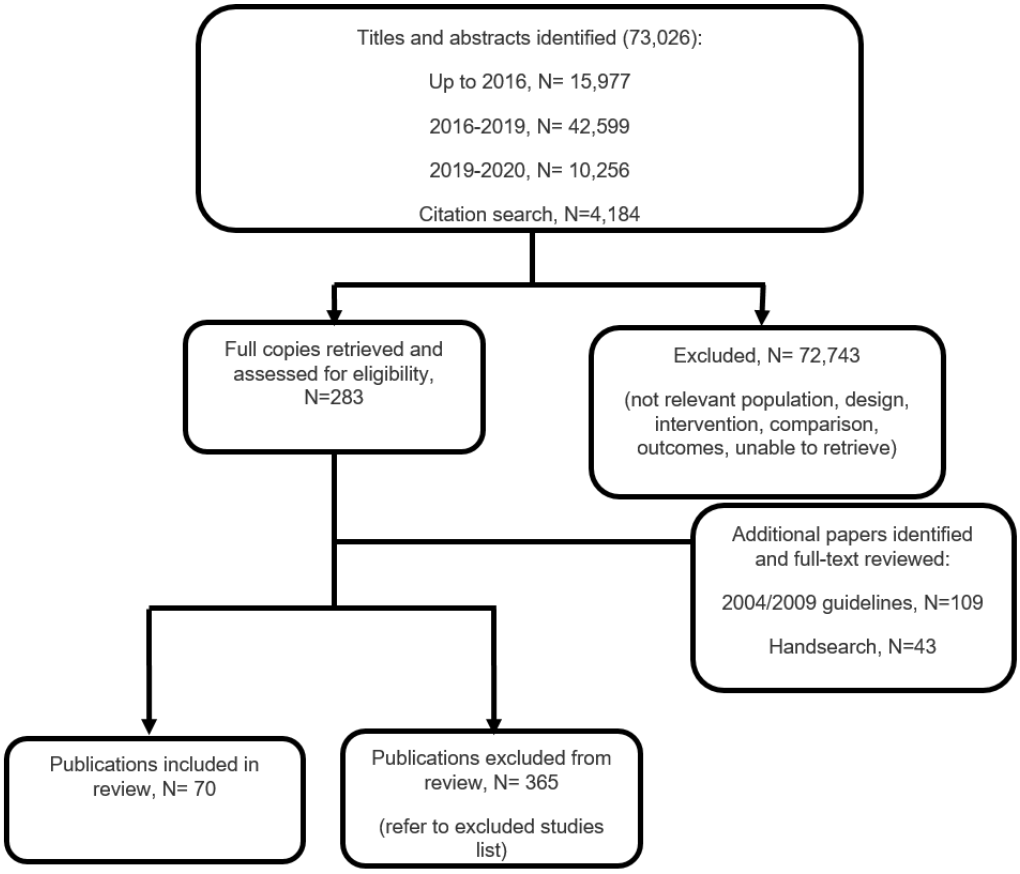
Date of search: 04/11/2021

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
#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 whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Please refer to the clinical evidence tables in supplement C – Clinical evidence tables for Evidence Review C Relapse prevention

Appendix E – Forest plots

Forest plots for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Comparison 1: Cognitive and cognitive behavioural therapies versus no treatment

Figure 2: Relapse at 35 weeks post-randomisation (ITT)

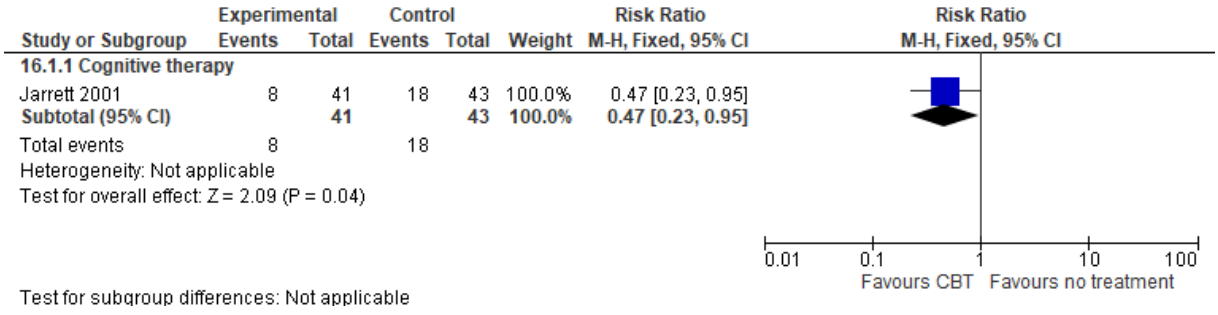
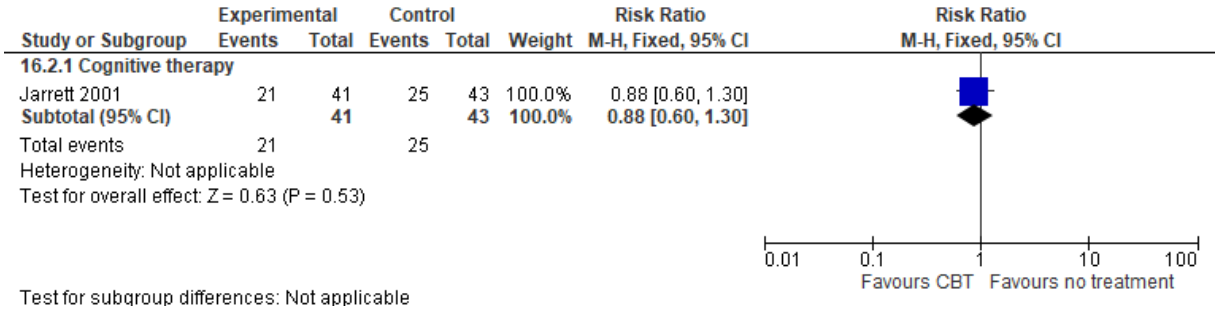


Figure 3: Relapse at 104 weeks post-randomisation (ITT)



Comparison 2: Cognitive and cognitive behavioural therapies versus TAU

Figure 4: Relapse at 124 weeks post-randomisation (ITT)

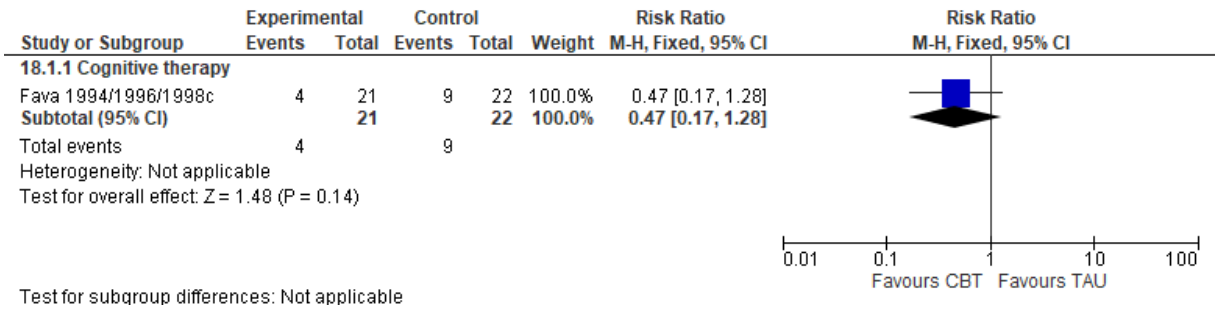


Figure 5: Relapse at 228 weeks post-randomisation (ITT)

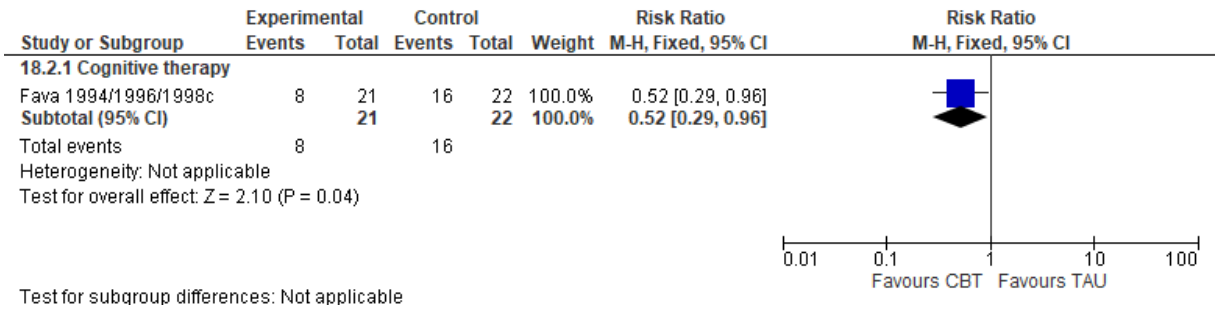
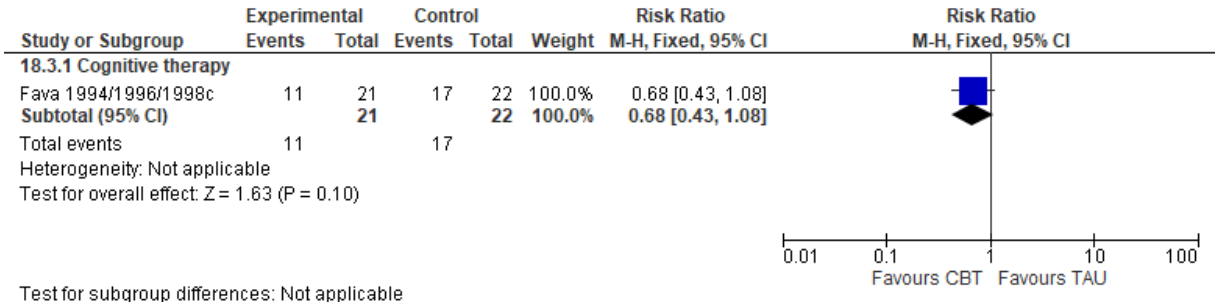


Figure 6: Relapse at 332 weeks post-randomisation (ITT)



Comparison 3: Cognitive and cognitive behavioural therapies + TAU versus TAU

Figure 7: Relapse at 13 weeks post-randomisation (ITT)

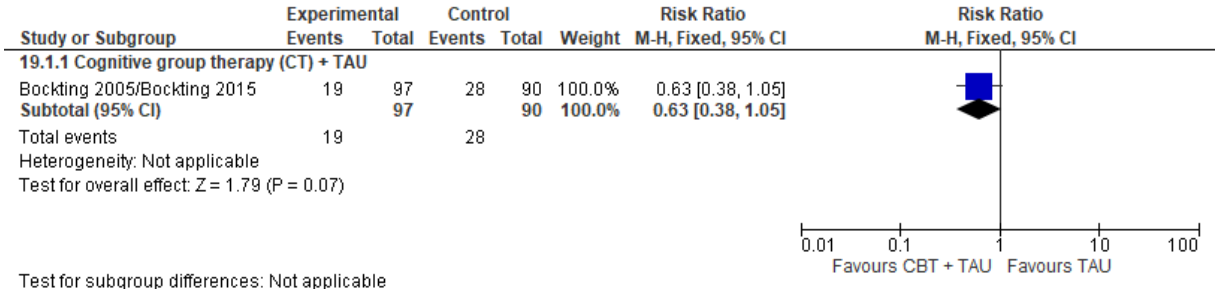


Figure 8: Relapse at 26 weeks post-randomisation (ITT)

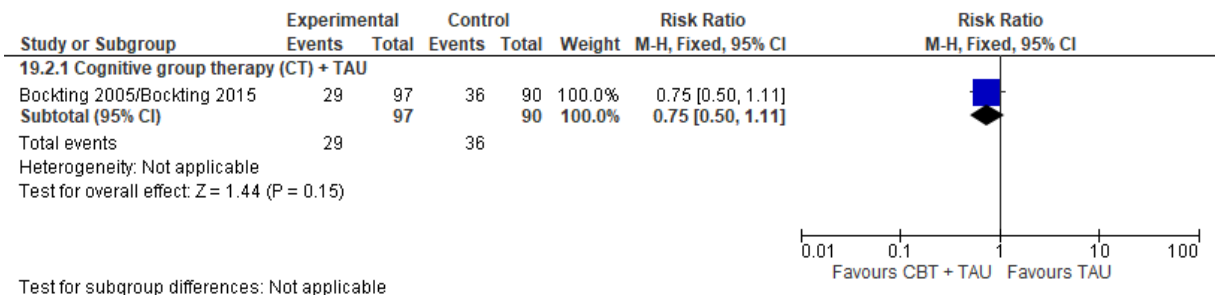


Figure 9: Relapse at 39 weeks post-randomisation (ITT)

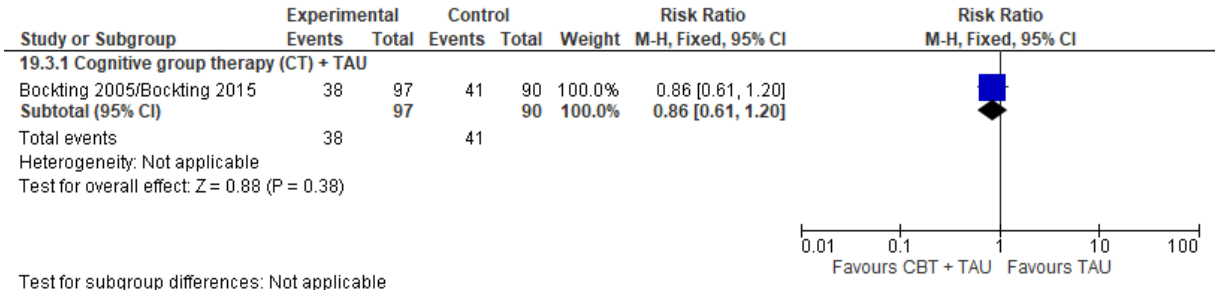


Figure 10: Relapse at 52-65 weeks post-randomisation (ITT)

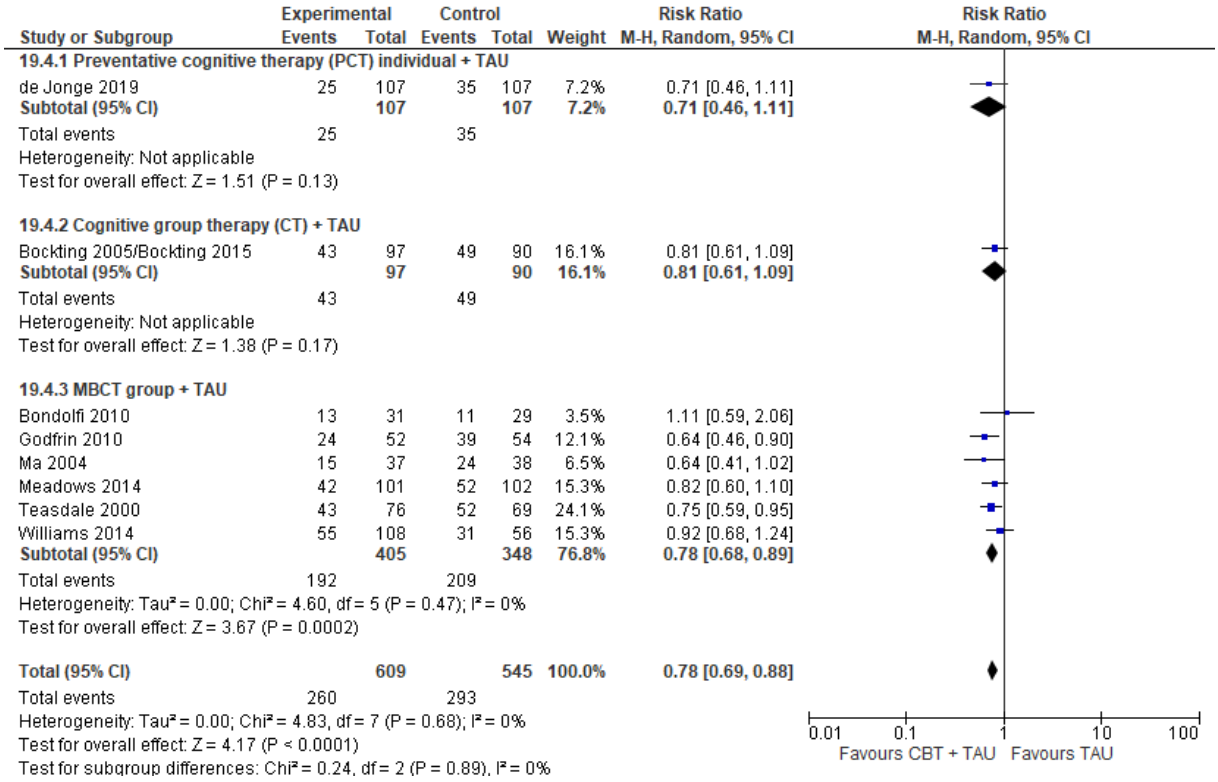


Figure 11: Relapse at 78 weeks post-randomisation (ITT)

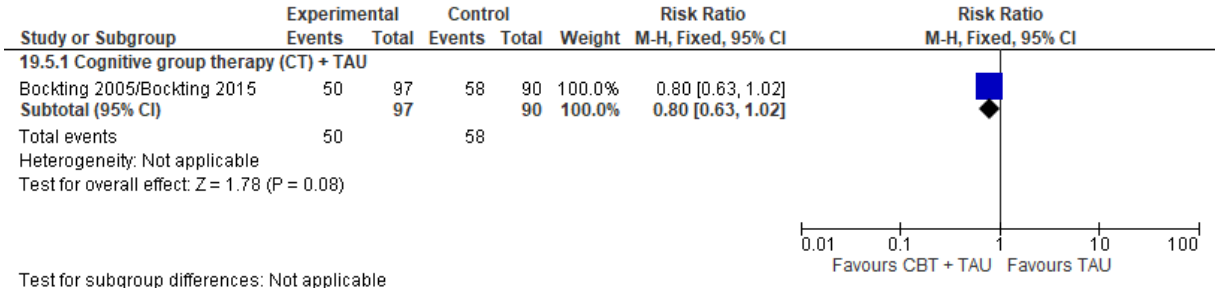


Figure 12: Relapse at 104-113 weeks post-randomisation (ITT)

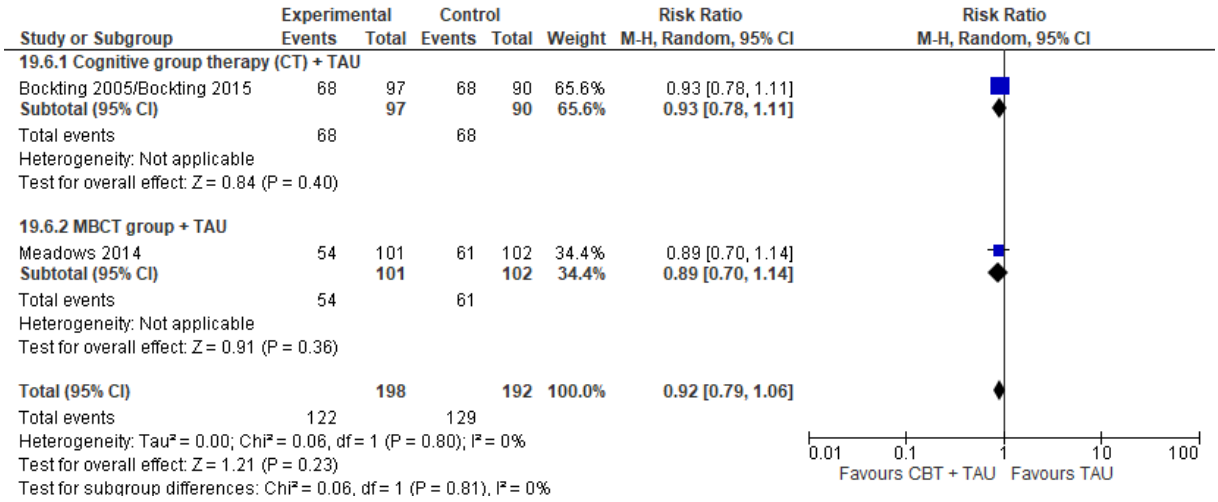


Figure 13: Relapse at 520 weeks post-randomisation (ITT)

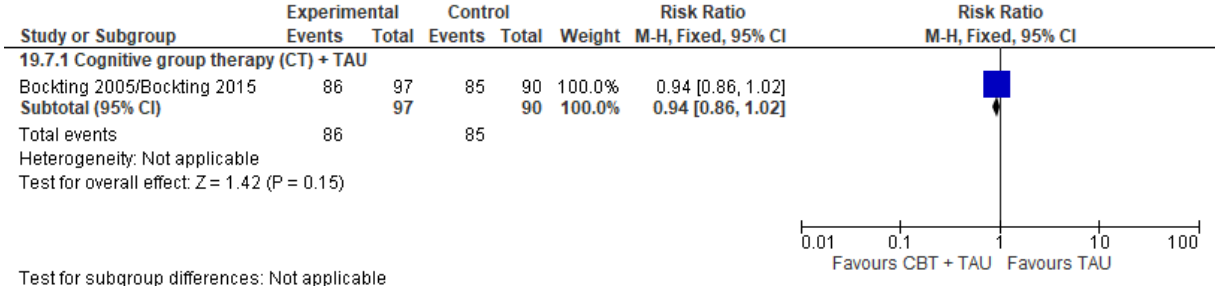


Figure 14: Quality of life impairment at 8 weeks post-randomisation

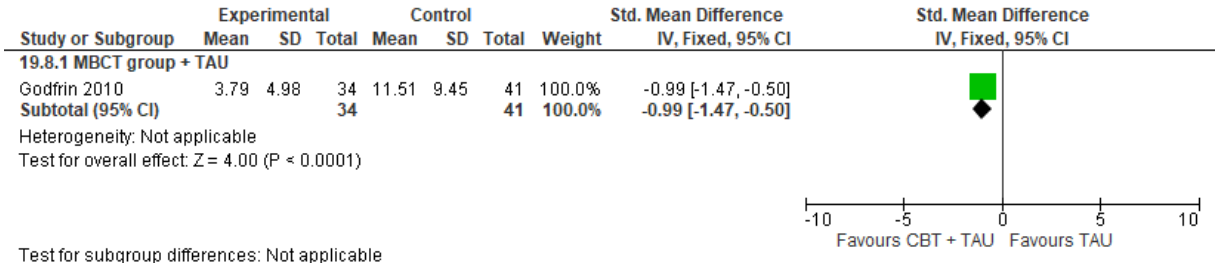


Figure 15: Quality of life impairment at 34 weeks post-randomisation

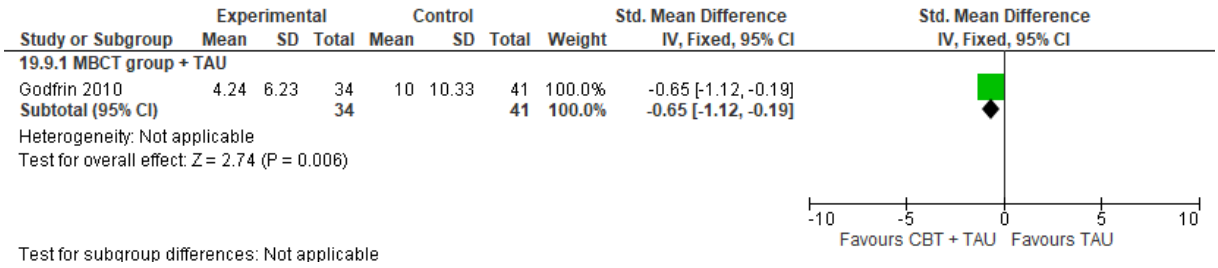
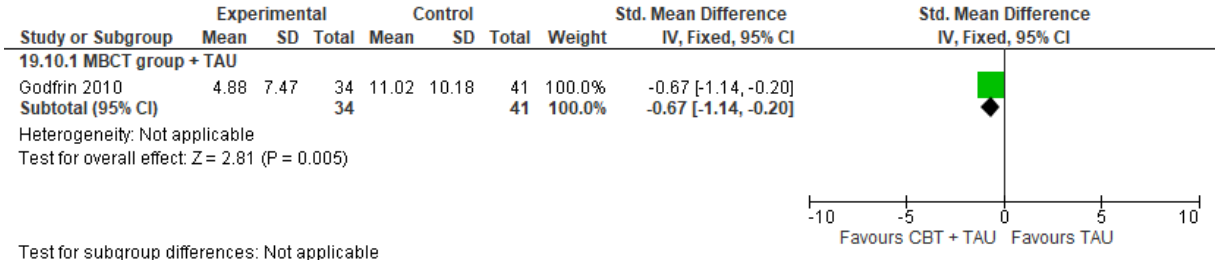


Figure 16: Quality of life impairment at 60 weeks post-randomisation



Comparison 4: Cognitive and cognitive behavioural therapies + TAU versus attention placebo + TAU

Figure 17: Relapse at 60 weeks post-randomisation (ITT)

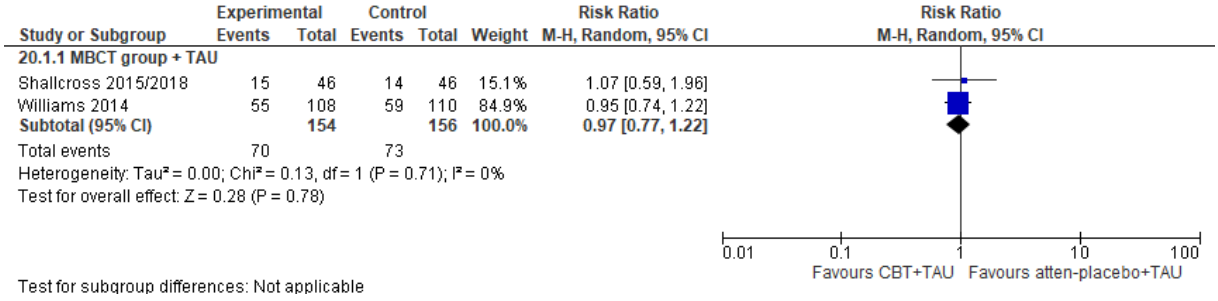


Figure 18: Relapse at 121 weeks post-randomisation (ITT)

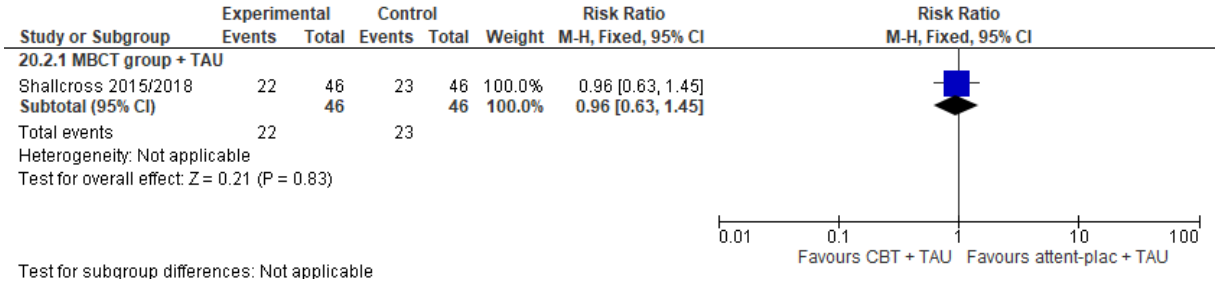


Figure 19: Quality of life change score at 8 weeks post-randomisation

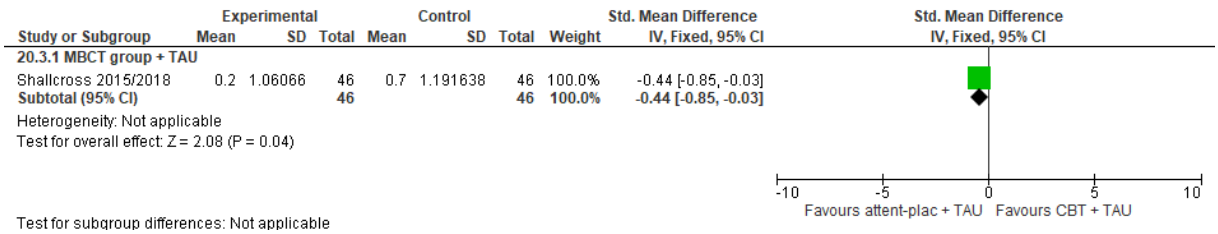


Figure 20: Quality of life change score at 34 weeks post-randomisation

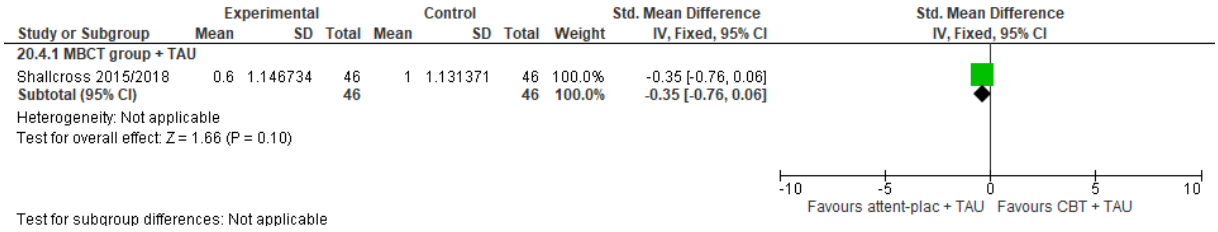


Figure 21: Quality of life change score at 60 weeks post-randomisation

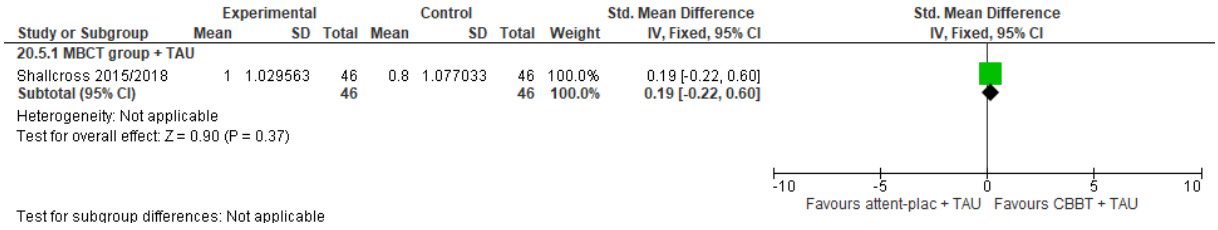
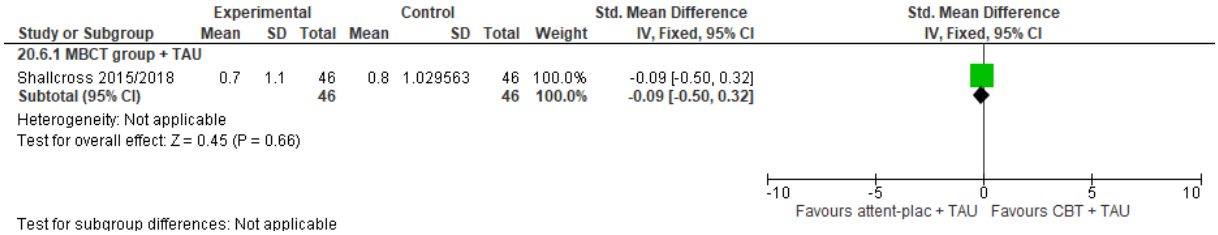


Figure 22: Quality of life change score at 121 weeks post-randomisation



Comparison 5: Cognitive and cognitive behavioural therapies versus pill placebo

Figure 23: Relapse at 35 weeks post-randomisation (ITT)

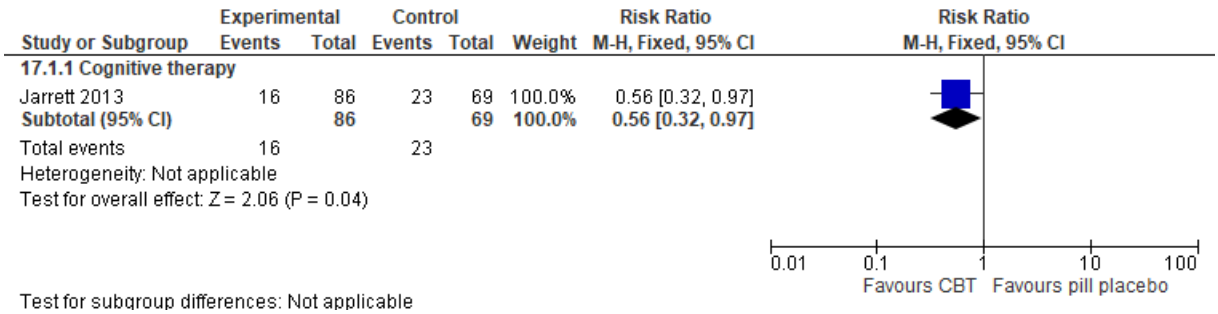


Figure 24: Relapse at 87 weeks post-randomisation (ITT)

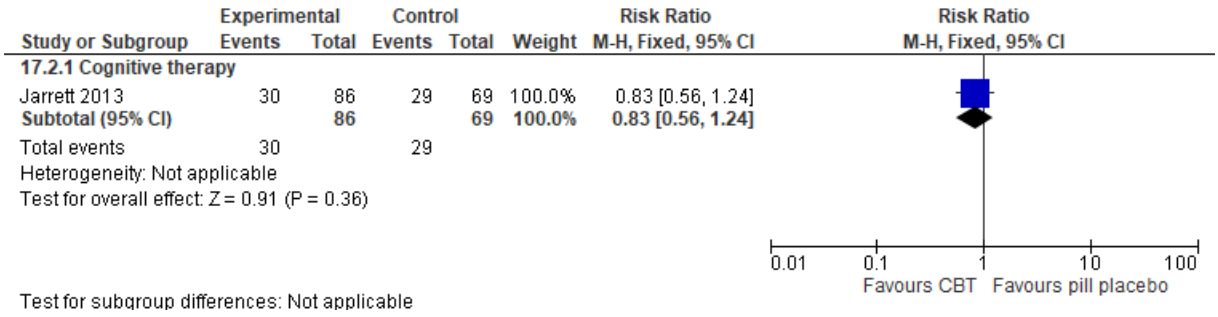
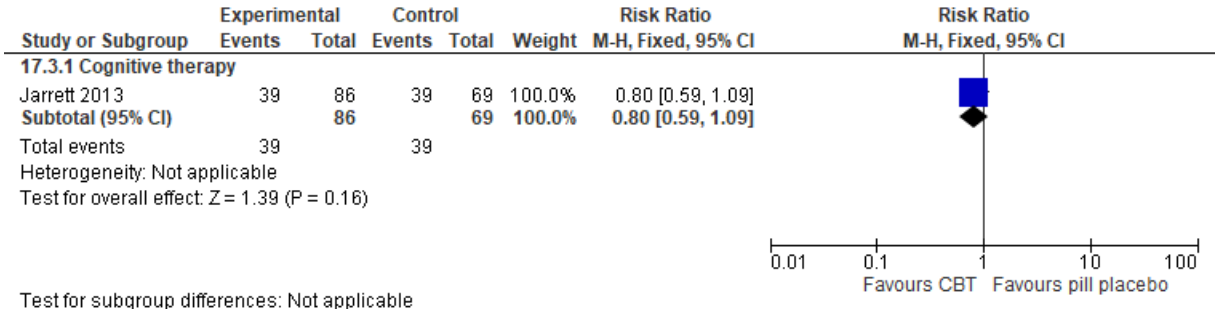
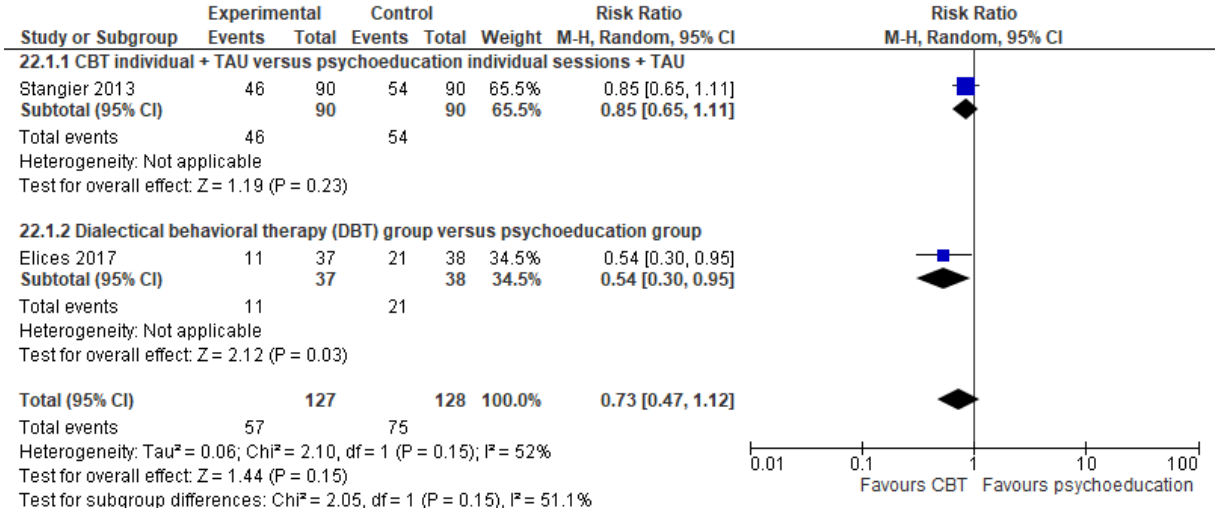


Figure 25: Relapse at 139 weeks post-randomisation (ITT)



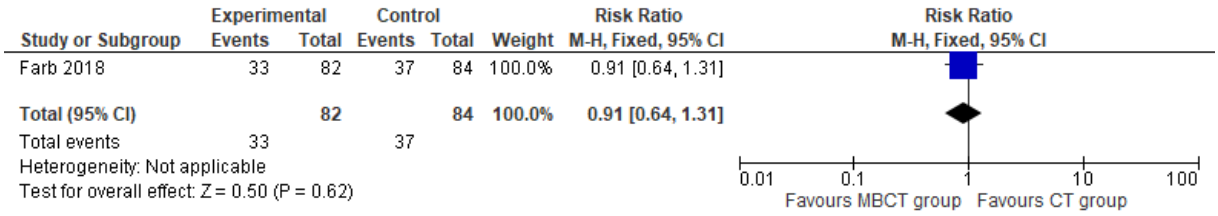
Comparison 6: Cognitive and cognitive behavioural therapies (+/- TAU) versus psychoeducation (+/- TAU)

Figure 26: Relapse at 62-87 weeks post-randomisation (ITT)



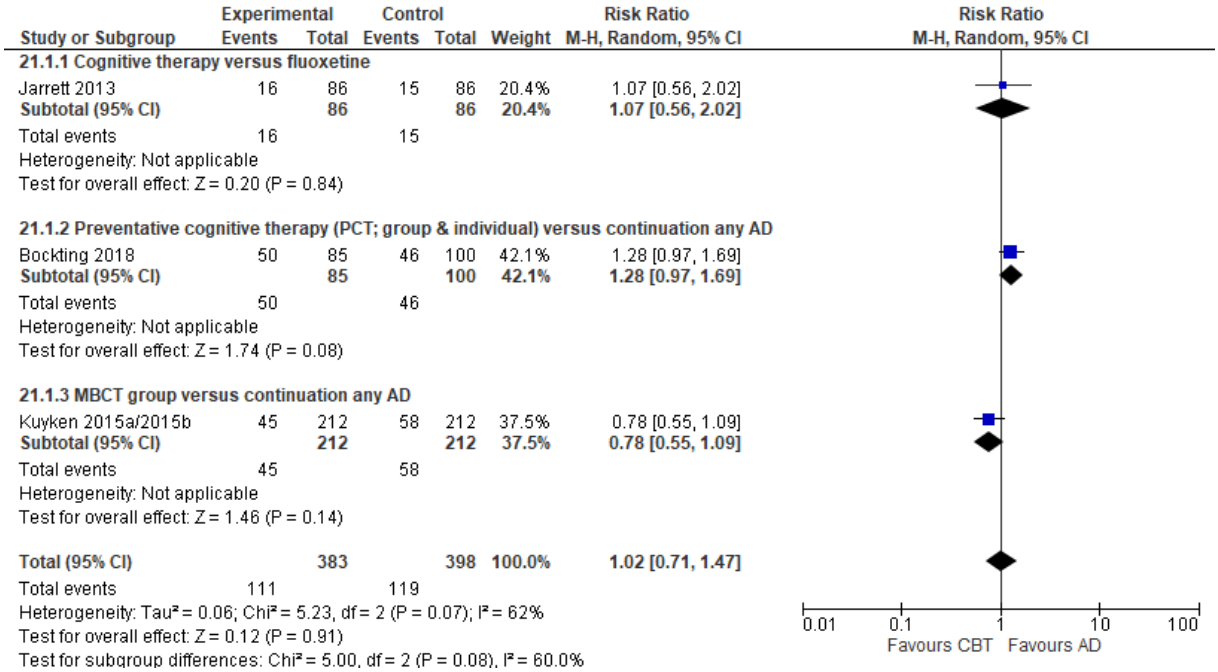
Comparison 7. Mindfulness-based cognitive therapy (MBCT) group (+ TAU) versus cognitive therapy group (+ TAU)

Figure 27: Relapse at 104 weeks post-randomisation (ITT)



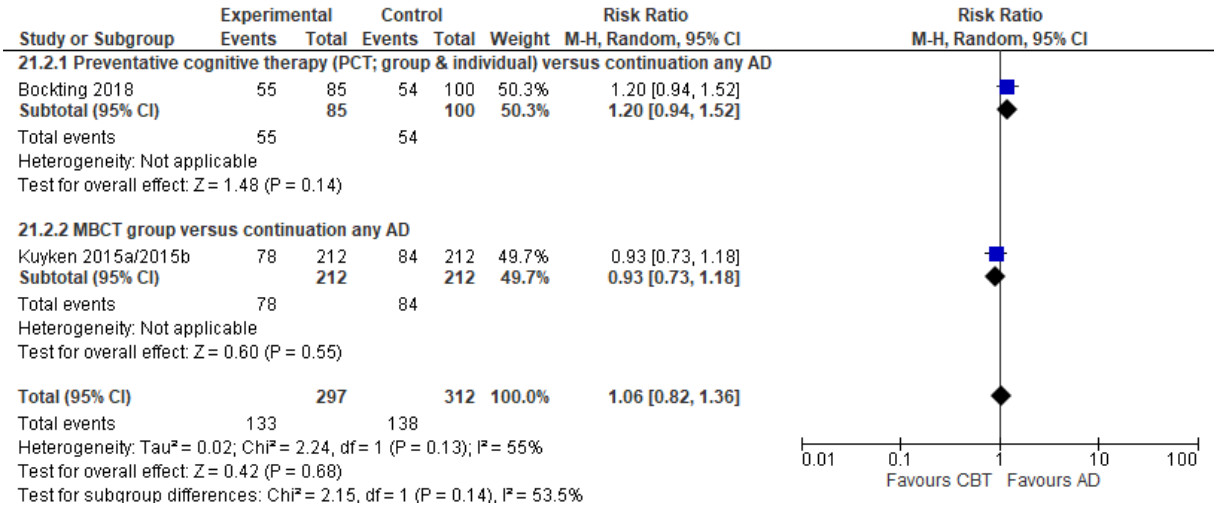
Comparison 8. Cognitive and cognitive behavioural therapies versus antidepressants

Figure 28: Relapse at 22-35 weeks post-randomisation (ITT)



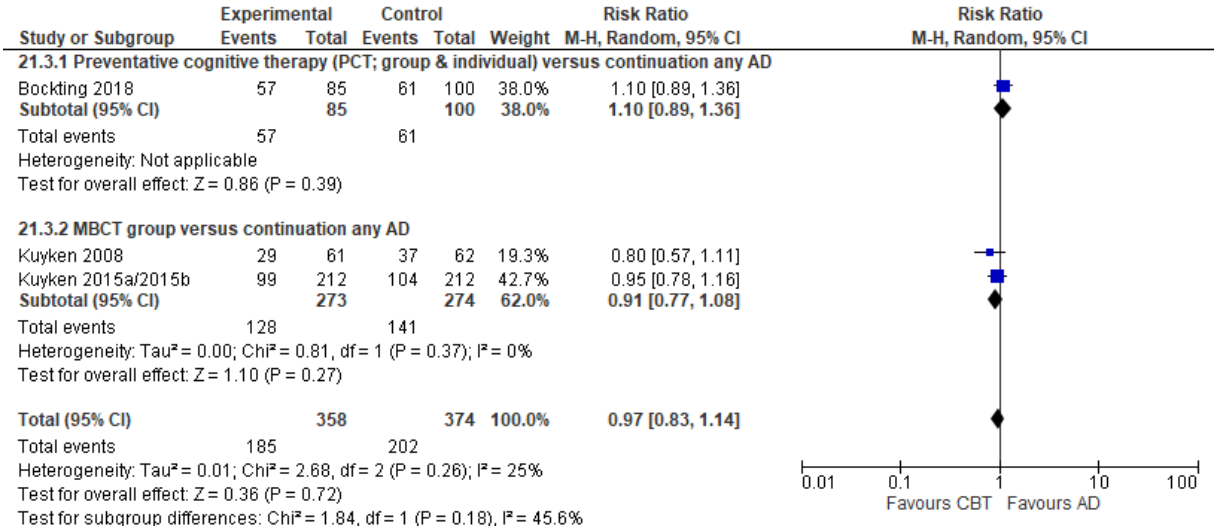
AD: antidepressants

Figure 29: Relapse at 43 weeks post-randomisation (ITT)



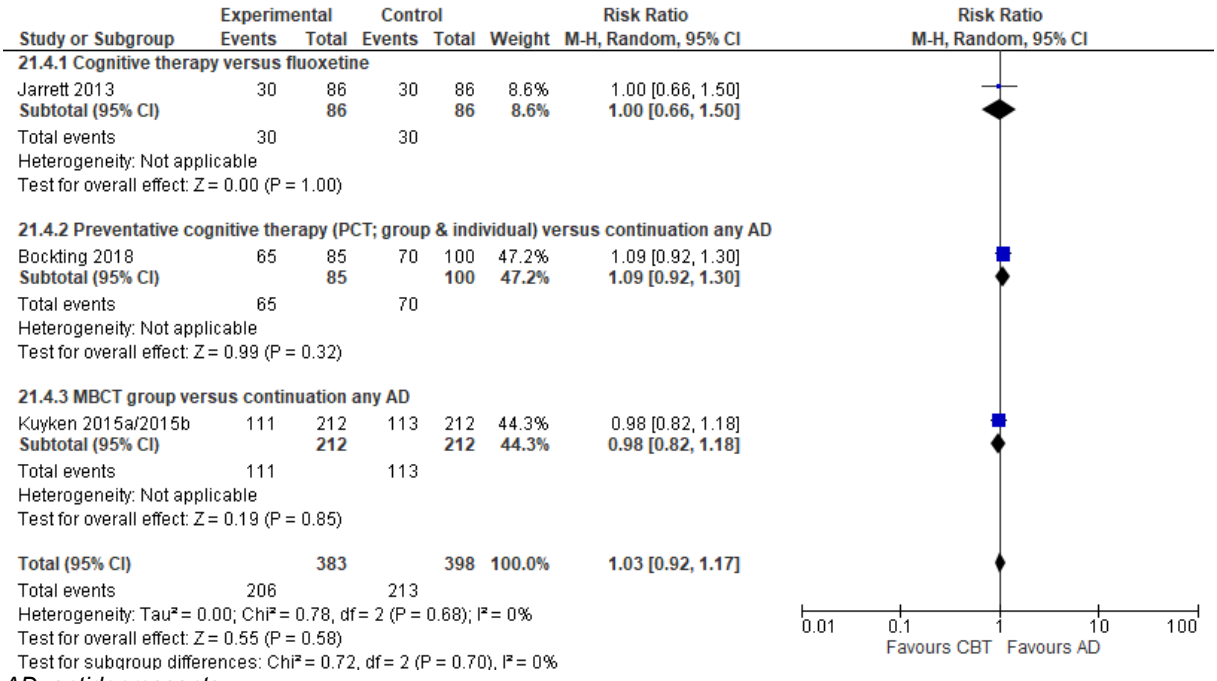
AD: antidepressants

Figure 30: Relapse at 57-65 weeks post-randomisation



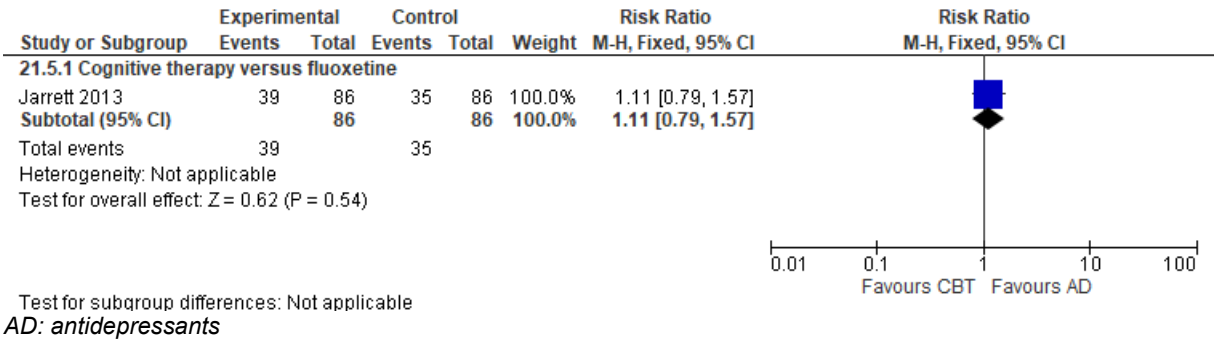
AD: antidepressants

Figure 31: Relapse at 87-100 weeks post-randomisation (ITT)



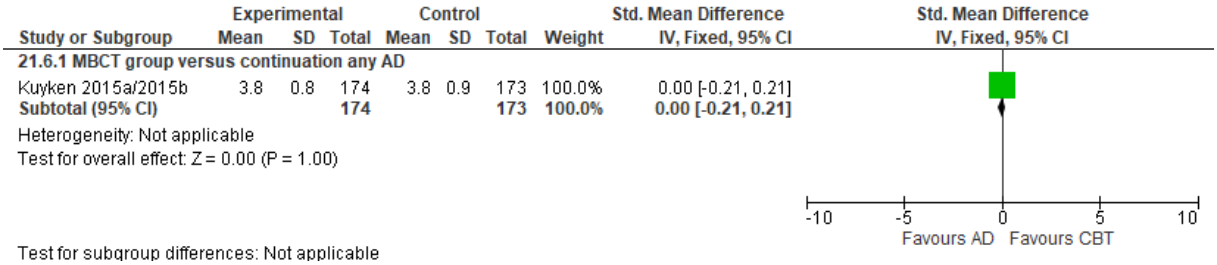
AD: antidepressants

Figure 32: Relapse at 139 weeks post-randomisation (ITT)



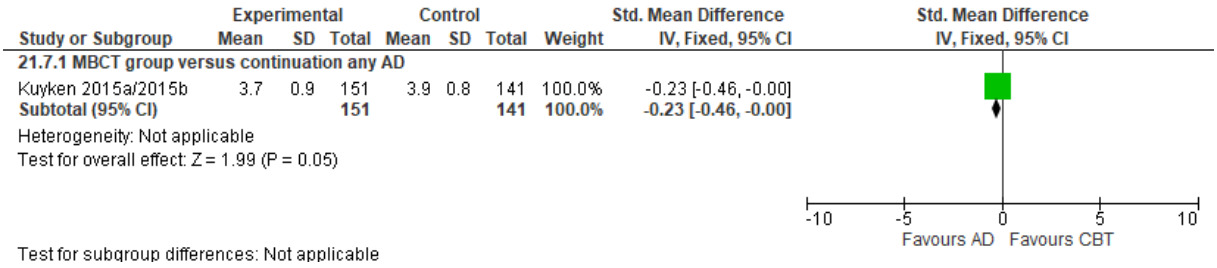
AD: antidepressants

Figure 33: Quality of life at 12 weeks post-randomisation



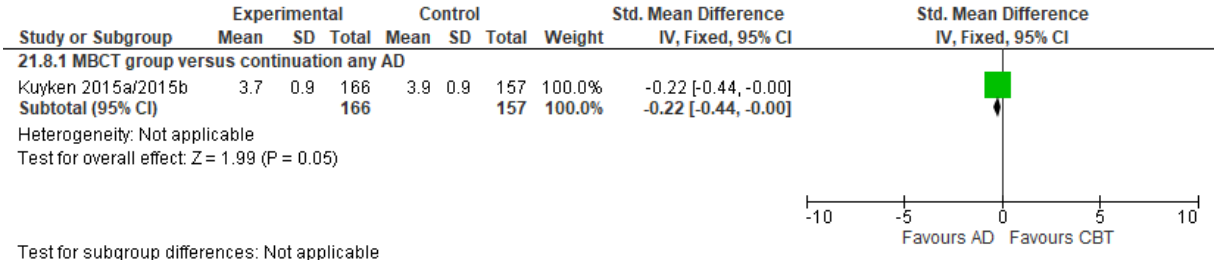
AD: antidepressants

Figure 34: Quality of life at 39 weeks post-randomisation



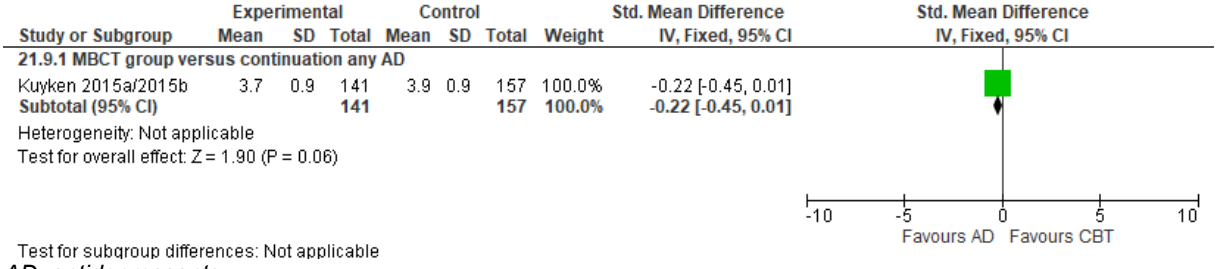
AD: antidepressants

Figure 35: Quality of life at 52 weeks post-randomisation



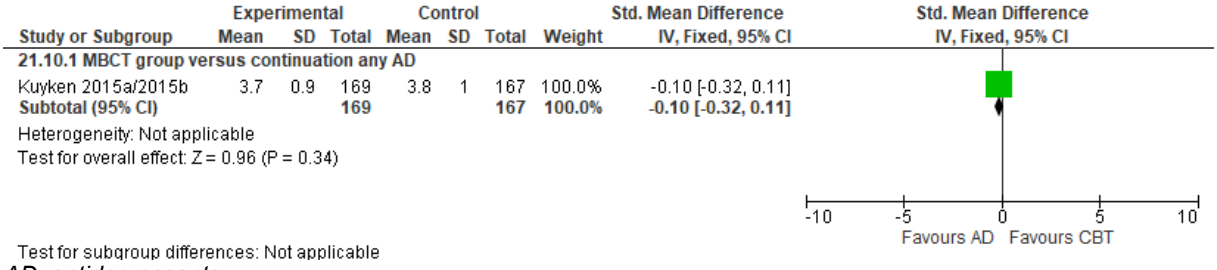
AD: antidepressants

Figure 36: Quality of life at 78 weeks post-randomisation



AD: antidepressants

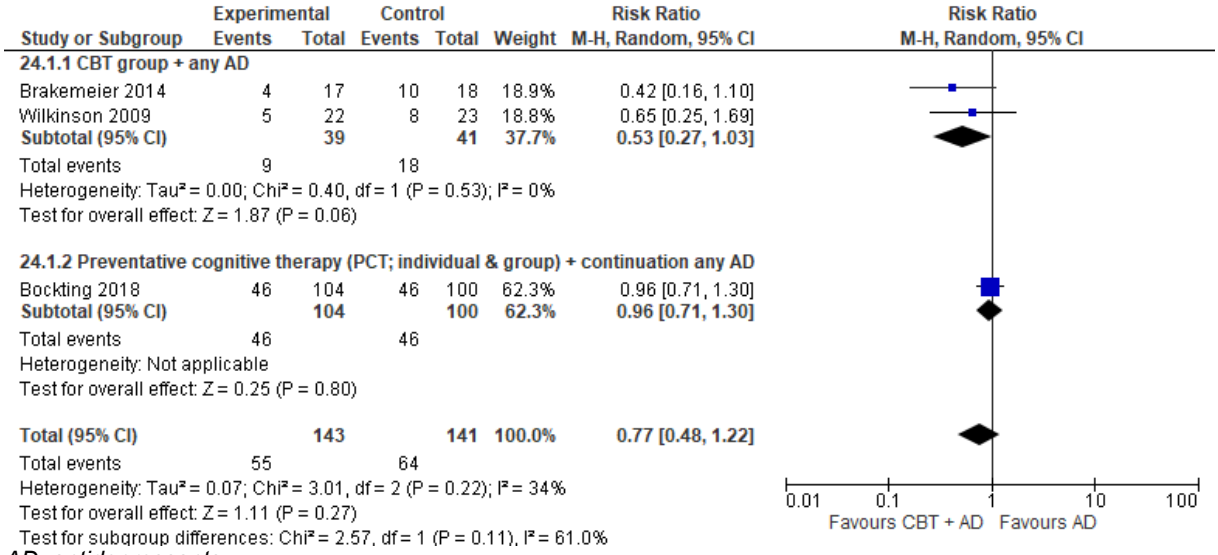
Figure 37: Quality of life at 104 weeks post-randomisation



AD: antidepressants

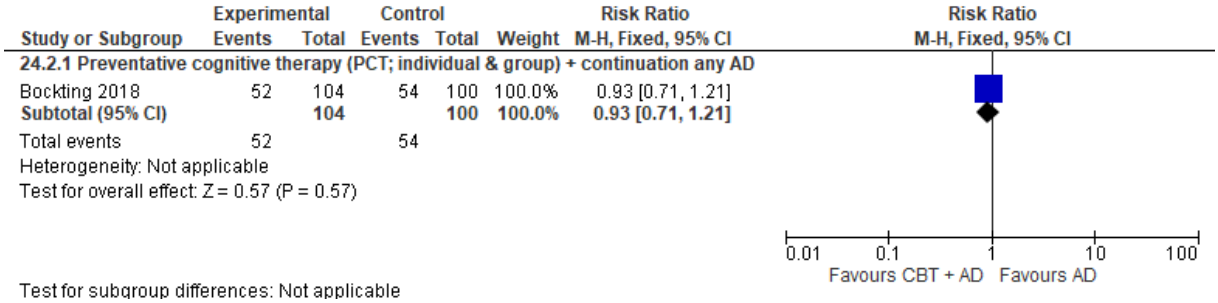
Comparison 9. Cognitive and cognitive behavioural therapies + antidepressants versus antidepressants

Figure 38: Relapse at 26-28 weeks post-randomisation (ITT)



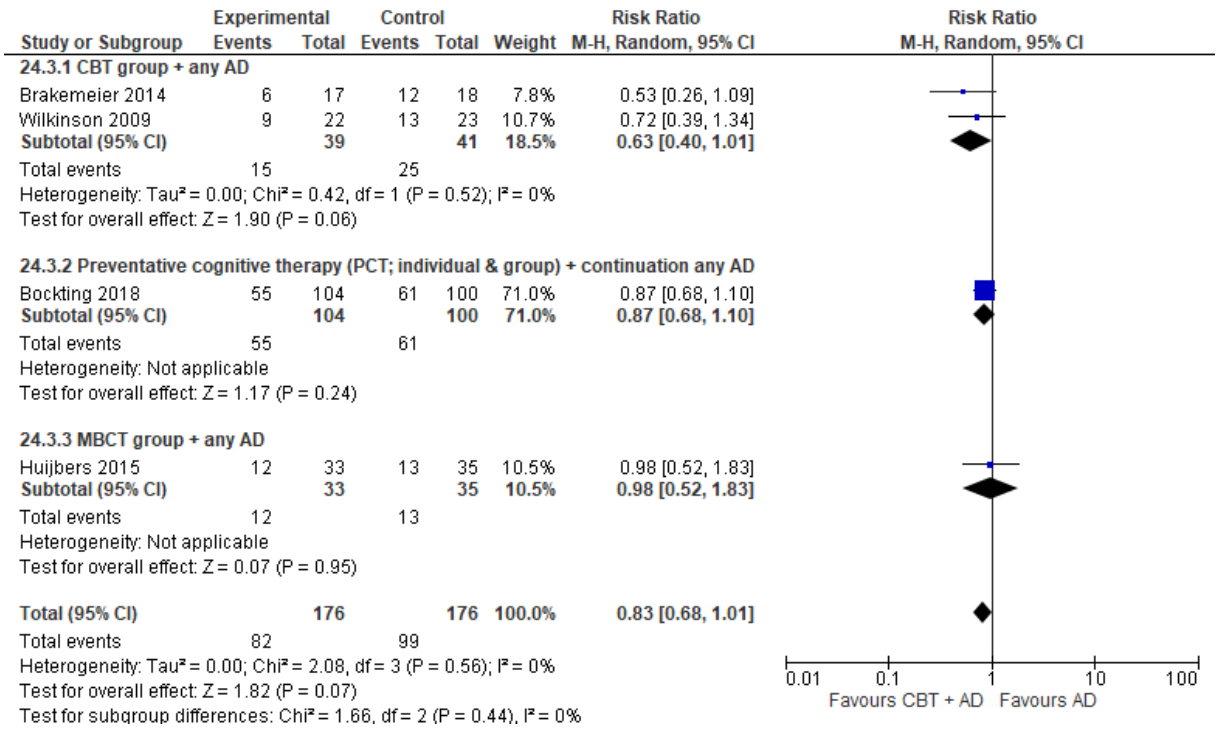
AD: antidepressants

Figure 39: Relapse at 43 weeks (ITT)



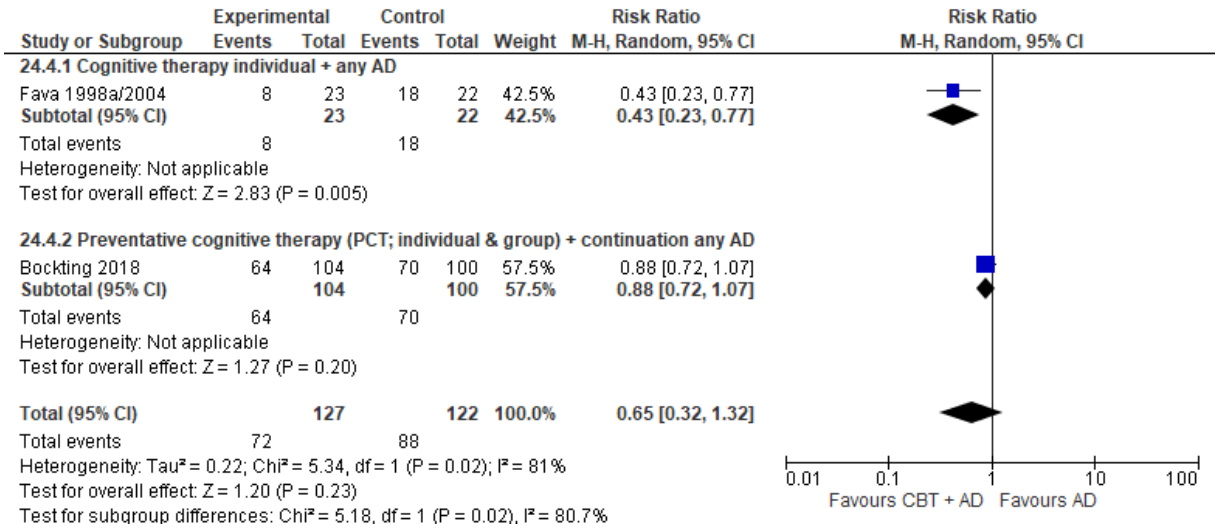
AD: antidepressants

Figure 40: Relapse at 52-65 weeks post-randomisation (ITT)



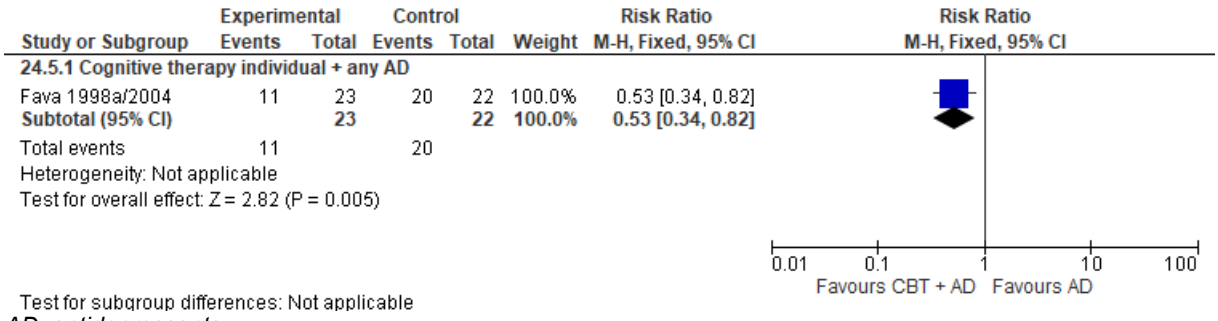
AD: antidepressants

Figure 41: Relapse at 100-104 weeks post-randomisation (ITT)



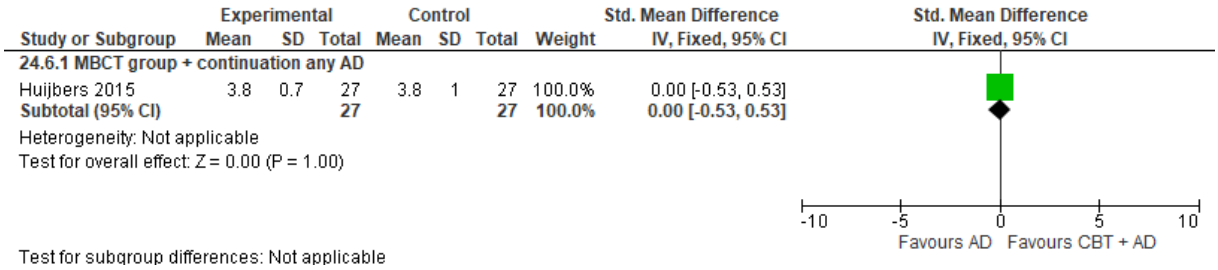
AD: antidepressants

Figure 42: Relapse at 310 weeks post-randomisation (ITT)



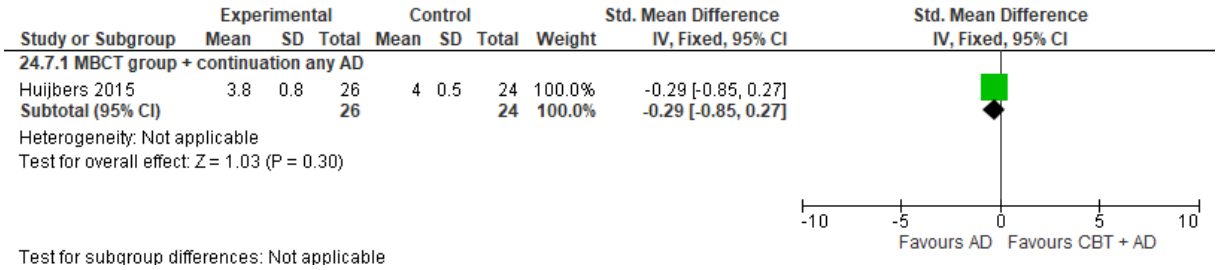
AD: antidepressants

Figure 43: Quality of life at 12 weeks post-randomisation



AD: antidepressants

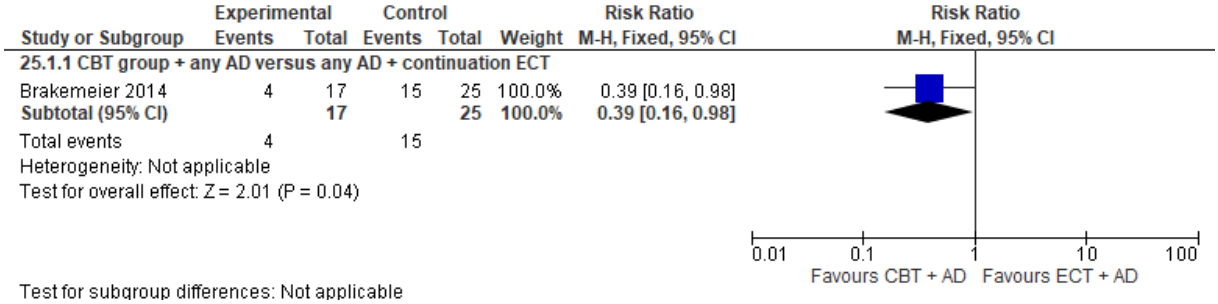
Figure 44: Quality of life at 65 weeks post-randomisation



AD: antidepressants

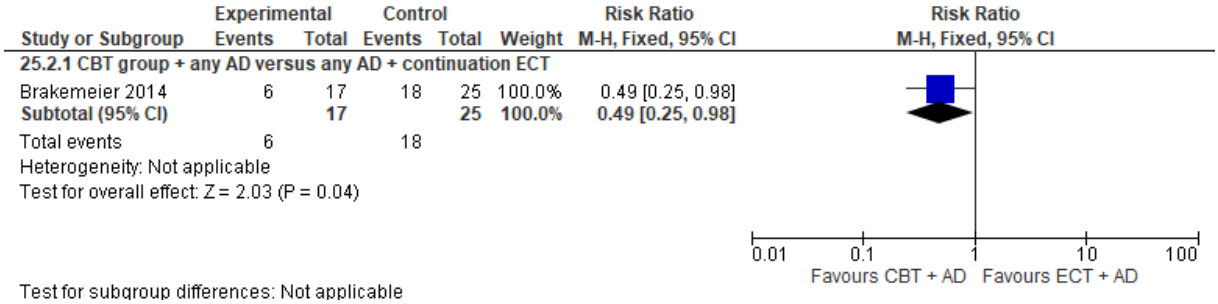
Comparison 10. Cognitive and cognitive behavioural therapies + antidepressants versus ECT + antidepressants

Figure 45: Relapse at 26 weeks post-randomisation (ITT)



AD: antidepressants

Figure 46: Relapse at 52 weeks post-randomisation (ITT)



AD: antidepressants

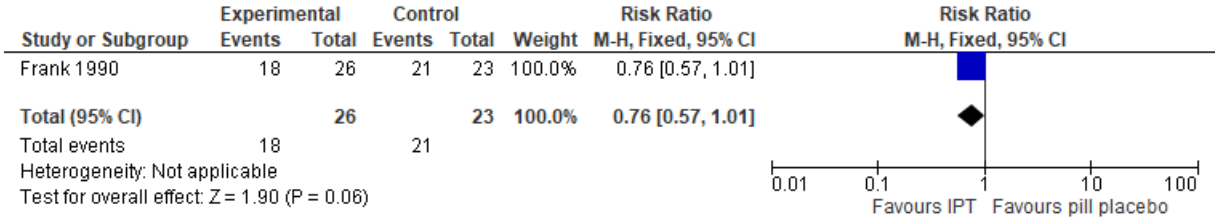
Comparison 11. Mindfulness-based cognitive therapy (MBCT) group + continuation antidepressant versus MBCT group (discontinuation antidepressant)

Figure 47: Relapse at 65 weeks post-randomisation (ITT)

AD: antidepressants

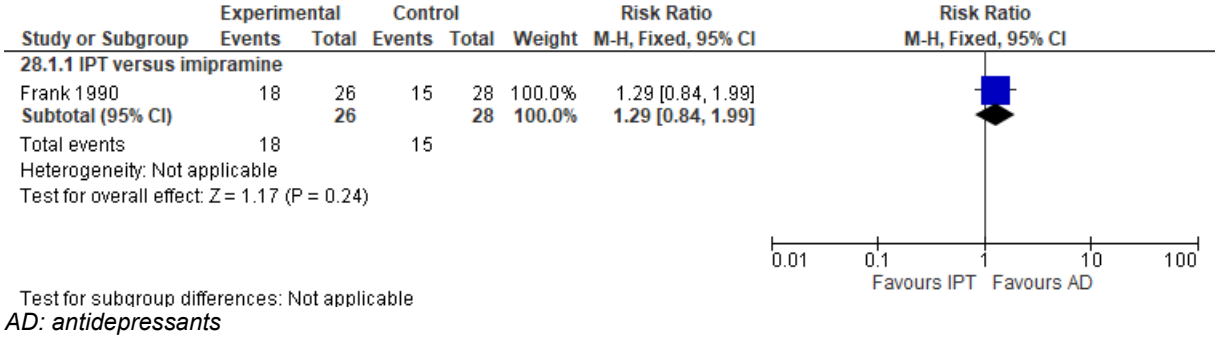
Comparison 12. Interpersonal therapy (IPT) versus pill placebo

Figure 48: Relapse at 156 weeks post-randomisation (ITT)



Comparison 13. Interpersonal therapy (IPT) versus antidepressant

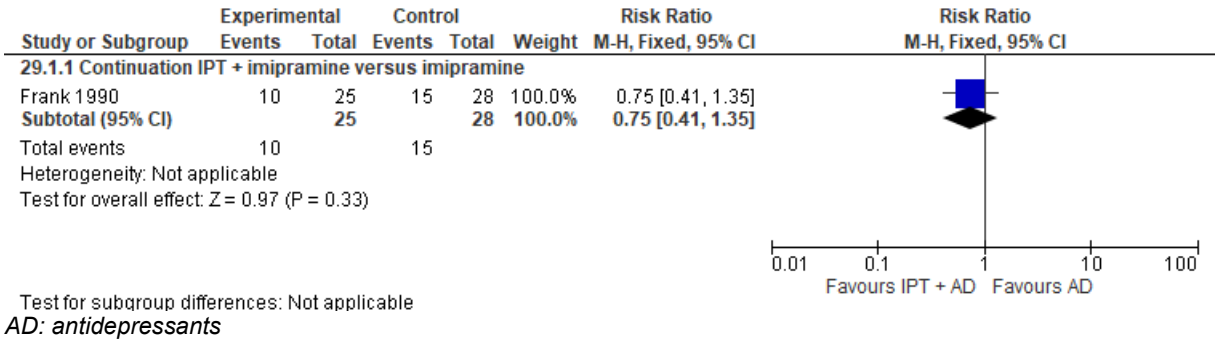
Figure 49: Relapse at 156 weeks post-randomisation (ITT)



AD: antidepressants

Comparison 14. Interpersonal therapy (IPT) + antidepressant versus antidepressant

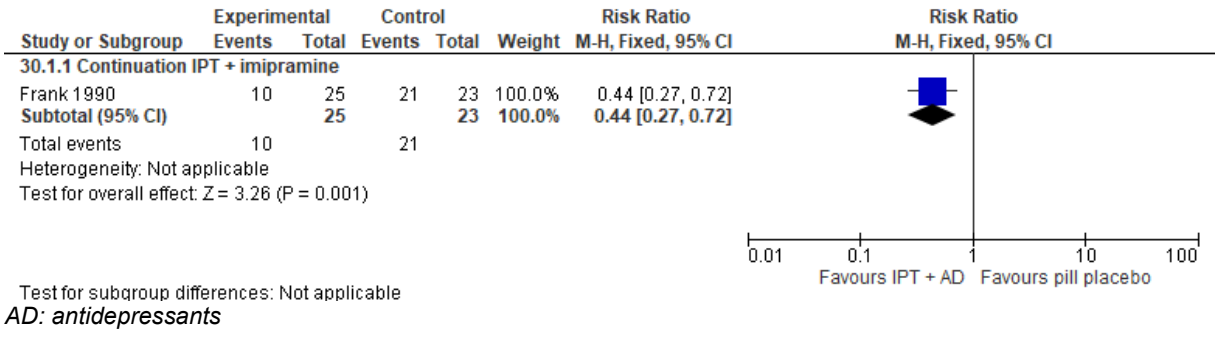
Figure 50: Relapse at 156 weeks post-randomisation (ITT)



AD: antidepressants

Comparison 15. Interpersonal therapy (IPT) + antidepressant versus pill placebo

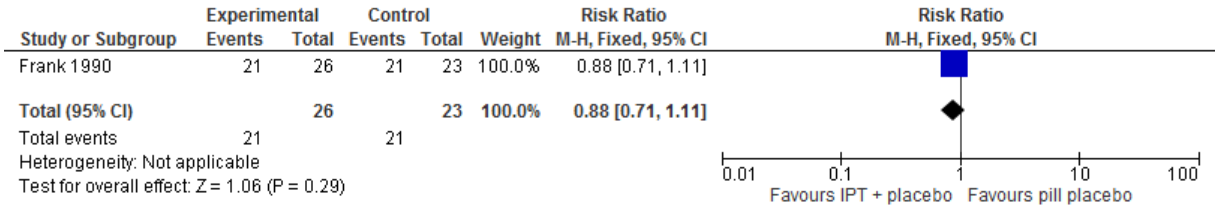
Figure 51: Relapse at 156 weeks post-randomisation (ITT)



AD: antidepressants

Comparison 16. Interpersonal therapy (IPT) + pill placebo versus pill placebo

Figure 52: Relapse at 156 weeks post-randomisation (ITT)



Comparison 17. Self-help + TAU versus TAU

Figure 53: Relapse at 12-14 weeks post-randomisation (ITT)

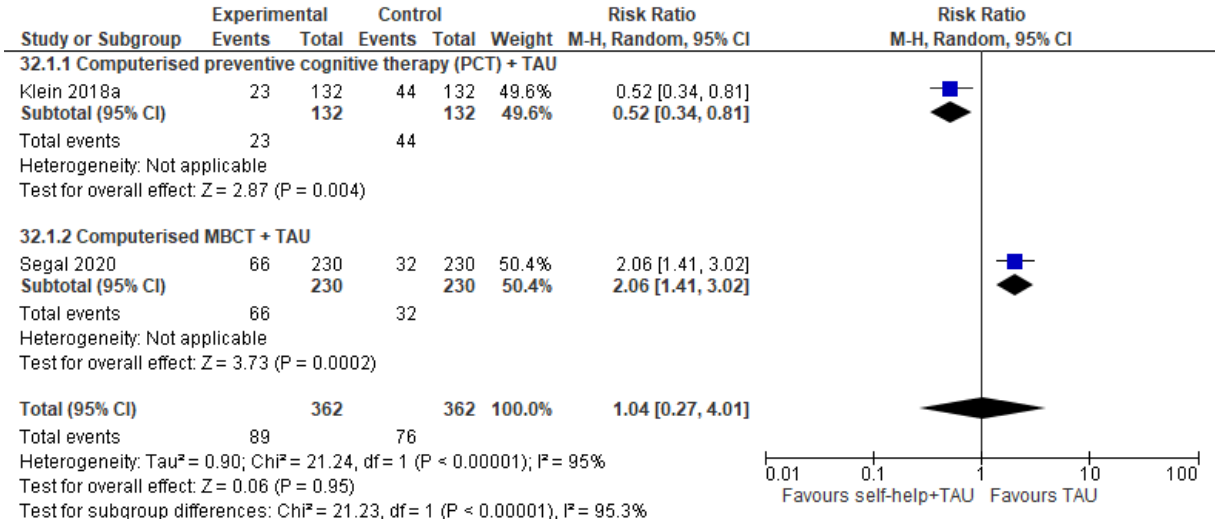


Figure 54: Relapse at 28 weeks post-randomisation (ITT)

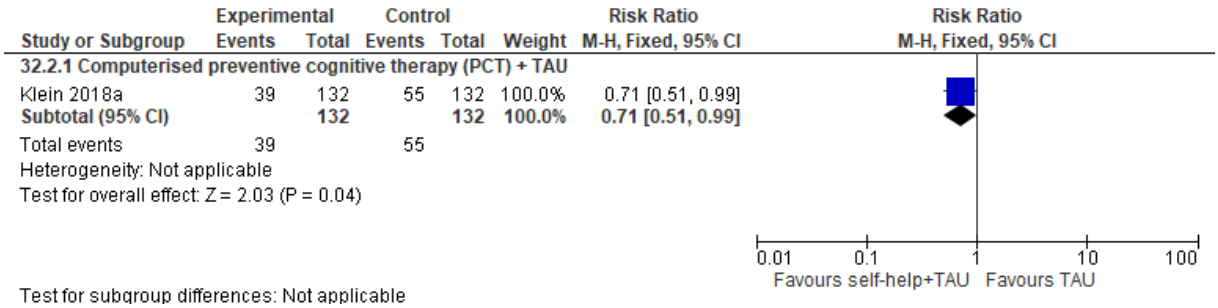


Figure 55: Relapse at 43 weeks post-randomisation (ITT)

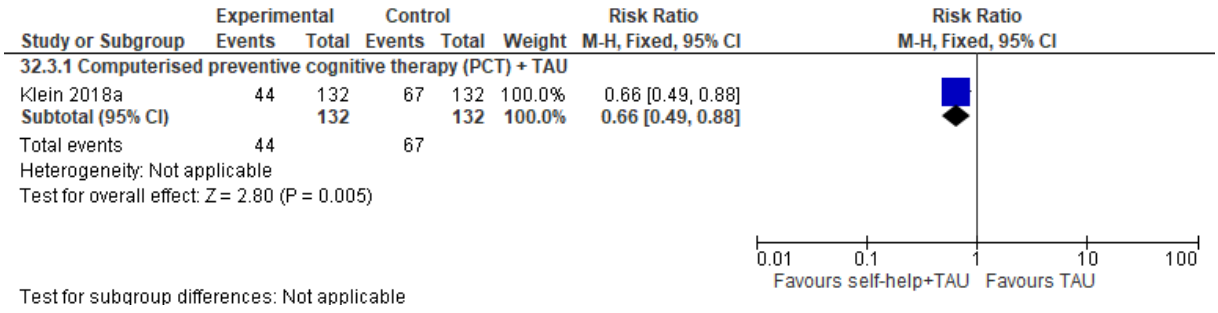


Figure 56: Relapse at 52-65 weeks post-randomisation (ITT)

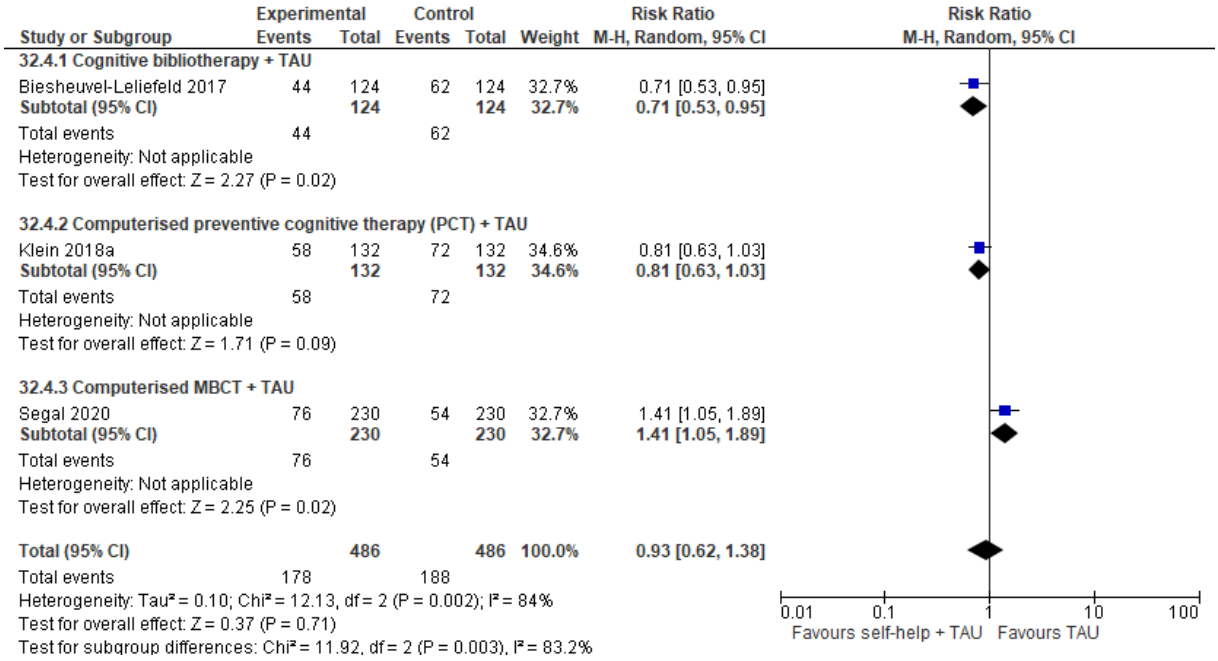


Figure 57: Relapse at 71 weeks post-randomisation (ITT)

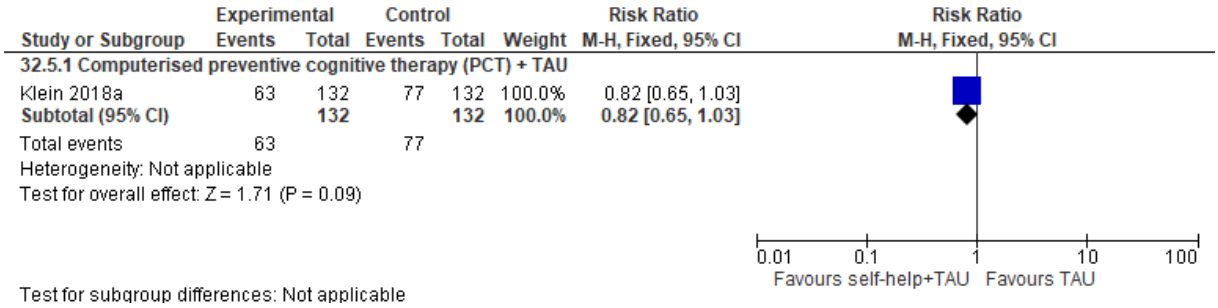


Figure 58: Relapse at 85 weeks post-randomisation (ITT)

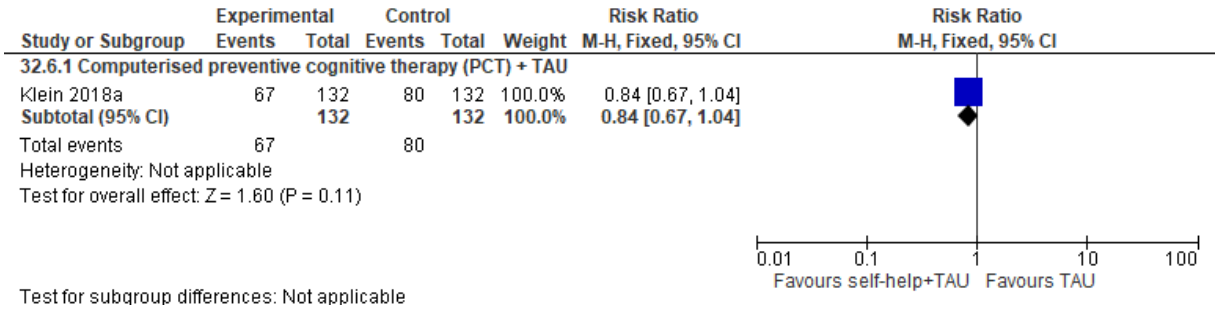


Figure 59: Relapse at 100 weeks post-randomisation (ITT)

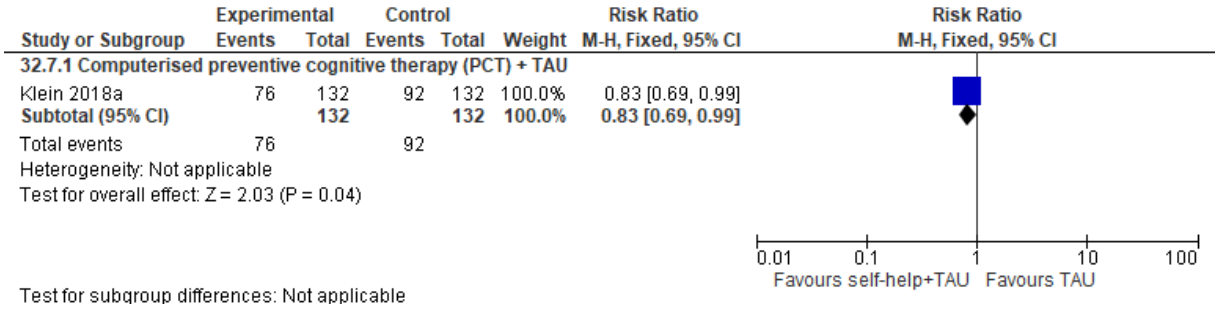


Figure 60: Quality of life at 26 weeks post-randomisation

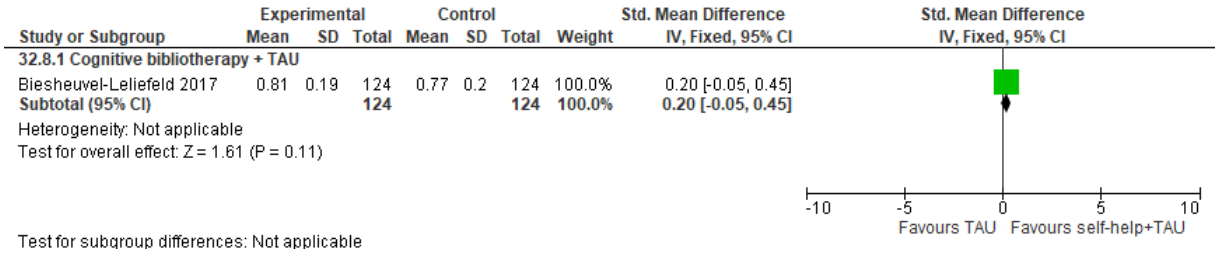


Figure 61: Quality of life at 52 weeks post-randomisation

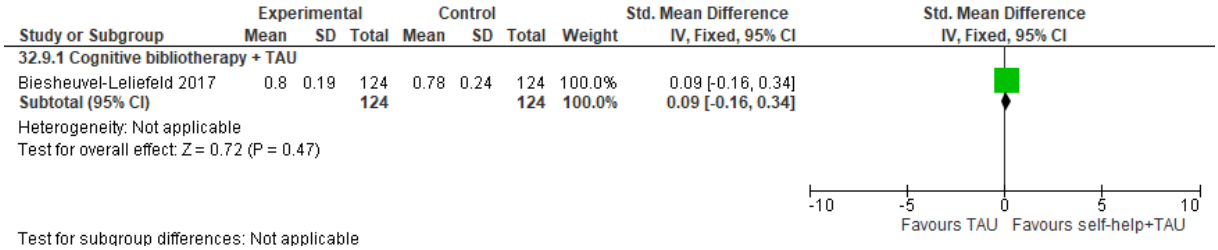


Figure 62: Quality of life mental health component at 12-26 weeks post-randomisation

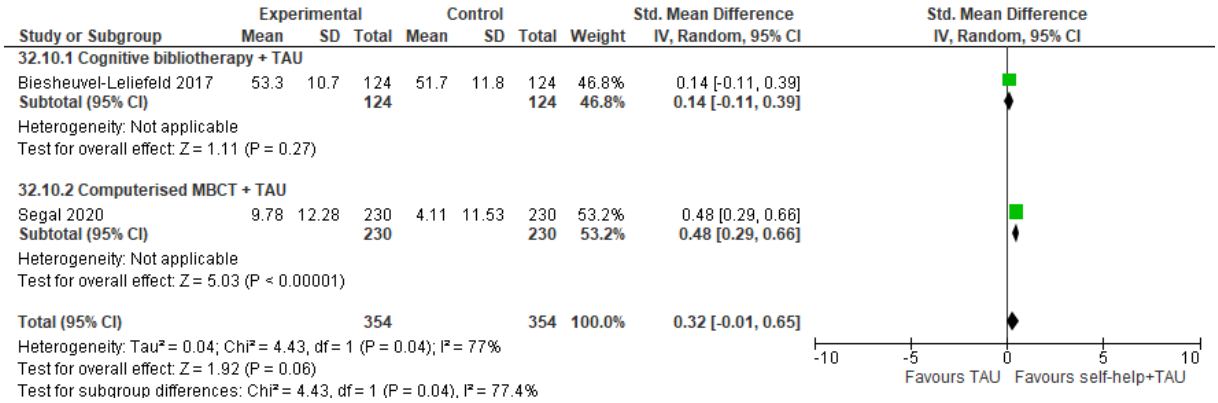


Figure 63: Quality of life physical health component at 12-26 weeks post-randomisation

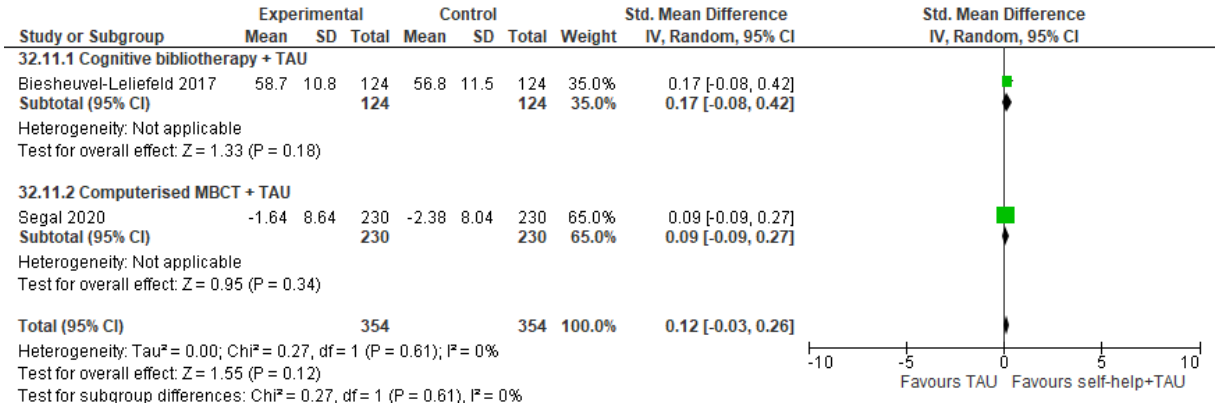


Figure 64: Quality of life mental health component at 52-65 weeks post-randomisation

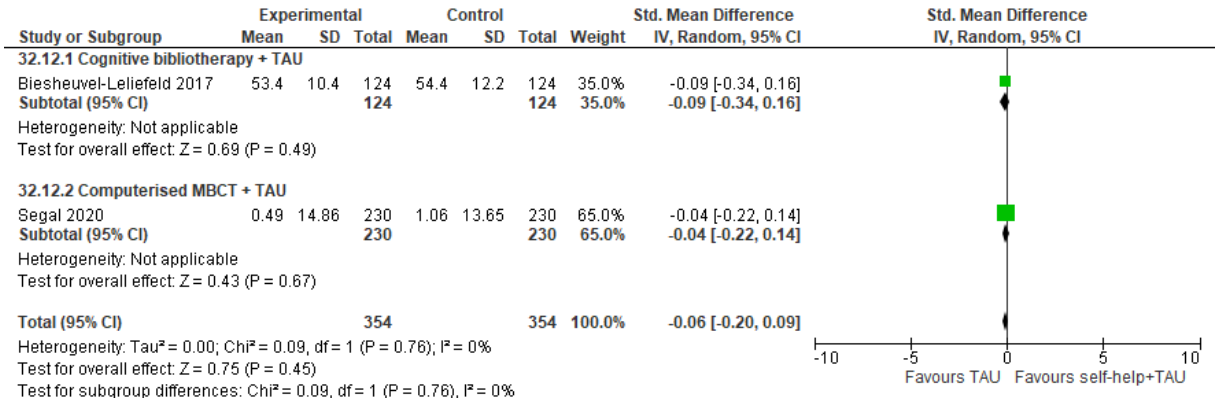
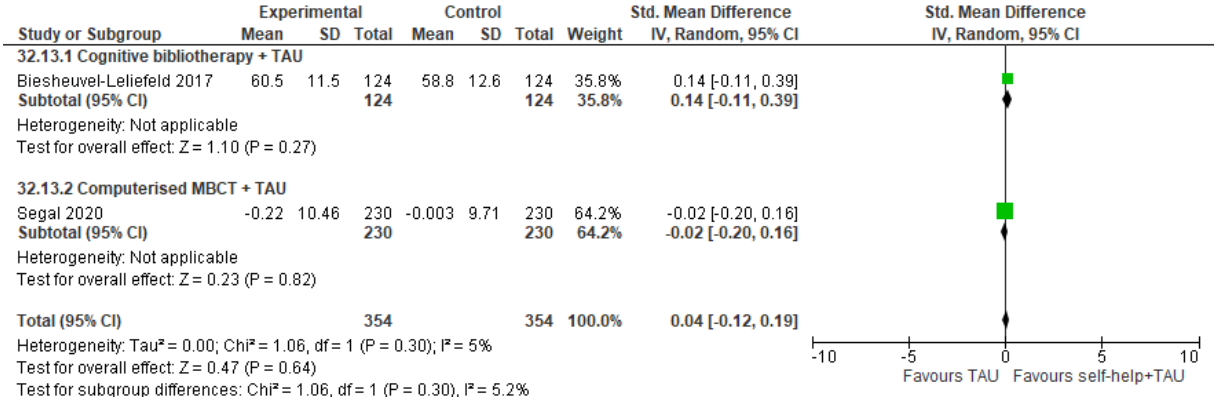


Figure 65: Quality of life physical health component at 52-65 weeks post-randomisation



Comparison 18. Self-help with support + TAU versus attention placebo + TAU

Figure 66: Relapse at 36 weeks post-randomisation (ITT)

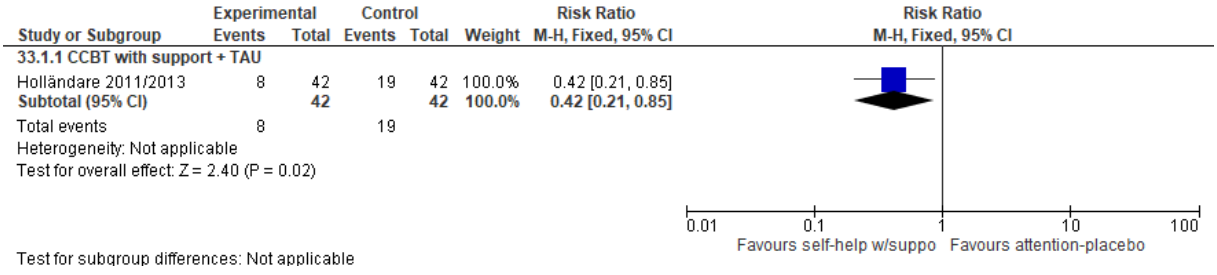


Figure 67: Relapse at 114 weeks post-randomisation (ITT)

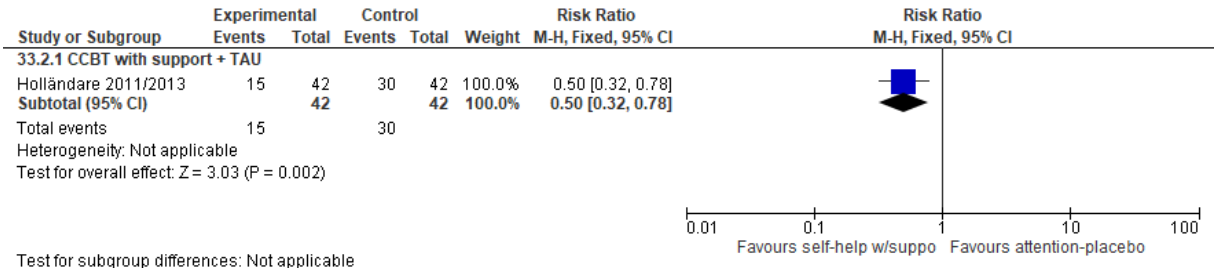


Figure 68: Quality of life change score at 10 weeks post-randomisation

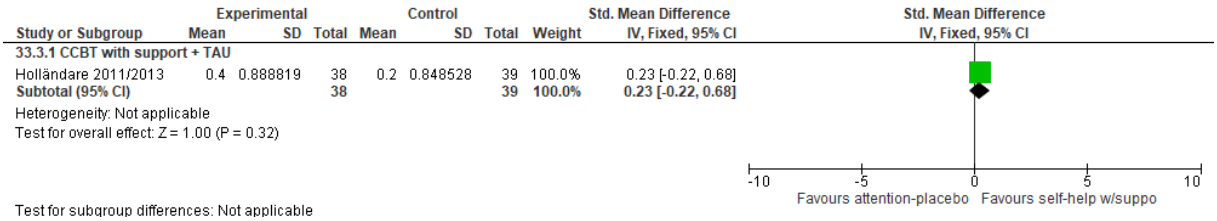


Figure 69: Quality of life change score at 36 weeks post-randomisation

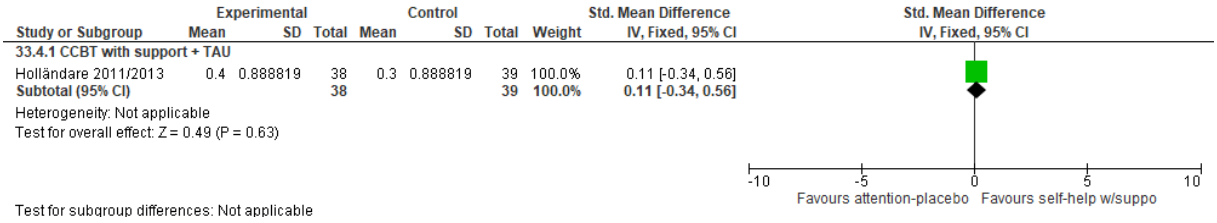


Figure 70: Quality of life change score at 62 weeks post-randomisation

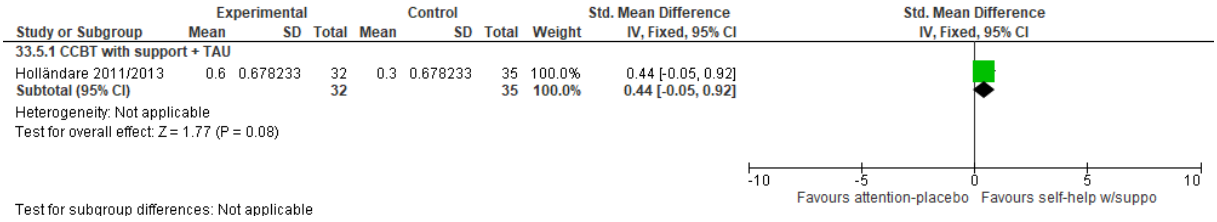
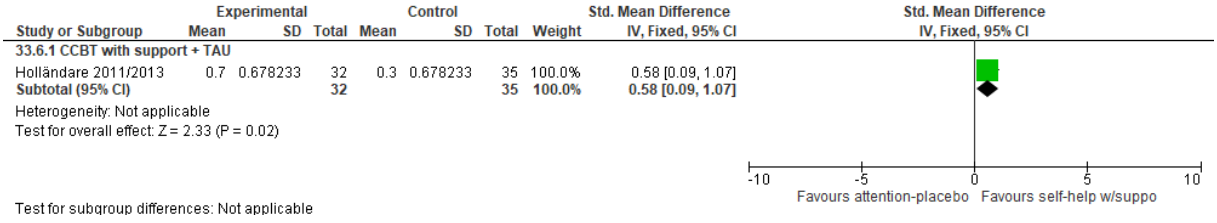


Figure 71: Quality of life change score at 114 weeks post-randomisation



Comparison 19. SSRIs versus pill placebo

Figure 72: Relapse at 16-36 weeks post-randomisation (ITT)

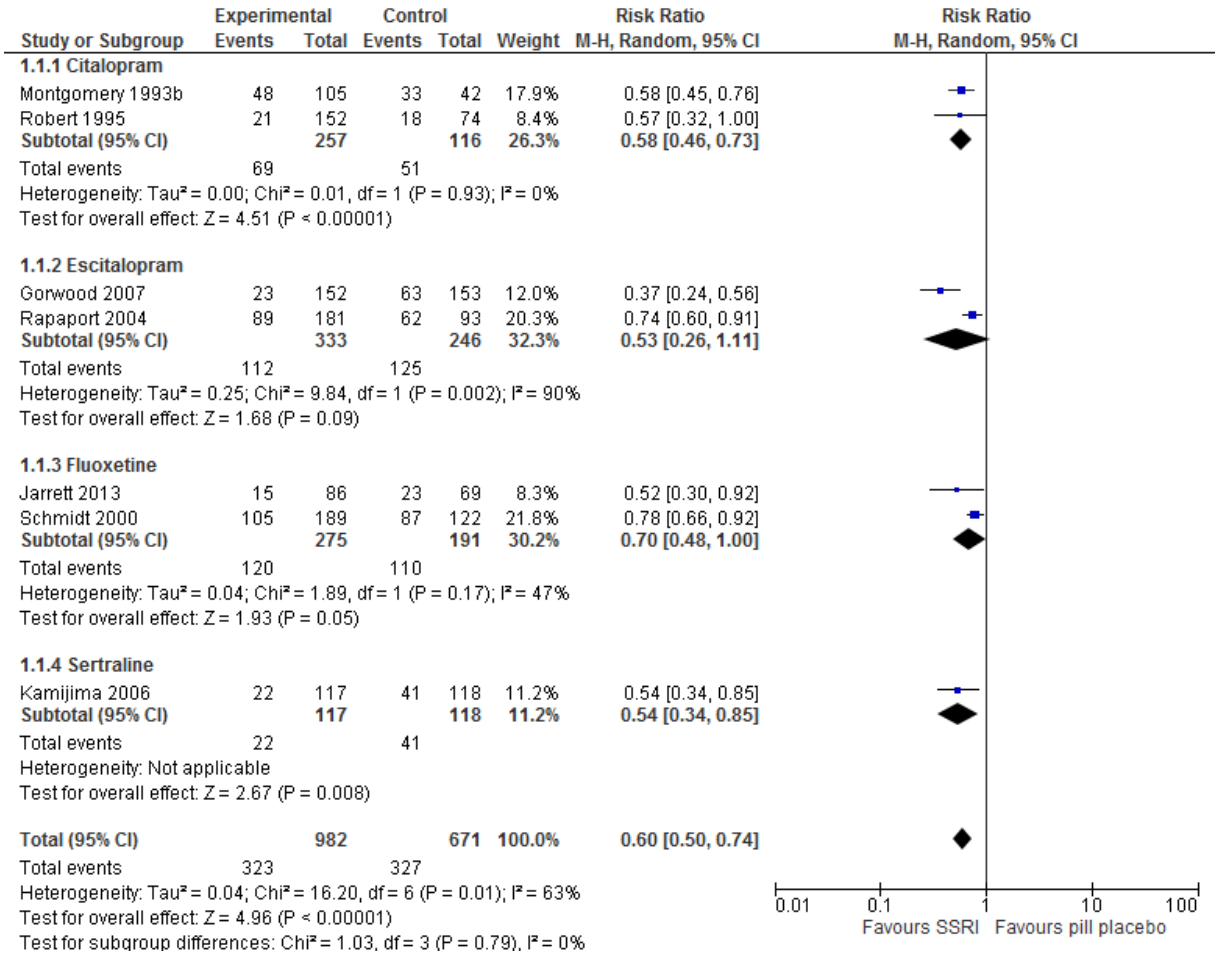


Figure 73: Relapse at 44-48 weeks post-randomisation (ITT)

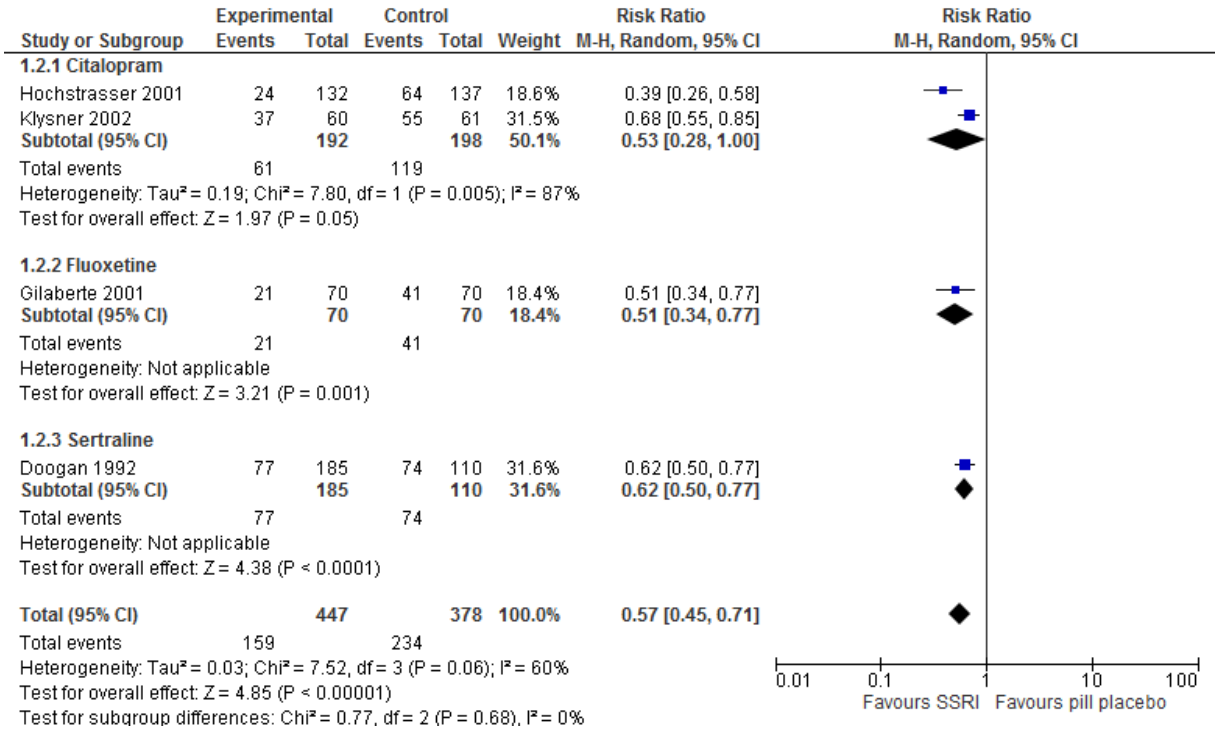


Figure 74: Relapse at 52-87 weeks post-randomisation (ITT)

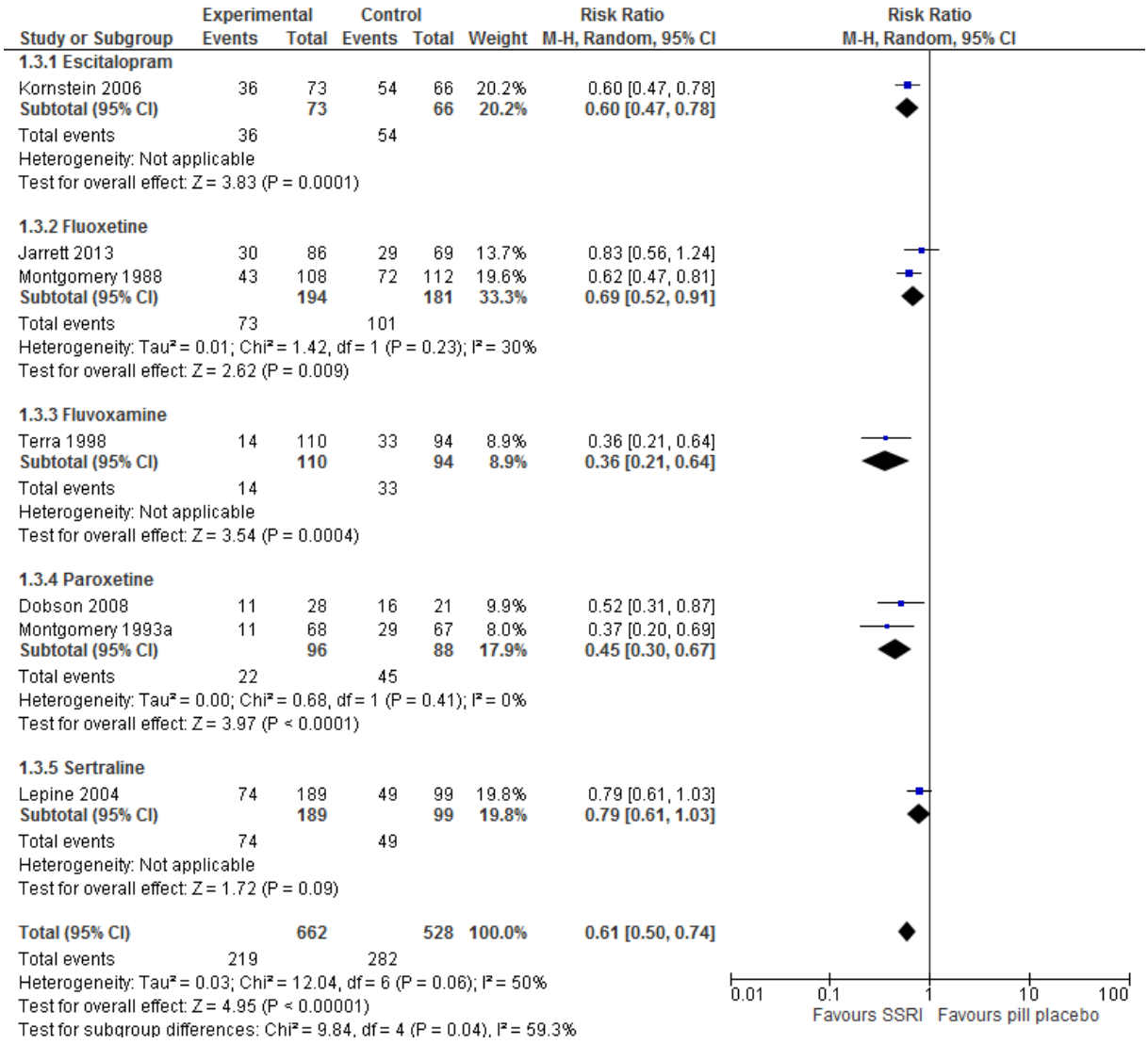


Figure 75: Relapse at 100-139 weeks post-randomisation (ITT)

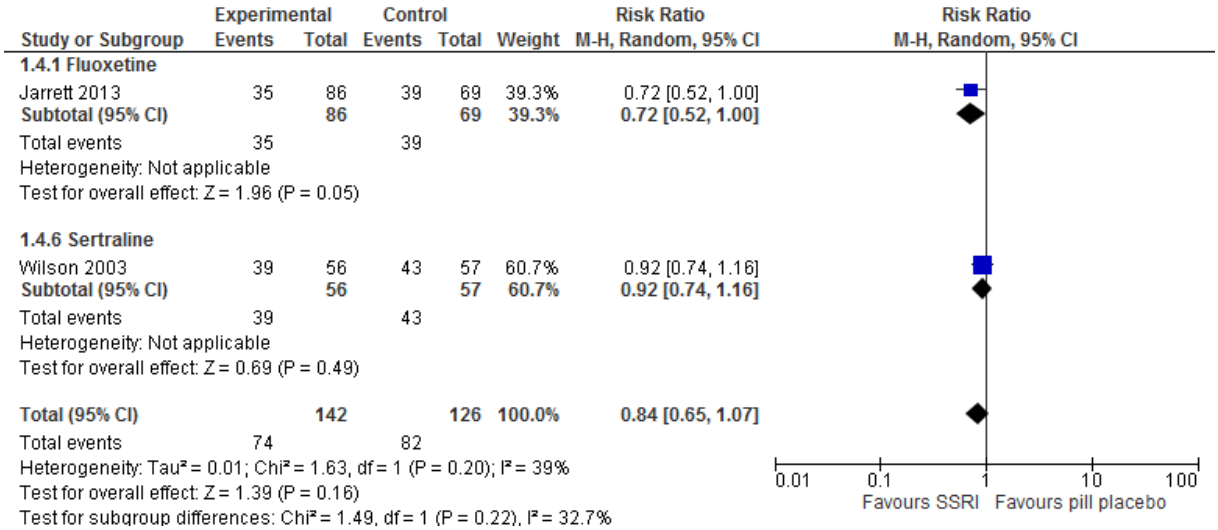
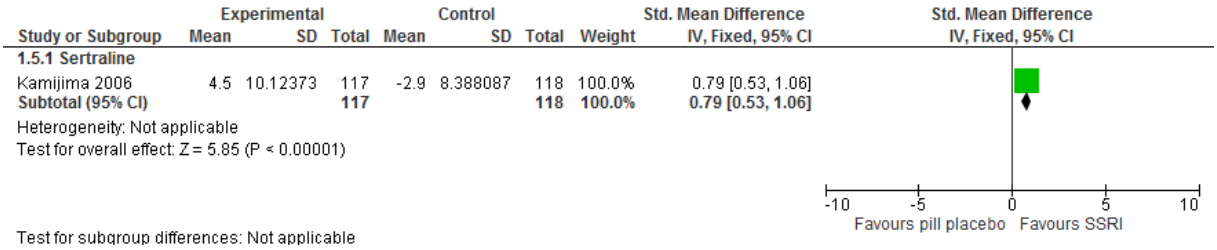
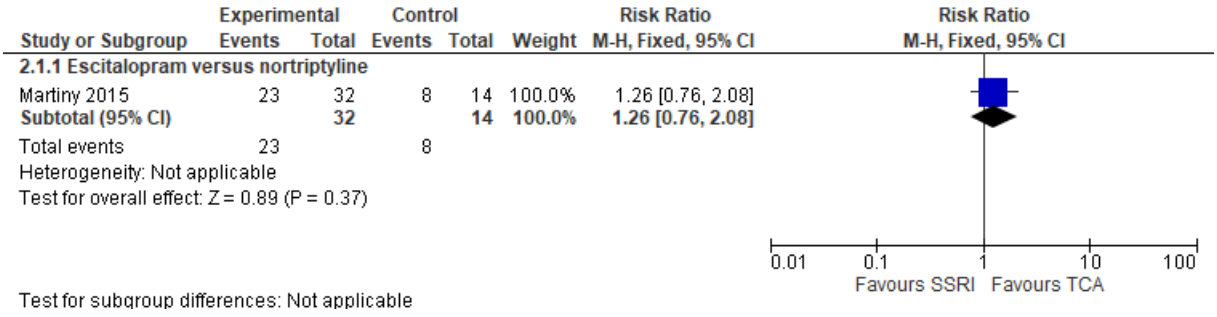


Figure 76: Quality of life change score at 16 weeks post-randomisation



Comparison 20. SSRI versus TCA

Figure 77: Relapse at 25 weeks post-randomisation (ITT)



Comparison 21. TCAs versus pill placebo

Figure 78: Relapse at 26-35 weeks post-randomisation (ITT)

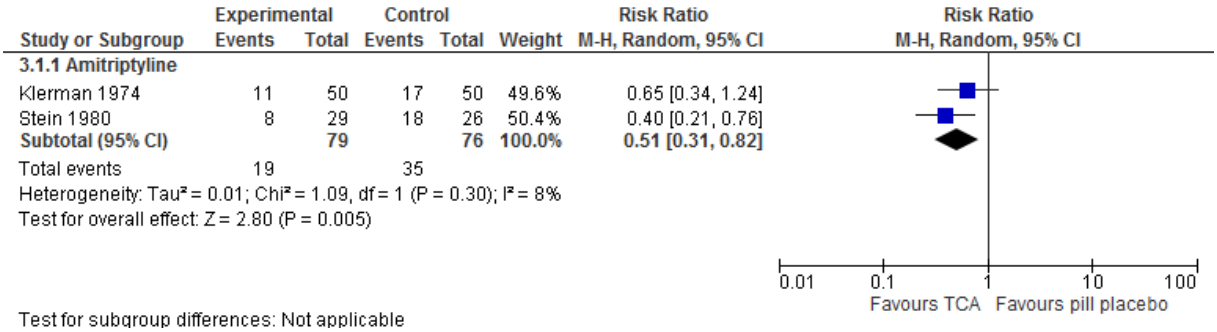


Figure 79: Relapse at 52 weeks post-randomisation (ITT)

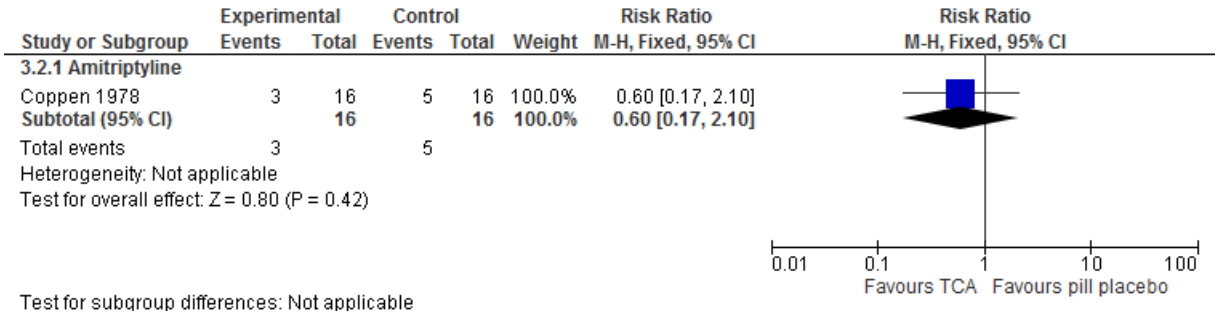
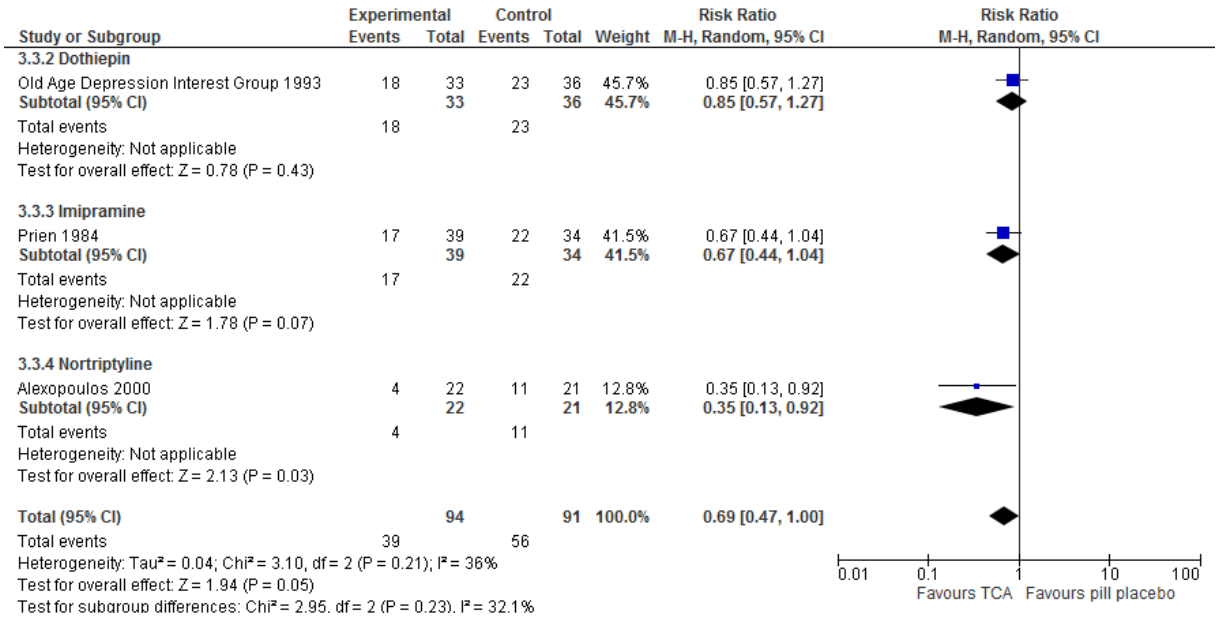
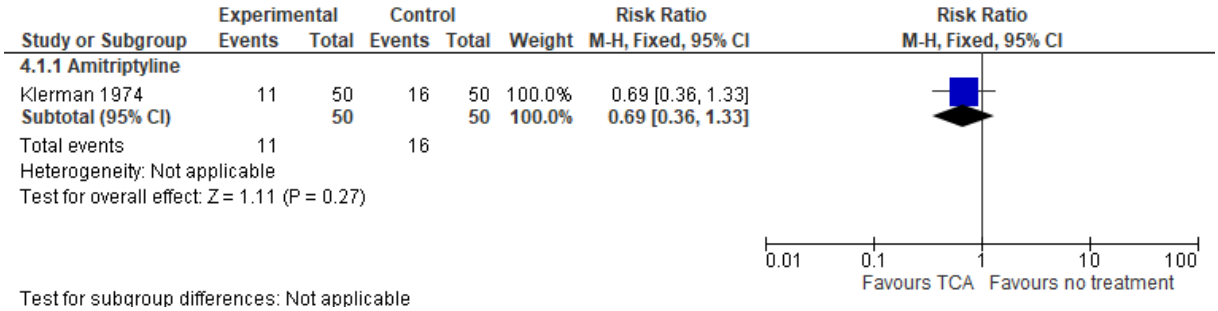


Figure 80: Relapse at 104 weeks post-randomisation (ITT)



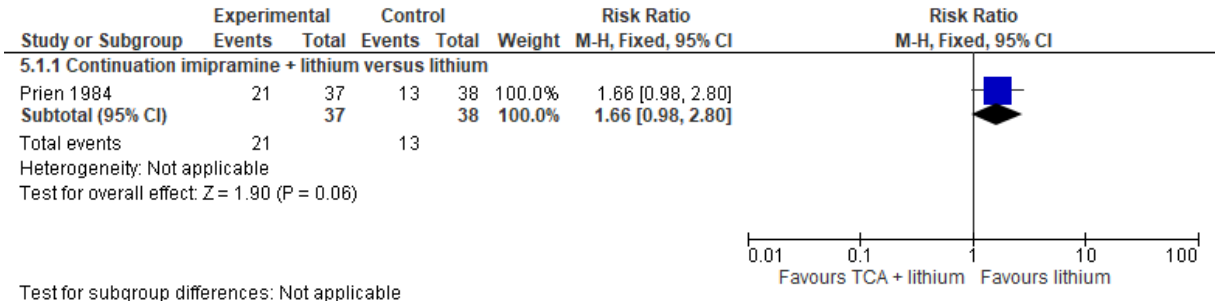
Comparison 22. TCA versus no treatment

Figure 81: Relapse at 35 weeks post-randomisation (ITT)



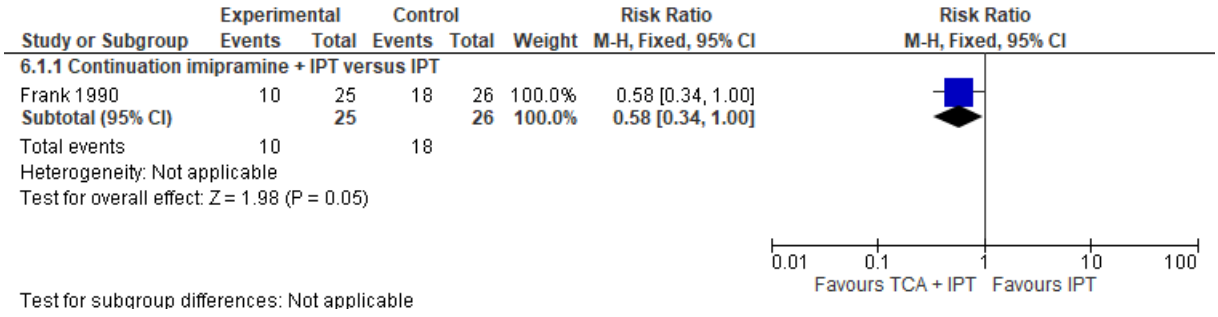
Comparison 23. TCA + lithium versus lithium

Figure 82: Relapse at 104 weeks post-randomisation (ITT)



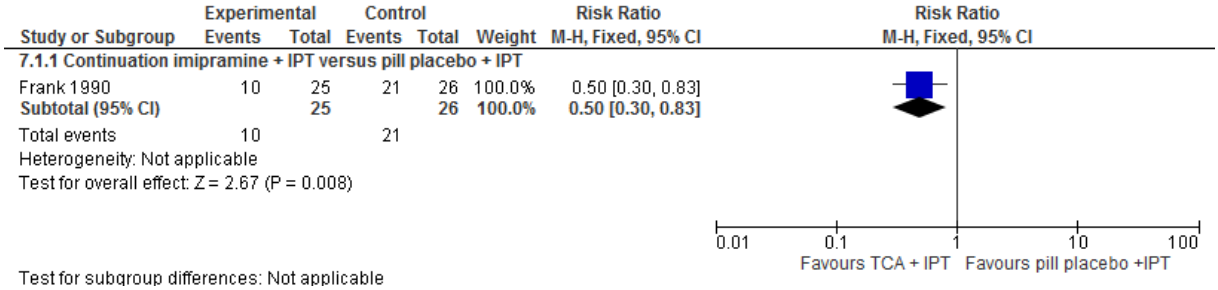
Comparison 24. TCA + IPT versus IPT

Figure 83: Relapse at 156 weeks post-randomisation (ITT)



Comparison 25. TCA + IPT versus pill placebo + IPT

Figure 84: Relapse at 156 weeks post-randomisation (ITT)



Comparison 26. SNRIs versus pill placebo

Figure 85: Relapse at 26 weeks post-randomisation (ITT)

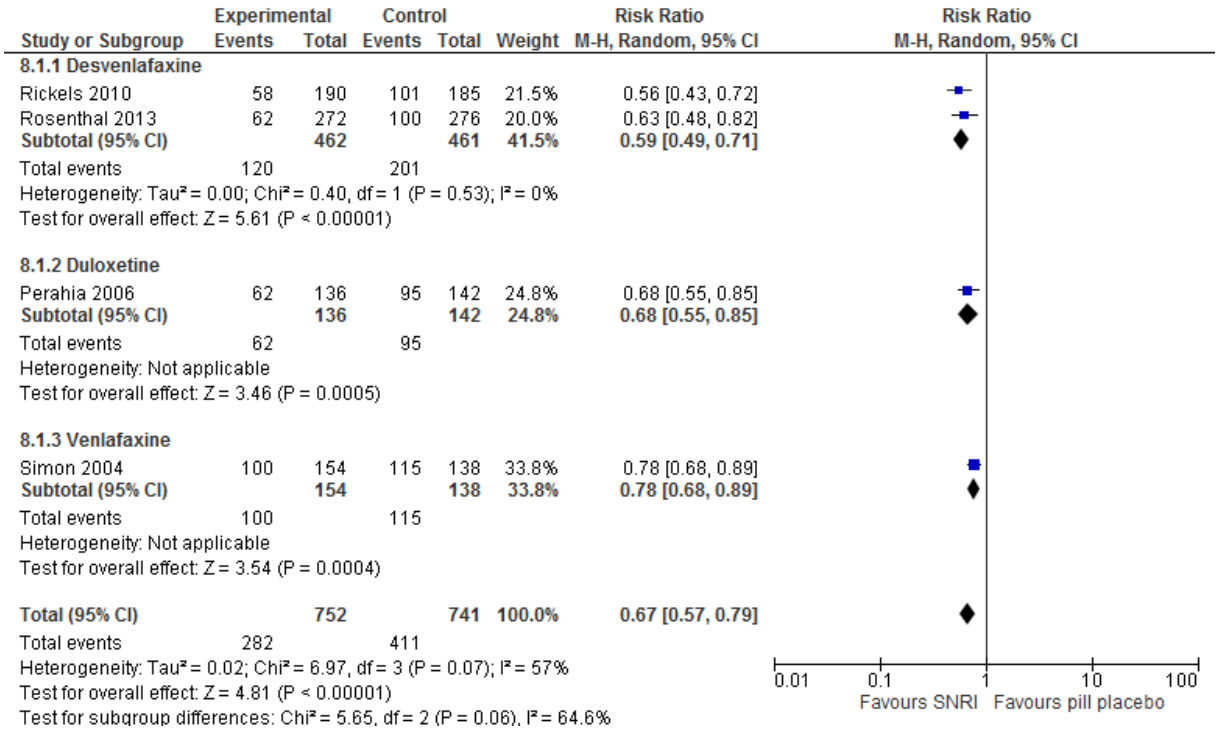


Figure 86: Relapse at 52 weeks post-randomisation (ITT)

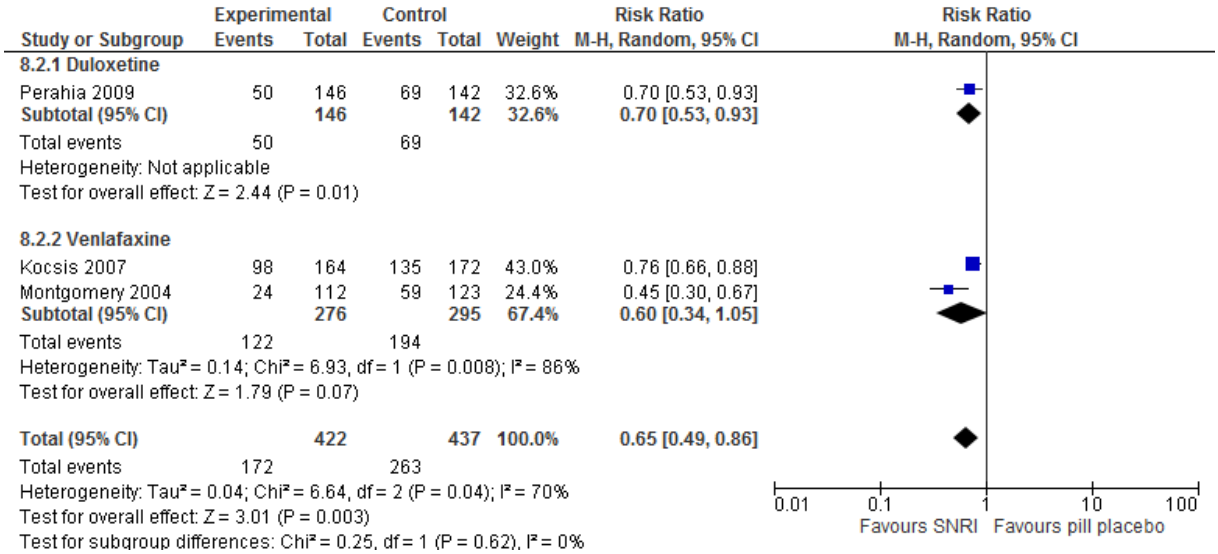


Figure 87: Functional impairment at 52 weeks post-randomisation

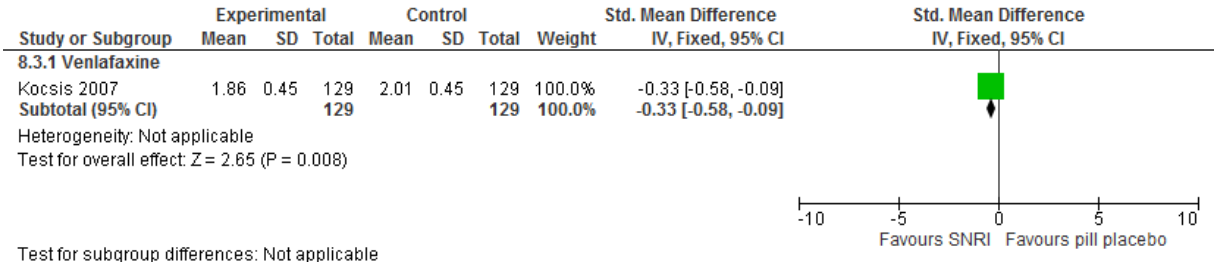


Figure 88: Functional impairment change score at 52 weeks post-randomisation

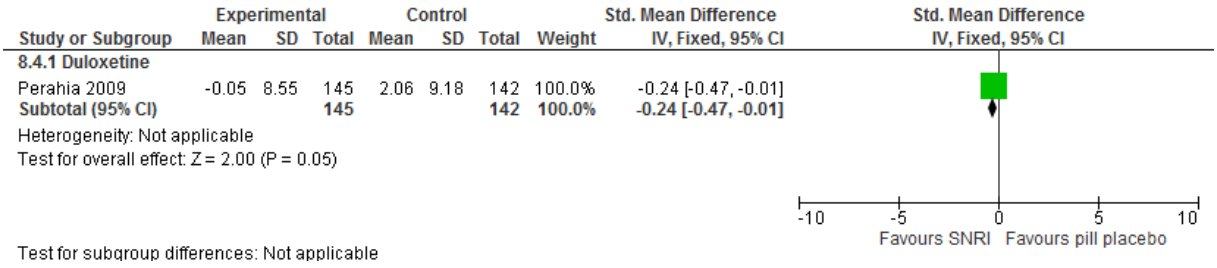


Figure 89: Quality of life at 52 weeks post-randomisation

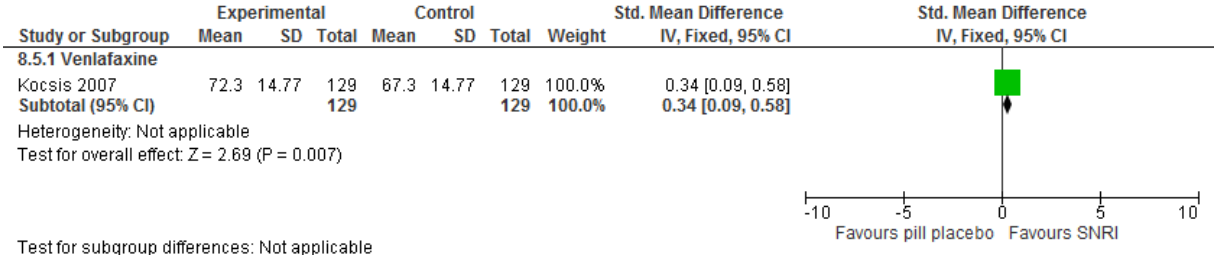


Figure 90: Quality of life physical component change score at 52 weeks post-randomisation

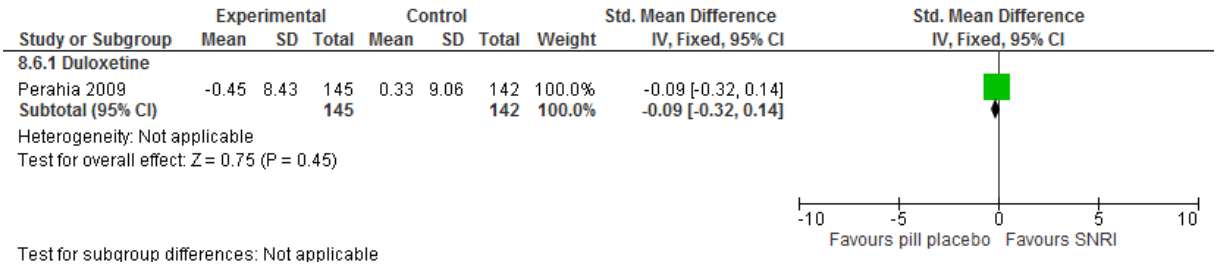
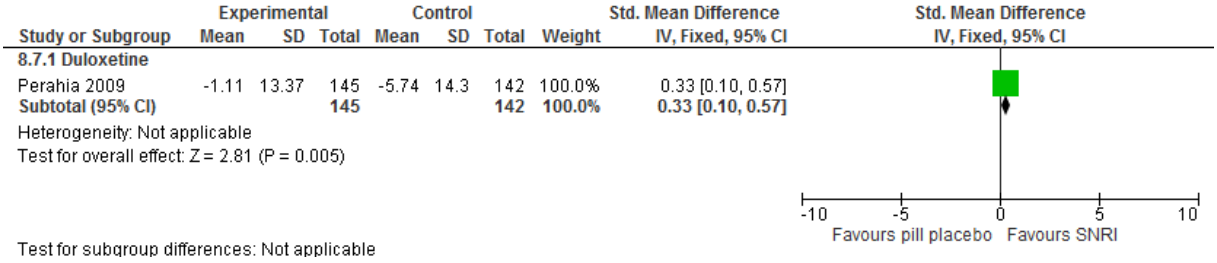


Figure 91: Quality of life mental component change score at 52 weeks post-randomisation



Comparison 27. Antipsychotic versus pill placebo

Figure 92: Relapse at 52 weeks post-randomisation (ITT)

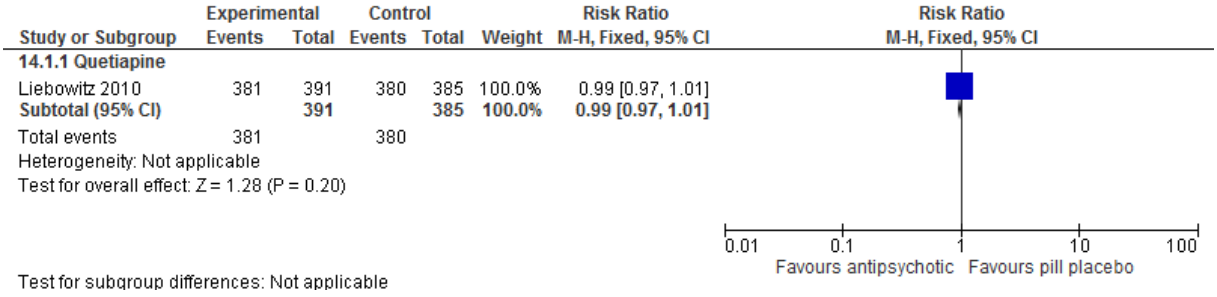


Figure 93: Sleeping difficulties change score at 52 weeks post-randomisation

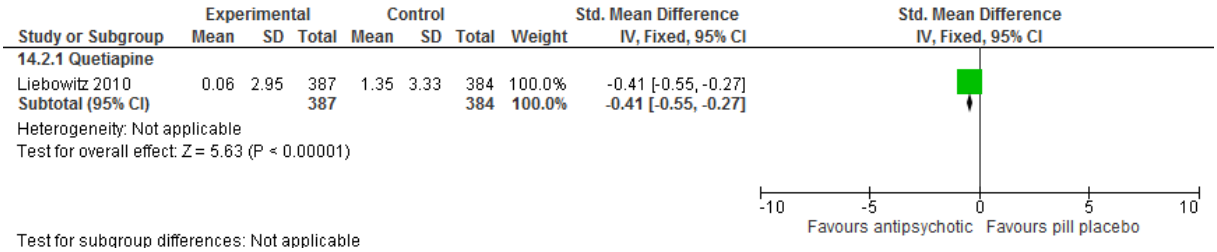
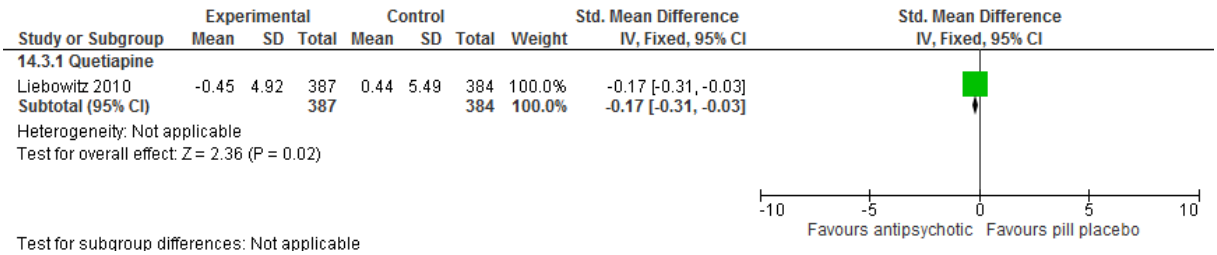
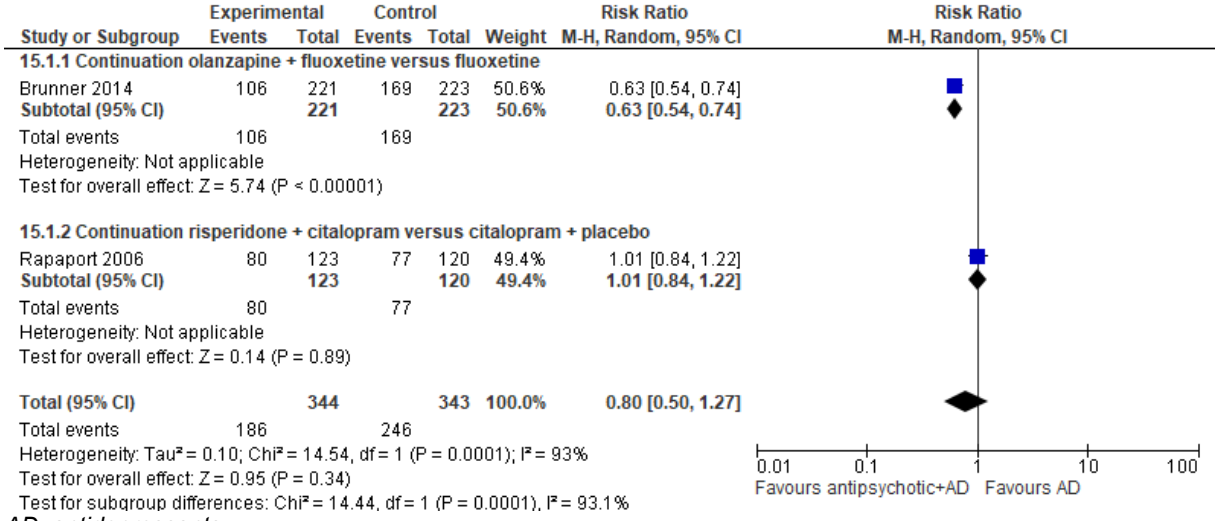


Figure 94: Functional impairment change score at 52 weeks post-randomisation



Comparison 28. Antipsychotics + antidepressant versus antidepressant

Figure 95: Relapse at 24-27 weeks post-randomisation (ITT)



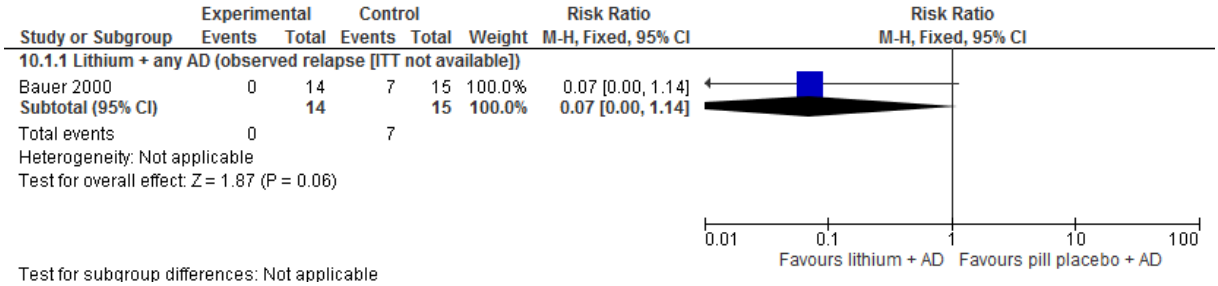
AD: antidepressants

Comparison 29. Lithium versus pill placebo

Figure 96: Relapse at 104 weeks post-randomisation (ITT)

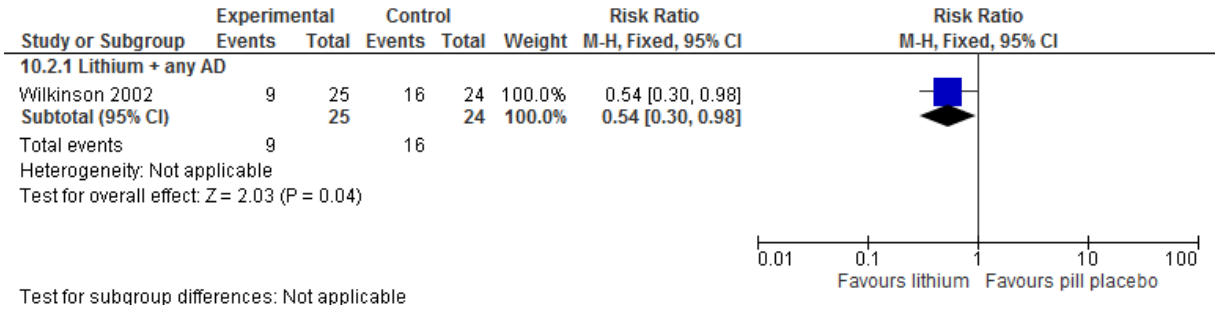
Comparison 30. Lithium + antidepressant versus pill placebo + antidepressant

Figure 97: Relapse at 16 weeks post-randomisation



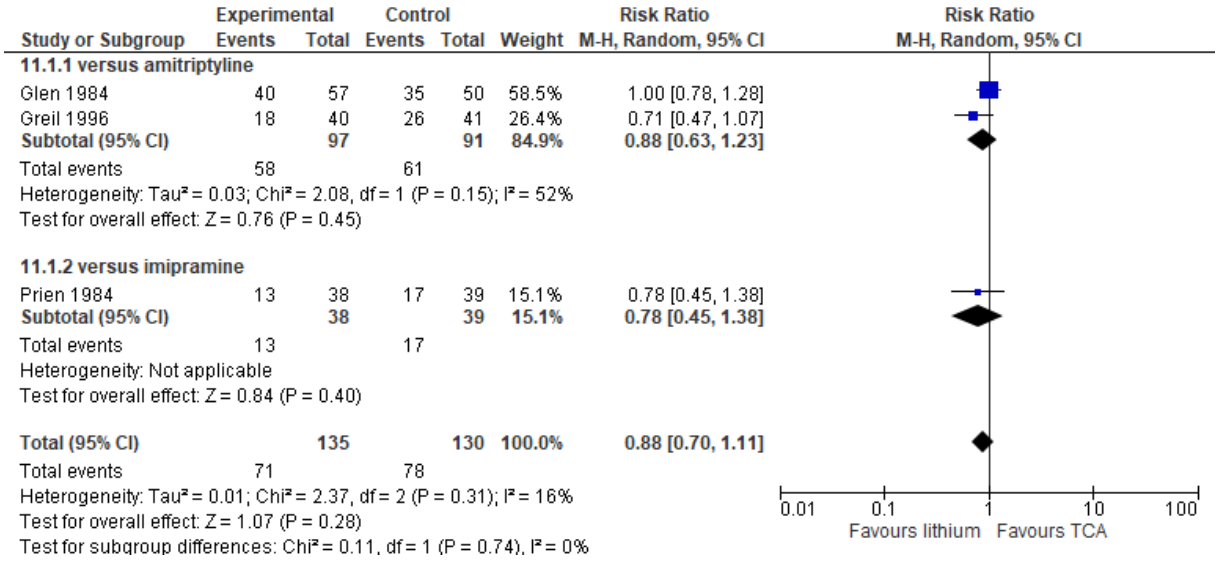
AD: antidepressants

Figure 98: Relapse at 104 weeks post-randomisation (ITT)



Comparison 31. Lithium versus TCAs

Figure 99: Relapse at 104-156 weeks post-randomisation (ITT)



Comparison 32. Lithium + TCA versus pill placebo

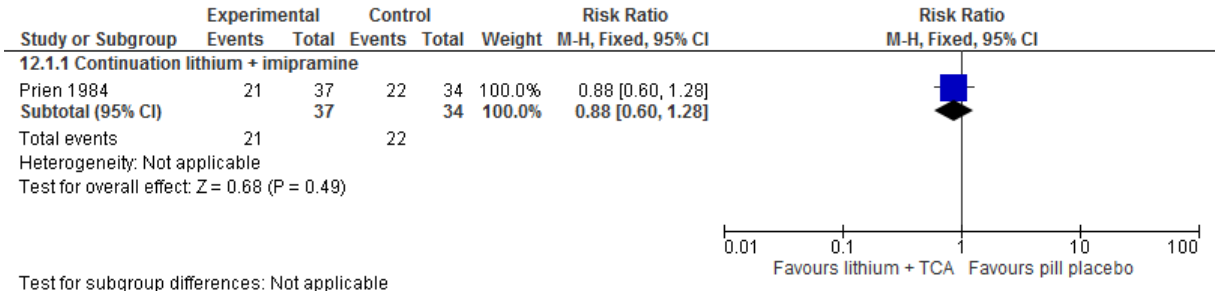
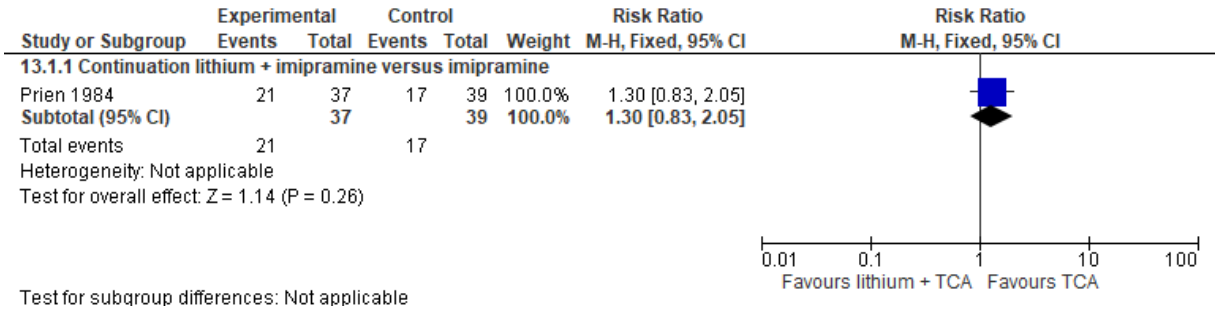


Figure 100: Relapse at 104 weeks post-randomisation (ITT)

Comparison 33. Lithium + TCA versus TCA

Figure 101: Relapse at 104 weeks post-randomisation (ITT)



Comparison 34. ECT + pharmacological intervention versus pharmacological intervention

Figure 102: Relapse at 24-26 weeks post-randomisation (ITT)

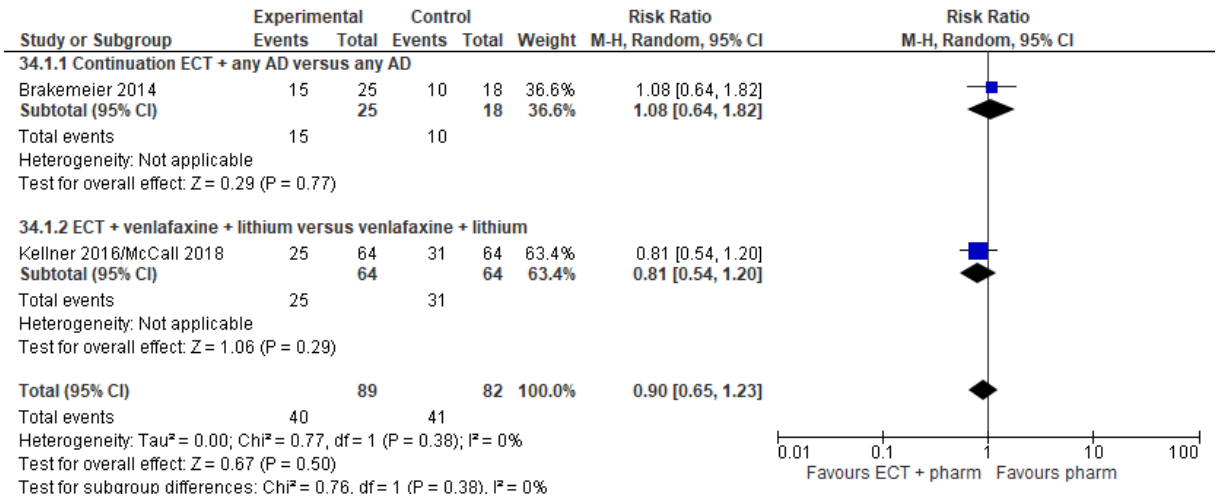


Figure 103: Relapse at 52 weeks post-randomisation (ITT)

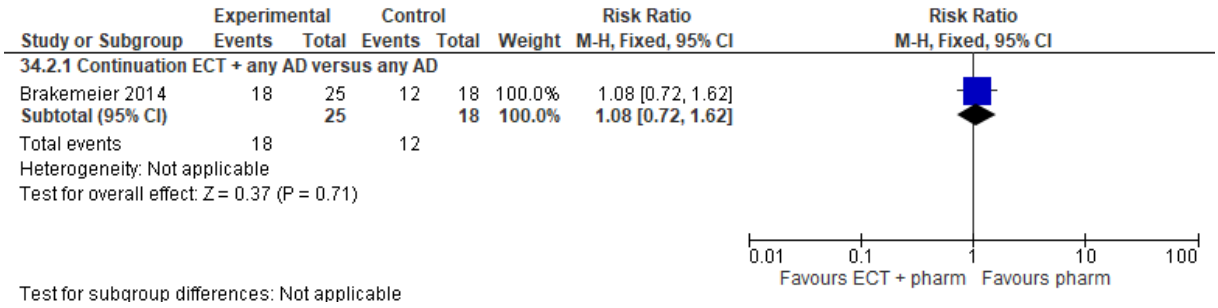


Figure 104: Quality of life physical component score (PCS) change score at 24 weeks post-randomisation

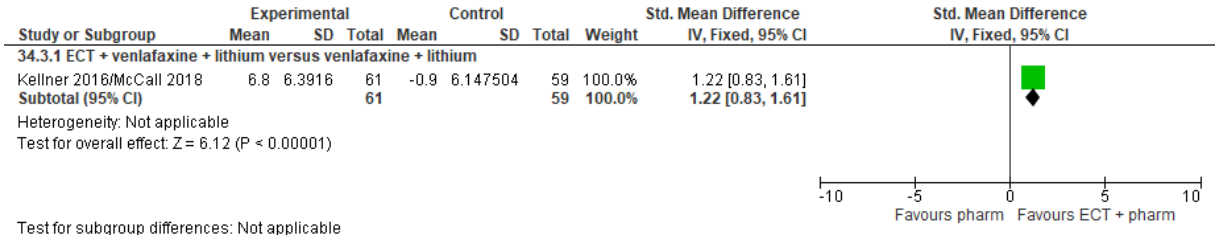
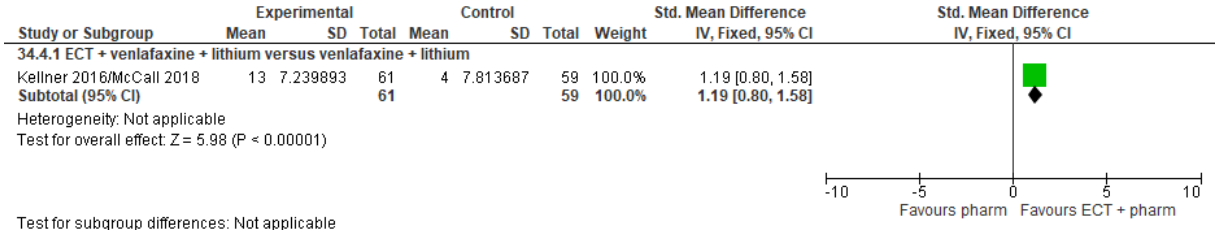


Figure 105: Quality of life mental component score (MCS) change score at 24 weeks post-randomisation



Appendix F – GRADE tables

GRADE tables for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Comparison 1: Cognitive and cognitive behavioural therapies versus no treatment

Table 37: Clinical evidence profile for comparison 1: cognitive and cognitive behavioural therapies versus no treatment

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies	No treatment	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 35 weeks post-randomisation (ITT) (follow-up mean 35 weeks; assessed with: Met DSM-IV criteria for MDD (i.e. LIFE PSR score of 5 or 6 for 2 weeks))												
1 (Jarrett 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/41 (19.5%)	18/43 (41.9%)	RR 0.47 (0.23 to 0.95)	222 fewer per 1000 (from 21 fewer to 322 fewer)	MODERATE	CRITICAL
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Met DSM-IV criteria for MDD (i.e. LIFE PSR score of 5 or 6 for 2 weeks))												
1 (Jarrett 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	21/41 (51.2%)	25/43 (58.1%)	RR 0.88 (0.6 to 1.3)	70 fewer per 1000 (from 233 fewer to 174 more)	LOW	CRITICAL

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; LIFE: longitudinal interval follow-up evaluation; MDD: major depressive disorder; PSR: psychiatric rating scale; RR: relative risk

[1] *95% CI crosses thresholds for both no effect and clinically important benefit*

[2] *95% CI crosses threshold for no effect and thresholds for both clinically important benefit and harm*

Comparison 2: Cognitive and cognitive behavioural therapies versus TAU

Table 38: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies versus TAU

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies	TAU	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 124 weeks post-randomisation (ITT) (follow-up mean 124 weeks; assessed with: RDC-defined episode of major depression)												
1 (Fava 1994/ 1996/ 1998c)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/21 (19%)	9/22 (40.9 %)	RR 0.47 (0.17 to 1.28)	217 fewer per 1000 (from 340 fewer to 115 more)	VERY LOW	CRITICAL
Relapse at 228 weeks post-randomisation (ITT) (follow-up mean 228 weeks; assessed with: RDC-defined episode of major depression)												
1 (Fava 1994/ 1996/ 1998c)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	8/21 (38.1%)	16/22 (72.7 %)	RR 0.52 (0.29 to 0.96)	349 fewer per 1000 (from 29 fewer to 516 fewer)	VERY LOW	CRITICAL
Relapse at 332 weeks post-randomisation (ITT) (follow-up mean 332 weeks; assessed with: RDC-defined episode of major depression)												
1 (Fava 1994/ 1996/ 1998c)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/21 (52.4%)	17/22 (77.3 %)	RR 0.68 (0.43 to 1.08)	247 fewer per 1000 (from 440 fewer to 62 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk; TAU: treatment as usual
[1] Significant group difference at baseline
[2] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm
[3] 95% CI crosses threshold for both no effect and clinically important benefit

Comparison 3: Cognitive and cognitive behavioural therapies + TAU versus TAU

Table 39: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies + TAU versus TAU

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + TAU	TAU	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 13 weeks post-randomisation (ITT) (follow-up mean 13 weeks; assessed with: Met DSM-IV criteria for relapse or recurrence (assessed with SCID-I))												
1 (Bockting 2005/ Bockting 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/97 (19.6%)	28/90 (31.1%)	RR 0.63 (0.38 to 1.05)	115 fewer per 1000 (from 193 fewer to 16 more)	VERY LOW	CRITICAL
Relapse at 26 weeks post-randomisation (ITT) (follow-up mean 26 weeks; assessed with: Met DSM-IV criteria for relapse or recurrence (assessed with SCID-I))												
1 (Bockting 2005/ Bockting 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/97 (29.9%)	36/90 (40%)	RR 0.75 (0.5 to 1.11)	100 fewer per 1000 (from 200 fewer to 44 more)	VERY LOW	CRITICAL
Relapse at 39 weeks post-randomisation (ITT) (follow-up mean 39 weeks; assessed with: Met DSM-IV criteria for relapse or recurrence (assessed with SCID-I))												
1 (Bockting 2005/ Bockting 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38/97 (39.2%)	41/90 (45.6%)	RR 0.86 (0.61 to 1.2)	64 fewer per 1000 (from 178 fewer to 91 more)	VERY LOW	CRITICAL
Relapse at 52-65 weeks post-randomisation (ITT) (follow-up 52-65 weeks; assessed with: Diagnostic criteria for major depression)												
8 (Bockting	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[2]	none	260/609 (42.7%)	293/545	RR 0.79 (0.7 to 0.89)	113 fewer per 1000 (from 59	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + TAU	TAU	Relative (95% CI)	Absolute		
2005/ Bockting 2015, Bondolfi 2010, de Jonge 2019, Godfrin 2010, Ma 2004, Meadows 2014, Teasdale 2000, Williams 2014)		risk of bias						(53.8 %)		fewer to 161 fewer)		
Relapse at 78 weeks post-randomisation (ITT) (follow-up mean 78 weeks; assessed with: Met DSM-IV criteria for relapse or recurrence (assessed with SCID-I))												
1 (Bockting 2005/ Bockting 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/97 (51.5%)	58/90 (64.4 %)	RR 0.8 (0.63 to 1.02)	129 fewer per 1000 (from 238 fewer to 13 more)	VERY LOW	CRITICAL
Relapse at 104-113 weeks post-randomisation (ITT) (follow-up 104-113 weeks; assessed with: Diagnostic criteria for major depression)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + TAU	TAU	Relative (95% CI)	Absolute		
2 (Bockting 2005/ Bockting 2015, Meadows 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122/198 (61.6%)	129/192 (67.2%)	RR 0.92 (0.79 to 1.06)	54 fewer per 1000 (from 141 fewer to 40 more)	VERY LOW	CRITICAL
Relapse at 520 weeks post-randomisation (ITT) (follow-up mean 520 weeks; assessed with: Met DSM-IV criteria for relapse or recurrence (assessed with SCID-I))												
1 (Bockting 2005/ Bockting 2015)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/97 (88.7%)	85/90 (94.4%)	RR 0.94 (0.86 to 1.02)	57 fewer per 1000 (from 132 fewer to 19 more)	LOW	CRITICAL
Quality of life impairment at 8 weeks post-randomisation (follow-up mean 8 weeks; measured with: Quality of Life in Depression Scale (QLDS); Better indicated by lower values)												
1 (Godfrin 2010)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	41	-	SMD 0.99 lower (1.47 to 0.5 lower)	MODERATE	IMPORTANT
Quality of life impairment at 34 weeks post-randomisation (follow-up mean 34 weeks; measured with: Quality of Life in Depression Scale (QLDS); Better indicated by lower values)												
1 (Godfrin 2010)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	34	41	-	SMD 0.65 lower (1.12 to 0.19 lower)	LOW	IMPORTANT
Quality of life impairment at 60 weeks post-randomisation (follow-up mean 60 weeks; measured with: Quality of Life in Depression Scale (QLDS); Better indicated by lower values)												
1 (Godfrin 2010)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	34	41	-	SMD 0.67 lower (1.14 to 0.2 lower)	LOW	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; RR: relative risk; SCID-I: structured clinical interview for DSM-IV axis I disorders; SMD: standardised mean difference; TAU: treatment as usual

[1] *Significant group difference at baseline*

[2] *95% CI crosses threshold for both no effect and clinically important benefit*

[3] *Unclear risk of detection bias (self-reported outcome)*

Comparison 4: Cognitive and cognitive behavioural therapies + TAU versus attention placebo + TAU

Table 40: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies + TAU versus attention placebo + TAU

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + TAU	Attention placebo + TAU	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 60 weeks post-randomisation (ITT) (follow-up mean 60 weeks; assessed with: Met DSM-IV criteria for relapse (assessed with SCID))												
2 (Shallcross 2015/ 2018, Williams 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	70/154 (45.5%)	73/156 (46.8%)	RR 0.97 (0.77 to 1.22)	14 fewer per 1000 (from 108 fewer to 103 more)	MODERATE	CRITICAL
Relapse at 121 weeks post-randomisation (ITT) (follow-up mean 121 weeks; assessed with: Met DSM-IV criteria for relapse (assessed with SCID))												
1 (Shallcross 2015/ 2018)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/46 (47.8%)	23/46 (50%)	RR 0.96 (0.63 to 1.45)	20 fewer per 1000 (from 185 fewer to 225 more)	VERY LOW	CRITICAL
Quality of life change score at 8 weeks post-randomisation (follow-up mean 8 weeks; measured with: Satisfaction with Life Scale (SWL); Better indicated by higher values)												
1 (Shallcross 2015/ 2018)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	46	46	-	SMD 0.44 lower (0.85 to 0.03 lower)	VERY LOW	IMPORTANT
Quality of life change score at 34 weeks post-randomisation (follow-up mean 34 weeks; measured with: Satisfaction with Life Scale (SWL); Better indicated by higher values)												
1 (Shallcross 2015/ 2018)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	46	46	-	SMD 0.35 lower (0.76 lower to 0.06 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + TAU	Attention placebo + TAU	Relative (95% CI)	Absolute		
Quality of life change score at 60 weeks post-randomisation (follow-up mean 60 weeks; measured with: Satisfaction with Life Scale (SWL); Better indicated by higher values)												
1 (Shallcross 2015/ 2018)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	46	46	-	SMD 0.19 higher (0.22 lower to 0.6 higher)	VERY LOW	IMPORTANT
Quality of life change score at 121 weeks post-randomisation (follow-up mean 121 weeks; measured with: Satisfaction with Life Scale (SWL); Better indicated by higher values)												
1 (Shallcross 2015/ 2018)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	46	46	-	SMD 0.09 lower (0.5 lower to 0.32 higher)	VERY LOW	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; RR: relative risk; SCID: structured clinical interview for DSM-IV axis I disorders; SMD: standardised mean difference; TAU: treatment as usual

[1] 95% CI crosses thresholds for both no effect and clinically important benefit

[2] Significant group difference at baseline

[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

[4] 95% CI crosses threshold for both no effect and clinically important harm (SMD -0.5 as better indicated by higher values for these outcomes)

Comparison 5: Cognitive and cognitive behavioural therapies versus pill placebo

Table 41: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 35 weeks post-randomisation (ITT) (follow-up mean 35 weeks; assessed with: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks))												
1 (Jarrett 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/86 (18.6%)	23/69 (33.3%)	RR 0.56 (0.32 to 0.97)	147 fewer per 1000 (from 10 fewer to 227 fewer)	MODERATE	CRITICAL
Relapse at 87 weeks post-randomisation (ITT) (follow-up mean 87 weeks; assessed with: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks))												
1 (Jarrett 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30/86 (34.9%)	29/69 (42%)	RR 0.83 (0.56 to 1.24)	71 fewer per 1000 (from 185 fewer to 101 more)	MODERATE	CRITICAL
Relapse at 139 weeks post-randomisation (ITT) (follow-up mean 139 weeks; assessed with: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks))												
1 (Jarrett 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39/86 (45.3%)	39/69 (56.5%)	RR 0.8 (0.59 to 1.09)	113 fewer per 1000 (from 232 fewer to 51 more)	MODERATE	CRITICAL

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; LIFE: longitudinal interval follow-up evaluation; MDD: major depressive disorder; PSR: psychiatric rating scale; RR: relative risk

[1] 95% CI crosses thresholds for both no effect and clinically important benefit

Comparison 6: Cognitive and cognitive behavioural therapies (+/- TAU) versus psychoeducation (+/- TAU)

Table 42: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies (+/- TAU) versus psychoeducation (+/- TAU)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies (+/- TAU)	Psychoeducation (+/- TAU)	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 62-87 weeks post-randomisation (ITT) (follow-up 62-87 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence)												
2 (Elices 2017, Stangier 2013)	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	57/127 (44.9%)	75/128 (58.6%)	RR 0.73 (0.47 to 1.12)	158 fewer per 1000 (from 311 fewer to 70 more)	VERY LOW	CRITICAL

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; RR: relative risk
[1] Significant group difference at baseline in study contributing >50% to weighting
[2] Considerable heterogeneity
[3] 95% CI crosses threshold for both no effect and clinically important benefit

Comparison 7. Mindfulness-based cognitive therapy (MBCT) group (+ TAU) versus cognitive therapy group (+ TAU)

Table 43: Clinical evidence profile for comparison mindfulness-based cognitive therapy (MBCT) group (+ TAU) versus cognitive therapy group (+ TAU)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mindfulness-based cognitive therapy (MBCT) group + TAU**	**Cognitive therapy group + TAU**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID))												
1 (Farb 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	33/82 (40.2%)	37/84 (44%)	RR 0.91 (0.64 to 1.31)	40 fewer per 1000 (from 159 fewer to 137 more)	VERY LOW	CRITICAL

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; RR: relative risk; SCID: structured clinical interview for DSM-IV axis I disorders; TAU: treatment as usual

[1] Significant group difference at baseline and unclear blinding of outcome assessment

[2] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Comparison 8. Cognitive and cognitive behavioural therapies versus antidepressants

Table 44: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies versus antidepressants

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies	AD	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 22-35 weeks post-randomisation (ITT) (follow-up 22-35 weeks; assessed with: Diagnostic criteria for major depression)												
3 (Bockting 2018, Kuyken 2015a/ 2015b, Jarrett 2013)	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[2]	none	111/383 (29%)	119/ 398 (29.9 %)	RR 1.02 (0.71 to 1.47)	6 more per 1000 (from 87 fewer to 141 more)	VERY LOW	CRITICAL
Relapse at 43 weeks post-randomisation (ITT) (follow-up mean 43 weeks; assessed with: Diagnostic criteria for major depression)												
2 (Bockting 2018, Kuyken 2015a/ 2015b)	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	133/297 (44.8%)	138/ 312 (44.2 %)	RR 1.03 (0.86 to 1.22)	13 more per 1000 (from 62 fewer to 97 more)	MODERATE	CRITICAL
Relapse at 57-65 weeks post-randomisation (follow-up 57-65 weeks; assessed with: Diagnostic criteria for major depression)												
3 (Bockting 2018, Kuyken 2008, Kuyke	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/358 (51.7%)	202/ 374 (54%)	RR 0.97 (0.83 to 1.14)	16 fewer per 1000 (from 92 fewer to 76 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies	AD	Relative (95% CI)	Absolute		
n 2015a/ 2015b)												
Relapse at 87-100 weeks post-randomisation (ITT) (follow-up 87-100 weeks; assessed with: Diagnostic criteria for major depression)												
3 (Bockting 2018, Kuyken 2015a/ 2015b, Jarrett 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	206/383 (53.8%)	213/ 398 (53.5 %)	RR 1.03 (0.92 to 1.17)	16 more per 1000 (from 43 fewer to 91 more)	HIGH	CRITICAL
Relapse at 139 weeks post-randomisation (ITT) (follow-up mean 139 weeks; assessed with: Met DSM-IV criteria for MDD (ie, LIFE PSR score of 5 or 6 for 2 consecutive weeks))												
1 (Jarrett 2013)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	39/86 (45.3%)	35/86 (40.7 %)	RR 1.11 (0.79 to 1.57)	45 more per 1000 (from 85 fewer to 232 more)	LOW	CRITICAL
Quality of life at 12 weeks post-randomisation (follow-up mean 12 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Kuyken 2015a/ 2015b)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	174	173	-	SMD 0 higher (0.21 lower to 0.21 higher)	MODERATE	IMPORTANT
Quality of life at 39 weeks post-randomisation (follow-up mean 39 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Kuyken 2015a/ 2015b)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	151	141	-	SMD 0.23 lower (0.46 lower to 0 higher)	MODERATE	IMPORTANT
Quality of life at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive and cognitive behavioural therapies**	**AD**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1 (Kuyken 2015a/ 2015b)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	166	157	-	SMD 0.22 lower (0.44 lower to 0 higher)	MODERATE	IMPORTANT
Quality of life at 78 weeks post-randomisation (follow-up mean 78 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Kuyken 2015a/ 2015b)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	141	157	-	SMD 0.22 lower (0.45 lower to 0.01 higher)	MODERATE	IMPORTANT
Quality of life at 104 weeks post-randomisation (follow-up mean 104 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Kuyken 2015a/ 2015b)	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	169	167	-	SMD 0.1 lower (0.32 lower to 0.11 higher)	MODERATE	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; LIFE: longitudinal interval follow-up evaluation; MDD: major depressive disorder; PSR: psychiatric rating scale; QOL: quality of life; RR: relative risk; SMD: standardised mean difference; WHOQOL-BREF: World Health Organization quality of life scale-abbreviated version

[1] Considerable heterogeneity

[2] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

[3] Unclear risk of detection bias (self-reported outcome)

Comparison 9. Cognitive and cognitive behavioural therapies + antidepressants versus antidepressants

Table 45: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies + antidepressants versus antidepressants

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + AD	AD	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 26-28 weeks post-randomisation (ITT) (follow-up 26-28 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
3 (Bockting 2018, Brakemeier 2014, Wilkinson 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55/143 (38.5%)	64/141 (45.4%)	RR 0.77 (0.48 to 1.22)	104 fewer per 1000 (from 236 fewer to 100 more)	MODERATE	CRITICAL
Relapse at 43 weeks (ITT) (follow-up mean 43 weeks; assessed with: Met DSM-IV-TR criteria for recurrence (assessed with SCID-I))												
1 (Bockting 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	52/104 (50%)	54/100 (54%)	RR 0.93 (0.71 to 1.21)	38 fewer per 1000 (from 157 fewer to 113 more)	MODERATE	CRITICAL
Relapse at 52-65 weeks post-randomisation (ITT) (follow-up 52-65 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
4 (Bockting 2018, Brakemeier 2014, Huijbers 2015,	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	82/176 (46.6%)	99/176 (56.3%)	RR 0.83 (0.68 to 1.01)	96 fewer per 1000 (from 180 fewer to 6 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive and cognitive behavioural therapies + AD	AD	Relative (95% CI)	Absolute		
Wilkinson 2009)												
Relapse at 100-104 weeks post-randomisation (ITT) (follow-up 100-104 weeks; assessed with: Diagnostic criteria for major depression)												
2 (Bockting 2018, Fava 1998a/ 2004)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[3]	none	72/127 (56.7%)	88/122 (72.1%)	RR 0.65 (0.32 to 1.32)	252 fewer per 1000 (from 490 fewer to 231 more)	VERY LOW	CRITICAL
Relapse at 310 weeks post-randomisation (ITT) (follow-up mean 310 weeks; assessed with: RDC-defined episode of major depression)												
1 (Fava 1998a/ 2004)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[1]	none	11/23 (47.8%)	20/22 (90.9%)	RR 0.53 (0.34 to 0.82)	427 fewer per 1000 (from 164 fewer to 600 fewer)	LOW	CRITICAL
Quality of life at 12 weeks post-randomisation (follow-up mean 12 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Huijbers 2015)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	27	27	-	SMD 0 higher (0.53 lower to 0.53 higher)	VERY LOW	IMPORTANT
Quality of life at 65 weeks post-randomisation (follow-up mean 65 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Huijbers 2015)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	26	24	-	SMD 0.29 lower (0.85 lower to 0.27 higher)	VERY LOW	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; QOL: quality of life; RDC: research diagnostic criteria; RR: relative risk; SCID-I: structured clinical interview for DSM-IV axis I disorders; SMD: standardised mean difference; WHOQOL-BREF: World Health Organization quality of life scale-abbreviated version

[1] 95% CI crosses thresholds for both no effect and clinically important benefit

[2] Very serious heterogeneity

[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

[4] Unclear randomisation method and allocation concealment, and blinding of outcome assessment unclear

[5] Significant group difference at baseline, and unclear risk of detection bias (self-reported outcome)

Comparison 10. Cognitive and cognitive behavioural therapies + antidepressants versus ECT + antidepressants

Table 46: Clinical evidence profile for comparison cognitive and cognitive behavioural therapies + antidepressants versus ECT + antidepressants

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive and cognitive behavioural therapies + antidepressant**	**ECT + antidepressant**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 26 weeks post-randomisation (ITT) (follow-up mean 26 weeks; assessed with: Relapse was declared if the patient was hospitalised for symptomatic worsening and/or when HAMD scores increased by ≥ 18 points at a continuation measurement time point or increased from baseline ≥ 10 points)												
1 (Brakemeier 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	4/17 (23.5%)	15/25 (60 %)	RR 0.39 (0.16 to 0.98)	366 fewer per 1000 (from 12 fewer to 504 fewer)	MODERATE	CRITICAL
Relapse at 52 weeks post-randomisation (ITT) (follow-up mean 52 weeks; assessed with: Relapse was declared if the patient was hospitalised for symptomatic worsening and/or when HAMD scores increased by ≥ 18 points at a continuation measurement time point or increased from baseline ≥ 10 points)												
1 (Brakemeier 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	6/17 (35.3%)	18/25 (72 %)	RR 0.49 (0.25 to 0.98)	367 fewer per 1000 (from 14 fewer to 540 fewer)	MODERATE	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RR: relative risk

[1] 95% CI crosses threshold for both no effect and clinically important benefit

Comparison 11. Mindfulness-based cognitive therapy (MBCT) group + continuation antidepressant versus MBCT group (discontinuation antidepressant)

Table 47: Clinical evidence profile for comparison mindfulness-based cognitive therapy (MBCT) group + continuation antidepressant versus MBCT group (discontinuation antidepressant)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mindfulness-based cognitive therapy (MBCT) group + continuation antidepresant**	**MBCT group (discontinuation antidepressants)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 65 weeks post-randomisation (ITT) (follow-up mean 65 weeks; assessed with: Met DSM-IV criteria for MDD (assessed with SCID-I))												
1 (Huijbers 2016a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47/121 (38.8%)	69/128 (53.9%)	RR 0.72 (0.55 to 0.95)	151 fewer per 1000 (from 27 fewer to 243 fewer)	VERY LOW	CRITICAL

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; MDD: major depressive disorder; RR: relative risk; SCID: structured clinical interview for DSM-IV axis I disorders

[1] Non-blind outcome assessment

[2] 95% CI crosses thresholds for both no effect and clinically important benefit

Comparison 12. Interpersonal therapy (IPT) versus pill placebo

Table 48: Clinical evidence profile for comparison interpersonal therapy (IPT) versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/26 (69.2%)	21/23 (91.3%)	RR 0.76 (0.57 to 1.01)	219 fewer per 1000 (from 393 fewer to 9 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Significant difference between groups at baseline and rapid tapering of acute treatment
[2] 95% CI crosses the threshold for both no effect and clinically important benefit

Comparison 13. Interpersonal therapy (IPT) versus antidepressant

Table 49: Clinical evidence profile for comparison interpersonal therapy (IPT) versus antidepressant

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT	Antidepressant	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/26 (69.2%)	15/28 (53.6%)	RR 1.29 (0.84 to 1.99)	155 more per 1000 (from 86 fewer to 530 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Significant difference between groups at baseline and rapid tapering of acute treatment
[2] 95% CI crosses threshold for both no effect and clinically important harm

Comparison 14. Interpersonal therapy (IPT) + antidepressant versus antidepressant

Table 50: Clinical evidence profile for comparison interpersonal therapy (IPT) + antidepressant versus antidepressant

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
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/25 (40%)	15/28 (53.6%)	RR 0.75 (0.41 to 1.35)	134 fewer per 1000 (from 316 fewer to 188 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Significant difference between groups at baseline and rapid tapering of acute treatment
[2] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

Comparison 15. Interpersonal therapy (IPT) + antidepressant versus pill placebo

Table 51: Clinical evidence profile for comparison interpersonal therapy (IPT) + antidepressant versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT + antidepressant	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/25 (40%)	21/23 (91.3%)	RR 0.44 (0.27 to 0.72)	511 fewer per 1000 (from 256 fewer to 667 fewer)	LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Significant difference between groups at baseline and rapid tapering of acute treatment

Comparison 16. Interpersonal therapy (IPT) + pill placebo versus pill placebo

Table 52: Clinical evidence profile for comparison interpersonal therapy (IPT) + pill placebo versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPT + pill placebo	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious [2]	none	21/26 (80.8%)	21/23 (91.3%)	RR 0.88 (0.71 to 1.11)	110 fewer per 1000 (from 265 fewer to 100 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Significant difference between groups at baseline and rapid tapering of acute treatment

[2] *95% CI crosses thresholds for both no effect and clinically important benefit*

Comparison 17. Self-help + TAU versus TAU

Table 53: Clinical evidence profile for comparison self-help + TAU versus TAU

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-help + TAU	TAU	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 12-14 weeks post-randomisation (ITT) (follow-up 12-14 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
2 (Klein 2018a, Segal 2020)	randomised trials	serious[1]	very serious[2]	no serious indirectness	very serious[3]	none	89/362 (24.6%)	76/362 (21%)	RR 1.04 (0.27 to 4.01)	8 more per 1000 (from 153 fewer to 632 more)	VERY LOW	CRITICAL
Relapse at 28 weeks post-randomisation (ITT) (follow-up mean 28 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID-I))												
1 (Klein 2018a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	39/132 (29.5%)	55/132 (41.7%)	RR 0.71 (0.51 to 0.99)	121 fewer per 1000 (from 4 fewer to 204 fewer)	MODERATE	CRITICAL
Relapse at 43 weeks post-randomisation (ITT) (follow-up mean 43 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID-I))												
1 (Klein 2018a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	44/132 (33.3%)	67/132 (50.8%)	RR 0.66 (0.49 to 0.88)	173 fewer per 1000 (from 61 fewer to 259 fewer)	MODERATE	CRITICAL
Relapse at 52-65 weeks post-randomisation (ITT) (follow-up 52-65 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
3 (Bieshevuvel-Leliefeld 2017, Klein 2018a, Segal 2020)	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[3]	none	178/486 (36.6%)	188/486 (38.7%)	RR 0.93 (0.62 to 1.38)	27 fewer per 1000 (from 147 fewer to 147 more)	VERY LOW	CRITICAL
Relapse at 71 weeks post-randomisation (ITT) (follow-up mean 71 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID-I))												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-help + TAU	TAU	Relative (95% CI)	Absolute		
1 (Klein 2018a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	63/132 (47.7%)	77/132 (58.3%)	RR 0.82 (0.65 to 1.03)	105 fewer per 1000 (from 204 fewer to 17 more)	MODERATE	CRITICAL
Relapse at 85 weeks post-randomisation (ITT) (follow-up mean 85 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID-I))												
1 (Klein 2018a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	67/132 (50.8%)	80/132 (60.6%)	RR 0.84 (0.67 to 1.04)	97 fewer per 1000 (from 200 fewer to 24 more)	MODERATE	CRITICAL
Relapse at 100 weeks post-randomisation (ITT) (follow-up mean 100 weeks; assessed with: Met DSM-IV criteria for relapse/recurrence (assessed with SCID-I))												
1 (Klein 2018a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	76/132 (57.6%)	92/132 (69.7%)	RR 0.83 (0.69 to 0.99)	118 fewer per 1000 (from 7 fewer to 216 fewer)	MODERATE	CRITICAL
Quality of life at 26 weeks post-randomisation (follow-up mean 26 weeks; measured with: European Quality of Life Five-Dimensions (3-level) Health Status Questionnaire (EQ-5D); Better indicated by lower values)												
1 (Bieshe uvel-Leliefel d 2017)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	124	-	SMD 0.2 higher (0.05 lower to 0.45 higher)	MODERATE	IMPORTANT
Quality of life at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: European Quality of Life Five-Dimensions (3-level) Health Status Questionnaire (EQ-5D); Better indicated by lower values)												
1 (Bieshe uvel-Leliefel d 2017)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	124	-	SMD 0.09 higher (0.16 lower to 0.34 higher)	MODERATE	IMPORTANT
Quality of life mental health component at 12-26 weeks post-randomisation (follow-up 12-26 weeks; measured with: 12-Item Short-Form Health Survey (SF-12) mental health component; Better indicated by lower values)												
2 (Bieshe uvel-Leliefel	randomised trials	serious[5]	serious[6]	no serious indirectness	serious[4]	none	354	354	-	SMD 0.32 higher (0.01	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-help + TAU	TAU	Relative (95% CI)	Absolute	Quality	Importance
d 2017, Segal 2020)										lower to 0.65 higher)		
Quality of life physical health component at 12-26 weeks post-randomisation (follow-up 12-26 weeks; measured with: 12-Item Short-Form Health Survey (SF-12) physical health component; Better indicated by lower values)												
2 (Bieshe uvel-Leliefel d 2017, Segal 2020)	randomise d trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	354	-	SMD 0.12 higher (0.03 lower to 0.26 higher)	MODERATE	IMPORTANT
Quality of life mental health component at 52-65 weeks post-randomisation (follow-up 52-65 weeks; measured with: 12-Item Short-Form Health Survey (SF-12) mental health component; Better indicated by lower values)												
2 (Bieshe uvel-Leliefel d 2017, Segal 2020)	randomise d trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	354	-	SMD 0.06 lower (0.2 lower to 0.09 higher)	MODERATE	IMPORTANT
Quality of life physical health component at 52-65 weeks post-randomisation (follow-up 52-65 weeks; measured with: 12-Item Short-Form Health Survey (SF-12) physical health component; Better indicated by lower values)												
2 (Bieshe uvel-Leliefel d 2017, Segal 2020)	randomise d trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	354	-	SMD 0.04 higher (0.12 lower to 0.19 higher)	MODERATE	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; RR: relative risk; SCID: structured clinical interview for DSM-IV axis I disorders; SMD: standardised mean difference; TAU: treatment as usual

[1] Unclear blinding of outcome assessment in study contributing >50% to weighting

[2] Very serious heterogeneity

[3] 95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm

[4] *95% CI crosses thresholds for both no effect and clinically important benefit*
[5] *Unclear risk of detection bias (self-reported outcome)*
[6] *Considerable heterogeneity*

Comparison 18. Self-help with support + TAU versus attention placebo + TAU

Table 54: Clinical evidence profile for comparison self-help with support + TAU versus attention placebo + TAU

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Self-help with support + TAU**	**Attention placebo + TAU**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 36 weeks post-randomisation (ITT) (follow-up mean 36 weeks; assessed with: Met DSM-IV criteria for MDD (assessed with SCID-I))												
1 (Holländare 2011/ 2013)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/42 (19%)	19/42 (45.2%)	RR 0.42 (0.21 to 0.85)	262 fewer per 1000 (from 68 fewer to 357 fewer)	LOW	CRITICAL
Relapse at 114 weeks post-randomisation (ITT) (follow-up mean 114 weeks; assessed with: Met DSM-IV criteria for MDD (assessed with SCID-I))												
1 (Holländare 2011/ 2013)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/42 (35.7%)	30/42 (71.4%)	RR 0.5 (0.32 to 0.78)	357 fewer per 1000 (from 157 fewer to 486 fewer)	MODERATE	CRITICAL
Quality of life change score at 10 weeks post-randomisation (follow-up mean 10 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Holländare 2011/ 2013)	randomised trials	serious [1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	38	39	-	SMD 0.23 higher (0.22 lower to 0.68 higher)	LOW	IMPORTANT
Quality of life change score at 36 weeks post-randomisation (follow-up mean 36 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Holländare	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	38	39	-	SMD 0.11 higher (0.34 lower	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-help with support + TAU	Attention placebo + TAU	Relative (95% CI)	Absolute		
2011/ 2013)										to 0.56 higher)		
Quality of life change score at 62 weeks post-randomisation (follow-up mean 62 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Holländare 2011/ 2013)	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	32	35	-	SMD 0.44 higher (0.05 lower to 0.92 higher)	LOW	IMPORTANT
Quality of life change score at 114 weeks post-randomisation (follow-up mean 114 weeks; measured with: WHOQOL-BREF - overall QOL; Better indicated by lower values)												
1 (Holländare 2011/ 2013)	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	32	35	-	SMD 0.58 higher (0.09 to 1.07 higher)	LOW	IMPORTANT

CI: confidence interval; DSM: diagnostic statistical manual; ITT: intention to treat; QOL: quality of life; RR: relative risk; SCID-I: structured clinical interview for DSM-IV axis I disorders; SMD: standardised mean difference; TAU: treatment as usual; WHOQOL-BREF: World Health Organization quality of life scale-abbreviated version

[1] Unclear blinding of outcome assessment

[2] 95% CI crosses thresholds for both no effect and clinically important benefit

[3] Unclear risk of detection bias (self-reported outcome)

Comparison 19. SSRIs versus pill placebo

Table 55: Clinical evidence profile for comparison SSRIs versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRI**	**Pill placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 16-36 weeks post-randomisation (ITT) (follow-up 16-36 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
7 (Gorwood 2007, Jarrett 2013, Kamijima 2006, Montgomery 1993b, Rapaport 2004, Robert 1995, Schmidt 2000)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias3	323/982 (32.9%)	327/671 (48.7%)	RR 0.6 (0.5 to 0.74)	195 fewer per 1000 (from 127 fewer to 244 fewer)	VERY LOW	CRITICAL
Relapse at 44-48 weeks post-randomisation (ITT) (follow-up 44-48 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
4 (Doogan 1992, Gilaberte 2001, Hochstrasser 2001, Klysner 2002)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	159/447 (35.6%)	234/378 (61.9%)	RR 0.57 (0.45 to 0.71)	266 fewer per 1000 (from 180 fewer to 340 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SSRI	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 52-87 weeks post-randomisation (ITT) (follow-up 52-87 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
7 (Dobson 2008, Jarrett 2013, Kornstein 2006, Lepine 2004, Montgomery 1993a, Montgomery 1988, Terra 1998)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	219/662 (33.1%)	282/528 (53.4%)	RR 0.61 (0.5 to 0.74)	208 fewer per 1000 (from 139 fewer to 267 fewer)	VERY LOW	CRITICAL
Relapse at 100-139 weeks post-randomisation (ITT) (follow-up 100-139 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
2 (Jarrett 2013, Wilson 2003)	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	74/142 (52.1%)	82/126 (65.1%)	RR 0.84 (0.65 to 1.07)	104 fewer per 1000 (from 228 fewer to 46 more)	VERY LOW	CRITICAL
Quality of life change score at 16 weeks post-randomisation (follow-up mean 16 weeks; measured with: Quality of Life, Enjoyment, and Satisfaction Scale (Q-LES-Q); Better indicated by lower values)												
1 (Kamijima 2006)	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	117	118	-	SMD 0.79 higher (0.53 to 1.06 higher)	LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

1 Randomisation method and allocation concealment unclear, blinding of outcome assessor unclear and abrupt or rapid tapering of acute treatment, for the majority of studies

2 Considerable heterogeneity (I^2>50%)

[3] *Trial funding from pharmaceutical companies*
[4] *Unclear blinding of outcome assessment, high risk of attrition and abrupt tapering of acute treatment (in study that accounts for >50% if weighting)*
[5] *95% CI crosses threshold for no effect and threshold for clinicall important benefit*
[6] *Unclear randomisation method and allocation concealment, unclear risk of detection bias (self-reported outcome), and rapid tapering of acute treatment*

Comparison 20. SSRI versus TCA

Table 56: Clinical evidence profile for comparison SSRI versus TCA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SSRI**	**TCA**	**Relative (95% CI)**	**Absolute**		
Relapse at 25 weeks post-randomisation (ITT) (follow-up mean 25 weeks; assessed with: HAMD score ≥ 16, present for 14 days)												
1 (Martiny 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	23/32 (71.9 %)	8/14 (57.1 %)	RR 1.26 (0.76 to 2.08)	149 more per 1000 (from 137 fewer to 617 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; ITT: intention to treat; RR: relative risk; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

1 Statistically significant group difference at baseline

2 95% CI crosses thresholds for clinically important benefit, no effect, and for clinically important harm

3 Trial funded by pharmaceutical company and stopped early due to due to low inclusion rate

Comparison 21. TCAs versus pill placebo

Table 57: Clinical evidence profile for comparison TCAs versus pill placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCA**	**Pill placebo**	**Relative (95% CI)**	**Absolute**		
Relapse at 26-35 weeks post-randomisation (ITT) (follow-up 26-35 weeks; assessed with: Not reported)												
2 (Klerman 1974, Stein 1980)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/79 (24.1 %)	35/76 (46.1%)	RR 0.51 (0.31 to 0.82)	226 fewer per 1000 (from 83 fewer to 318 fewer)	LOW	CRITICAL
Relapse at 52 weeks post-randomisation (ITT) (follow-up mean 52 weeks; assessed with: An increase in morbidity sufficiently severe to warrant admission to hospital)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCA	Pill placebo	Relative (95% CI)	Absolute		
1 (Coppen 1978)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	3/16 (18.8 %)	5/16 (31.3%)	RR 0.6 (0.17 to 2.1)	125 fewer per 1000 (from 259 fewer to 344 more)	VERY LOW	CRITICAL
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
3 (Alexopoulos 2000, Old Age Depression Interest Group 1993, Prien 1984)	randomised trials	serious [5]	no serious inconsistency	no serious indirectness	serious[2]	none	39/94 (41.5 %)	56/91 (61.5%)	RR 0.69 (0.47 to 1)	191 fewer per 1000 (from 326 fewer to 0 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; TCA: tricyclic antidepressant

[1] Unclear randomisation method and allocation concealment, unclear blinding of outcome assessment, and abrupt tapering of acute treatment

[2] 95% CI crosses threshold for no effect and clinically important benefit

[3] 95% CI crosses thresholds for clinically important benefit, no effect, and for clinically important harm

[4] Funding from pharmaceutical company

[5] Unclear allocation concealment and unclear blinding of outcome assessment (in studies contributing >50% to the weighting)

Comparison 22. TCA versus no treatment

Table 58: Clinical evidence profile for comparison TCA versus no treatment

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCA**	**No treatment**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 35 weeks post-randomisation (ITT) (follow-up mean 35 weeks; assessed with: Not reported)												
1 (Klerman 1974)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/50 (22%)	16/50 (32%)	RR 0.69 (0.36 to 1.33)	99 fewer per 1000 (from 205 fewer to 106 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; TCA: tricyclic antidepressant
1 Unclear randomisation method and allocation concealment, unclear blinding of outcome assessment, and abrupt tapering of acute treatment
2 95% CI crosses thresholds for clinically important benefit, no effect, and clinically important harm

Comparison 23. TCA + lithium versus lithium

Table 59: Clinical evidence profile for comparison TCA + lithium versus lithium

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TCA + lithium**	**Lithium**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Clinical condition satisfied the RDC for definite major depressive disorder and GAS rating of 60 or less or terminated due to adverse reaction)												
1 (Prien 1984)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/37 (56.8%)	13/38 (34.2%)	RR 1.66 (0.98 to 2.8)	226 more per 1000 (from 7 fewer to 616 more)	LOW	CRITICAL

CI: confidence interval; GAS: global assessment scale; ITT: intention to treat; RDC; research diagnostic criteria; RR: relative risk; TCA: tricyclic antidepressant
1 Unclear randomisation method and allocation concealment, and abrupt tapering of acute treatment

2 95% CI crosses thresholds for no effect and clinically important harm

Comparison 24. TCA + IPT versus IPT

Table 60: Clinical evidence profile for comparison TCA + IPT versus IPT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCA + IPT	IPT	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/25 (40%)	18/26 (69.2%)	RR 0.58 (0.34 to 1)	291 fewer per 1000 (from 457 fewer to 0 more)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; IPT: interpersonal therapy; ITT: intention to treat; RDC; research diagnostic criteria; RR: relative risk; TCA: tricyclic antidepressant
1 Significant group difference at baseline and rapid tapering of acute treatment
2 95% CI crosses thresholds for both no effect and clinically important benefit

Comparison 25. TCA + IPT versus pill placebo + IPT

Table 61: Clinical evidence profile for comparison TCA + IPT versus pill placebo + IPT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCA + IPT	Pill placebo + IPT	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 156 weeks post-randomisation (ITT) (follow-up mean 156 weeks; assessed with: Met the RDC for major depressive disorder, HAMD score ≥15, and Raskin severity score ≥7)												
1 (Frank 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/25 (40%)	21/26 (80.8%)	RR 0.5 (0.3 to 0.83)	404 fewer per 1000 (from 137 fewer to 565 fewer)	VERY LOW	CRITICAL

CI: confidence interval; HAMD: Hamilton depression rating scale; IPT: interpersonal therapy; ITT: intention to treat; RDC; research diagnostic criteria; RR: relative risk; TCA: tricyclic antidepressant

[1] Significant group difference at baseline and rapid tapering of acute treatment

[2] 95% CI crosses threshold for both no effect and clinically important benefit

Comparison 26. SNRIs versus pill placebo

Table 62: Clinical evidence profile for comparison SNRIs versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SNRI**	**Pill placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 26 weeks post-randomisation (ITT) (follow-up mean 26 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
4 (Perahia 2006, Rickels 2010, Rosenthal 2013, Simon 2004)	randomised trials	serious [1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	282/752 (37.5%)	411/741 (55.5%)	RR 0.67 (0.57 to 0.79)	183 fewer per 1000 (from 116 fewer to 239 fewer)	VERY LOW	CRITICAL
Relapse at 52 weeks post-randomisation (ITT) (follow-up mean 52 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
3 (Kocsis 2007, Montgomery 2004, Perahia 2009)	randomised trials	serious [4]	serious[2]	no serious indirectness	serious[5]	reporting bias[3]	172/422 (40.8%)	263/437 (60.2%)	RR 0.65 (0.49 to 0.86)	211 fewer per 1000 (from 84 fewer to 307 fewer)	VERY LOW	CRITICAL
Functional impairment at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Social Adjustment Scale - Self Report (SAS-SR); 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	SNRI	Pill placebo	Relative (95% CI)	Absolute		
1 (Kocsis 2007)	randomised trials	serious [4]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	129	129	-	SMD 0.33 lower (0.58 to 0.09 lower)	VERY LOW	IMPORTANT
Functional impairment change score at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Sheehan Disability Scale (SDS); Better indicated by lower values)												
1 (Perahia 2009)	randomised trials	serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	145	142	-	SMD 0.24 lower (0.47 to 0.01 lower)	LOW	IMPORTANT
Quality of life at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Quality of Life, Enjoyment, and Satisfaction Scale (Q-LES-Q); Better indicated by lower values)												
1 (Kocsis 2007)	randomised trials	serious [4]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	129	129	-	SMD 0.34 higher (0.09 to 0.58 higher)	VERY LOW	IMPORTANT
Quality of life physical component change score at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Medical Outcomes Study Short Form 36 (SF-36) physical component score (PCS); Better indicated by lower values)												
1 (Perahia 2009)	randomised trials	serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	145	142	-	SMD 0.09 lower (0.32 lower to 0.14 higher)	LOW	IMPORTANT
Quality of life mental component change score at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Medical Outcomes Study Short Form 36 (SF-36) mental component score (MCS); Better indicated by lower values)												
1 (Perahia 2009)	randomised trials	serious [4]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	145	142	-	SMD 0.33 higher (0.1 to 0.57 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; SNRI: serotonin and norepinephrine reuptake inhibitors; RR: relative risk

1 Unclear randomisation method and allocation concealment, and rapid tapering of acute treatment

2 Considerable heterogeneity

3 Trials funded by pharmaceutical companies

4 Unclear randomisation method and allocation concealment, and unclear blinding of outcome assessment (in studies contributing >50% to the weighting)

5 95% CI crosses thresholds for both clinically important benefit and no effect

Comparison 27. Antipsychotic versus pill placebo

Table 63: Clinical evidence profile for comparison antipsychotic versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 52 weeks post-randomisation (ITT) (follow-up mean 52 weeks; assessed with: A depressive event was defined as ≥1 of the following: (a) initiation of pharmacological treatment by the investigator to treat depression or self-medication with prohibited medications for ≥1 week, (b) hospitalization for depressive symptoms, (c) MADRS score ≥18 at 2 consecutive assessments 1 week apart, or at the final assessment if patient discontinued, (d) CGI-S score ≥5, and (e) suicide attempt or discontinuation from the study due to imminent risk of suicide)												
1 (Liebowitz 2010)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	381/391 (97.4%)	380/385 (98.7%)	RR 0.99 (0.97 to 1.01)	10 fewer per 1000 (from 30 fewer to 10 more)	VERY LOW	CRITICAL
Sleeping difficulties change score at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Pittsburgh Sleep Quality Index (PSQI); Better indicated by lower values)												
1 (Liebowitz 2010)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	387	384	-	SMD 0.41 lower (0.55 to 0.27 lower)	VERY LOW	IMPORTANT
Functional impairment change score at 52 weeks post-randomisation (follow-up mean 52 weeks; measured with: Sheehan Disability Scale (SDS); Better indicated by lower values)												
1 (Liebowitz 2010)	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	387	384	-	SMD 0.17 lower (0.31 to 0.03 lower)	VERY LOW	IMPORTANT

CI: confidence interval; CGI-S: clinical global impression-severity; ITT: intention to treat; MADRS: Montgomery-Asberg depression rating scale; RR: relative risk; SMD: standardised mean difference

[1] Unclear randomisation method and allocation concealment, unclear blinding of outcome assessment, high risk of attrition bias and abrupt tapering of acute treatment

[2] Trial funded by pharmaceutical company

[3] 95% CI crosses threshold for both no effect and clinically important benefit

Comparison 28. Antipsychotics + antidepressant versus antidepressant

Table 64: Clinical evidence profile for comparison antipsychotics + antidepressant versus antidepressant

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antipsychotic + antidepressant**	**Antidepressant**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 24-27 weeks post-randomisation (ITT) (follow-up 24-27 weeks; assessed with: Scored above clinical threshold on a validated depression scale)												
2 (Brunner 2014, Rapaport 2006)	randomised trials	serious [1]	very serious[2]	no serious indirectness	very serious[3]	reporting bias[4]	186/344 (54.1%)	246/343 (71.7%)	RR 0.8 (0.5 to 1.27)	143 fewer per 1000 (from 359 fewer to 194 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
1 Rapid/abrupt tapering of acute treatment
2 Very serious heterogeneity
3 95% CI crosses thresholds for no effect and for clinically important benefit and harm
4 Trials funded by pharmaceutical companies

Comparison 29. Lithium versus pill placebo

Table 65: Clinical evidence profile for comparison lithium versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lithium**	**Pill placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Clinical condition satisfied the RDC for definite major depressive disorder and GAS rating of 60 or less or terminated due to adverse reaction)												
1 (Prien 1984)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/38 (34.2 %)	22/34 (64.7%)	RR 0.53 (0.32 to 0.88)	304 fewer per 1000 (from 78 fewer to 440 fewer)	LOW	CRITICAL

CI: confidence interval; GAS: global assessment scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk
[1] Unclear randomisation method and allocation concealment, and abrupt tapering of acute treatment
[2] 95% CI crosses thresholds for both no effect and clinically important benefit

Comparison 30. Lithium + antidepressant versus pill placebo + antidepressant

Table 66: Clinical evidence profile for comparison lithium + antidepressant versus pill placebo + antidepressant

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium + antidepressant	Pill placebo + antidepressant	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 16 weeks post-randomisation (follow-up mean 16 weeks; assessed with: Met DSM-III-R criteria for a current major depressive episode; HAMD score of at least 15; CGI-S score of at least 4)												
1 (Bauer 2000)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/14 (0%)	7/15 (46.7%)	RR 0.07 (0 to 1.14)	434 fewer per 1000 (from 467 fewer to 65 more)	LOW	CRITICAL
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Subjects, in the opinion of the responsible psychiatrist, requiring an increase or change in antidepressants, admission for ECT or scoring greater than or equal to 13 points on the MADRS were considered to have relapsed)												
1 (Wilkinson 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	9/25 (36%)	16/24 (66.7%)	RR 0.54 (0.3 to 0.98)	307 fewer per 1000 (from 13 fewer to 467 fewer)	LOW	CRITICAL

CI: confidence interval; CGI-S: clinical global impression-severity; DSM: diagnostic statistical manual; ECT: electroconvulsive therapy; HAMD: Hamilton depression rating scale; ITT: intention to treat; MADRS: Montgomery-Asberg depression rating scale; RR: relative risk

1 Unclear randomisation method and allocation concealment, and rapid tapering of acute treatment

2 95% CI crosses thresholds for both no effect and clinically important benefit

3 Trial funded by pharmaceutical company

Comparison 31. Lithium versus TCAs

Table 67: Clinical evidence profile for comparison lithium versus TCAs

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium	TCA	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 104-156 weeks post-randomisation (ITT) (follow-up 104-156 weeks; assessed with: Diagnostic criteria for major depression or scored above clinical threshold on a validated depression scale)												
3 (Glen 1984, Greil 1996, Prien 1984)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/135 (52.6 %)	78/130 (60 %)	RR 0.88 (0.7 to 1.11)	72 fewer per 1000 (from 180 fewer to 66 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; TCA: tricyclic antidepressant
+ Unclear blinding of, or non-blind, outcome assessment, and rapid/abrupt tapering of acute treatment (in studies contributing >50% to weighting)
+ 95% CI crosses thresholds for both no effect and clinically important benefit

Comparison 32. Lithium + TCA versus pill placebo

Table 68: Clinical evidence profile for comparison lithium + TCA versus pill placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium + TCA	Pill placebo	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Clinical condition satisfied the RDC for definite major depressive disorder and GAS rating of 60 or less or terminated due to adverse reaction)												
1 (Prien 1984)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/37 (56.8%)	22/34 (64.7%)	RR 0.88 (0.6 to 1.28)	78 fewer per 1000 (from 259 fewer to 181 more)	VERY LOW	CRITICAL

CI: confidence interval; GAS: global assessment scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk; TCA: tricyclic antidepressant
[1] Unclear randomisation method and allocation concealment, and abrupt tapering of acute treatment
[2] 95% CI crosses thresholds for no effect, clinically important benefit, and clinically important harm

Comparison 33. Lithium + TCA versus TCA

Table 69: Clinical evidence profile for comparison lithium + TCA versus TCA

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lithium + TCA	TCA	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 104 weeks post-randomisation (ITT) (follow-up mean 104 weeks; assessed with: Clinical condition satisfied the RDC for definite major depressive disorder and GAS rating of 60 or less or terminated due to adverse reaction)												
1 (Prien 1984)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/37 (56.8%)	17/39 (43.6%)	RR 1.3 (0.83 to 2.05)	131 more per 1000 (from 74 fewer to 458 more)	LOW	CRITICAL

CI: confidence interval; GAS: global assessment scale; ITT: intention to treat; RDC: research diagnostic criteria; RR: relative risk; TCA: tricyclic antidepressant

1 Unclear randomisation method and allocation concealment, and abrupt tapering of acute treatment

2 95% CI crosses thresholds for no effect and clinically important harm

Comparison 34. ECT + pharmacological intervention versus pharmacological intervention

Table 70: Clinical evidence profile for comparison ECT + pharmacological intervention versus pharmacological intervention

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECT + pharm	Pharm	Relative (95% CI)	Absolute	Quality	Importance
Relapse at 24-26 weeks post-randomisation (ITT) (follow-up 24-26 weeks; assessed with: Scored above clinical threshold on a validated depression scale)												
2 (Brakemeier 2014, Kellner 2016/ McCall 2018)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/89 (44.9%)	41/82 (50%)	RR 0.9 (0.65 to 1.23)	50 fewer per 1000 (from 175 fewer to 115 more)	VERY LOW	CRITICAL
Relapse at 52 weeks post-randomisation (ITT) (follow-up mean 52 weeks; assessed with: Relapse was declared if the patient was hospitalized for symptomatic worsening and/or when HAMD scores increased by ≥ 18 points at a continuation measurement time point or increased from baseline ≥ 10 points)												
1 (Brakemeier 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	18/25 (72%)	12/18 (66.7%)	RR 1.08 (0.72 to 1.62)	53 more per 1000 (from 187 fewer to 413 more)	LOW	CRITICAL
Quality of life physical component score (PCS) change score at 24 weeks post-randomisation (follow-up mean 24 weeks; measured with: Medical Outcomes Study Short Form 36 (SF-36) physical component score (PCS); Better indicated by lower values)												
1 (Kellner 2016/ McCall 2018)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	59	-	SMD 1.22 higher (0.83 to 1.61 higher)	LOW	CRITICAL
Quality of life mental component score (MCS) change score at 24 weeks post-randomisation (follow-up mean 24 weeks; measured with: Medical Outcomes Study Short Form 36 (SF-36) mental component score (MCS); Better indicated by lower values)												
1 (Kellner 2016/ McCall 2018)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	59	-	SMD 1.19 higher (0.8 to 1.58 higher)	LOW	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; HAMD: Hamilton depression rating scale; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] Significant group difference at baseline in study contributing >50% to weighting

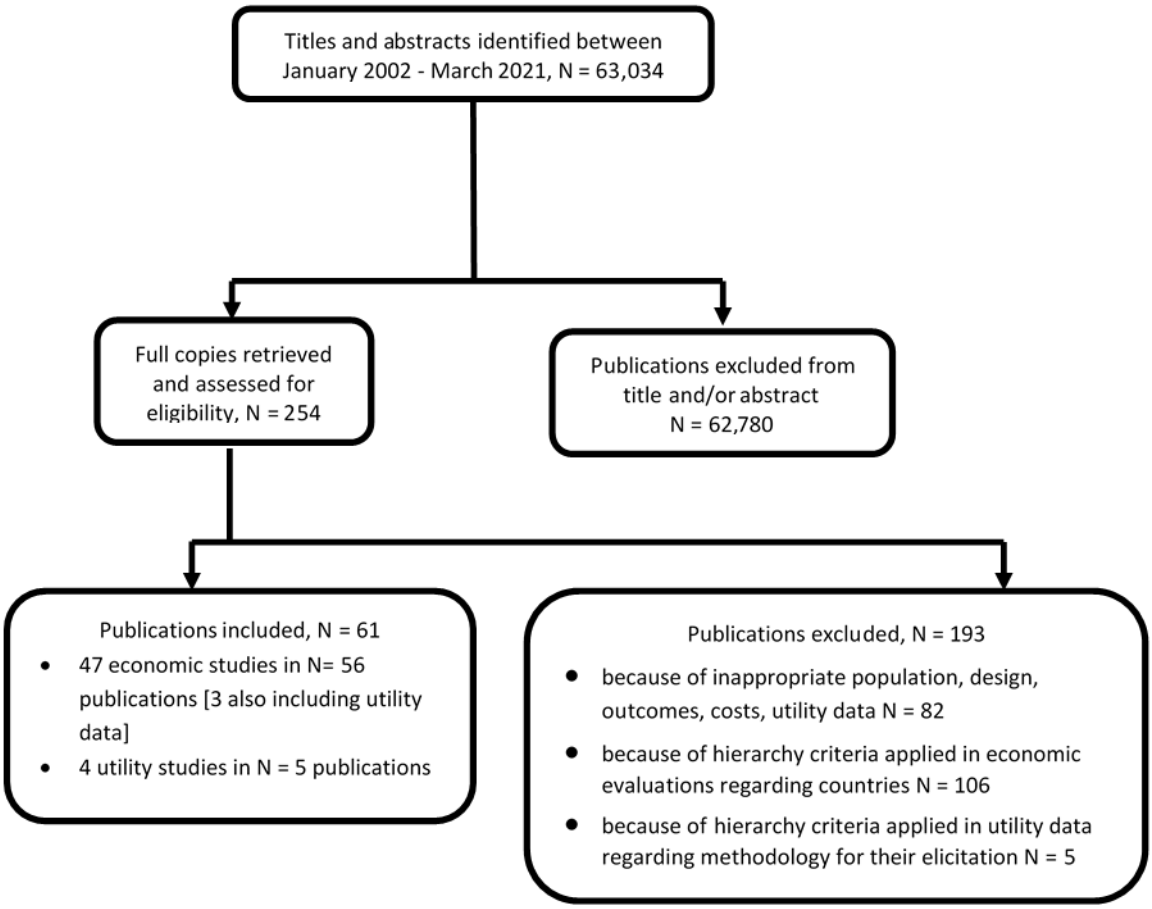
[2] *95% CI crosses thresholds for both no effect and clinically important benefit*
[3] *95% CI crosses threshold for no effect, and thresholds for both clinically important benefit and harm*
[4] *Significant group difference at baseline and unclear risk of detection bias (self-reported outcome)*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

A global health economics search was undertaken for all areas covered in the guideline. Figure 106 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 106. 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



Appendix H – Economic evidence tables

Economic evidence tables for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Table 71: Economic evidence tables for mindfulness-based cognitive therapy versus maintenance antidepressant treatment

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kuyken 2008 UK Cost effectiveness analysis	Interventions: Mindfulness-based cognitive therapy with support to taper or discontinue antidepressant treatment, comprising 8 x 2 hour group sessions over consecutive weeks, with 4 follow-up sessions in the following year (MBCT) Maintenance antidepressant treatment plus medication adherence monitoring (AD)	Adults with ≥ 3 previous major depressive episodes, on a therapeutic dose of maintenance antidepressants over the last 6 months, and currently either in full or partial remission from the most recent episode. Exclusion criteria: organic brain damage, comorbid diagnoses of current substance dependence, current/past psychosis, bipolar disorder, persistent antisocial behaviour, persistent self -injury requiring clinical management/therapy, unable to engage with MBCT for physical, practical, or other reasons, formal concurrent psychotherapy	Costs: MBCT, medication, hospital (inpatient, outpatient, emergency department) and community health and social services (e.g., primary care, social work, complementary therapies), plus productivity losses. Mean NHS/PSS cost per person: MBCT: $2076, AD: $1577 Mean societal cost per person (SD): MBCT: $3373 ($4002), AD: $2915 ($4838); difference $457 (95%CI -$1130 to $2043, p=0.87) Primary outcome measure: time to and % of relapse/recurrence Secondary outcomes: severity/duration of relapses/recurrences, severity of residual depressive symptoms, number of comorbid psychiatric diagnoses, quality of life using the WHO Quality of Life instrument (WHOQOL-BREF). Percentage of people relapsing: MBCT: 47%; ADs: 60%	ICER of MCBT-TS vs AD: $439/additional relapse or recurrence prevented and $23/depression-free day (NHS/PSS perspective) $962 /additional relapse or recurrence prevented and $50 /depression-free day (societal perspective) Probability of MBCT-TS being cost-effective at zero willingness to pay for preventing an additional relapse /recurrence: 0.42; probability of MBCT-TS exceeds 0.50 at willingness to pay ≥ $1,000 per relapse / recurrence averted (societal perspective)	Perspective: NHS/PSS (and societal) Currency: international $ Cost year: 2006 Time horizon: 15 months Discounting: NA Applicability: partially applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Pragmatic single-blind parallel 2-group RCT Source of efficacy data: RCT (Kuyken 2008); (N=123, completers n=115) Source of resource use data: RCT (N=123, completers=115) Source of unit costs: national sources	Hazard ratio 0.63 (95%CI 0.39 to 1.04, p=0.07) Difference in secondary outcomes: MBCT more effective than AD in reducing residual depressive symptoms and psychiatric comorbidity and in improving quality of life in the physical and psychological domains.		
Kuyken 2015a/2015b UK Cost effectiveness and cost-utility analysis	Interventions: Mindfulness-based cognitive therapy with support to taper or discontinue antidepressant treatment, comprising 8 x 2.25 hour group sessions, normally over consecutive weeks, with 4 refresher sessions offered roughly every 3 months for the following year (MBCT) Maintenance antidepressant treatment plus GP support in maintaining a therapeutic level of	Adults with ≥ 3 previous major depressive episodes, in full or partial remission from their most recent episode, and on a therapeutic dose of maintenance antidepressants Exclusion criteria: current major depressive episode, comorbid diagnoses of current substance misuse, organic brain damage, current or past psychosis including bipolar disorder, persistent antisocial behaviour, persistent self-injury needing clinical management or therapy, formal concurrent psychotherapy. Pragmatic single-blind parallel 2-group RCT	Costs: MBCT, medication, inpatient & outpatient care, A&E, ambulance, staff time (GP, practice nurse, district nurse, health visitor, community psychiatric nurse, midwife, community psychiatrist, clinical psychologist, occupational therapist, physiotherapist, counselling, art/drama/music therapist, chiropodist, dietician, social worker, support worker), advice service, day centre Plus out-of-pocket expenses and productivity losses Mean health and social care cost per person (SD): MBCT: £2485 (£4077), AD: £2360 (£4206); difference £124 (95%CI -£750 to £973, p=0.80). Mean societal cost per person (SD): MBCT: £3204 (£4012), AD: £2755 (£4465); difference £449 (95%CI -£842 to £1286, p=0.68)	Using primary outcome: ICER of MBCT vs AD: £4,955 (NHS/PSS perspective) or £10,604 (societal perspective) per additional relapse or recurrence averted Using QALYs, MBCT is dominated by AD Using any of the outcomes, the probability of MBCT-TS being cost-effective did not exceed 0.49 (NHS/PSS perspective) or 0.52 (societal perspective)	Perspective: NHS/PSS (and societal) Currency: GBP£ Cost year: 2012 Time horizon: 2 years Discounting: 3.5% Applicability: directly applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	medication over 2 years (AD)	Source of efficacy data: RCT (Kuyken 2015a/2015b); (N=424, completers=366) Source of resource use data: RCT (N=424, completers=248) Source of unit costs: national sources	Primary outcome measure: time to and % of relapse/recurrence Secondary outcomes: depression-free days recorded by the depression module of the Structured Clinical Interview for DSM–IV (SCID), residual depressive symptoms assessed by the GRID-HAMD and the BDI, psychiatric and medical comorbidity using the relevant SCID modules and the Medical Symptom Checklist (MSCL), respectively, quality of life using the WHO Quality of Life instrument (WHOQOL-BREF) and the EQ-5D-3L (used to estimate QALYs) Percentage of people relapsing: MBCT: 44%; ADs: 47% Hazard ratio 0.89 (95%CI 0.67 to 1.18, p=0.43) Difference in secondary outcomes: no statistically significant differences QALYs: MBCT: 1.49; ADs: 1.53		

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Table 72: Economic evidence profile for mindfulness-based cognitive therapy versus maintenance antidepressant treatment in people at high risk of relapse whose depression has responded to pharmacological treatment

Study and country	Limitations	Applicability	Other comments	Incremental cost[1]	Incremental effect	ICER[1]	Uncertainty
Kuyken 2008 UK	Minor limitations[2]	Partially applicable[3]	Outcome: % of people avoiding relapse	£412	13%	£363/relapse prevented (adjusted)	Not statistically significant differences in costs or outcomes
Kuyken 2015a/2015b UK	Minor limitations[4]	Directly applicable[5]	Outcomes: % of people avoiding relapse and QALYs	£140	3% -0.04	£5,573/relapse prevented (adjusted) Dominated	Not statistically significant differences in costs or outcomes Probability of MBCT being cost-effective less than 0.50 at any WTP per QALY gained

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment as usual; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 15 months, analysis conducted alongside RCT (N=125; completers n=115); national unit prices used. statistical analyses conducted, including bootstrapping; CEACs presented for societal perspective
3. UK study; NHS & PSS perspective (societal perspective reported separately); outcome measure was percentage of relapses avoided; no QALYs estimated
4. Time horizon 2 years, analysis conducted alongside RCT (N=424, completers=366); national unit prices used. Statistical analyses conducted, including bootstrapping; CEACs presented
5. UK study; NHS & PSS perspective (societal perspective reported separately); outcome measure was percentage of relapses avoided and QALYs based on EQ-5D ratings (UK tariff)

Table 73: Economic evidence profile for maintenance SSRIs versus GP care (SSRIs tapering) in people at medium risk of relapse whose depression has responded to SSRIs

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[1]	Incremental effect	ICER (£/effect)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	£156	0.018	£8,626	Probability of SSRIs being cost-effective at WTP £20,000/QALY: 0.88 Conclusions sensitive to use of a higher hazard ratio of antidepressant vs pill placebo (GP care), use of narrower utility gains and increase in the risk of side effects from antidepressant use

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; SSRI: selective serotonin reuptake inhibitor; WTP: willingness to pay
1. Costs reported in 2020 UK pounds.
2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Table 74: Economic evidence profile for maintenance SNRIs versus GP care (SNRIs tapering) in people at medium risk of relapse whose depression has responded to SNRIs

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[1]	Incremental effect	ICER (£/effect)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	£170	0.011	£15,011	Probability of SNRIs being cost-effective at WTP £20,000/QALY: 0.65 Conclusions sensitive to use of a higher hazard ratio of antidepressant vs pill placebo (GP care), use of narrower utility gains and increase in the risk of side effects from antidepressant use

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; SNRI: serotonin and norepinephrine reuptake inhibitor; WTP: willingness to pay
1. Costs reported in 2020 UK pounds.
2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Table 75: Economic evidence profile for maintenance TCAs versus GP care (TCAs tapering) in people at medium risk of relapse whose depression has responded to TCAs

Study and country	Limitations	Applicability	Other comments	Incremental cost (£)[1]	Incremental effect	ICER (£/effect)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	£108	0.018	£5,896	Probability of TCAs being cost-effective at WTP £20,000/QALY: 0.84 Conclusions sensitive to use of a higher hazard ratio of antidepressant vs pill placebo (GP care), use of narrower utility gains and increase in the risk of side effects from antidepressant use

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TCA: tricyclic antidepressant; WTP: willingness to pay
1. Costs reported in 2020 UK pounds.
2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Table 76: Economic evidence profile for psychological and pharmacological interventions versus GP care and no treatment in people at medium risk of relapse whose depression has responded to psychological treatment

Study and country	Limitations	Applicability	Other comments	Incremental cost (£) vs GP care[1]	Incremental effect vs GP care	NMB (£)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	Individual CT/CBT £807 AD £256 No treatment -£53	Individual CT/CBT: 0.016 AD: -0.001 No treatment: -0.012	GP care £131,525 No treatment £131,344 AD £131,258 Individual CT/CBT £131,034	Probability of being cost-effective: GP care 0.47, no treatment 0.43, AD 0.07, individual CT/CBT 0.03. Results sensitive to use of narrower utility gains and experiencing more severe depression in case of relapse. Individual CT/CBT becomes most cost effective option if number of sessions is reduced to 4

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; NMB: net monetary benefit; QALY: quality-adjusted life year; WTP: willingness to pay

1. Costs reported in 2020 UK pounds.
2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Table 77: Economic evidence profile for maintenance pharmacological, psychological and combined treatments versus GP care and antidepressant drug tapering in people at high risk of relapse whose depression has responded to pharmacological treatment

Study and country	Limitations	Applicability	Other comments	Incremental effect vs GP care (AD taper)[1]	Incremental cost vs GP care (AD taper)	NMB (£)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	Primary analysis AD 0.050 MBCT & AD 0.070 MBCT & AD tapering 0.063 group CT/CBT & AD 0.069 individual CT/CBT & AD 0.075 individual CT/CBT & AD tapering 0.046 Secondary analysis AD 0.050 MBCT & AD 0.070 MBCT & AD tapering 0.063 group CT/CBT & AD 0.066	Primary analysis AD £126 MBCT & AD £676 MBCT & AD tapering £491 group CT/CBT & AD £472 individual CT/CBT & AD £1,019 individual CT/CBT & AD tapering £825 Secondary analysis AD £126 MBCT & AD £676 MBCT & AD tapering £491 group CT/CBT & AD £479 individual CT/CBT & AD £1,019	Primary analysis group CT/CBT & AD £128,879 AD £128,838 MBCT & AD tapering £128,730 MBCT & AD £128,676 individual CT/CBT & AD £128,432 individual CT/CBT & AD tapering £128,065 GP care & AD tapering £127,960 Secondary analysis cCBT with support & AD £129,663 individual psychoeducation & AD £128,971 cCBT & AD £128,892 AD £128,842 group CT/CBT & AD £128,793	Probability of being cost-effective: Primary analysis group CT/CBT & AD not estimated; AD 0.39; MBCT & AD tapering 0.24; MBCT & AD 0.15; individual CT/CBT & AD 0.04; individual CT/CBT & AD tapering 0.18; GP care & AD tapering 0.00 Secondary analysis cCBT with support & AD not estimated; individual psychoeducation & AD 0.51; cCBT & AD 0.22; AD 0.05; group CT/CBT & AD 0.11; MBCT & AD tapering 0.08; MBCT & AD 0.01; individual CT/CBT & AD 0.01; individual CT/CBT & AD tapering 0.02; GP care & AD tapering 0.00

Study and country	Limitations	Applicability	Other comments	Incremental effect vs GP care (AD taper)[1]	Incremental cost vs GP care (AD taper)	NMB (£)[1]	Uncertainty[1]
				individual CT/CBT & AD 0.075 individual CT/CBT & AD tapering 0.058 individual psychoeducation & AD 0.063 cCBT & AD 0.056 cCBT with support & AD 0.094	individual CT/CBT & AD tapering £851 individual psychoeducation & AD £240 cCBT & AD £188 cCBT with support & AD £182	MBCT & AD tapering £128,732 MBCT & AD £128,681 individual CT/CBT & AD £128,434 individual CT/CBT & AD tapering £128,260 GP care & AD tapering £127,960	Results sensitive to use of narrower utility gains Individual CT/CBT & AD becomes most cost-effective option if number of sessions is reduced to 4. MBCT & AD tapering becomes most cost-effective option if it is delivered in a less resource intensive way (by 1 therapist to 12 participants) Options that include antidepressants become less cost-effective when risk of side effects increases

AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs reported in 2020 UK pounds.
2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Table 78: Economic evidence profile for psychological and pharmacological interventions versus GP care and no treatment in people at high risk of relapse whose depression has responded to psychological treatment

Study and country	Limitations	Applicability	Other comments	Incremental effect vs GP care[1]	Incremental cost vs GP care	NMB (£)[1]	Uncertainty[1]
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY In [] intervention	individual CT/CBT 0.038 AD 0.012 No treatment -0.026	individual CT/CBT £775 AD £236 No treatment -£38 [MBCT £486]	[cCBT with support £129,557] [Individual psychoeducation £128,230]	Probability of being cost-effective: <u>Primary analysis</u>

Study and country	Limitations	Applicability	Other comments	Incremental effect vs GP care[1]	Incremental cost vs GP care	NMB (£)[1]	Uncertainty[1]
			s considered in secondary analysis only	[MBCT 0.014] [group CT/CBT 0.002] [individual psychoeducation 0.012] [cCBT without support -0.015] [cCBT with support 0.071]	[group CT/CBT £319] [individual psychoeducation £57] [cCBT without support £63] [cCBT with support -£84]	GP care £128,055 AD £128,054 individual CT/CBT £128,031 MBCT £127,854 group CT/CBT £127,775 cCBT without support £127,697 No treatment £127,564	GP care 0.25; AD 0.28; individual CT/CBT 0.20; no treatment 0.27 <u>Secondary analysis</u> cCBT with support not estimated individual psychoeducation 0.38; GP care 0.13; AD 0.13; individual CT/CBT 0.05; MBCT 0.04; group CT/CBT 0.12; CBT without support 0.11; no treatment 0.04 Results sensitive to use of narrower utility gains, increase in previous number of episodes, and reduction in severity of depression. Individual CT/CBT becomes most cost-effective option if number of sessions is reduced to 4. MBCT becomes most cost-effective option if it is delivered in a less resource intensive way (by 1 therapist to 12 participants)

AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; QALY: quality-adjusted life year; WTP: willingness to pay

1. Costs reported in 2020 UK pounds.

2. Decision-analytic Markov model, time horizon 10 years; relative effects based on guideline systematic review and pairwise meta-analysis; baseline effects derived from review of naturalistic studies; disutility and costs due to common side effects considered – disutility and costs due to serious (but less common) side effects not considered; resource use based on published data from a large naturalistic study (N=88,935) supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented

3. UK study; NHS & PSS perspective; QALYs based on EQ-5D measurements and the UK population tariff

Appendix J – Economic analysis

Economic evidence analysis for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Introduction – objective of economic modelling

The choice of interventions for preventing relapse in adults whose depression has responded to treatment was identified by the committee and the guideline health economist as an area with potentially major resource implications. Existing economic evidence in this area was limited and did not cover all relevant interventions. The clinical evidence in the area of relapse prevention was judged to be sufficient and of adequate quality to inform primary economic modelling. Based on the above considerations, an economic model was developed to assess the relative cost effectiveness of interventions aiming at preventing relapse in adults whose depression has responded to treatment in the UK.

It is noted that the term 'relapse' is typically used to refer to a new episode of depression following incomplete or only brief recovery (e.g. less than 4 months of being well), whereas the term 'recurrence' usually means a new episode following a period of recovery lasting more than 4 months. Also, 'remission' is defined as a relatively brief period during which an improvement of sufficient magnitude is observed so that the individual no longer meets syndromal criteria for the disorder and has no more than minimal symptoms, whereas 'recovery' is defined as an extended asymptomatic phase, which lasts more than 6 months. For the purposes of modelling, the term 'relapse' is used to capture new depressive episodes occurring either within or beyond 4 months of a recovery phase and the terms 'remission' and 'recovery' are used interchangeably to capture any period where a person with depression no longer meets syndromal criteria for the disorder, regardless of the duration of this period.

Economic modelling methods

Population

The study population of the economic model comprised adults whose depression has responded to treatment for an acute depressive episode.

The economic analysis focused on populations treated in primary care, as this is the setting where the majority of the study population is treated in routine practice. Moreover, populations treated in secondary care may have more severe and complex depression including comorbidities, so some aspects of care may be more difficult to determine and quantify in economic modelling. On the other hand, the committee acknowledged that the majority of RCTs in the area of relapse prevention have been conducted in secondary care settings. This may suggest that the study populations had a higher level of severity of depression, or may simply reflect clinical practice patterns at the time and in the countries in which the RCTs were conducted. Due to lack of relevant data from primary care settings, efficacy data were derived from RCTs conducted in secondary care and this is acknowledged as a limitation of the data and the economic analysis.

The committee suggested that the economic model take account of different predictors of relapse in depression, such as age, severity of initial depression, residual symptoms, psychiatric comorbidities, and number of previous episodes. However, identifying different

sub-groups according to predictors of relapse within the evidence base was beyond the scope of the review question on relapse prevention.

Nevertheless, the number of previous depressive episodes is a well-established predictor of relapse (Keller 1981; Kessing 1999; Mueller 1999; Solomon 2000) and therefore this factor was explored further in the context of the economic analysis. The majority of RCTs included in the guideline systematic review of interventions for relapse prevention provided some information on the minimum or mean number of previous episodes experienced by the study participants, and these details were used to identify studies in people with low risk of relapse (no previous depressive episodes), medium risk of relapse (1-2 previous episodes) and high risk of relapse (3+ previous episodes), as suggested by the committee (Table 79). Very few studies included participants who had responded to treatment of their first depressive episode. Some studies provided information on interventions tested in participants with a mean of 1-2 previous episodes. The majority of trials included participants with a mean number of episodes that was greater than 3. Some studies did not provide any information on the number of previous episodes experienced by the study participants. These data were too sparse to indicate a differential treatment effect according to the number of previous episodes. However, since the number of previous episodes is a predictor of relapse, the economic analysis considered populations with a medium risk of relapse (1-2 previous episodes) and a high risk of relapse (3+ previous episodes) to explore the impact of relapse preventive interventions on costs and benefits according to the number of previous episodes experienced by the study population. The number of previous episodes experienced by each population determined their baseline risk of relapse (i.e. the risk of relapse under standard care and without the assessed intervention) and also the range of interventions assessed in the economic model, as determined by available evidence (for example, some interventions, such as mindfulness-based cognitive therapy (MBCT), have been tested primarily in populations with a high risk of relapse, as determined by a number of at least 3 previous episodes). Due to sparseness of relevant data, the same treatment effect was used in the two populations (that is, at medium and high risk of relapse, respectively, according to their number of previous depressive episodes).

In order to quantify epidemiological parameters and estimate economic model inputs, the base-case analysis for people with 1-2 previous episodes utilised baseline relapse data for people with 1 previous episode, and the analysis for people with 3+ episodes utilised baseline relapse data on people with 3 previous episodes.

Regarding the severity of the depressive episodes, the economic analysis assumed that people at medium risk of relapse would experience less severe depression if they relapsed and populations at high risk of relapse would experience more severe depression if they relapsed. The definition of less severe and more severe depression was used to classify the study populations in the review questions on interventions for the treatment of a new episode of depression and is provided in evidence review B. This assumption (i.e. relapse to less or more severe depression) affected only the utility values of the remission state utilised in the economic model structure, owing to lack of efficacy data specific to symptom severity level. People with less severe depression were assumed to always experience less severe depression if they relapsed over the duration of the analysis; similarly, populations with more severe depression were assumed to always experience more severe depression if they relapsed over the time horizon of the model. This assumption was necessary in order to populate the economic model. The selection of populations in terms of risk and severity of depression aimed to cover a wide range of adults whose depression has responded to treatment presenting in routine clinical practice.

Based on the above categorisations of the study population, the following scenarios were tested in economic analysis for people treated in primary care:

- People at medium risk of relapse (1-2 previous episodes) who experienced less severe depression if they relapsed

- People at high risk of relapse (3+ previous episodes) who experienced more severe depression if they relapsed

In a scenario explored in sensitivity analysis, people at medium risk of relapse were assumed to experience more severe depression if they relapsed, and people at high risk of relapse were assumed to experience less severe depression if they relapsed.

The cohorts assessed in the economic model were divided into sub-groups, depending on the acute treatment they had received for their depressive episode that led to remission of the episode. Two broad cohort categories were selected, reflecting the availability of clinical data: cohorts that responded to acute pharmacological treatment with antidepressants; and cohorts that responded to acute psychological treatment. People who responded to antidepressant drug treatment were further sub-divided into 3 sub-groups according to the class of antidepressant they had been receiving as acute treatment: SSRI, SNRI, and TCA, respectively. Cohorts that responded to acute combined psychological and pharmacological treatment, as well as cohorts with previously treatment-resistant depression, who had received acute or maintenance pharmacological treatment other than antidepressants (e.g. lithium or antipsychotic drugs) or ECT were not assessed in the economic analysis, due to the sparseness of relevant data and the fact that these sub-groups represent a smaller part of the study population (so they were considered as of lower priority for economic analysis).

Table 79: Population characteristics in relapse prevention RCTs considered in the economic analysis

Study ID	Comparison	Number of previous episodes (excluding the most recent one)		Risk of relapse
		Inclusion criterion?	Mean (SD)	
SSRIs received as acute treatment prior to randomisation				
Doogan1992	Sertraline vs pill placebo	No	69% of participants ≥ 1	Medium or high
Kamijima 2006		At least 1 episode	3.5 (4.1)	High
Wilson 2003		No	0 for 72.5% of participants	Low
Gilaberte 2001	Fluoxetine vs pill placebo	At least 1 episode in last 5 years	2.45 (1.36) in last 5years	Medium
Montgomery 1988		At least 1 episode in last 5 years	3.79 (4.1)	High
Schmidt 2000		No	72% of participants ≥ 1	Medium or high
Terra 1998	Fluvoxamine vs pill placebo	At least 2 episodes in last 5 years	3.5 (1.4)	High
Gorwood 2007	Escitalopram vs pill placebo	No	Not reported	?
Kornstein 2006		At least 2 episodes, 1 in last 5 years	5.22 (4.72)	High
Rapaport 2004		No	Not reported	?
Hochstrasser 2001	Citalopram vs pill placebo	At least 2 episodes, 1 in last 5 years	Median/arm: 4 (2-15); 3 (2-20)	High
Klysner 2002		No	0 for 85% of participants; maximum 2	Low
Montgomery 1993b		No	Not reported	?
Robert 1995		No	Not reported	?
Dobson 2008	Paroxetine vs pill placebo	No	1.12 (1.30)	Medium
Montgomery 1993a		At least 2 episodes in last 4 years	2 for 20% of participants; 3-4 for 56%; 5+ for 24%	High
Franchini 1998	Paroxetine vs paroxetine	At least 1 episode in last 18 months	6.4 (2.5)	High
SNRIs received as acute treatment prior to randomisation				
Perahia 2006	Duloxetine vs pill placebo	At least 1 episode	Not reported	Medium or high
Perahia 2009		At least 2 episodes in last 5 years	4.2 (1.95)	High
Kocsis 2007	Venlafaxine vs pill placebo	At least 2 episodes, 1 in last 5 years	Not reported	Medium or high
Montgomery 2004		At least 1 episode in last 5 years	1.4 (0.72) in past 5 years	Medium
Simon 2004		No	Not reported	?

Study ID	Comparison	Number of previous episodes (excluding the most recent one)		Risk of relapse
		Inclusion criterion?	Mean (SD)	
Rickels 2010	Desvenlafaxine vs pill placebo	No	Not reported	?
Rosenthal 2013		No	2.12 (4.7)	Medium
TCAs received as acute treatment prior to randomisation				
Coppen 1978	Amitriptyline vs pill placebo	No	0 for 34% of participants, max 2	Medium
Klerman 1974		No	1 for majority	Medium
Stein 1980		No	≥ 1 for 56% of participants	Medium
Alexopoulos 2000	Nortriptyline vs pill placebo	No	0 for 30% participants, 1 for 47.5%, 2 for 14.5%, 3+ for 8%	Medium
Non-specified AD received as acute treatment prior to randomisation				
Fava 1994/ 1996/1998c	Individual CBT (AD taper) vs clinical management [TAU] (AD taper)	No	Not reported	?
Fava 1998a/2004	Individual CBT + AD vs AD	At least 2 episodes	3.55 (0.79)	High
Wilkinson 2009	group CBT + AD vs AD	No	0 for 31%, 1 for 20%, 3-5 for 31%, >5 for 18% of participants	Medium to high
Franchini 1997/2000a	Sertraline vs fluvoxamine	At least 1 episode in last 18 months	7.0 (2.3)	High
Huijbers 2015	MBCT + AD vs AD	At least 2 episodes	7.4 (7.1)	High
Huijbers 2016a	MBCT + AD vs MBCT (AD taper)	At least 2 episodes	5.75 (4.75)	High
Kuyken 2008	MBCT (AD taper) vs AD	At least 6 episodes	Median 6; 35% ≥ 9	High
Kuyken 2015a/2015b		At least 6 episodes	46% ≥ 5	High
Lepine 2004	Sertraline vs pill placebo	At least 2 episodes in last 4 years	50% ≥ 5	High
CBT/CT received as acute treatment either immediately or months prior to randomisation				
de Jonge 2019	Individual CBT + TAU vs TAU	At least 2 episodes	Median 3 (IQR 2-5)	High
Jarrett 2001	Individual CT vs no treatment	At least 1 episode	2.3 (0.15)	Medium
Jarrett 2013	Individual CT vs fluoxetine vs pill placebo	At least 1 episode	Median 3	High
Various treatments received in acute phase and/or prior to randomisation – TAU received as maintenance treatment				

Study ID	Comparison	Number of previous episodes (excluding the most recent one)		Risk of relapse
		Inclusion criterion?	Mean (SD)	
Biesheuvel-Leliefeld 2017	Cognitive bibliotherapy + TAU vs TAU	At least 2 episodes	2-3 for 52% and 4+ for 48% of participants	High
Bockting 2005/2015	Group CT + TAU vs TAU	At least 2 episodes in last 5 years	>2 for 82% of participants	High
Farb 2018	MBCT + TAU vs group CT + TAU	No	2.9	High
Bondolfi 2010	MBCT + TAU vs TAU	At least 3 episodes (2 in last 5 years, 1 in last 2 years)	median 4	High
Godfrin 2010		At least 2 episodes	not reported	Likely high
Ma 2004		At least 1 episode in past 5 years	median 2	Medium
Meadows 2014		At least 1 episode	8.8 (11.9)	High
Teasdale 2000		At least 1 episode in past 5 years	median 3	High
Shallcross 2015/2018	MBCT + TAU vs attention placebo + TAU	No	≥ 2 for 94.5% of participants	Medium or high
Williams 2014	MBCT + TAU vs attention placebo + TAU vs TAU	At least 2 episodes, 1 in past 2 years	>3 for 77% of participants	High
Segal 2020	cMBCT + TAU vs TAU	No	6.5 (3.1)	High
Holländare 2011/2013	cCBT with support + TAU vs attention placebo + TAU	No	4.96	High
Klein 2018a	cCT (no support) + TAU vs TAU	At least 1 episode	median 3	High
Old Age Depression Interest Group 1993	Dothiepine vs pill placebo	No	not reported	?
Stangier 2013	Individual CBT + TAU vs individual psychoeducation + TAU	At least 2 episodes	6.4 (7.3)	High

Risk of relapse defined as follows: 1st episode suggests low risk; 1-2 previous episodes suggest medium risk; 3+ previous episodes suggest high risk
AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT; cognitive therapy; IQR: interquartile range;MBCT: mindfulness-based cognitive therapy; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant
'c' before a treatment denotes computerised therapy

Starting age of modelled population

The age of cohorts considered in the economic model was determined by the mean age of onset of depression in adults and the number of previous episodes that people experienced. Kessler 2005 reported the results of a national comorbidity household survey in the US, according to which the median age-of-onset of depression was 32 years (interquartile range 19-44 years). In a Swedish longitudinal cohort study of 3,563 people followed up for 30-49 years, the median age at first onset of depression was reported to be around 35 years (Mattisson 2007). A large (n=20,198) Scottish family-based population study designed to identify the genetic determinants of common diseases, including major depression disorder, reported a mean age of onset of major depressive disorder of 31.7 years (SD 12.3 years) among 2,726 participants that met DSM-IV criteria for current and/or past major depression disorder (Fernandez-Pujals 2015). On the other hand, Andrade 2003 did a review of results of community epidemiological surveys on major depressive episodes that were carried out in 10 countries in America, Europe and Asia (UK was not included in these countries); the authors reported a median age of onset of major depression in the early to mid-twenties in all countries other than Japan (late twenties) and the Czech Republic (early thirties). Based on this evidence and following the committee's expert advice, the age of onset of major depression in the cohorts considered in the model was set at 32 years.

According to the committee's expert opinion, the mean interval between 2 consecutive depressive episodes in people who experience relapses is about 2 years. Therefore, for modelling purposes, people with 1 previous episode remitting from their current episode were assumed to be 34 years old, and people with 3 previous episodes remitting from their current episode were assumed to be 38 years of age.

Percentage of women in the study population

The percentage of women in each cohort were estimated to be 56%, based on weighted epidemiological data on depressive episodes reported in the most recent adult psychiatric morbidity household survey conducted in England (McManus 2016).

Determining the age and gender mix of the cohorts was necessary in order to estimate mortality risks in the model.

Interventions assessed

The range of interventions assessed in the economic analysis was determined by the availability of relevant clinical data included in the guideline systematic review. All interventions included in the NMAs that informed effects for each cohort assessed in the economic model were considered in the economic analysis, i.e.there was no requirement for a minimum amount of data for an intervention to be considered in the economic analysis.

Maintenance pharmacological treatments comprised commonly used antidepressants including SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), SNRIs (duloxetine, venlafaxine, desvenlafaxine), and TCAs (amitriptyline and nortriptyline). Maintenance psychological treatments included MBCT, group CT/CBT, individual CT/CBT, individual psychoeducation, and self-help (represented by computerised CBT) with support or without (with minimal) support.

Inactive comparators included no treatment and GP care; the latter reflects pill placebo trial arms and comprises visits to health professionals without any active pharmacological or psychological intervention being received (but with possible antidepressant drug tapering, if an antidepressant had been received as acute treatment).

Different interventions were assessed in people who had responded to pharmacological or psychological treatment received as acute therapy, according to the availability of respective clinical data and their risk for future relapses. Moreover, some interventions were only considered for people at high risk of relapse (whose depression has responded to either pharmacological or psychological acute treatment) because they had been tested only on populations at high risk of relapse.

People who had responded to acute pharmacological treatment moved on to one of the following maintenance treatment options:

- Cohorts at medium risk of relapse (1 previous episode):
  - continuation of the same drug they had been receiving as acute treatment, i.e. an SSRI, SNRI, or TCA. Each class was represented in the analysis by the most commonly used antidepressant within the class, according to national prescription data, among those with a BNF (British National Formulary 2021) indication for use to treat depression. For SSRIs this was sertraline; for SNRIs venlafaxine; and for TCAs nortriptyline (NHS Business Services Authority 2020)
  - gradual discontinuation of antidepressant treatment (tapering) and GP care; this option reflected care in RCT pill placebo arms. It needs to be noted that discontinuation of antidepressant was done abruptly in the pill placebo arms of some RCTs that informed the economic analysis, i.e. pill placebo replaced the drug immediately, while in other studies the drug was tapered (mostly within a short time period, up to 4 weeks) and eventually replaced by pill placebo. Antidepressants are associated with withdrawal symptoms if they are discontinued abruptly, thus increasing the relative effect of maintenance antidepressant treatment, meaning that the overall treatment effect of maintenance antidepressant treatment versus antidepressant tapering is likely to have been exaggerated in the clinical review and, consequently, in the economic analysis (Van Leeuwen 2021). Withdrawal symptoms may affect patients' willingness to stop antidepressants and be confounded with relapse/recurrence, so future studies should distinguish between these events (Maund 2019).
- Cohorts at high risk of relapse (3 previous episodes):
  - continuation of the same drug they had been receiving as acute treatment; as data for this analysis were derived mostly from studies assessing a mixture of antidepressants (therefore no drug-specific efficacy data were available), the economic analysis used sertraline for costing purposes, because this is the most commonly used antidepressant for the treatment of depression in adults (NHS Business Services Authority 2020)
  - gradual discontinuation of antidepressant treatment (tapering) and GP care
  - gradual discontinuation of antidepressant treatment (tapering) and initiation of MBCT
  - combination therapy comprising continuation of drug treatment and addition of MBCT
  - combination therapy comprising continuation of drug treatment and addition of group CT/CBT
  - combination therapy comprising continuation of drug treatment and addition of individual CT/CBT
  - gradual discontinuation of antidepressant treatment (tapering) and initiation of individual CT/CBT
  - combination therapy comprising continuation of drug treatment and addition of individual psychoeducation
  - combination therapy comprising continuation of drug treatment and addition of computerised CBT without/with minimal support
  - combination therapy comprising continuation of drug treatment and addition of computerised CBT with support.

The options that included psychological treatment were considered only in cohorts at high risk of relapse because they have been tested specifically in populations with a high number of previous depressive episodes, and thus at high risk of relapse, in the trials included in the guideline systematic review.

People who had received acute psychological treatment prior to remission, moved on to one of the following maintenance treatment options:

- Cohorts at medium risk of relapse (1 previous episode):
  - maintenance psychological treatment with individual CT
  - maintenance pharmacological treatment, represented by fluoxetine, as this was the only drug for which evidence was available in this population
  - GP care, reflected in RCT pill placebo arms
  - no treatment.
- Cohorts at high risk of relapse (3 previous episodes):
  - maintenance psychological treatment with individual CT
  - maintenance pharmacological treatment, represented by fluoxetine, for consistency with the cohort at medium risk of relapse
  - GP care
  - no treatment
  - MBCT
  - group CT/CBT
  - individual psychoeducation
  - self-help (represented by computerised CBT) without/with minimal support
  - self-help (represented by computerised CBT) with support.

The last 4 options were considered only in cohorts at high risk of relapse because they have been tested specifically in populations with a high number of previous depressive episodes, and thus at high risk of relapse, in the trials included in the guideline systematic review.

One study included in the guideline systematic review (Elices 2017) compared group dialectical behavioural therapy versus group psychoeducation. These interventions were

Model structure

A Markov model was constructed using Microsoft Office Excel 2016. The model estimated the total costs and benefits associated with provision of each of the treatment options in each cohort of adults with depression that has responded to acute treatment. The structure of the model, which aimed to simulate the course of depression and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of adults whose depression has responded to acute pharmacological or psychological treatment were initiated on relevant treatment options, according to the type of acute treatment they had received, as described earlier. Separate models were developed for the various sub-populations considered in the analysis, depending on the type of the acute treatment of the depressive episode they responded to.

The model, which was run in yearly cycles, included 3 health states: relapse (depressive episode), remission, and death. Within each year, people could remain in the same state or move from one state to another, with the exception of death, which was an absorbing state (so people in this state always remained in it). For every new episode of relapse, people entered separate relapse states (i.e. separate depressive episodes) so that their number of previous episodes could be tracked and the appropriate future risk of relapse that is

dependent on the number of previous episodes could be applied. In addition, within each new episode of relapse, people entered tunnel relapse states, so that the time they remained in every relapse (depressive episode) could be estimated and a time-dependent probability of remission could be applied. People achieving remission also entered tunnel remission states, so that the time they remained in remission could be estimated and a time-dependent probability of relapse could be applied.

The time horizon of the analysis was 10 years, which allowed assessment of longer-term costs and benefits associated with relapse prevention treatment without introducing high complexity associated with the number of tunnel states that would be required were the model run over a longer period of time. A half-cycle correction was applied; this practically means that all events in the model occurred in the middle of each cycle.

Maintenance pharmacological (antidepressant) treatment was received during the first 2 years of the model; maintenance psychological treatment was received within the first year of the model. Benefits of all treatments were assumed to be enjoyed over the first 2 years of the model, according to available evidence on pharmacological and psychological interventions aiming at relapse prevention and the committee's expert opinion. Therefore, over the first 2 years in the model, the risk of relapse experienced by the cohorts was determined by their baseline risk of relapse and the effects of the maintenance treatment option received by each cohort. If people relapsed during this period of 2 years, maintenance treatment was discontinued and the preventative benefit of maintenance treatment ceased at the point of relapse. Beyond the period of the first 2 years, all cohorts were subject to the same baseline risk of relapse according to their number of previous episodes and the time (years) spent in remission. The model did not assess future maintenance treatments beyond those received over the first 1-2 years of the model.

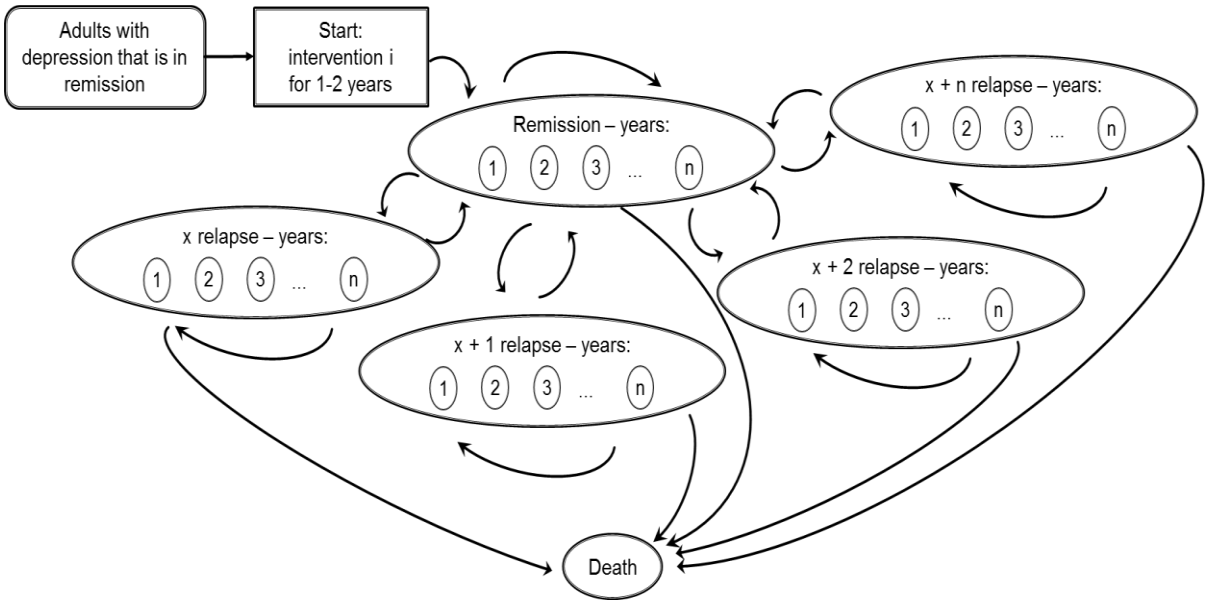
The baseline risk of relapse for each cohort depended on the time people remained in remission (the longer people stayed in remission, the lower their risk of relapse) and their number of previous episodes (the higher the number of their previous episodes, the higher their risk of relapse). The probability of remission for each cohort depended on the time people remained in relapse, i.e. a depressive episode (the longer people stayed in relapse, the lower their probability of remission).

The model did not consider probabilities and events associated with conversion to bipolar depression. This is a potential outcome that was not considered in the model due to sparseness of relevant data and the complexity entailed in modelling this outcome and associated future events.

People who received maintenance pharmacological treatment were assumed to experience common antidepressant side effects (such as headaches, nausea, agitation, sedation, or sexual dysfunction) resulting in a reduction in their health-related quality of life (HRQoL) over a period of up to 2 years during which they received maintenance antidepressant treatment. They were also assumed to incur extra costs for the management of their side effects, which comprised additional GP visits and pharmacological treatment.

The structure of the economic model of relapse prevention is shown in Figure 107.

Figure 107. Schematic diagram of the relapse prevention economic model structure



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE 2014). Costs consisted of intervention costs (drug acquisition, staff time for provision of maintenance pharmacological and psychological therapies and equipment and materials for self-help), as well as other costs associated with the management of future relapses, which included drug acquisition, primary care, hospitalisation, outpatient visits, psychological therapies, and accident and emergency visits. Costs of management of common side effects from antidepressants in people receiving maintenance pharmacological treatment alone or in combination and healthcare costs incurred by people in remission (potentially unrelated to the treatment of depression) were also considered in the analysis. The cost year was 2020.

The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the health states of remission or relapse, as well as utility decrements due to common side effects associated with maintenance antidepressant treatment.

Efficacy data

Selection of efficacy data and methods of evidence synthesis

Efficacy data (relative effects on the risk of relapse) for the relapse prevention interventions considered in the economic modelling were derived from the RCTs included in the guideline systematic review of interventions aiming at relapse prevention. Data were synthesised in pairwise meta-analysis or network meta-analysis (NMA) conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003). NMA is a generalisation of pairwise meta-analysis to data structures that include, for example, A vs. B, B vs. C and A vs. C trials (Lu 2004). NMA strengthens inferences concerning the relative effect of two treatments by including both direct and indirect treatment comparisons. This means that NMA allows estimation of the relative effects of treatments that may not have been directly compared in RCTs. Simultaneous estimation of all relative effects for any number of treatments is possible provided that treatments are connected in a single 'network of evidence' – that is, every treatment is linked to at least one of the other treatments under assessment through

direct comparisons (Caldwell 2005; Mavridis 2015). For each analysis conducted, we present network plots, which depict all treatments by nodes and show which treatments have been directly compared in the RCTs included in the respective NMA, by connecting them with a direct line.

A binomial likelihood and cloglog link linear model was used (Dias 2011a) to allow estimation of hazard ratios of each maintenance treatment versus pill placebo, which were then applied onto the baseline risk of relapse (which reflected the effect of GP care) in the first and second year of the economic analyses (after this period people returned to the baseline risk of relapse that corresponded to their number of previous episodes and the number of years spent in remission). Although, as discussed under 'Baseline risk of relapse', the risk of relapse in people with depression that is in remission is reduced over time following a Weibull distribution, the cloglog link linear model was considered appropriate to use; this is because (1) hazard ratios of pairs of interventions were assumed to be constant over time, (2) the shape parameter gamma of the Weibull distribution did not vary with time and, (3) in each RCT considered in the NMA, events across arms referred to the same follow-up time point.

Pill placebo was selected as the baseline comparator because it was the most commonly used control in the studies included in the NMAs: it was the only control used in trials of people whose depression had responded to pharmacological treatment, and it had also been used as a control in trials of people whose depression had responded to psychological treatment. Moreover, the committee advised that treatment with pill placebo could be assumed to reflect routine GP care, for which baseline risks of relapse were available.

It should be noted that some RCTs included in the NMAs reported data only at treatment endpoint; other RCTs reported data both at treatment endpoint and at various follow-up periods. Finally, a number of RCTs reported only data at follow-up periods that were beyond the treatment endpoint, but no treatment endpoint data were reported. In studies reporting multiple data points, data as close to 52 weeks from treatment initiation as possible were obtained, to match the length of the Markov model cycle. In a few studies where treatment ran beyond 52 weeks but 52-week data were available, 52-week data were extracted and included in the appropriate NMA.

The WinBUGS code used to synthesise the data, for both random and fixed effect models, is shown in Table 80. It is a simplified code compared with the 'standard' cloglog link linear model (Dias 2011a) in that the time parameter has been removed since hazard ratios are time-independent and events in each study refer to the same follow-up time. Additional code was added to constrain the log-hazard to the range (-3, 10), to avoid numerical errors in computation (Ntzoufras 2009); this range practically covers all plausible values on the log-hazard scale.

In each analysis fixed and random effects models were tested, as appropriate. Goodness of fit of each model was assessed using the total residual deviance (totresdev) and the deviance information criteria (DIC) tool. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points. A difference between the total residual deviance and the number of data points of <5 was considered acceptable (Spiegelhalter 2002). Heterogeneity in the random effects models, expressed by the between-study standard deviation (SD), was also checked. Details on the interventions, data and type of model used (i.e. fixed or random effects) in each NMA are reported in the respective sub-sections for each population, as discussed below.

Table 80. WinBUGS codes used to synthesise data in all NMAs that informed the guideline economic modelling of interventions aiming at preventing relapses in people whose depression has responded to acute treatment

Binomial likelihood, cloglog link

Random Effects model

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
#       cloglog(p[i,k]) <- mu[i] + delta[i,k]
# model for linear predictor
   eta[i,k] <-  mu[i] + delta[i,k]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras 2009 (Chapter 7)
   cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-xi2))
     -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LHR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LHR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LHR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# cloglog truncation values
xi1 <- 10
xi2 <- 3
```

Binomial likelihood, cloglog link

```
# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lhr[c,k] <- (d[k]-d[c])
log(hr[c,k]) <- lhr[c,k]
}
}
}   # *** PROGRAM ENDS
```

Fixed Effect model

```
# Binomial likelihood, cloglog link
# Fixed effect model for multi-arm trials
model{                    # *** PROGRAM STARTS
for(i in 1:ns){               # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
#       cloglog(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# model for linear predictor
   eta[i,k] <-  mu[i] + d[t[i,k]] - d[t[i,1]]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras 2009 (Chapter 7)
   cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-xi2))
      -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
      rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm

# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# cloglog truncation values
xi1 <- 10
xi2 <- 3

# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lhr[c,k] <- (d[k]-d[c])
log(hr[c,k]) <- lhr[c,k]
}
}
}   # *** PROGRAM ENDS
```

Each WinBUGS model was run with an initial burn-in period of 100,000 iterations, followed by 100,000 further iterations, thinned by 10 so as to obtain 10,000 iterations for use in the probabilistic economic model.

The models utilised uninformative prior parameters. Three different sets of initial values were used and convergence was tested by visual inspection of the Brooks Gelman-Rubin diagram. In addition, convergence of the models was assessed by checking the autocorrelation and the Kernel density plots within WinBUGS.

Inconsistency checks

A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A vs. B trial is the same as the relative effect between A and B estimated indirectly from A vs. C and B vs. C trials. In other words, it is assumed that there is agreement between the direct and indirect evidence informing the treatment contrasts [this has also been termed the similarity or transitivity assumption (Mavridis 2015)]. Inconsistency arises when there is a conflict between direct evidence (from an A vs. B trial) and indirect evidence (gained from A vs. C and B vs. C trials) and can only be statistically assessed when there are closed loops of evidence on three treatments that are informed by at least three distinct trials (van Valkenhoef 2016a). The assumption of consistency between indirect and direct evidence was explored by undertaking global inconsistency tests, which compared the fit of the 'base-case' model (fixed or random effects) that assumes consistency with a model which allows for inconsistency between direct an indirect evidence (also known as an unrelated mean effects model; the latter is equivalent to having separate, unrelated meta-analyses for every pair-wise contrast while assuming a common between-study variance parameter across all comparisons in the case of random effects models. Improvement in model fit (or a substantial reduction in heterogeneity) in the inconsistency model compared with the NMA consistency model indicates evidence of inconsistency (Dias 2010 & 2011b). Deviance plots, in which the posterior mean deviance of the individual data points in the inconsistency model are plotted against their posterior mean deviance in the consistency model, were inspected in order to identify studies which may have contributed to loops of evidence where inconsistency may be present. Where global inconsistency was identified, local tests using the node-splitting approach, implemented in R using the gemtc package were planned to be performed. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2011b; van Valkenhoef 2016b). Inconsistency checks followed the approach described in Daly 2020.

The WinBUGS code used to check global inconsistency across NMAs is shown in Table 81.

Table 81. WinBUGS code used to perform global inconsistency checks to the NMAs that informed the guideline economic modelling of interventions aiming at preventing relapses in people whose depression has responded to acute treatment

Binomial likelihood, cloglog link – inconsistency model
Random Effects model

# Binomial likelihood, cloglog link – inconsistency model 	
# Random effects model for multi-arm trials 	
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS

Binomial likelihood, cloglog link – inconsistency model

```
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
#       cloglog(p[i,k]) <- mu[i] + delta[i,k]
# model for linear predictor
   eta[i,k] <-  mu[i] + delta[i,k]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras 2009 (Chapter 7)
   cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-xi2))
      -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LHR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LHR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,1],t[i,k]] + sw[i,k]
# precision of LHR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

for (k in 1:nt) { d[k,k] <- 0 } # set effects of k vs k to zero
for (c in 1:(nt-1)) {
for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) } }  # priors for all mean treatment effects
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# cloglog truncation values
xi1 <- 10
xi2 <- 3
}   # *** PROGRAM ENDS
```

Fixed Effect model

```
# Binomial likelihood, cloglog link – inconsistency model
# Fixed effect model for multi-arm trials
model{                    # *** PROGRAM STARTS
for(i in 1:ns){              # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
#       cloglog(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# model for linear predictor
```

Binomial likelihood, cloglog link – inconsistency model

```
   eta[i,k] <-  mu[i] + d[t[i,1],t[i,k]]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras 2009 (Chapter 7)
   cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-xi2))
      -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
       rhat[i,k] <- p[i,k] * n[i,k]         # expected value of the numerators
#Deviance contribution
       dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[])           #Total Residual Deviance

# vague priors for treatment effects
for (k in 1:nt) { d[k,k] <- 0 }  # set effects of k vs k to zero
for (c in 1:(nt-1)) {
   for (k in (c+1):nt){
     d[c,k] ~ dnorm(0,.0001)    # priors for all mean treatment effects# cloglog truncation values
xi1 <- 10
xi2 <- 3
}   # *** PROGRAM ENDS
```

Efficacy data for people at medium risk of relapse whose depression has responded to acute pharmacological treatment

Efficacy data for this analysis were derived from pairwise meta-analysis of pharmacological relapse prevention RCTs in populations whose depression has responded to (the same as maintenance) acute pharmacological treatment that were included in the guideline systematic review. Treatment endpoint effects were synthesised using the cloglog model described above, with separate analyses for SSRIs (represented in the economic model by sertraline), SNRIs (represented in the economic model by venlafaxine), and TCAs (represented in the economic model by nortriptyline). Effects were expressed as hazard ratios of relapse for each drug class versus pill placebo which were applied onto the baseline relapse risk over the first 2 years of the economic analysis, during which pharmacological maintenance treatment was received. After two years of maintenance pharmacological treatment people in the model returned to the baseline risk of relapse that corresponded to their number of previous episodes and the number of years they spent in remission.

Table 82 shows the RCT data considered in the analysis of people at medium risk of relapse whose depression has responded to acute pharmacological treatment.

Table 82: Studies, interventions [T] and efficacy data (number of relapses [n] and number randomised [N]) considered in the analysis for people at medium risk of relapse whose depression has responded to acute pharmacological treatment

Study ID	Time point (weeks)	Drug	Arm 1			Arm 2			Arm 3		
			T	n	N	T	n	N	T	n	N
SSRIs											
Doogan1992	44	Sertraline	2	77	185	1	74	110	NA	NA	NA
Kamijima 2006	16		2	22	117	1	41	118	NA	NA	NA

Study ID	Time point (weeks)	Drug	Arm 1			Arm 2			Arm 3		
			T	n	N	T	n	N	T	n	N
Wilson 2003	100		2	39	56	1	43	57	NA	NA	NA
Lepine 2004[2]	78		2	37	95	2	37	94	1	49	99
Gilaberte 2001	48	Fluoxetine	2	21	70	1	41	70	NA	NA	NA
Montgomery 1988	52		2	43	108	1	72	112	NA	NA	NA
Schmidt 2000	25		2	105	189	1	87	122	NA	NA	NA
Terra 1998	52	Fluvoxamine	2	14	110	1	33	94	NA	NA	NA
Gorwood 2007	24	Escitalopram	2	23	152	1	63	153	NA	NA	NA
Kornstein 2006	52		2	36	73	1	54	66	NA	NA	NA
Rapaport 2004	36		2	89	181	1	62	93	NA	NA	NA
Hochstrasser 2001	48	Citalopram	2	24	132	1	64	137	NA	NA	NA
Klysner 2002	48		2	37	60	1	55	61	NA	NA	NA
Robert 1995	24		2	21	152	1	18	74	NA	NA	NA
Montgomery 1993b	24		2	22	48	2	26	57	1	33	42
Dobson 2008	52	Paroxetine	2	11	28	1	16	21	NA	NA	NA
Montgomery 1993a	52		2	11	68	1	29	67	NA	NA	NA
Franchini 1998	121		2	8	34	2	18	34	NA	NA	NA
SNRIs											
Perahia 2006	26	Duloxetine	2	62	136	1	95	142	NA	NA	NA
Perahia 2009	52		2	50	146	1	69	142	NA	NA	NA
Kocsis 2007	52	Venlafaxine	2	98	164	1	135	172	NA	NA	NA
Montgomery 2004	52		2	24	112	1	59	123	NA	NA	NA
Simon 2004	26		2	100	154	1	115	138	NA	NA	NA
Rickels 2010	26	Desvenlafaxine	2	58	190	1	101	185	NA	NA	NA
Rosenthal 2013	26		2	62	272	1	100	276	NA	NA	NA
TCAs											
Coppen 1978	52	Amitriptyline	2	3	16	1	5	16	NA	NA	NA
Klerman 1974	35		2	11	50	1	17	50	NA	NA	NA
Stein 1980	26		2	8	29	1	18	26	NA	NA	NA
Alexopoulos 2000	104	Nortriptyline	2	4	22	1	11	21	NA	NA	NA

Treatment codes: 1 pill placebo; 2 antidepressant drug
SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Results of the pairwise meta-analysis: people at medium risk of relapse whose depression has responded to acute pharmacological treatment

For the analysis of SSRI data (35 data points), the random effects model (SD = 0.23; totresdev = 36.76; DIC = 224.49) was selected as it demonstrated a better fit compared with the fixed effect model (totresdev = 48.95; DIC = 228.57). The between-study SD in the random effects model suggested moderate heterogeneity when compared with the size of the intervention effect estimate.

For the analysis of SNRI data (14 data points), the fixed effect model (totresdev = 12.94; DIC = 96.18) was preferred as it showed an equally good fit to the random effects model (SD = 0.11; totresdev = 12.87; DIC = 98.04).

Similarly, for the analysis of TCA data (8 data points), the fixed effect model (totresdev = 7.54; DIC = 40.44) was preferred as it showed an equally good fit to the random effects model (SD = 0.70; totresdev = 7.33; DIC = 41.84).

The resulting hazard ratios of each antidepressant drug class versus pill placebo (which represented GP care in the economic model) are shown in Table 83.

Table 83. Results of the pairwise meta-analysis that informed the economic analysis for people at medium risk of relapse whose depression has responded to acute pharmacological treatment

AD drug class	N AD	Mean hazard ratio v pill placebo (95% CIs)	N pill placebo	Type of model
SSRIs	1,975	0.46 (0.38 to 0.54)	1,496	random effects
SNRIs	1,174	0.55 (0.48 to 0.62)	1,178	fixed effect
TCAs	117	0.40 (0.24 to 0.63)	113	fixed effect

AD: antidepressant; CIs: confidence intervals; N: number of participants randomised in each comparison of AD class vs pill placebo; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Efficacy data for people at high risk of relapse whose depression has responded to acute pharmacological treatment

Efficacy data for this analysis were derived from synthesis of data obtained from psychological and pharmacological relapse prevention RCTs in populations whose depression has responded to acute pharmacological treatment that were included in the guideline systematic review.

Psychological RCTs in these populations assessed maintenance psychological interventions instead of, or in addition to, antidepressants; these studies did not use specific antidepressant drugs (or drug classes), so that no class-specific effect could be obtained for antidepressants. To synthesise psychological and pharmacological study data, an overall antidepressant treatment effect was estimated out of all studies (pharmacological and psychological) and utilised in the analysis. This overall treatment effect was applied to sertraline, which was the drug used in the analysis for this population regarding drug acquisition cost.

In addition to the above studies, a number of studies included participants whose depression had responded to a range of acute treatments, including both pharmacological and psychological interventions. The vast majority of these studies considered maintenance treatments added to treatment as usual [TAU] vs TAU alone (as seen in Table 79); TAU comprised a range of treatments that could include no treatment, help from the family doctor or other routine healthcare if requested, antidepressant use, or depression relapse active monitoring. These studies (and respective interventions) were considered only for people at high risk of relapse, since they had been tested predominantly (if not exclusively) in populations at high risk of relapse. In order to incorporate this evidence into the economic analysis, these studies were included in the data synthesis for people at high risk of relapse whose depression has responded to acute pharmacological treatment in a secondary analysis. As in this population TAU comprises antidepressant treatment, the relative effect of psychological intervention plus TAU versus TAU alone that was estimated in these studies was assumed to reflect the relative effect of the psychological intervention plus antidepressant versus antidepressant alone.

Data from the above studies were synthesised in two NMAs (one for the primary analysis and one for the secondary analysis) using the cloglog link linear model, as described earlier.

Both random and fixed effects models were tested. Some RCTs reported data only at treatment endpoint, other RCTs reported data both at treatment endpoint and at various follow-up periods and a number of RCTs reported follow-up but not treatment endpoint data. In studies reporting multiple data points, data reported as close to 52 weeks from treatment initiation as possible were obtained, to match the length of the Markov model cycle. In total, 38 studies with 79 arms and 7,471 participants were included in the primary analysis and 53 studies with 110 arms and 10,084 participants were included in the secondary analysis.

Studies, interventions and efficacy data included in the guideline systematic review that were considered in the NMA of interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment are shown in

Table 84. The network plots of interventions included in the NMA primary and secondary analysis are shown in Figure 108.

Table 84: RCTs, interventions [T] and efficacy data (number of relapses [n] and number randomised [N] in each arm) considered in the analysis for people at high risk of relapse whose depression has responded to acute pharmacological treatment

Study ID	Time point (weeks)	Arm 1			Arm 2			Arm 3		
		T	n	N	T	n	N	T	n	N
Doogan1992	44	2	77	185	1	74	110	NA	NA	NA
Kamijima 2006	16	2	22	117	1	41	118	NA	NA	NA
Wilson 2003	100	2	39	56	1	43	57	NA	NA	NA
Gilaberte 2001	48	2	21	70	1	41	70	NA	NA	NA
Montgomery 1988	52	2	43	108	1	72	112	NA	NA	NA
Schmidt 2000	25	2	105	189	1	87	122	NA	NA	NA
Terra 1998	52	2	14	110	1	33	94	NA	NA	NA
Gorwood 2007	24	2	23	152	1	63	153	NA	NA	NA
Kornstein 2006	52	2	36	73	1	54	66	NA	NA	NA
Rapaport 2004	36	2	89	181	1	62	93	NA	NA	NA
Hochstrasser 2001	48	2	24	132	1	64	137	NA	NA	NA
Klysner 2002	48	2	37	60	1	55	61	NA	NA	NA
Robert 1995	24	2	21	152	1	18	74	NA	NA	NA
Montgomery 1993b	24	2	22	48	2	26	57	1	33	42
Dobson 2008	52	2	11	28	1	16	21	NA	NA	NA
Montgomery 1993a	52	2	11	68	1	29	67	NA	NA	NA
Franchini 1998	121	2	8	34	2	18	34	NA	NA	NA
Perahia 2006	26	2	62	136	1	95	142	NA	NA	NA
Perahia 2009	52	2	50	146	1	69	142	NA	NA	NA
Kocsis 2007	52	2	98	164	1	135	172	NA	NA	NA
Montgomery 2004	52	2	24	112	1	59	123	NA	NA	NA
Simon 2004	26	2	100	154	1	115	138	NA	NA	NA
Rickels 2010	26	2	26	58	1	190	101	NA	NA	NA
Rosenthal 2013	26	2	26	62	1	272	100	NA	NA	NA
Coppen 1978	52	2	3	16	1	5	16	NA	NA	NA
Klerman 1974	35	2	11	50	1	17	50	NA	NA	NA

Study ID	Time point (weeks)	Arm 1			Arm 2			Arm 3		
		T	n	N	T	n	N	T	n	N
Stein 1980	26	2	8	29	1	18	26	NA	NA	NA
Alexopoulos 2000	104	2	4	22	1	11	21	NA	NA	NA
Lepine 2004[1]	78	2	37	95	2	37	94	1	49	99
Franchini 1997/2000a	104	2	10	32	2	9	32	NA	NA	NA
Huijbers 2015	65	4	12	33	2	13	35	NA	NA	NA
Huijbers 2016	65	4	47	121	3	69	128	NA	NA	NA
Kuyken 2008	65	3	29	61	2	37	62	NA	NA	NA
Kuyken 2015	65	3	99	212	2	104	212	NA	NA	NA
Wilkinson 2009	52	5	9	22	2	13	23	NA	NA	NA
Fava 1998a/2004	104	6	8	23	2	18	22	NA	NA	NA
Fava 1994/1996/1998c[2]	124	7	4	21	1	9	22	NA	NA	NA
Bockting 2018[3]	57	6	55	104	7	57	85	2	61	100
Bockting 2005/2015[4]	52	5	43	97	2	49	90	NA	NA	NA
Bondolfi2010[4]	60	4	13	31	2	11	29	NA	NA	NA
Farb 2018[4]	104	4	33	82	5	37	84	NA	NA	NA
Godfrin2010[4]	56	4	24	52	2	39	54	NA	NA	NA
Ma2004[4]	60	4	15	37	2	24	38	NA	NA	NA
Meadows 2014[4]	60	4	42	101	2	52	102	NA	NA	NA
Teasdale 2000[4]	60	4	43	76	2	52	69	NA	NA	NA
Williams 2014[4]	60	4	55	108	2	31	56	11	59	110
Shallcross 2015/2018[4]	60	4	15	46	11	14	46	NA	NA	NA
Old Age Depression Interest Group 1993[4]	52	2	13	33	1	21	36	NA	NA	NA
Stangier 2013[4]	87	6	46	90	8	54	90	NA	NA	NA
Biesheuvel-Leliefeld 2017[4]	52	9	44	124	2	62	124	NA	NA	NA
Holländare 2011/2013[4]	36	10	8	42	11	19	42	NA	NA	NA
Klein 2018a[4]	57	9	58	132	2	72	132	NA	NA	NA
Segal 2020[4]	65	9	76	230	2	54	230	NA	NA	NA

Treatment codes: 1 pill placebo; 2 AD; 3 MBCT + AD tapering; 4 MBCT + AD; 5 group CT/CBT + AD; 6 individual CT/CBT + AD; 7 individual CT/CBT + AD tapering; 8 individual psychoeducation + AD; 9 self-help (without or with minimal support) + AD; 10 self-help with support + AD; 11 attention placebo + AD

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy

[1]This study compared sertraline versus pill placebo in people who had not received sertraline as acute treatment; hence, it has been included in this analysis but not in the class-specific pharmacological treatment for people at medium risk of relapse, who had remitted following specified pharmacological treatment, which was continued as maintenance treatment.

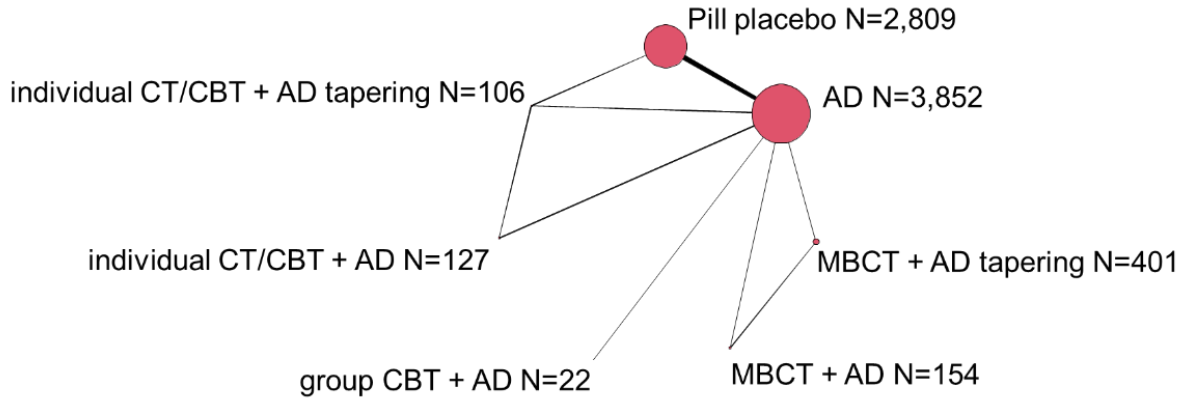
[2]The study compared individual CT + AD tapering versus clinical management + AD tapering; the latter was coded as pill placebo to allow connection of the study to the network

[3]Active interventions were coded as 'individual CT/CBT + AD' and 'individual CT/CBT + AD tapering'; however, in each arm, a number of people received group CT/CBT.

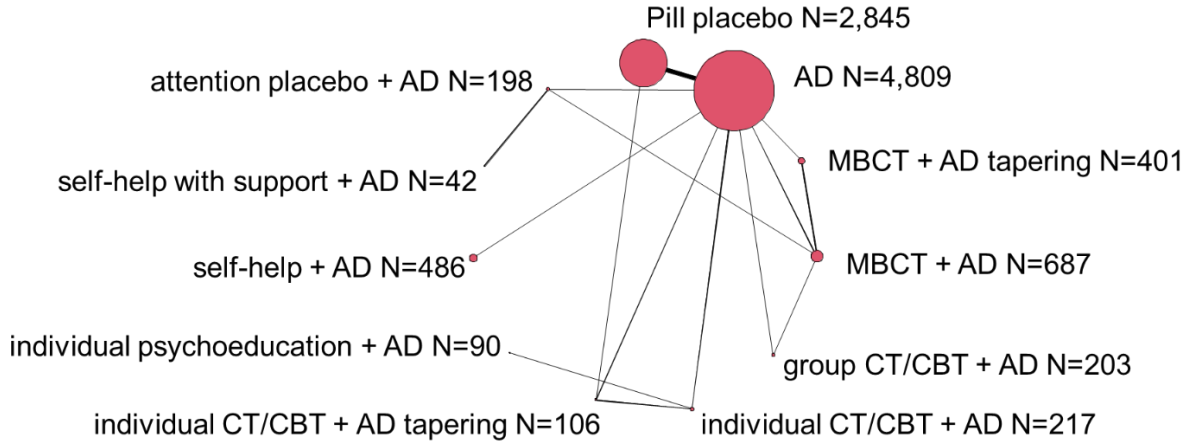
[4]These studies recruited people whose depression had responded to various acute treatments and were considered only in secondary analysis. In studies that compared an intervention added to TAU vs TAU alone, TAU in this population was assumed to reflect AD.

Figure 108. Network plots of interventions included in the NMA of treatments for people at high risk of relapse whose depression has responded to acute pharmacological treatment

A. primary analysis



B. secondary analysis



The width of the lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy

Results of the network meta-analysis: people at high risk of relapse whose depression has responded to acute pharmacological treatment

The random effects model demonstrated a better fit for the data, for both the primary and the secondary analysis. Heterogeneity (between-trial standard deviation) was low-to-moderate when compared with the size of the intervention effect estimates. No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as the two models showed no differences in their fit or in the between-study standard deviation (Table 85). The deviance plot showed no considerable improvements in the prediction of data points by the inconsistency model compared with the consistency model, in both the primary and the secondary analyses (Figure 109). Therefore, no further inconsistency checks using the node-splitting approach were undertaken.

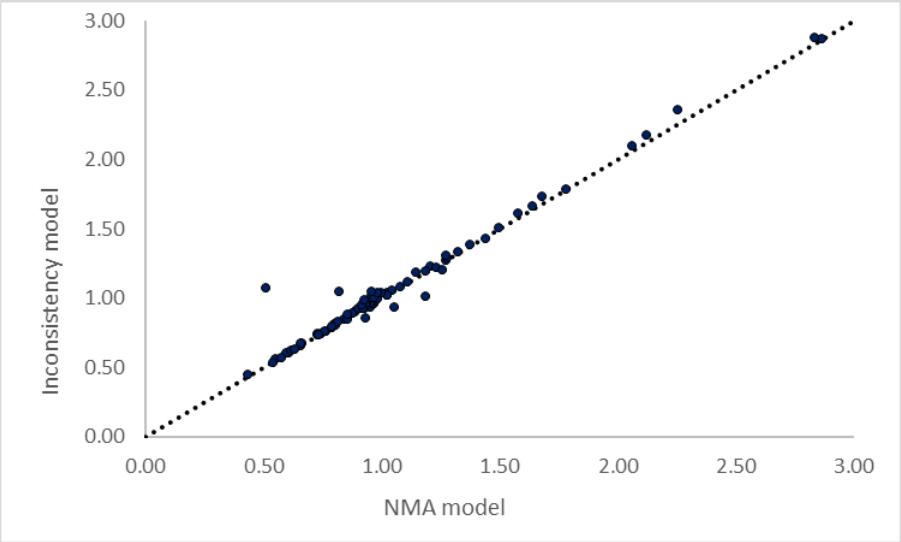
Table 85. Model fit statistics for fixed and random effects models and inconsistency models in analysis for people at high risk of relapse whose depression has responded to acute pharmacological treatment

Model	Between Study Heterogeneity – SD			Posterior mean residual deviance[1]	DIC[2]
	Posterior mean	Posterior median	95% CrI		
Primary analysis					
Fixed effect – consistency	Non applicable			98.93	504.35
Random effects – consistency	0.17	0.17	0.03 to 0.32	83.43	500.84
Random effects - inconsistency	0.17	0.17	0.02 to 0.32	84.53	503.76
Secondary analysis					
Fixed effect – consistency	Non-applicable			137.30	706.28
Random effects - consistency	0.18	0.18	0.06 to 0.30	112.20	698.13
Random effects - inconsistency	0.20	0.20	0.08 to 0.32	112.70	702.86

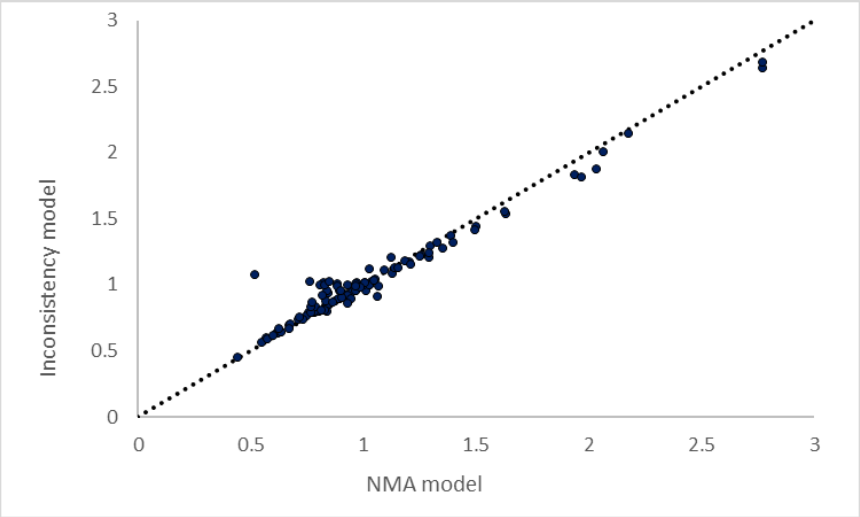
1 compared to 79 total data points (primary analysis); and 110 total data points (secondary analysis)
2 lower values preferred
CrI: credible intervals; DIC: Deviance information criterion; SD: standard deviation

Figure 109. Deviance contributions for the random effects consistency and inconsistency models for people at high risk of relapse whose depression has responded to acute pharmacological treatment

a. primary analysis



b. secondary analysis



The results of the random effects models that informed the economic analysis (hazard ratios of all interventions versus pill placebo) are shown in Table 86.

Table 86. Results of the NMA that informed the economic analysis for people at high risk of relapse whose depression has responded to acute pharmacological treatment (random effects model)

Comparison	Mean hazard ratio (95% CrI)
Primary analysis	
AD vs pill placebo	0.50 (0.44 to 0.55)
MBCT (AD taper) vs pill placebo	0.46 (0.31 to 0.64)
MBCT + AD vs pill placebo	0.34 (0.19 to 0.55)
Group CT/CBT + AD vs pill placebo	0.35 (0.12 to 0.79)
Individual CT/CBT + AD vs pill placebo	0.30 (0.18 to 0.46)
Individual CT/CBT (AD taper) vs pill placebo	0.51 (0.30 to 0.78)
Secondary analysis	
AD vs pill placebo	0.49 (0.44 to 0.55)
MBCT (AD taper) vs pill placebo	0.46 (0.32 to 0.63)
MBCT + AD vs pill placebo	0.34 (0.26 to 0.43)
Group CT/CBT + AD vs pill placebo	0.37 (0.24 to 0.54)
Individual CT/CBT + AD vs pill placebo	0.30 (0.18 to 0.46)
Individual CT/CBT (AD taper) vs pill placebo	0.50 (0.29 to 0.79)
Individual psychoeducation + AD vs pill placebo	0.40 (0.18 to 0.76)
Self-help without/with minimal support + AD vs pill placebo	0.45 (0.32 to 0.61)
Self-help with support + AD vs pill placebo	0.15 (0.04 to 0.35)
Attention placebo + AD vs pill placebo	0.39 (0.24 to 0.59)

AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMA: network meta-analysis

Efficacy data for people at medium or high risk of relapse whose depression has responded to acute psychological treatment

Efficacy data for this analysis were derived from synthesis of data obtained from pharmacological and psychological relapse prevention RCTs in populations whose depression has responded to acute psychological treatment that were included in the guideline systematic review.

In addition, studies that included participants whose depression had responded to a range of acute treatments, including both pharmacological and psychological interventions, were considered in a secondary analysis. The vast majority of these studies assessed maintenance treatments added to treatment as usual [TAU] vs TAU alone. These studies (and respective interventions) were considered only for people at high risk of relapse whose depression has responded to acute psychological treatment, since they had been tested predominantly (if not exclusively) in populations at high risk of relapse. As in populations who have responded to acute psychological treatment TAU comprises no (further) treatment, the relative effect of psychological intervention plus TAU versus TAU alone that was estimated in these studies was assumed to equal the relative effect of psychological intervention versus no treatment.

Data from the above studies were synthesised in a NMA using the cloglog linear model. A single NMA was run for both people at medium risk of relapse and those at high risk of relapse, and for primary and secondary analysis, because the additional studies and comparisons relevant to people at high risk of relapse, which were considered in secondary analysis, made different comparisons and did not create any loops with the evidence for people at medium risk of relapse (with the exception of one small study [N=66] of antidepressant versus pill placebo). Both random and fixed effects models were tested. Some RCTs reported data only at treatment endpoint, other RCTs reported data both at treatment endpoint and at various follow-up periods and a number of RCTs reported follow-up but not treatment endpoint data. In studies reporting multiple data points, data reported as close to 52 weeks from treatment initiation as possible were obtained, to match the length of the Markov model cycle. In total, 18 studies with 38 arms and 3,152 participants were included in the analysis.

Studies, interventions and efficacy data included in the guideline systematic review that were considered in the NMA of interventions for people at medium or high risk of relapse whose depression has responded to acute psychological treatment are shown in Table 87. The network plots of interventions included in the NMAs, both in primary and secondary analysis, are shown in Figure 110.

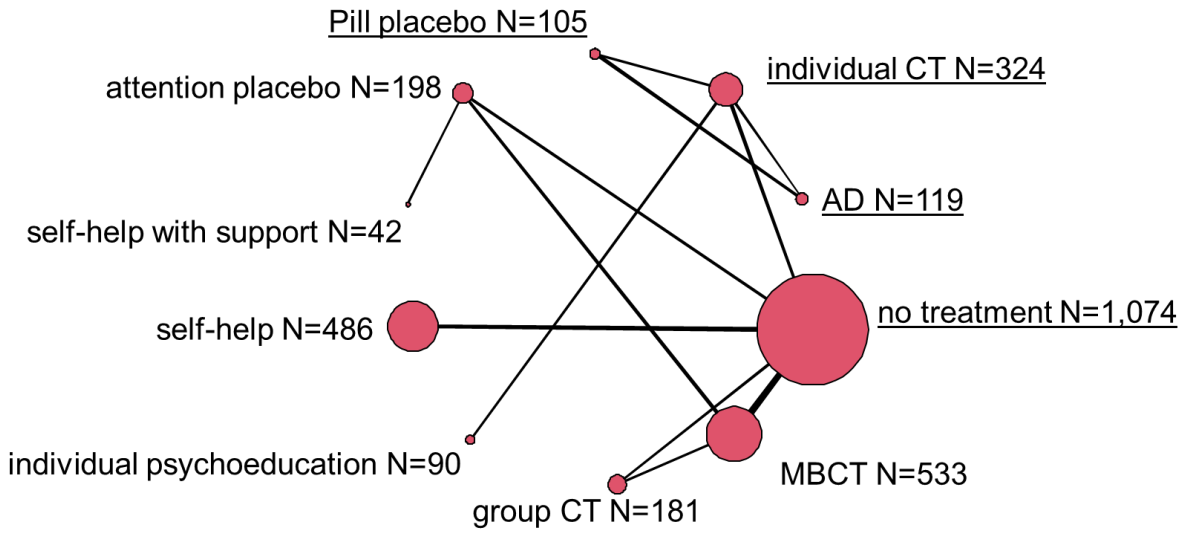
Table 87: Studies, interventions [T] and efficacy data (number of relapses [n] and number randomised [N] in each arm) considered in the analysis for people at medium and/or high risk of relapse whose depression has responded to acute psychological treatment

Study ID	Time point (weeks)	Arm 1			Arm 2			Arm 3		
		T	n	N	T	n	N	T	n	N
Jarrett2001	35	2	8	41	4	18	43	NA	NA	NA
Jarrett2013	56	2	39	86	1	40	69	3	48	86
de Jonge 2019[1]	65	2	25	107	4	35	107	NA	NA	NA
Bockting 2005/2015[2]	52	6	43	97	4	49	90	NA	NA	NA
Bondolfi2010[2]	60	5	13	31	4	11	29	NA	NA	NA
Farb 2018[2]	104	5	33	82	6	37	84	NA	NA	NA
Godfrin2010[2]	56	5	24	52	4	39	54	NA	NA	NA

Study ID	Time point (weeks)	Arm 1			Arm 2			Arm 3		
		T	n	N	T	n	N	T	n	N
Ma2004[2]	60	5	15	37	4	24	38	NA	NA	NA
Meadows 2014[2]	60	5	42	101	4	52	102	NA	NA	NA
Teasdale 2000[2]	60	5	43	76	4	52	69	NA	NA	NA
Williams 2014[2]	60	5	55	108	4	31	56	10	59	110
Shallcross 2015/2018[2]	60	5	15	46	10	14	46	NA	NA	NA
Old Age Depression Interest Group 1993[2]	52	3	13	33	1	21	36	NA	NA	NA
Stangier 2013[2]	87	2	46	90	7	54	90	NA	NA	NA
Biesheuvel-Leliefeld 2017[2]	52	8	44	124	4	62	124	NA	NA	NA
Holländare 2011/2013[2]	36	9	8	42	10	19	42	NA	NA	NA
Klein 2018a2[2]	57	8	58	132	4	72	132	NA	NA	NA
Segal 2020[2]	65	8	76	230	4	54	230	NA	NA	NA

Treatment codes: 1 pill placebo; 2 individual CT/CBT; 3 AD; 4 no treatment; 5 MBCT; 6 group CT/CBT; 7 individual psychoeducation; 8 self-help (without or with minimal support); 9 self-help with support; 10 attention placebo
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy
[1]This study compared individual CT + TAU vs TAU in people whose depression responded to acute individual CT, reporting that TAU comprises no treatment. The comparison was thus coded as individual CT vs no treatment.
[2]These studies recruited people whose depression had responded to various acute treatments and were considered only in secondary analysis. In studies that compared an intervention added to TAU vs TAU alone, TAU in this population was assumed to reflect no treatment.

Figure 110. Network plot of interventions included in the NMA of treatments for people at medium and/or high risk of relapse whose depression has responded to acute psychological treatment. Underlined are treatments considered for people at medium and/or high risk of relapse in primary analysis



The width of the lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy

Results of the network meta-analysis: people at medium or high risk of relapse whose depression has responded to acute psychological treatment

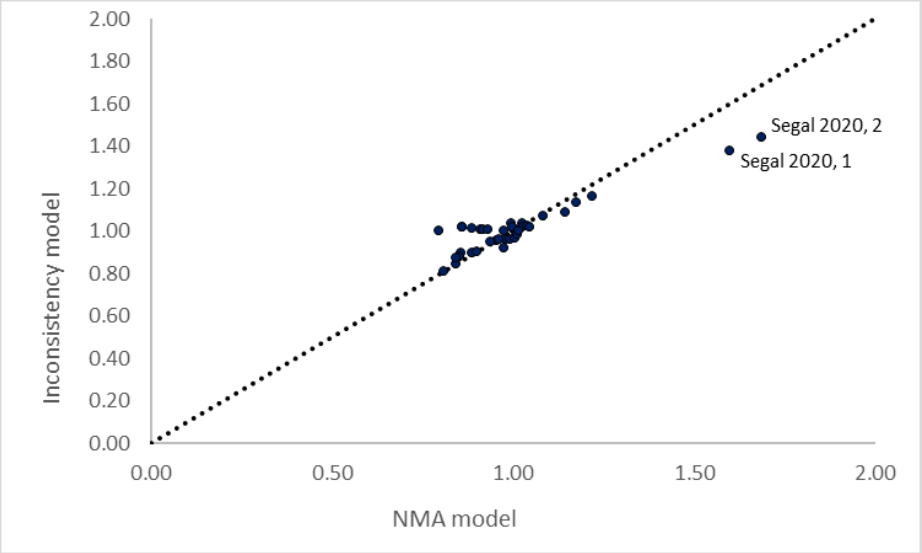
The random effects model demonstrated a better fit for the data. Heterogeneity (between-trial standard deviation) was moderate when compared with the size of the intervention effect estimates. No evidence of inconsistency was found through comparison of the consistency and inconsistency random effects models, as the two models showed no differences in their fit or in the between-study standard deviation (Table 88). The deviance plot showed no considerable improvements in the prediction of data points by the inconsistency model compared with the consistency model (Figure 111). There was only some evidence of improvement for Segal 2020, a 2-arm study that compared self-help without or with minimal support with no treatment. The study did not form any loop in the network and therefore did not contribute to potential evidence of inconsistency. This study was the only negative trial of self-help without or with minimal support in the network (the network included 2 positive studies of self-help compared with no treatment) and therefore it has contributed to the network's heterogeneity. As no evidence of inconsistency was found from the global inconsistency checks and the inspection of the deviance plot, no further inconsistency checks using the node-split approach were undertaken.

Table 88. Model fit statistics for fixed and random effects models and inconsistency models in analysis for people at high risk of relapse whose depression has responded to acute psychological treatment

Model	Between Study Heterogeneity - SD			Posterior mean residual deviance[1]	DIC[2]
	Posterior mean	Posterior median	95% CrI		
Fixed effect – consistency	Non applicable			48.55	252.12
Random effects – consistency	0.27	0.26	0.06 to 0.56	38.04	247.80
Random effects - inconsistency	0.33	0.31	0.08 to 0.69	38.27	249.76

1 compared to 38 total data points
2 lower values preferred
CrI: credible intervals; DIC: Deviance information criterion; SD: standard deviation

Figure 111. Deviance contributions for the random effects consistency and inconsistency models for people at high risk of relapse whose depression has responded to acute psychological treatment



The results of the random effects model that informed the economic analysis (hazard ratios of all interventions versus pill placebo and versus no treatment) are shown in Table 89.

Table 89. Results of the NMA that informed the economic analysis for people at medium and/or high risk of relapse whose depression has responded to acute psychological treatment (random effects model)

Comparison	Mean hazard ratio (95% CrI) - NMA
individual CT/CBT vs pill placebo	0.67 (0.31 to 1.26)
AD vs pill placebo	0.81 (0.43 to 1.37)
no treatment vs pill placebo	1.28 (0.45 to 2.95)
MBCT vs pill placebo	0.89 (0.29 to 2.14)
group CT vs pill placebo	1.01 (0.30 to 2.56)
individual psychoeducation vs pill placebo	0.92 (0.29 to 2.20)
self-help without/with minimal support vs pill placebo	1.17 (0.37 to 2.85)
self-help with support vs pill placebo	0.40 (0.07 to 1.33)
attention placebo vs pill placebo	1.03 (0.30 to 2.63)
individual CT/CBT vs no treatment	0.52 (0.29 to 1.01)
AD vs no treatment	0.61 (0.26 to 1.69)
MBCT vs no treatment	0.70 (0.51 to 0.93)
group CT vs no treatment	0.79 (0.44 to 1.33)
individual psychoeducation vs no treatment	0.79 (0.26 to 1.77)
self-help without/with minimal support vs no treatment	0.92 (0.59 to 1.33)
self-help with support vs no treatment	0.31 (0.08 to 0.82)
attention placebo vs no treatment	0.80 (0.43 to 1.36)

AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMA: network meta-analysis

Baseline risks of relapse and remission - overview

The baseline risks of relapse and remission were estimated from data obtained from a review of long-term observational (or 'naturalistic' or 'longitudinal') studies conducted in primary or secondary care that reported data on relapse rates over long periods of time in people who had remitted from a depressive episode and/or long-term data on (non-)recovery rates in people in a depressive episode. In this type of studies the treatment is not assigned by design and is not under the control of the investigators. The review included 12 studies conducted in primary care (Coryell 1991; Eaton 2008; Hardeveld 2013; Mattisson 2007; Nuggerud-Galeas 2020; Ormel 1993; Riihimäki 2014; Skodol 2011; Stegenga 2012; van Weel-Baumgarten 1998; Yiend 2009), 16 studies conducted in secondary care (Bukh 2016; Gonzales 1985; Holma 2008; Kanai 2003; Keller 1981, 1984 & 1992; Kennedy 2003; Kiloh 1988; Lee 1988; Lehman 1988; Maj 1992; Melartin 2004; Mueller 1996 & 1999; Solomon 2000) and 1 study conducted in both primary and secondary care settings (Comijs 2015) that reported relapse and/or chronicity (i.e. non-recovery) data on people with depression. The studies were identified from 3 systematic reviews of naturalistic studies (Hardeveld 2010; Steinert 2014; van Weel-Baumgarten 2000) and further committee's expert advice; additional studies were identified by scanning the reference lists of publications suggested by the committee.

The reported risks of relapse in the 1st year, 2nd to 5th years and 6th year and above following remission, together with risks of non-recovery over time reported in each study are provided in Table 90.

Table 90: Risks of relapse in years following remission and risks of chronicity (non-recovery) of a depressive episode as reported in the naturalistic studies included in the guideline review

Study ID	Population characteristics	Relapse risk following remission			Risk of chronicity (non-recovery)
		Year 1	Years 2-5	Years 6+	
Primary care – community settings					
Coryell 1991	396 nonclinical individuals in the US who had had major depression that ended before the initial evaluation			Year 6: 0.34	
Eaton 2008	92 adults with a first episode of major depression in a community setting in the US followed up for 10 years.	Graph: 0.06	Year 2: 0.25 (according to the graph, it is 0.19)	Year 10: 0.45	Year 10: 0.15 (chronicity defined as people not remaining free for longer than 1 year)
Hardeveld 2013	687 people from the general Dutch population with a lifetime DSM-III-R diagnosis of major depression but without a current major depressive episode or dysthymia. Participants had to be at least 6 months in remission. 3-year follow-up & modelled projection of relapses.	0.03	Year 2: 0.05 Year 5: 0.13	Year 10: 0.23 Year 20: 0.42	
Magnil 2013	Primary care cohort of 51 people >60 years of age diagnosed with mild or moderate major depression, who completed 5 assessments over 2 years of follow-up in Sweden.				Year 2: 0.71
Mattisson 2007	Community sample of 3563 people in Sweden followed in 1947, 1957, 1972 & 1997. 344 people had their first onset of depression during the follow-up and were analysed in this study.	Graph: 0.09	Graph: Year 2: 0.12 Year 5: 0.21	Year 10: 0.29	
Nuggerud-Galeas 2020	Retrospective data analysis of a primary care sample of 957 adults who had been diagnosed with depression between 2001-2017 in Spain. Mean age at diagnosis 50 for men, 53 for women. It is not known whether first diagnosis within this period represented first episode of depression.		Men: Year 4.97: 0.35 Women: Year 4.37: 0.43	Men: Year 8.54: 0.47 Year 12.29: 0.48 Women: Year 8.16: 0.59	

Study ID	Population characteristics	Relapse risk following remission			Risk of chronicity (non-recovery)
		Year 1	Years 2-5	Years 6+	
				Year 11.66: 0.63	
Ormel 1993	20 people with depression among 201 people with common mental health problems receiving primary-care in the Netherlands				Year 3.5: 0.12
Riihimäki 2014	137 people with DSM-IV depressive disorder in Finnish primary care; 122 completed a 5-year follow-up including 102 with a research diagnosis of major depression		Year 5: 0.51 [from full or partial remission]		Year 5: 0.10 (no full or partial remission) 0.31(no full remission)
Skodol 2011	1,996 participants in a national US survey who met criteria for major depression, followed-up for 3 years	Not considered as only relapse after 1 year was estimated, those who relapsed in shorter periods of time were not included in estimates. Also, denominator included people with persistent major depression			Year 3: 0.15
Stegenga 2012	174 people with major depression in Dutch primary care, followed over 39 months.	0.11	Year 3: 0.18		Year 3: 0.17
van Weel-Baumgarten 1998	222 people with depression before January 1984 in Dutch primary care followed up for 10 years	Graph: 0.10	Graph: Year 2: 0.18 Year 3: 0.26 Year 5: 0.31	Year 10: 0.40	
Yiend 2009	37 people attending UK primary care services followed for 23 years (73% with first episode); 23% on antidepressants at the time of the study (mean length of time on antidepressants during follow up 39.7 months); 24.3% received no pharmacological treatment. No patients were continuously medicated throughout follow up.			Year 10: 0.50 Year 23: 0.62	Year 23: 0.00
Secondary care – inpatient and/or outpatient settings					
Bukh 2016	301 adult in- (60.8%) or out-patients with a validated diagnosis of a single depressive episode from 2005 to 2007 in Denmark	0.09	Year 2: 0.15 Year 5: 0.32		Year 1: 0.71 Year 2: 0.42 Year 5: 0.17

Study ID	Population characteristics	Relapse risk following remission			Risk of chronicity (non-recovery)
		Year 1	Years 2-5	Years 6+	
Gonzales 1985	59 outpatients with unipolar major depression who had completed CBT and were followed for 1-3 years in the US	0.31			Year 1: 0.31
Holma 2008	163 people in Finland with DSM-IV major depression receiving mainly outpatient care, followed up over 5 years between 1997 and 2004.		Year 5: 0.71		Year 5: 0.01 (no full or partial remission) 0.12 (no full remission)
Kanai 2003	95 people who had recovered from unipolar major depression, followed for 6 years, recruited mostly from secondary settings (22/23 centres) in Japan. Participants had not received antidepressant or antipsychotic medication in the 3 months prior to the start of the study	0.21	Year 2: 0.30 Year 5: 0.42	Year 6: 0.14	
Keller 1981	101 in- or out-patients in a current episode of major depression, of whom 75 recovered, followed for 1 year in the US	0.21 (major depression) 0.36 (depressive symptoms)			Year 1: 0.29
Keller 1984	97 US people with an episode of major depressive disorder and no history of chronic minor depression who sought treatment at five university medical centres in the US				Year 2: 0.21
Kennedy 2003	70 people receiving psychiatric secondary care, predominantly inpatient (76%) in the UK, with moderate to severe depression, followed up for 8-11 years. At follow up, 59% received at least 5 years of antidepressant treatment and only 15% received less than a year of antidepressant treatment. Over follow-up people maintained regular contact with their GPs and mental health teams for psychiatric review or treatment.	0.25	Year 2: 0.33	Graph: Year 8: 0.65	Year 11: 0.08

Study ID	Population characteristics	Relapse risk following remission			Risk of chronicity (non-recovery)
		Year 1	Years 2-5	Years 6+	
Kiloh 1988	133 Australian inpatients with primary depressive illness between 1966 and 1970 were followed up for an average of 15 years.			Year 15: 0.76	Year 15: 0.17
Lee 1988	89 inpatients with primary depressive illness in London in 1965-66 followed for 18 years			Year 18: 0.95	Year 18: 0.15
Lehman 1988	65 depressed Canadians followed for 11 years; 52% were receiving psychiatric treatment predominately as outpatients at follow-up.			Year 11: 0.78	
Maj 1992	72 people in specialist care in Italy who had recovered from an episode of non-psychotic major depression, evaluated bimonthly for a period ranging from 20 to 108 months (median 66 months).	0.37	Year 5: 0.75		
Melartin 2004	269 secondary care psychiatric outpatients and inpatients diagnosed with a new episode of DSM-IV major depression in Finland		Year 1.5: 038		
Keller 1992 Mueller 1996	431 people with major depression in secondary care in the US, followed for 10 years				Year 1: 0.30 Year 2: 0.19 Year 4: 0.13 Year 5: 0.12 Year 10: 0.07
Mueller 1999	380 people who recovered from an index episode of major depressive disorder and 105 people who subsequently remained well for at least 5 years after recovery in outpatient specialist care in the US, followed for up to 15 years; people could be taking antidepressants and possibly ECT over time. Of those who eventually experienced a relapse, 77% were receiving no antidepressant treatment during the month just before the relapse.	Graph: 0.25	Graph: Year 2: 0.42 Year 3: 0.52	Year 15: 0.85 (Kaplan-Meier curve)	

Study ID	Population characteristics	Relapse risk following remission			Risk of chronicity (non-recovery)
		Year 1	Years 2-5	Years 6+	
Solomon 2000	318 people in inpatient and outpatient care in the US with unipolar major depressive disorder prospectively followed for 10 years Number of previous episodes: 0: 38%; 1: 24%; 2: 13%; 3+: 25% During the 4 weeks immediately before the onset of the first three prospectively observed relapses, 47%-50% of all subjects received no pharmacotherapy. During the 4 weeks immediately before the onset of the fourth and fifth prospectively observed relapses, one-third of the subjects received no pharmacotherapy.	0.25	Year 2: 0.42 Year 5: 0.60 2nd relapse: Year 2: 59% Year 5: 74% 3rd relapse: Year 2: 62% Year 5: 79% 4th relapse: Year 2: 62% 5th relapse: Year 2: 74% Number of relapses refer to prospectively observed relapses during the study, not lifetime relapses.		
Mixed primary and secondary care settings					
Comijs 2015	199 people ≥ 60 years of age with major depression attending either mental health care facilities or primary care in the Netherlands, followed up for 2 years				Year 2: 0.44

Baseline risk of relapse after a single (first) depressive episode (i.e. in people with no previous depressive episodes)

The committee's expert opinion and inspection of the available naturalistic data suggested that the risk of relapse to a depressive episode over time is dependent on time, and is likely to follow a Weibull distribution, in which the relapse rate is proportional to a power of time. People have a higher risk of relapse in the early years following remission, and this risk is reduced with every year they remain in remission; the cumulative hazard rate for the Weibull distribution is given by the following mathematical formula:

$$H(t) = \lambda t^{\gamma}$$

where lambda (λ) and gamma (γ) are the scale and shape parameters of the distribution, respectively.

When gamma >1, then the risk increases over time; when it equals 1, then the risk is constant with time and the distribution is exponential. When gamma < 1, then the risk is reduced over time. For example, the risk of relapse over time (years) from the previous depressive episode, for different rates of change in the risk of relapse (expressed by the gamma parameter) over time, assuming a first-year relapse risk of 0.25 (lambda = 0.288), is shown in Figure 112. Figure 113 shows survival curves of hypothetical cohorts of 1,000 adults with depression in remission and at risk of relapse, for different rates of change in the risk of relapse (expressed by the 'gamma' parameter) over time, and the same first-year risk of relapse of 0.25.

Figure 112. Change in the risk of relapse over time from previous depressive episode, for different rates of change in the risk of relapse ('gamma' parameter) over time, and a first-year relapse risk of 0.25

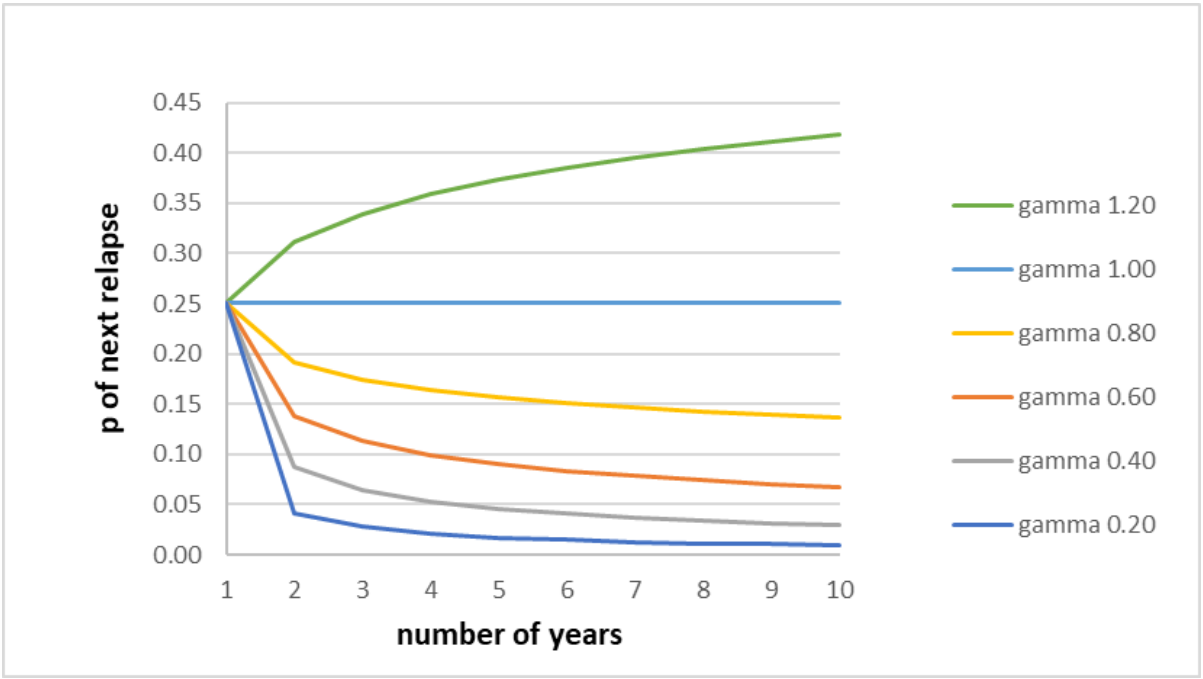
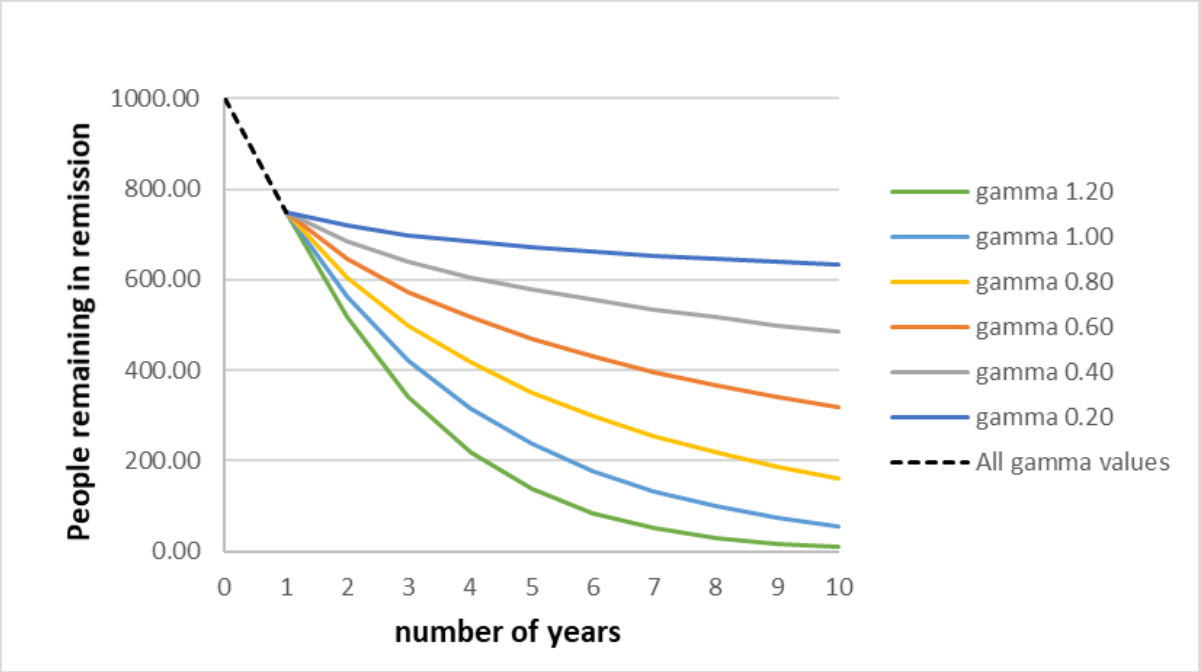


Figure 113. Survival curves of hypothetical cohorts of 1,000 adults with depression in remission and at risk of relapse for different rates of change in the risk of relapse ('gamma' parameter) over time, and a first-year relapse risk of 0.25



Once people relapse and subsequently remit, their risk of relapse to the next episode increases again, and is dependent on the time they have spent in remission following resolution of their previous episode.

There is evidence that the risk of relapse increases with the number of previous episodes, and this was taken into account in the economic model. Therefore, it was decided to estimate the baseline risk of relapse after the first depressive episode (i.e. in people with no previous depressive episodes) as a first step, and then model the baseline risk of relapse in the cohorts examined in the economic analysis according to their number of previous depressive episodes.

In order to estimate the risk of relapse over time and determine the underlying Weibull distribution after a single (first) depressive episode, the committee advised that data from Eaton 2008 and Mattisson 2007 be synthesised; both studies included low-risk community cohorts, which were consistent with the model study population, who were followed up for long periods following remission of their first depressive episode. Both publications included graphs showing the time to relapse after the first episode of depression by gender. Digital software (http://www.digitizeit.de) was used to read and extract the proportions of people free from episode at each year of the study, up to 10 years. Subsequently, the numbers of people relapsing over time were approximated, based on the number of participants in each study. Data on men and women were similar, suggesting that there is no difference in the risk of relapse over time by gender. Retrospective data from Nuggerud-Galeas 2020, which referred to recurrence after a first depressive episode in a primary care cohort, were also inspected. The study reported time to next recurrence over a period of 16 years. The study sample had a mean age at first episode of 52 years and was characterised by considerably higher risk of relapse compared with the samples in Eaton 2008 and Mattisson 2007. The authors acknowledged the high mean age at onset compared with available epidemiological data and admitted that participants in the study might have had previous episodes of depression that had not been recorded. Therefore, this study was not considered further for data synthesis.

Data from Eaton 2008 and Mattisson 2007 were synthesised in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003), in order to estimate the parameters of the underlying Weibull distribution (lambda and gamma). Both fixed and random effects models over lambda were tested, while a fixed effect was assumed for gamma across studies. Goodness of fit of each model was assessed using the residual deviance (resdev) and the DIC tool. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points. Heterogeneity in the random effects model, expressed by the between-study standard deviation (SD), was also checked. The models were run with an initial burn-in period of 20,000 iterations, followed by 100,000 further iterations, thinned by 10 so as to obtain 10,000 iterations for use in the probabilistic economic model. Uninformative prior parameters and two different sets of initial values were used; convergence was tested by visual inspection of the Brooks Gelman-Rubin diagram. In addition, convergence of the models was assessed by checking the autocorrelation and the Kernel density plots within WinBUGS. The WinBUGS code used to synthesise the relapse data and estimate the underlying Weibull distribution parameters is provided in Table 91. The fixed and random effects model fit statistics are shown in Table 92, suggesting somewhat better fit for the random effects model (lower resdev and DIC), although no model gave a perfect fit. However, it was noted that the random effects model was based on 2 studies only, a number that is not adequate to accurately estimate the between study SD, so the SD estimate depends on the prior used. On the other hand, Eaton 2008 is a small study compared with Mattisson 2007, and the fixed effect model outputs rely mainly on the larger Mattisson 2007 study. Following these considerations, the simpler, fixed effect model was selected. The outputs of the analysis are shown in Table 93. It can be seen that gamma has a value of less than 1, suggesting that the risk of relapse is reduced over time.

Table 91. WinBUGS code used for synthesis of relapse data in people who are in remission following a single (first) depressive episode, and for synthesis of remission data in people with depression, in order to estimate the parameters of the underlying Weibull distributions

WinBUGS code used for synthesis of relapse data

Fixed effect model

```
model   {
  for( i in 1 :ndata) {
     r.int[i] ~ dbin(p[i],n.int[i])
     p[i] <-  1-exp(-lambda*(pow(t[i],gamma) - pow(t0[i],gamma)))
           rhat[i]<-n.int[i]*p[i]
           dev[i]<-  2 * (r.int[i] * (log(r.int[i])-log(rhat[i]))  +  (n.int[i]-r.int[i]) * (log(n.int[i]-r.int[i]) -
log(n.int[i]-rhat[i])))
  }
           resdev<- sum(dev[])

lambdalog ~ dnorm(0.0,0.1)
log(lambda)<-lambdalog

log(gamma) <-  gammalog
gammalog ~ dnorm(0.0,0.1)

dummy[1]<-r[1]
dummy[2]<-n[1]
dummy[3]<-s[1]
}
```

Random effects model

```
model   {
```

WinBUGS code used for synthesis of relapse data

```
  for( i in 1 :ndata) {
     r.int[i] ~ dbin(p[i],n.int[i])
     p[i] <- 1-exp(-lambda[s[i]]*(pow(t[i],gamma) - pow(t0[i],gamma)))
           rhat[i]<-n.int[i]*p[i]
           dev[i]<-  2 * (r.int[i] * (log(r.int[i])-log(rhat[i]))  +  (n.int[i]-r.int[i]) * (log(n.int[i]-r.int[i]) -
log(n.int[i]-rhat[i])))
  }
           resdev<- sum(dev[])

for (j in 1:nstudy){
                     log(lambda[j]) <- lambdalog[j]
                     lambdalog[j]~dnorm(mean.lambdalog,prec.lambdalog)
}

mean.lambdalog ~ dnorm(0.0,0.1)
prec.lambdalog<-pow(sd.lambdalog,-2)
sd.lambdalog~dunif(0,2)
log(mean.lambda) <- mean.lambdalog

log(gamma) <-  gammalog
gammalog ~ dnorm(0.0,0.1)

dummy[1]<-r[1]
dummy[2]<-n[1]
}
```

Table 92: Model fit statistics for fixed and random effects models in synthesis of relapse data in people who are in remission following a single (first) depressive episode

Model	Between Study Heterogeneity - SD			Posterior mean residual deviance[1]	DIC[2]
	Posterior mean	Posterior Median	95% CrI		
Fixed effect	Non applicable			54.48	154.80
Random effects	0.87	0.77	0.14 to 1.91	47.51	148.92

1 compared to 40 total data points
2 lower values preferred
CrI: credible intervals; DIC: Deviance information criterion; SD: standard deviation

Table 93: Results of the data synthesis undertaken in WinBUGS to determine the parameters of the underlying Weibull distribution of the risk of relapse over time, in people who are in remission following a single (first) episode

Parameter	Mean	SD	Median	95% credible intervals
Lambda	0.09	0.01	0.09	0.07 to 0.12
Gamma	0.63	0.06	0.63	0.52 to 0.75

A comparison of the mean modelled cumulative risk of relapse over time (that was utilised in the economic analysis) and the observed cumulative risk of relapse that was extracted from the graphs included in the studies by Eaton 2008 and Mattisson 2007 is provided in Table 94, which suggests that the modelled values are a good approximation of the values observed in the longitudinal studies, taking into account their relative weight in the analysis

(the study sample in Mattison 2007 was considerably larger than the study sample in Eaton 2008). The estimated Weibull distribution parameters were used to inform the economic model; more specifically, the time-dependent relapse risk informed the relapse risk in each of the tunnel remission states of the economic model.

Table 94: Cumulative relapse risk over time following remission from a single (first) depressive episode in primary care: modelled and observed risks

Time (years)	Mean modelled risk	Observed risk Eaton 2008		Observed risk Mattisson 2007	
		Men [N=22]	Women [N=70]	Men [N=116]	Women [N=228]
1	0.09	0.09	0.06	0.08	0.09
2	0.13	0.14	0.20	0.11	0.13
3	0.17	0.23	0.24	0.14	0.17
4	0.20	0.23	0.27	0.18	0.19
5	0.22	0.23	0.31	0.18	0.22
6	0.25	0.23	0.31	0.20	0.23
7	0.27	0.23	0.37	0.22	0.25
8	0.29	0.23	0.43	0.24	0.27
9	0.31	0.32	0.47	0.26	0.28
10	0.32	0.32	0.50	0.28	0.29

Effect of the number of previous depressive episodes on the baseline risk of relapse

There is ample evidence to suggest that the number of previous episodes is a predictor of relapse (Bockting 2006; Hardeveld 2010; Keller 1981; Kessing 1999; Mueller 1999; Solomon 2000).

Kessing 1999 reported the results of a case register study that included all hospital admissions with primary affective disorder in Denmark during 1971–1993. A total of 7,925 unipolar patients were included in the study. The authors reported that the risk of relapse increased with every new episode; the mean hazard ratio of relapse with every additional episode was 1.15 (95% CI 1.11-1.18).

Mueller 1999 analysed prospective follow-up data of up to 15 years on the course of major depression for 380 people receiving outpatient specialist care in the US, who recovered from an index episode of major depression. The authors reported a similar mean adjusted odds ratio of relapse for every additional episode of 1.18 (95% CI 1.06-1.31).

The economic model utilised the hazard ratio reported in Kessing 1999 in order to estimate the increase in the risk of relapse within each year in remission for every additional depressive episode. Applying this ratio onto the estimated relapse risk for people with one single (no previous) episode allowed estimation of the baseline relapse risk for people with one previous episode and people with three previous episodes (that is, the two populations of interest in the economic analysis). It also allowed estimation of the relapse risk in future remission states (reflecting further previous episodes of relapse) in the model.

The populations in the naturalistic studies that were considered in order to estimate the baseline relapse risk received a range of interventions that were assumed to correspond to GP care (pill placebo arms) in the economic model. Therefore, the estimated baseline risk of relapse was applied onto the GP care arms of the economic models, according to the study population (i.e. people having experienced 1 or 3 previous episodes before their 'index' remitted episode).

Probability of remission after relapse

The economic model took into account the chronicity, that is, the lack of recovery characterising a proportion of depressive episodes. The annual probability of recovery following a relapse of a depressive episode was estimated based on a synthesis of relevant chronicity data included in the review of naturalistic studies in primary care settings. The committee noted the limited availability of relevant data in primary care (Table 90). Eaton 2008 reported a probability of persistence of 0.15 over 10 years that suggests a higher chronicity than that observed in secondary care studies; this figure referred to people not remaining free from a depressive episode for at least 1 year, which the committee considered as an unusual criterion for determining chronicity compared with definitions of chronicity in the other studies included in the review. Therefore, this study was not further considered for the estimation of chronicity in the economic model. Riihimäki 2014 reported that the probability of people with depression not reaching full remission in 5 years was 0.30, which is a high figure compared with data on people in primary care reported by Skodol 2011 and Stegenga 2012. Bukh 2016 reported also high chronicity rates compared with other studies in secondary care (Year 1: 0.71; Year 2: 0.42) and was not further considered. In addition, Magnil 2013 and Comijs 2015 reported high chronicity rates in older adults (Year 2: 0.71 and 0.44, respectively) and, likewise, were not further considered in the analysis. On the other hand, Stegenga 2012 reported a rather low chronicity risk in Year 1 (0.17) compared with other studies and was also no further considered. In the remaining studies included in the review of longitudinal data, chronicity risks ranged between 0.29-0.31 in the first year (Gonzales 1985; Keller 1981; Keller 1992); 0.19-0.21 over 2 years (Keller 1984 & 1992), 0.15 over 3 years (Skodol 2011), 0.13 over 4 years (Keller 1992), 0.12 over 5 years (Holma 2008; Keller 1992), and 0.07 over 10 years (Mueller 1996), which the committee considered a reasonable reflection of the course of depression in clinical practice.

These data suggest that the probability of recovery may also follow a Weibull distribution, with the rate of recovery being higher over the first years of an episode and decreasing with time. As with relapse data, recovery data were synthesised in WinBUGS 1.4.3 testing both a fixed and a random effects models over lambda, while a fixed effect was assumed for gamma across studies, in order to estimate the parameters of the underlying Weibull distribution (lambda and gamma). Goodness of fit of each model was assessed using the resdev and the DIC tool. Heterogeneity in the random effects model, expressed by the between-study standard deviation (SD), was also checked. The models were run with an initial burn-in period of 20,000 iterations, followed by 100,000 further iterations, thinned by 10 so as to obtain 10,000 iterations for use in the probabilistic economic model. Uninformative prior parameters and two different sets of initial values were used; convergence was tested by visual inspection of the Brooks Gelman-Rubin diagram. In addition, convergence of the models was assessed by checking the autocorrelation and the Kernel density plots within WinBUGS. The WinBUGS code used to synthesise the recovery data and estimate the underlying Weibull distribution parameters is the same with the one used for synthesis of relapse data, shown in Table 91. The fixed and random effects model fit statistics are shown in Table 95, suggesting a similar fit for random and fixed effects models, although no model gave a perfect fit. Therefore the simpler, fixed effect model was selected. The outputs of this analysis are shown in Table 96. It can be seen that gamma has a value that is lower than 1, suggesting that the probability of recovery is reduced over time.

Table 95: Model fit statistics for fixed and random effects models in synthesis of recovery data in people with depression

Model	Between Study Heterogeneity - SD			Posterior mean residual deviance[1]	DIC[2]
	Posterior mean	Posterior Median	95% CrI		
Fixed effect	Non applicable			26.70	83.86

Model	Between Study Heterogeneity - SD			Posterior mean residual deviance[1]	DIC[2]
	Posterior mean	Posterior Median	95% CrI		
Random effects	0.07	0.05	0.00 to 0.22	26.18	85.09

1 compared to 11 total data points
2 lower values preferred
CrI: credible intervals; DIC: Deviance information criterion; SD: standard deviation

Table 96: Results of data synthesis undertaken in WinBUGS to determine the parameters of the underlying Weibull distribution of probability of recovery over time, in people in a depressive episode

Parameter	Mean	SD	Median	95% Credible intervals
Lambda	1.16	0.04	1.16	1.08 to 1.24
Gamma	0.42	0.03	0.42	0.37 to 0.47

A comparison of the mean modelled probability of remaining in a depressive episode over time (that was utilised in the economic analysis) and the observed proportions of people remaining in a depressive episode reported in the studies included in the analysis is provided in Table 97, which suggests that the modelled values are a good approximation of the values observed in the longitudinal studies. The estimated Weibull distribution parameters were used to inform the economic model; more specifically, the time-dependent probability of recovery informed each of the tunnel relapse states of the economic model.

Table 97: Probability of remaining in a depressive episode (chronicity) over time: modelled and observed probabilities

Time (years)	Mean modelled probability	Probabilities reported in the literature
1	0.31	Gonzales 1985: 0.31; Keller 1981: 0.29; Keller 1992: 0.30
2	0.21	Keller 1984: 0.21; Keller 1992: 0.19
3	0.16	Skodol 2011: 0.15
4	0.12	Keller 1992: 0.13
5	0.10	Holma 2008: 0.12; Keller 1992: 0.12
6	0.08	
7	0.07	
8	0.06	
9	0.05	
10	0.05	Keller 1992 (Mueller 1996): 0.07

Probability of development of side effects from antidepressant treatment

Treatment with antidepressants is associated with the development of various side effects. These can be serious, including death, attempted suicide or self-harm, falls, fractures, stroke or transient ischaemic attack, epilepsy/seizures, myocardial infarction, hyponatraemia and upper gastrointestinal bleeding (Coupland 2011; Coupland 2018; Jakobsen 2017) or less serious but more common, such as headaches, nausea and other gastrointestinal symptoms, dizziness, agitation, sedation, sexual dysfunction, tremor, sweating, fatigue, dry mouth, sleepiness during the day or sleeplessness, weight gain and arrhythmia (Anderson 2012; Bet 2013; Jakobsen 2017; Uher 2009).

Serious side effects from antidepressants are costly to treat and are likely to reduce the quality of life more significantly, in people who experience them. However, they do not occur

frequently. Coupland 2011 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in older people with depression, in a retrospective cohort study that utilised data from 60,746 people aged 65 and over diagnosed as having a new episode of depression, obtained across 570 general practices in the UK between 1996 and 2008. The authors reported that SSRIs were associated with the highest adjusted hazard ratios for falls (1.66, 95%; CIs 1.58 to 1.73) and hyponatraemia (1.52; 95% CIs 1.33 to 1.75) compared with when antidepressants were not being used, while a group of 'other antidepressants' defined according to the British National Formulary, which included mirtazapine and venlafaxine among others, was associated with the highest adjusted hazard ratios for all-cause mortality (1.66; 95% CIs 1.56 to 1.77), attempted suicide or self-harm (5.16; 95% CIs 3.90 to 6.83), stroke/transient ischaemic attack (1.37; 95% CIs 1.22 to 1.55), fracture (1.64; 95% CIs 1.46 to 1.84), and epilepsy/seizures (2.24; 95% CIs 1.60 to 3.15), compared with when antidepressants were not being used. However, for most of these side effects, with the exception of all-cause mortality, the difference in absolute risks between people who received antidepressants and those who were not taking antidepressants during the assessment period was small (lower than 1%) with few exceptions: considering the drugs and classes that were included in the guideline economic analysis, for SSRIs, the absolute increase in risk of falls compared with people who were not taking antidepressants was 2.21%. It is noted that these data were derived from older adults with depression, who are likely to have a higher baseline risk for these events compared with younger populations. Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants, is expected to be lower than that observed between respective groups in older populations.

Similarly, Coupland 2018 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in 238,963 adults aged 20-64 years registered with general practices across the UK, who had a first diagnosis of depression between 2000 and 2011. Relative to other antidepressant treatment classes, SSRIs were associated with the highest adjusted hazard ratios for falls (1.48, 95%; CIs 1.39 to 1.59), and fracture (1.30; 95% CIs 1.21 to 1.39), compared with when antidepressants were not being used, while TCAs were associated with the highest adjusted hazard ratios for upper gastrointestinal bleeding (1.43; 95% CIs 1.13 to 1.81) and all cause mortality (1.92; 95% CIs 1.68 to 2.19). Other antidepressants were associated with the highest adjusted hazard ratio for adverse drug reaction (2.81; 95% CIs 2.11 to 3.75). Again, the difference in absolute risks between people who received antidepressants and those who were not receiving antidepressants during the assessment period was very small (e.g. difference 0.001% in falls between people under SSRIs and those under no antidepressant treatment; 0.002% in fractures between people under other antidepressants and those under no antidepressant treatment). Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants is very small and expected to have a negligible impact on costs and HRQoL.

Jakobsen 2017 conducted a systematic review and meta-analysis to assess the effects (including adverse events) of SSRIs versus pill placebo, 'active' placebo, or no intervention in adult participants with major depressive disorder. The authors reported that SSRIs significantly increased the risks of serious adverse events (odds ratio 1.37; 95% CI 1.08 to 1.75) corresponding to 31/1000 SSRI participants experiencing a serious adverse event compared with 22/1000 control participants (this is a 0.9% difference).

Bet 2013 assessed the risk of common side effects in 846 adults with depression and/or anxiety who received antidepressant monotherapy on 927 occassions, recruited from primary care and specialist mental health settings in the Netherlands. Participants were asked to fill in a short 12-question antidepressant side effect checklist, to self-report patient-perceived common side effects related to their antidepressant therapy. Common side effects included sleeplessness, sleepiness during the day, restlessness, muscle spasms and twitching, dry mouth, profuse sweating, sexual dysfunction, nausea, constipation, diarrhea,

weight gain and dizziness. Large percentages of participants in the study reported at least 1 side effect as shown in Table 98.

Table 98: Percentages of people under antidepressant medication reporting zero, 1-2 or 3 side effects and above (from Bet 2013)

Antidepressant	N	% reporting zero side effects	% reporting 1-2 side effects	% reporting ≥ 3 side effects
SSRI	584	36%	33%	31%
TCA	97	28%	33%	39%
Venlafaxine	145	27%	37%	36%
Mirtazapine	58	36%	40%	24%
Other	19	47%	26%	26%

However, it is not known whether these common side effects have a significant impact on HRQoL or lead to the use of additional healthcare resources, e.g. trigger extra GP visits. Moreover, as this was an uncontrolled study, it cannot be determined whether the side effects reported were indeed a result of antidepressant use.

Cascade 2009 conducted a cross-sectional study on approximately 700 patients receiving SSRI medication, to explore the prevalence of side effects and their impact on HRQoL and healthcare service contacts. The study reported that 38% of study participants experienced a side effect. However, only 25% of the side effects were considered “very bothersome” or “extremely bothersome” by the respondents. Moreover, regardless of how bothersome the side effects were, only 40% of SSRI users mentioned the side effects to their prescribing physicians.

Anderson 2012 estimated the prevalence of common side effects such as headaches, nausea or vomiting, agitation sedation and sexual dysfunction associated with treatment with antidepressants, by undertaking a retrospective analysis of data derived from a large US managed care claims form on 40,017 people aged 13 years and above, of whom 36,400 were adults aged 19 years and above, who were newly diagnosed with depression and were initiated on antidepressant monotherapy between 1998 and 2008. Antidepressant groups included, among others, SSRIs, SNRIs, and TCAs. The mean time of exposure to antidepressants was 198 days (range 1-2,993 days). The authors reported that the most common side effects of those assessed were headaches, followed by nausea. The prevalence, rates of experiencing at least one of the 5 common side effects considered in the study, and the estimated length of time of people experiencing at least one common side effect for the antidepressants of interest in the economic analysis are shown in Table 99.

Table 99: Prevalence, rates and length of time experiencing at least one common side effect of antidepressants in adults with depression (from Anderson 2012)

Antidepressant	N	% developing ≥ 1 side effect	Rate[1] experiencing ≥ 1 side effect	Length of time with ≥ 1 side effect (years)
SSRI	23,620	7.0%	0.117	1.68
SNRI	4,762	9.2%	0.150	1.63
TCA	776	6.7%	0.152	2.26

1 per person-years

The committee considered the available evidence and agreed that, although side effects are common, only a proportion of them have a measurable impact on HRQoL and result in an increase in healthcare resource use, and have thus an impact on the cost effectiveness of antidepressant treatments. This is supported by data reported in Cascade 2009. They also expressed the view that studies asking specifically participants to self-report the presence of

side effects (such as the Bet 2013 study) tend to overestimate the prevalence of side effects in the study population, in particular as these use uncontrolled study designs and the causality between the antidepressant use and the reported side effects is not established. Using data from Bet 2013 (or other similar study designs) to inform the risk of side effects for pharmacological treatment options in the economic model would overestimate the impact of side effects on the relative cost-effectiveness between pharmacological and non-pharmacological treatments, especially as psychological treatments are assumed to have zero risks of side effects.

On the other hand, the committee expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, such as those reported in Anderson 2012, are more representative of the risk of side effects that have an impact on HRQoL and healthcare costs. Therefore, the committee agreed to use the data reported in Anderson 2012 in order to inform the base-case economic analysis on the risk of side effects from antidepressant medication use. The economic model took into account the percentage of people experiencing at least 1 side effect for each antidepressant of interest (and their combinations with psychological treatment where relevant), and the length of time those people spent experiencing at least 1 common side effect.

People who had responded to acute pharmacological treatment were assumed to have already received antidepressant treatment for 12 weeks prior to entering the economic model (and therefore to have started experiencing common side effects from antidepressants prior to entering the model). For those people, the length of time in the model if they experienced at least 1 common side effect was 2 years (equal to the total duration of maintenance antidepressant treatment) if they received TCAs; people who experienced side effects after receiving SSRIs or SNRIs did so for the 1st year of maintenance treatment, and for 0.43 and 0.38, respectively, of their time in the 2nd year of maintenance antidepressant treatment. People who received non-specified antidepressant treatment were assumed to experience at least 1 common side effect at a probability and duration equal to those receiving SSRIs, as this is the most commonly prescribed antidepressant class for people with depression.

In people who had responded to acute psychological treatment and moved on to antidepressant maintenance treatment, those who subsequently experienced common side effects from the antidepressant (SSRI) did so in the first 1st year of maintenance treatment and for 0.68 of their time in the 2nd year of maintenance treatment.

The model considered the impact of common side effects on treatment costs and people's HRQoL.

After consideration of all available data on the risk of side effects from antidepressant medication use, in a sensitivity analysis, the committee advised that a risk of side effects of 40% be explored, as the higher end of the risk that might have an impact on HRQoL and management costs.

No side effects were considered for people receiving non-pharmacological maintenance interventions; however, people receiving non-pharmacological interventions are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Anderson 2012 was an uncontrolled study and did not examine the rate of side effects that were attributable to drugs. Therefore, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness.

The economic model did not incorporate the impact of less common but more severe side effects on costs and people's HRQoL, as this would require most complex modelling and detailed data on the course and management of these side effects. However, omission of these severe side effects is not expected to have considerably affected the results of the

economic analysis, due to their low incidence in the study population. Nevertheless, omission of less common but severe side effects from the economic analysis may have potentially overestimated the cost effectiveness of pharmacological and combined treatments regarding the risk of severe side effects associated with drugs.

Mortality

Depression is associated with an increased risk of mortality relative to the general population. A comprehensive systematic review of 293 studies that assessed the increased risk of people with depression relative to non-depressed individuals, which included 1,813,733 participants (135,007 depressed and 1,678,726 non-depressed) reported a risk ratio of mortality in depressed relative to non-depressed participants of 1.64 (95% CI 1.56 to 1.76). After adjustment for publication bias, the risk ratio was reduced to 1.52 (95% CI 1.45 to 1.59) (Cuijpers 2014). The adjusted figure was applied onto general mortality statistics for the UK population (Office for National Statistics 2020), to estimate the absolute annual mortality risk in people experiencing a depressive episode relative to people not experiencing a depressive episode within each cycle of the model. People with a depressive episode were assumed to be at increased mortality risk due to depression in the years they experienced a depressive episode (i.e. while they were in the relapse health state). The same mortality risk was assumed for both men and women experiencing a relapse, as no gender-specific data were reported in the study. People not experiencing a depressive episode in each model cycle were assumed to be subject to the mortality risk of the general UK population.

It is acknowledged that the mortality risk ratio refers to depressed versus non-depressed individuals and not versus the general population. The UK general population already includes a proportion of people with major depression: according to the latest adult psychiatric morbidity survey for England, 3.3% of adults suffered from depression in 2014 (McManus 2016); therefore the economic analysis has slightly overestimated the annual mortality risk for people experiencing a depressive episode as well as for those not experiencing a depressive episode. This is a limitation of the analysis owing to lack of more relevant data, which, nevertheless, is expected to have had a negligible effect on the cost effectiveness results.

Utility data and estimation of quality adjusted life years (QALYs)

In order to express outcomes in the form of QALYs, the health states of the economic model (remission, relapse) need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic review of utility data on depression-related heath states identified 7 studies that reported utility data corresponding to depression-related health states, which were derived from EQ-5D measurements on adults with depression valued by the general UK population (Kaltenthaler 2006; Koeser 2015; Kolovos 2017; Mann 2009; Sapin 2004; Sobocki 2006 & 2007; Soini 2017). Four of the studies analysed EQ-5D data obtained from adults with depression or common mental health problems participating in RCTs, 3 of which were conducted in the UK (Kaltenthaler 2006, Mann 2009, Koeser 2015) and 1 in various European countries, including the UK (Soini 2017). One study reported findings from an individual patient-level meta-analysis of EQ-5D data from 1629 adults mainly with depression (a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands (Kolovos 2017). The other 2 studies analysed naturalistic primary care EQ-5D data from adults with depression in France (Sapin 2004) and Sweden (Sobocki 2006 & 2007). All studies reported utility values associated with severity of

depression (i.e. mild, moderate or severe) and/or states of depression relating to treatment response (i.e. response, remission, no response) and were thus relevant to the health states considered in the guideline economic modelling. All studies defined health states using validated measures of depressive symptoms, such as the BDI, the HAMD-17, the PHQ-9, the MADRS, the CGI, the CES-D, the HADS-D or the IDS-SR (inventory of depressive symptomatology self-report).

An overview of the study characteristics, the methods used to define health states, and the health-state utility values reported by each of the studies is provided in Table 100.

Table 100: Summary of available EQ-5D derived health-state utility data for depression (UK tariff)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
Kaltenthaler 2006	Analysis of EQ-5D and CORE-OM data obtained from 62 people with common mental health problems participating in a multi-centre RCT of supervised self-help CBT in the UK (Richards 2003). CORE-OM data were first mapped onto the BDI, which was used to categorise people into 3 groups of mild to moderate, moderate to severe and severe depression. BDI cut-off scores used for categorisation were not reported. EQ-5D utility value for no depression obtained from age- and gender-matched normal population in the UK (Kind 1999).	No depression Mild to moderate depression Moderate to severe Severe	NA NR NR NR	0.88 (0.22) 0.78 (0.20) 0.58 (0.31) 0.38 (0.32)
Koeser 2015	Analysis of EQ-5D and HAMD17 data obtained from people with recurrent depression in full or partial remission participating in a RCT of MBCT in the UK (N=123) (Kuyken 2008). Definition of health states by HAMD scores: remission ≤ 7; response 8-14; no response ≥ 15	Remission Response No response	NR NR NR	0.80 (0.02) 0.62 (0.04) 0.48 (0.05)
Kolovos 2017	Analysis of EQ-5D and symptom scale score data (CES-D or MADRS or PHQ-9 or IDS-SR or HADS-D) from 1629 adults mainly with depression (although a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands; 4979 observations considered. Definition of health states by CES-D score: remission 0-15; minor 16-19; mild 20-25; moderate 26-30; severe 31-60; definition of health states by MADRS score: remission 0-8; minor 9-18; mild 19-26; moderate 27-34; severe 35-60; definition of health states by PHQ-9 score: remission 0-4; minor 5-9; mild 10-14; moderate 15-19; severe 20-27; definition of health states by IDS-SR score: remission 0-13; minor 14-25; mild 26-38; moderate 39-48; severe 49-84; definition of health states by HADS-D score: remission 0-7; minor 8-13; mild 14-19; moderate 20-25; severe 26-52.	Minor Mild Moderate Severe Remission	NR NR NR NR NR	0.62 (0.58-0.65) 0.57 (0.54-0.61) 0.52 (0.49-0.56) 0.39 (0.35-0.43) 0.70 (0.67-0.73)
Mann 2009	Analysis of EQ-5D and PHQ-9 data collected from 114 people with depression participating in a cluster RCT of collaborative care across 19 UK primary care practices based in urban and rural communities (Richards 2008). Definition of health states by PHQ-9 score: mild 5-9; moderate 10-14; moderately severe 15-19; severe 20-27	Mild Moderate Moderate to severe Severe	10 24 39 35	0.65 (0.23) 0.66 (0.21) 0.56 (0.27) 0.34 (0.29)
Sapin 2004	Analysis of EQ-5D and MADRS data collected from 250 people with major depression recruited from 95 French primary care practices for inclusion in an 8-week follow-up cohort. Definition of health states by MADRS score: remission MADRS ≤ 12; response at least 50% reduction in the	Response – remission Response – no remission No response	144 34 46	0.85 (0.13) 0.72 (0.20) 0.58 (0.28)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
	MADRS baseline score over 8 weeks. Baseline mean MADRS score 32.7 (SD 7.7)	Baseline	250	0.33 (0.25)
Sobocki 2006 & 2007	Analysis of EQ-5D and CGI-S and CGI-I data collected from 447 adults with depression enrolled in a naturalistic longitudinal observational 6-month study conducted in 56 primary care practices in 5 regions of Sweden. People who started a new or changed antidepressant treatment were eligible for inclusion. Definition of health states by CGI-S score: mild 2-3; moderate 4; severe 5-7; remission 'much or very much improved' score (1-2) combined with clinical judgement	Mild Moderate Severe Remission No remission	110 268 69 207 191	0.60 (0.54 to 0.65) 0.46 (0.30 to 0.48) 0.27 (0.21 to 0.34) 0.81 (0.77 to 0.83) 0.57 (0.52 to 0.60)
Soini 2017	Analysis of EQ-5D, MADRS and HAMD data obtained from people with depression and an inadequate response to a SSRI/SNRI participating in a RCT of vortioxetine versus agomelative in a multi-national RCT conducted in inpatient and outpatient settings in 14 European countries, including the UK (N=501) (Montgomery 2014). Mean MADRS score at baseline: 28.9; remission defined as MADRS score ≤10 or HAMD score ≤7	Baseline Remission No remission	NR NR NR	0.54 0.85 0.62

N: number of participants who provided ratings on each state
BDI: Beck Depression Inventory; CBT: cognitive behavioural therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CGI-I: Clinical Global Impression – Improvement scale; CGI-S: Clinical Global Impression – Severity scale; CI: confidence intervals; CORE-OM: Clinical Outcomes in Routine Evaluation – Outcome Measure); HADS-D: Hospital Anxiety and Depression Scale Depression subscale; HAMD: Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfulness Based Cognitive Therapy; NR: not reported; PHQ: Patient Health Questionnaire; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; RCT: randomised controlled trial; SD: standard deviation

All reported utility data comply with the NICE criteria on selection of utility data for use in NICE economic evaluations (NICE 2013). The data from Kaltenthaler 2006 were derived following mapping of CORE-OM data onto BDI data; however, the BDI cut-off scores used to determine the health states by depressive symptom severity were not reported, and therefore it is not clear the exact level of symptom severity the resulting utility scores correspond to. All other studies provided details on the scale cut-off scores used to determine the depression-related health states by severity or by response to treatment. Mann 2009 used the original PHQ-9 cut-off scores to determine severity levels of depression. However, it is noted that a PHQ-9 score of 5-9, which corresponded to the state of mild depression according to the PHQ-9 manual, is also below the cut-off point for clinically detected depression (Gilbody 2007a & 2007b). Kolovos 2017 used a number of different scales to determine severity levels of depression in their study sample, with cut-off scores being determined based on the literature and not necessarily to scale manuals.

The economic model of interventions aiming at relapse prevention used data from Sobocki 2006 & 2007. This was decided because the study provided data that could be linked to all states included in the model, i.e. relapse to less severe depression (the value of 0.60 for mild depression was used), relapse to more severe depression (a weighted average of the utility of moderate and severe depression of 0.42 was used) and remission (0.81) and was based on a larger study sample compared with the rest studies providing utility data, with the exception of Kolovos 2017. Remission was defined in the study as an improved or very much improved score on the CGI-Improvement scale, combined with a clinical judgement by the treating doctor of being in full remission. It is acknowledged that this definition of remission may actually indicate response to treatment not reaching full remission. Nevertheless, although all cohorts enter the model in full remission, a proportion of people in the cohorts remitting from future episodes might not experience full remission and might have some residual symptoms, and therefore the utility value of remission based on the improved or very much improved CGI-I score is likely to express the utility of people in future remission states. It is noted that the value of 0.81 corresponding to the state of 'remission' in Sobocki 2006 & 2007 is very close to the utility value of remission (0.80) reported in Koeser 2015 and between the values of 0.72 and 0.85 corresponding to the states of 'response not reaching remission' and 'response reaching remission', respectively, that were reported by Sapin 2004 (who defined response and remission based on MADRS scores), which indicates that the value utilised in the model may reflect a utility between partial and full remission that is closer to the utility of the latter. It is noted that Soini 2017 also reports a value of 0.85 for remission, determined as a MADRS score ≤10 or a HAMD score ≤7. On the other hand, the utility value reported in Sobocki 2006 & 2007 is higher than the value of remission of 0.70 reported by Kolovos 2017. The latter study reported values for minor and mild depression of 0.62 and 0.57, respectively, the average of which (0.60) is consistent with the value (0.60) reported in Sobocki 2006 & 2007 for mild depression, and utility values for moderate and severe depression of 0.52 and 0.39, respectively, the average of which (0.46) is somewhat higher but broadly consistent with the value estimated for more severe depression (0.42) using the data reported in Sobocki 2006 & 2007.

In sensitivity analysis, the lower value of 0.70 for remission from Kolovos 2017 and the higher values of 0.65 and 0.56 for people relapsing to less severe depression and more severe depression from Mann 2009 were tested in a more conservative scenario.

According to the committee's expert opinion, an average depressive episode lasts 6 months. This estimate is supported by data from a prospective study on 250 adults with a newly originated (first or recurrent) major depressive episode, drawn from a prospective epidemiological Dutch survey on 7,046 people in the general population (Spijker 2002). According to this study, the mean duration of a recurrent episode was 6.1 months (95% CI 4.7-7.5). The economic model assumed that people experiencing a depressive episode that resolved in the next year (i.e. people who spent only a year in the depressive episode and

then moved to the remission state in the next cycle), experienced a reduction in their HRQoL for 6 months out of the 12 months of the cycle they remained in the 'relapse' (depressive) state. Thus, people relapsing to depressive episodes that lasted only for one year were assumed to have the utility of remission for 6 months and the utility of depression (less or more severe) for another 6 months. However, people whose depressive episode was expected to last for at least 2 cycles (years), were attached the utility of depression over the number of years they remained in relapse, except their final year in the relapse state, in which they were assumed to have the utility of depression for 6 months and the utility of remission for the remaining 6 months in the cycle.

Side effects from medication are expected to result in a reduction in utility scores of adults with depression. Sullivan 2004 applied regression analysis on EQ-5D data (UK tariffs) obtained from participants in the 2000 national USA Medical Expenditure Panel Survey to derive age-adjusted utility values for health states associated with depression and with side effects of antidepressants. Health states were defined based on descriptions in the International Classification of Diseases (9th Edition) (ICD-9) and the Clinical Classification Categories (CCC) (clinically homogenous groupings of ICD-9 codes derived by the Agency for Healthcare Research and Quality). Table 101 shows the health states determined by Sullivan 2004 and the corresponding utility values obtained from regression analysis of EQ-5D data. The mean utility decrements due to side effects from antidepressants ranged from -0.044 (diarrhoea) to -0.129 (excitation, insomnia and anxiety), with a mean decrement of -0.087. This mean utility decrement was applied to the proportion of people who experienced side effects from maintenance antidepressant treatment alone or in combination, over the period they experienced side effects from antidepressant treatment, i.e. over 1.68 years if thy received SSRIs, 1.63 years if they received SNRIs, and 2 years if they received TCAs.

Table 101: Summary of EQ-5D derived health-state utility data for side effects from antidepressants (UK tariff)

Study	Definition of health states	Health state	Mean (95% CI)
Sullivan 2004	Censored least absolute deviations (CLAD) regression analysis of EQ-5D data from the 2000 national US Medical Expenditure Panel Survey (MEPS) [http://meps.ahrq.gov/mepsweb/] Definitions of health states Gastrointestinal symptoms (GI): average Diarrhoea: clinical classification categories (CCC) - Agency for Healthcare Research and Quality): 144 regional enteritis Dyspepsia: CCC 138 oesophageal disorders Nausea & constipation: assumed average of GI Sexual: ICD-9 302 sexual disorders Excitation: average Insomnia: assumed equal to anxiety Anxiety: CCC 072 anxiety, somatoform, dissociative disorders Headache: CCC 084 headache Drowsiness & other: assumed average of all side effects Untreated depression ICD-9 311 depressive disorder; CLAD 25% Treated depression: ICD-9 311 depressive disorder; CLAD 75%; baseline utility estimate (not a decrement)	GI symptoms Diarrhoea Dyspepsia Nausea Constipation Sexual Excitation Insomnia Anxiety Headache Drowsiness Other Untreated depression Treated depression	-0.065 (-0.082 to -0.049) -0.044 (-0.056 to -0.034) -0.086 (-0.109 to -0.065) -0.065 (-0.082 to -0.049) -0.065 (-0.082 to -0.049) -0.049 (-0.062 to -0.037) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.115 (-0.144 to -0.087) -0.085 (-0.107 to -0.065) -0.085 (-0.107 to -0.065) -0.268 (-0.341 to -0.205) 0.848 (0.514 to 0.971)

Intervention resource use and costs

Intervention costs were estimated by combining resource use associated with each intervention with appropriate unit costs (drug acquisition costs, healthcare professional unit costs, and costs of equipment and infrastructure, as relevant).

Maintenance pharmacological interventions

Pharmacological intervention costs consisted of drug acquisition and GP visit costs. In addition to the 3 class-representative drugs (sertraline for SSRIs, venlafaxine for SNRIs, nortriptyline for TCAs), the model also considered GP care (reflected in the pill placebo arms of the relapse prevention RCTs). The cost of fluoxetine maintenance treatment was also estimated, as fluoxetine was considered as a treatment option in people whose depression has responded to acute psychological treatment.

The average daily dosage for each drug was determined according to optimal clinical practice (BNF 2021), following confirmation by the committee in order to reflect routine clinical practice in the NHS, and was consistent with dosages reported in the RCTs that were included in the systematic review of interventions for relapse prevention in adults with depression.

Maintenance pharmacological treatment lasted 2 years, based on available relevant evidence and previous NICE guidance. The model assumed gradual discontinuation (tapering) of the drug at the end of maintenance treatment, which was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) in the last 3 months of maintenance treatment, according to routine optimal clinical practice, as advised by the committee. Provision of maintenance pharmacological treatment involved 6 GP contacts in the 1st year of treatment and another 3 in the 2nd year; three extra GP visits were assumed during the tapering period.

GP care (reflecting RCT pill placebo arms) comprised 3 GP contacts in the 1st year and 1 contact in the 2nd year of treatment. For people in remission following pharmacological treatment who subsequently received GP care as maintenance treatment option, a tapering period in the first 3 months of GP care was assumed, which included 3 months of antidepressant administration in a linearly reduced dose (starting from optimal dose until no drug was received) plus 3 extra GP visits.

These resource use estimates were based on the committee's expert advice; they represent UK routine clinical practice but may be less resource intensive than some of the descriptions of medical resource use in pharmacological trial protocols, where resource use is more intensive than routine clinical practice.

The drug acquisition costs and the GP unit cost were taken from national sources (Curtis 2020, NHS Business Services Authority 2021). The lowest reported price for each drug was used, including prices of generic forms, where available. The reported GP unit cost included remuneration, direct care staff costs and other practice expenses, practice capital costs and qualification costs. The latter represented the investment costs of pre-registration and postgraduate medical education, annuitised over the expected working life of a GP; ongoing training costs were not considered due to lack of available information. The unit cost per patient contact was estimated taking into account the GPs' working time as well as the ratio of direct (surgeries, clinics, telephone consultations & home visits) to indirect (referral letters, arranging admissions) patient care, and time spent on general administration.

Intervention costs of maintenance pharmacological treatment and of GP care (reflected in RCT pill placebo arms) are shown in Table 102.

Table 102: Intervention costs of maintenance pharmacological treatments considered in the guideline economic analysis on relapse prevention (2020 prices)

Drug	Mean daily dosage	Drug acquisition cost[1]	2-year drug cost	2-year total intervention cost (drug and GP[2])
Sertraline	50% 50mg; 25% 100mg; 15% 150mg; 10% 200mg	50mg, 28 tab, £2.78 100mg, 28 tab, £4.32	£107.62[3]	£575.62
Venlafaxine XR	150mg	150mg, 28 tab, £3.90	£95.41[3]	£563.41
Nortriptyline	75mg	25mg, 100 tab, £2.90	£59.60[3]	£527.60
Fluoxetine[4]	20mg	20mg, 30 cap, £1.20	£27.40	£495.40
GP care [& 3 month drug tapering] (pill placebo)	Linear reduction over 1 month	As above, depending on tapered acute drug treatment (if applicable)	£0-£7.07[5]	£156.00[6]-£280.07

[1] NHS Business Services Authority 2021
[2] GP cost includes 6 GP visits in the 1st year and 3 GP visits in the 2nd year, plus 3 visits during tapering (committee's expert opinion); GP unit cost £36 per patient contact lasting 9.22 minutes (Curtis & Burns, 2016)
[3] includes 3 months' tapering
[4] Fluoxetine was considered as a treatment option in people whose depression has responded to acute psychological treatment.
[5] Depends on whether tapering is required (i.e. whether acute treatment was pharmacological and which drug was used); range of drug cost reflects range of drug acquisition cost during tapering
[6] Lower estimate does not include tapering visits

Maintenance psychological interventions

Maintenance psychological therapies comprised a number of individual or group sessions delivered by a range of healthcare professionals. Resource use estimates of each maintenance psychological therapy in terms of number and duration of sessions, mode of delivery and number of therapists and participants in the case of group interventions were determined by resource use data described in respective RCTs that were included in the guideline systematic review, modified by the committee to represent clinical practice in the UK; where trial resource use was very different to routine UK practice, a sensitivity analysis was undertaken, testing the impact of using routine UK resource use estimates on the results of the analysis.

Individual CT/CBT was delivered by agenda for change (AfC) band 7 high intensity therapists with a range of background qualifications, including clinical psychologists, counsellors, therapists that started their career as psychological well-being practitioners (PWPs), nurses (the latter is more often seen in secondary care), etc. (NHS England and Health Education England 2016a). High-intensity interventions delivered in groups, such as group CT/CBT and group MBCT were delivered by one AfC band 7 high intensity therapist, who led the delivery of the therapy, supported by one AfC band 6 therapist, who might be, for example, a PWP who had received additional IAPT training or a trainee clinical psychologist. Low intensity psychological interventions (individual psychoeducation, self-help with support, self-help without or with minimaly support) were delivered by an AfC band 5 low intensity therapist, who in Improving Access to Psychological Therapies (IAPT) services is usually a PWP. These assumptions were based on the committee's expert advice regarding the delivery of psychological interventions in routine clinical practice (predominantely IAPT services), although it is acknowledged that there may be further variation in the types of therapists delivering psychological interventions across different settings in the UK.

Therapist unit costs were estimated using a combination of data derived from national sources and included wages/salary, salary on-costs, capital and other overheads, qualification costs, and the cost of monthly supervision where relevant. In estimating the unit

cost of each type of therapist per hour of client contact, the ratio of direct (face-to-face) to indirect time (reflecting time for preparation of therapeutic sessions and other administrative tasks) of the therapist was also taken into account. This ratio of direct to indirect time was either directly obtained, where available, from national sources (Curtis 2020) or estimated by the committee, using their expertise and after taking into account relevant information in the same document.

Unit cost elements associated with wages/salary, salary on-costs, capital and other overheads were obtained, for each salary band level, from national data for community-based health care scientific and professional staff (Curtis 2020).

Qualification costs were estimated from a variety of sources. The qualification cost of a PWP was assumed to equal a 1-year cost of a AfC Band 4 health professional, which is the salary of PWP trainees (https://www.healthcareers.nhs.uk/explore-roles/psychological-therapies/roles/psychological-wellbeing-practitioner). The qualification cost of a band 7 high intensity therapist is variant, ranging from the qualification cost of a therapist originally trained as PWP to the qualification cost of a clinical psychologist (NHS England and Health Education England 2016b). Other high intensity therapists (counsellors, nurses) have qualification costs that lie between the PWP and the clinical psychologist qualification cost. For simplicity, the mean qualification cost of a band 7 high intensity therapist was calculated as the average between the PWP and the clinical psychologist qualification cost. In addition, for all band 7 high intensity therapists, regardless of their background qualifications, an additional IAPT high intensity therapist training cost of £10,000 (committee's expert advice) was estimated. The qualification cost of a band 6 therapist was estimated as the average between the PWP qualification cost (plus the £10,000 IAPT training cost) and a clinical psychology year 2 trainee cost (NHS England and Health Education England 2016b). Delivery of MBCT by high intensity therapists requires extra training that is not included in qualification costs. This training cost was estimated to approximate on average £18,000 per trainee, based on published fees for MBCT training courses offered by the Universities of Oxford and Bangor. All qualification costs were uplifted, where needed, to 2020 prices using the NHS cost inflation index (Curtis 2020) and annuitised using the formula reported in Netten 1998, assuming a useful working life ranging between 23-25 years, a time from obtaining the qualification until retirement ranging between 41-44 years, and an equal distribution of the useful working life over the period until retirement, due to lack of specific information on this distribution.

Other ongoing training costs of healthcare professionals delivering psychological interventions were not considered, because no relevant data are available. It is noted that this approach is consistent with the lack of consideration of ongoing training costs in the estimation of the reported GP unit cost, also due to lack of relevant data.

The committee also advised that supervision costs be considered in the estimation of the therapist unit costs, as supervision is essential for the delivery of psychological therapies and may incur considerable costs. According to the British Association for Behavioural and Cognitive Therapies (2016), high intensity therapists should receive regular supervision in groups of no more than 6 participants, with a mean duration of 1.5 hour per month for a full time practitioner. Based on this information, supplemented with the committee's expert advice, the supervision cost estimated for high intensity therapists comprised 1.5 hour of individual supervision per month, delivered by a Band 7 (50%) or Band 8a (50%) therapist. Low intensity therapists were assumed to receive 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4 by a band 6 PWP. The supervision cost included the cost of the supervisor's time, but not the cost of the supervised therapist's time, as this is indirectly included in the unit cost of each therapist.

Using the above information and assumptions, the unit costs of each therapist providing psychological interventions considered in the model are summarised in Table 103. Details on

the methods of estimation of each unit cost are provided in Table 104, Table 105 and Table 106.

Table 103: Unit costs of therapists delivering psychological interventions used in the guideline economic analysis (2020 prices)

Type of therapist	Unit cost[1]	Details
PWP (Band 5)	£50	See Table 104
High intensity therapist Band 7	£110	See Table 105
High intensity MBCT therapist Band 7	£112	See Table 105
Therapist Band 6	£89	See Table 106
Therapist Band 6 with training in MBCT	£91	See Table 106

1 per hour of client contact
MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 104: Unit cost of psychological well-being practitioner band 5 (2020 prices)

Cost element	Cost	Source
Wages – salary – annual	£25,023	Curtis 2020; costs for community-based scientific and professional staff AfC band 5
Salary on-costs – annual	£7,437	
Overheads, staff – annual	£7,953	
Overheads, non-staff – annual	£12,400	
Capital overheads – annual	£5,237	
Qualifications – annuitised	£4,141	Based on a 1-year cost of £50,659 for community-based scientific and professional staff AfC band 4 (i.e. salary level of PWP trainee) (Curtis 2020), annuitised using the formula by Netten 1998, assuming a useful working life of 25 years, a period life up to retirement of 44 years, and an equal distribution of the useful working life over the period until retirement.
Supervision – annual	£1,249	Assuming 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4, for a period of 42.6 weeks per year (working time per year), by a band 6 PWP (with unit cost per hour estimated using salary cost elements from Curtis 2020 plus annuitised qualification cost of £4,141).
SUM of unit costs	**£63,440**	
Working time (hours/year)	1,599	Curtis 2020
Total cost per hour	**£40**	
Ratio of direct to indirect time*	1-to-0.25	assumption - committee's expert opinion
Cost/hour of direct contact	**£50**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change

Table 105: Unit cost of high intensity therapist band 7 (with and without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£41,226		Curtis 2020; costs for community-based scientific and professional staff AfC band 7
Salary on-costs – annual	£13,024		

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Overheads, staff – annual	£13,291		
Overheads, non-staff – annual	£20,723		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£10,821	£12,485	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from 3-year training cost of clinical psychologist (NHS England and Health Education England 2016b) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 23 years, a time up to retirement of 42 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from Curtis 2020 and qualification costs for therapists with/without MBCT training).
SUM of unit costs	**£105,359**	**£107,038**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£66**	**£67**	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£110**	**£112**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 106: Unit cost of therapist band 6 (with/without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£33,734		Curtis 2020; costs for community-based scientific and professional staff AfC band 6
Salary on-costs – annual	£10,440		
Overheads, staff – annual	£10,823		
Overheads, non-staff – annual	£16,875		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£7,527	£9,190	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist trainee in year 2. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from training cost of clinical psychologist up to 2 years of training (NHS England and Health Education England 2016b), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from Curtis 2020 and qualification costs for band 7 and 8 therapists with/without MBCT training).
SUM of unit costs	**£85,673**	**£87,352**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£54**	**£55**	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£89**	**£91**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

In addition, according to the committee's expert advice, people receiving maintenance psychological therapy had 2 contacts with a GP during maintenance treatment.

The intervention costs of computerised self-help therapies included the cost of the provider of digital mental health programmes and related equipment required for their delivery (personal computers [PCs] and capital overheads). The cost of provision of a computerised CBT programme per client by the main provider of digital mental health programmes comprised a fixed fee of £39, which is independent of the number of sessions attended (committee's expert advice). The annual costs of hardware and capital overheads (space around the PC) were based on reported estimates made for the economic analysis undertaken to inform the NICE Technology Appraisal on computerised CBT for depression and anxiety (Kaltenthaler 2006). Kaltenthaler 2006 estimated that one PC can serve around 100 people with mental disorders treated with computerised programmes per year. Assuming that a PC is used under full capacity (that is, it serves no less than 100 people annually, considering that it is available for use not only by people with depression, but also by people with other mental health conditions), the annual cost of hardware and capital overheads was divided by 100 users, leading to a hardware and capital overheads cost per user of £14 (2020 price). It must be noted that if users of such programmes can access them from home or a public library, then the cost of hardware and capital overheads to the NHS is zero.

Details on the resource use and total costs of maintenance psychological interventions are provided in Table 107.

Table 107: Intervention costs of maintenance psychological therapies considered in the guideline economic analysis on relapse prevention (2020 prices)

Intervention	Resource use details	Total intervention cost per person[1]
MBCT	8 group sessions + 4 group booster sessions lasting 2 hours each; 2 MBCT therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 48 therapist hours per group and 6 therapist hours per service user	£608 + £78
Group CT/CBT	8 group sessions lasting 2 hours each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 32 therapist hours per group and 4 therapist hours per service user	£398 +£78
Individual CT/CBT	10 individual sessions with a band 7 HI therapist lasting 1 hour each	£1,098 +£78
Individual psychoeducation	10 individual sessions with a band 5 PWP lasting 20 minutes each	£165 +£78
Computerised CBT without support	Fixed cost of provider of digital mental health programmes is £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006). Cost includes 30 minutes of setup time by a band 5 PWP.	£78 + £78
Computerised CBT with support	1 session of 30 minutes and 7 sessions of 15 minutes each = 2.25 therapist hours per service user (band 5 PWP); fixed cost of provider of digital mental health programmes £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006)	£165 + £78

1 cost of psychological intervention plus 2 GP visits, at a GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020); cost of psychological intervention based on resource use combined with unit cost of therapists per hour of direct contact with client, estimated as described in Table 103, Table 104, Table 105, and Table 106.
CBT: cognitive behavioural therapy; CT: cognitive therapy; HI: high intensity; MBCT: mindfulness based cognitive therapy; PWP: psychological wellbeing practitioner

The committee considered the resource use associated with individual CT/CBT (Table 107) to be substantially higher than the level of intensity of maintenance psychological treatment received in routine UK practice. For this reason a sensitivity analysis was carried out that tested the impact of reducing the number of individual CT/CBT sessions down to 4, on the results of the economic analysis.

Combined maintenance pharmacological and psychological intervention

The intervention cost of combined maintenance pharmacological and psychological intervention was estimated as the sum of the intervention costs of the individual pharmacological and psychological treatment components.

In cohorts receiving combination treatment, no extra GP visits were added onto the psychological intervention cost, since people were already receiving GP care as part of their antidepressant treatment.

Cost of relapse and remission states

The cost of relapse and remission states in the economic model was estimated based primarily on data from Byford 2011. This was a naturalistic, longitudinal study that aimed to estimate the health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database between 2001 and 2006. The study analysed 12-month healthcare resource use data on 88,935 adults with depression and in receipt of at least two antidepressant prescriptions (for amitriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) in the first 3 months after the index prescription. The study provided data on resource relating to medication (antidepressant use and concomitant medication such as anxiolytics, hypnotics, mood stabilizers and neuroleptics), GP contacts, psychological therapy, psychiatrist and other specialist contacts, inpatient stays and accident and emergency attendances. Data were reported separately for people who remitted within 12 months, and those who did not remit. In addition, the study included graphs showing the change in healthcare costs overtime by timing of remission (separate graph lines were provided for people with very early remission defined as 1-4 months after onset of the depressive episode, early remission occurring 5-9 months after onset of the episode, late remission occurring 9-12 months after onset of the depression episode, and for people not achieving remission by 12 months). According to the study, among study participants who successfully ceased antidepressant treatment within the first 12 months (most probably remitters), 40% ceased within 4 months of the index prescription and almost 80% ceased within 8 months. This suggests that the costs incurred after remission did not include maintenance pharmacological treatment costs but were instead healthcare costs unrelated to depression.

The resource use and cost data reported in Byford 2011 for people with depression who remitted and those who did not remit within 12 months from the index prescription, uplifted to 2020 prices using the hospital & community health services index (HCHSI) up to year 2016 and then the NHS cost inflation index (NHSCII) up to year 2020 (Curtis 2020) are presented in Table 108.

Healthcare resource use and cost data from this study were modified following the committee's advice and attached to the model health states: data on people in a depressive episode who remitted within 12 months in the study were attached onto people in the relapse state of the model in their final year before remission (or in their first year of episode of their depressive episode lasted only over one model cycle). Resource use and cost data on people who did not remit within 12 months in the naturalistic study were used as the basis for estimating healthcare costs incurred by people who remained in a depressive episode for longer than one year and were applied to all years in a relapse state except the year before remission. Costs incurred after remission was achieved (which were possible to obtain from

the study's published graphs using digital software) were used to estimate annual healthcare costs associated with the remission state of the model.

Following the committee's advice, some of the resource use and drug acquisition cost data reported in the paper were modified, to reflect current clinical practice and the fact that some drugs are now available off-patent. Where detailed resource use data were provided, these were combined with appropriate 2020 unit costs; where only cost figures were available, these were uplifted to 2020 prices using the HCHSI up to year 2016 and then the NHSCII up to year 2020 (Curtis 2020), so that all costs in the guideline economic analysis reflected 2020 prices.

Table 108: 12-month resource use and costs of adults with depression reported in Byford 2011 (cost figures uplifted to 2020 prices)

Resource use element	Remitters (n=53,654)					Non-remitters (n=35,281)				
	Resource use			Cost		Resource use			Cost	
	Use %	Mean	SD	Mean	SD	Use %	Mean	SD	Mean	SD
Antidepressant use				£89	£58				£205	£91
Number of prescriptions	100	4.8	3.2			100	11.1	5.7		
Cumulative duration (days)		155.2	101.5				358.7	158.4		
Time on treatment (days)		129.8	73.7				283.9	63.8		
Concomitant medication				£36	£182				£86	£362
Anxiolytics – BZD (days)	8.2	32.4	241.7			12.6	69.5	458.5		
Anxiolytics – other (days)	0.7	0.8	15.0			1.1	1.6	23.7		
Hypnotics – BZD (days)	11.4	39.8	258.7			16.9	84.0	552.1		
Hypnotics – Z drugs (days)	9.2	7.5	44.4			12.9	16.4	71.6		
Hypnotics – other (days)	0.5	0.8	22.1			0.6	1.5	30.3		
Mood stabilizers – Li (days)	1.2	6.0	47.9			3.1	12.7	90.2		
Mood stabilizers – antiepileptic (days)	4.7	2.2	31.5			6.2	8.5	72.4		
Neuroleptics – typical (days)	0.2	0.4	11.2			0.5	1.4	25.9		
Neuroleptics – atypical (days)	0.7	3.0	54.8			1.1	8.3	120.0		
Service use										
GP visits	100	12.9	8.9	£471	£324	100	17.3	10.4	£669	£373
GP phone calls	55.2	2.5	4.3			86.7	5.4	6.1		
Psychological therapy contacts	0.2	0.0	0.1	£0	£5	0.2	0.0	0.1	£0	£8
Psychiatrist contacts	2.9	0.0	0.3	£96	£167	5	0.1	0.4	£124	£199
Other specialist contacts	38.6	0.6	1.1			44.9	0.8	1.2		
Hospitalisations [admissions]	5.2	0.1	0.4	£176	£915	5.7	0.1	0.4	£205	£1,060
Accident and emergency attendances	3.1	0.0	0.3	£6	£40	3.3	0.1	0.3	£6	£40
TOTAL COST				**£874**	**£1,128**				**£1,296**	**£1,352**

Costs for each healthcare cost category associated with the treatment of people with depression who remitted and those who did not remit within 12 months from their index episode were estimated as follows:

Cost of antidepressants and concomitant medication – relapse and remission states

The committee noted that a number of antidepressant drugs have become generic since the time the study was conducted, and this would have resulted in a reduction in the antidepressant costs reported in the study. In order to attach up-to-date drug acquisition costs to the antidepressant use reported in the study for 2001-2006, the following methodology was used: based on national prescription cost data for England in 2006 and 2019 - the most recent year for which relevant data existed - (NHS The Information Centre 2007; NHS Business Services Authority 2020), the ratio of the net ingredient cost (NIC) per antidepressant prescription item of 2019 relative to 2006 (which was the cost year used in the study by Byford and colleagues) was calculated; this was 0.29 (NIC per antidepressant prescription item was 9.39 in 2006 and 2.7 in 2019), and suggests that the mean cost per prescription has been reduced by more than 60%. Subsequently, the mean acquisition cost of antidepressants in 2015 was adjusted to be 50% lower than the cost reported in 2006.

Similarly to the methodology described above, for each category of concomitant medication, the ratio of the NIC per prescription item of 2019 relative to 2006 was calculated, and this was applied as a weighted ratio (according to the concomitant medication usage reported in the study) onto the cost of concomitant medication reported in the study, to adjust the total cost of concomitant medication to 2020 price.

The NICs per prescription items for antidepressants and the broad categories of concomitant medication in years 2006 and 2019 as well as the resulting ratios of 2019:2006 NICs are provided in Table 109.

Table 109: Net ingredient cost (NIC) per prescription item for antidepressants and categories of concomitant medication in 2006 and 2019

Drug category	NIC 2006	NIC 2019	Ratio NIC 2019:2006
Antidepressants	9.39	2.70	0.29
Anxiolytics	3.66	4.96	1.36
Hypnotics	2.75	4.96	1.80
Mood stabilizers – Li carbonate	1.72	2.26	1.31
Mood stabilizers – antiepileptic	21.54	10.75	0.50
Neuroleptics	38.83	10.28	0.26

Source: NHS, The Information Centre 2007; NHS Business Services Authority 2020

Byford 2011 reported that among study participants who successfully ceased antidepressant treatment within the first 12 months (most probably remitters), 40% ceased within 4 months of the index prescription and almost 80% ceased within 8 months. On the other hand, among participants who did not meet criteria for remission, 60% discontinued antidepressant treatment at some point over the 12-month study period but resumed within 6 months of antidepressant cessation and 40% received continuous antidepressant treatment over the 12-month study period.

Following the committee's expert opinion and previous NICE guideline recommendations on optimal duration of maintenance antidepressant treatment after remission of a depressive episode, the economic model assumed that antidepressant treatment for each depressive episode lasted in total 2 years at minimum; more specifically, it lasted over the duration of the depressive episode (i.e. over the whole period people spent in a relapse state) plus the first year into remission. Therefore, the adjusted estimated 12-month antidepressant cost for

remitters was applied to all remitters in the model over their first year of remission, to reflect continuation of maintenance pharmacological treatment according to NICE guidance.

GP visits and phone contacts – relapse and remission state

To estimate associated costs, relevant resource use for remitters and non-remitters reported in Byford 2011 was combined with respective unit costs (Curtis 2020).

Moreover, 3 extra GP visits were estimated for those who remitted in their first year of remission, to reflect extra resource use and costs associated with maintenance pharmacological treatment.

Cost of psychological therapy – relapse state

The committee noted that Byford 2011 reported a very low usage of psychological therapies. This is attributable to two reasons: first, because people in that study were selected due to their receiving antidepressant therapy, and second, because psychological therapy was not widely offered at the time the study was conducted (which was prior to the establishment of the IAPT programme in the UK).

According to NHS England, IAPT end of year data suggested that the percentage of people referred to IAPT services and receiving psychological therapies among those presenting to their GP and being eligible for psychological treatment reached 16.8% in 2016 (NHS England 2016).

Radhakrishnan 2013 reported costs of IAPT services in 5 East-of-England region Primary Care Trusts. Costs were estimated using treatment activity data and gross financial information, along with assumptions about how these financial data could be broken down. Data referred to 8,464 clients who attended at least 2 psychological treatment sessions (of whom 4,844 completed treatment). Using baseline PHQ-9 score bands to assess severity of depression, 2146 patients (25.4%) were classified as having moderate depressive symptoms, 1987 patients (23.5%) had moderate-severe depressive symptoms and 1787 patients (21.1%) presented with severe depressive symptoms. Based on the data reported in the study, the weighted mean cost per course of IAPT treatment per person (including people who completed treatment, those who dropped out, people who declined treatment and also people who were judged not to be suitable for treatment) was estimated to reach £799 (2020 prices). This unit cost was multiplied by the percentage of people receiving psychological therapy to estimate the cost of psychological treatment in the economic cohort, which was added to the annual cost of both people who remained in the relapse state, and those who moved to remission in the next model cycle.

The committee advised that people receiving psychological therapy still have GP contacts and some may also receive combination therapy. Therefore the costs of psychological treatment were added to the total cost associated with the relapse state, without other costs being reduced.

Cost of secondary care – relapse state

The cost of hospitalisation, psychiatrist visits, visits to other specialists and accident and emergency attendances was estimated by multiplying relevant resource use reported in Byford 2011 by respective NHS reference unit costs (NHS Improvement 2020) uplifted to 2020 prices using the HCHSI and NHSCII (Curtis 2020).

For hospitalisation, the mean cost per elective admission in NHS care was used. The committee expressed the opinion that a proportion of hospitalisations in the cohort should be due to their depressive episode. However, this proportion was not possible to estimate.

Therefore the committee decided to use the mean total cost per admission in the NHS as a conservative estimate of the cost of hospitalisation (since admissions to psychiatric wards are more expensive).

Cost of the remission state

According to the graphs presented in Byford 2011, the data of which were possible to extract using digital software (http://www.digitizeit.de), the 3-month costs after people had reached remission were approximately £100, thus the annual costs of remission reached £400 (2006 prices). Since the paper reports that over 40% of participants who successfully ceased antidepressant treatment ceased within 4 months of the index prescription and almost 80% ceased within 8 months, this cost figure appears not to be associated with maintenance treatment of the depressive episode, but is rather a 'generic' healthcare cost incurred by people in remission that is unrelated to treatment of depression. This cost was uplifted to 2020 prices using the HCHSI and NHSCII, resulting in a 2020 cost figure of £533 per year.

The figure of £533 was used to represent the annual healthcare cost of people in remission in the economic model. In the first year of remission following relapse, the annual cost of maintenance antidepressant drug treatment (£19) incurred by people in remission was added to this figure, as well as the cost of 3 GP visits (£117).

An overview of the healthcare costs associated with each health state in the guideline economic model and the methods for their estimation is shown in Table 110 and Table 111.

In the first 2 years of the model, the intervention cost of maintenance treatment was added onto the cost of the remission state, unless people relapsed within this period; in this case the intervention cost of maintenance treatment was added onto the cost of the remission state up to the point of relapse.

Table 110: Annual healthcare costs associated with the state of relapse in the guideline economic analysis (2020 prices)

Resource use element	Annual cost of relapse		Comments
	People remaining in relapse state in next model cycle	Last year of relapse prior to moving to remission	
Antidepressants	£44	£19	Cost reported by Byford 2011 for non-remitters and remitters, respectively, multiplied by the estimated net ingredient cost per antidepressant prescription item ratio for 2019:2006 (Table 109). Cost for non-remitters was used in both calculations to reflect antidepressant usage over 12 months, as remitters in the study ceased pharmacological treatment within a period of less than 12 months, which is inconsistent with current recommended clinical practice for maintenance antidepressant treatment.
Concomitant medication	£96	£41	Cost reported by Byford 2011 for non-remitters and remitters, respectively, multiplied by the estimated net ingredient cost per prescription item ratio for 2019:2006 (Table 109), weighted according to the concomitant medication usage reported in the study.
GP visits	£676	£502	Estimated by multiplying relevant resource use for non-remitters and remitters reported by Byford 2011 with the GP unit cost of £39 per patient contact lasting 9.22 minutes for 2020 (Curtis 2020).
GP phone calls	£45	£21	Estimated by multiplying resource use for non-remitters and remitters reported by Byford 2011 with the unit cost of £8 per GP telephone call (Curtis 2020).
Psychological therapy contacts	£133	£133	Estimated by combining the percentage (16.8%) of people referred to and receiving IAPT psychological therapies in 2016 (NHS England 2016) with the estimated weighted mean cost per course of IAPT treatment per person (£799), including people who completed treatment, those who dropped out, people who declined treatment and also people who were judged not to be suitable for treatment (Radhakrishnan 2013), expressed in 2020 prices using the HCHSI and NHSCII (Curtis 2020). This cost was added to the annual cost of both people who remained in the relapse state and those who transitioned to the remission state in the next model cycle.
Psychiatrist contacts	£11	£6	Estimated by multiplying relevant resource use for non-remitters and remitters reported in Byford 2011 with the NHS unit cost of £158 per contact with a mental health specialist team for adults and elderly (NHS Improvement 2020), after uplifting to 2020 price using the NHSCII inflation index (Curtis 2020).

Resource use element	Annual cost of relapse		Comments
	People remaining in relapse state in next model cycle	Last year of relapse prior to moving to remission	
Other specialist contacts	£100	£80	Estimated by multiplying relevant resource use for non-remitters and remitters reported by Byford 2011 with the mean NHS unit cost of £130 per outpatient attendance (NHS Improvement 2020), uplifted to 2020 price using the NHSCII (Curtis 2020).
Hospitalisations [admissions]	£333	£292	Estimated by multiplying relevant resource use for non-remitters and remitters reported by Byford 2011 with the mean NHS unit cost of £4,168 per admission in NHS care (NHS Improvement 2020), after uplifting to 2020 price using the NHSCII (Curtis 2020).
Accident and emergency attendances	£8	£7	Estimated by multiplying relevant resource use for non-remitters and remitters reported by Byford 2011 with the mean NHS unit cost per £170 for accident and emergency services (outpatient attendances) (NHS Improvement 2020), after uplifting to 2020 price using the NHSCII (Curtis 2020).
TOTAL COST	**£1,449**	**£1,102**	

HCHSI: hospital & community health services index; NSHCII: NHS cost inflation index

Table 111: Annual healthcare costs associated with the state of remission in the guideline economic analysis (2020 prices)

Resource use element	Annual cost of remission	Comments
Healthcare cost – all years of remission	**£528**	3-month healthcare cost of people having achieved remission obtained from graphs published by Byford 2011, read using digital software (http://www.digitizeit.de), extrapolated to 12 months and uplifted to 2020 prices using the HCHSI and NHSCII (Curtis 2020).
Maintenance antidepressant therapy – 1st year extra cost	**£136**	Additional cost reflecting optimal duration of maintenance antidepressant therapy following remission, comprising an annual antidepressant drug cost equal to that estimated for remitters and 3 GP contacts at the GP unit cost of £39 per patient contact lasting 9.22 minutes for 2020 (Curtis and Burns, 2020).

HCHSI: hospital & community health services index; NSHCII: NHS cost inflation index

Cost of management of common side effects from antidepressant treatment

People who experienced common side effects were assumed to have one extra GP contact every 3 months costing £39 (Curtis 2020) and to consume a cost of £10 per year for medication relating to the management of common side effects (e.g. paracetamol or anti-inflammatory drugs for headaches).

Discounting

Costs and benefits were discounted at an annual rate of 3.5% in the second year of the Markov component of the model as recommended by NICE 2014.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates); this approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each intervention) were averaged across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The distributions of the hazard ratios of all treatments versus pill placebo (reflecting GP care) were obtained from the NMAs, defined directly from values recorded in each of the 10,000 iterations performed in WinBUGS. The baseline risk of relapse after a single (first) episode and the risk of recovery were both determined by a Weibull distribution, as described earlier in methods. The probability distributions of the Weibull parameters (gamma and lambda) were defined directly from values recorded in each of the 10,000 iterations performed in WinBUGS. This allowed the correlation between the Weibull parameters to be taken into account. The hazard ratio of the risk of relapse for every additional depressive episode was given a log-normal distribution.

Utility values were assigned a beta distribution after applying the method of moments on data reported in the relevant literature. The proportion of women in the sample and the proportion of people experiencing side effects were also assigned a beta distribution. The risk ratio of mortality was assigned a log-normal distribution.

Uncertainty in intervention costs was taken into account by assigning probability distributions around the number of GP contacts and the number of individually delivered psychological therapy sessions. The number of therapist sessions per person attending group psychological interventions was not assigned a probability distribution because the number of group sessions remains the same, whether a participant attends the full course of treatment or a lower number of sessions. Drug acquisition costs were not given a probability distribution as these costs are set and are characterised by minimal uncertainty. However, if people receiving maintenance pharmacological therapy attended fewer GP visits than the mode in the second year of maintenance treatment, then they were assumed to be prescribed smaller amounts of medication than optimal, and to subsequently incur lower drug acquisition costs. Unit costs of healthcare staff (GPs and clinical psychologists) were assigned a normal distribution. Healthcare costs associated with the states of relapse and recovery were assigned a gamma distribution.

Table 112 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Table 112: Input parameters (deterministic values and probability distributions) that informed the economic models of interventions for relapse prevention in adults whose depression has responded to acute treatment

Input parameter	Mean deterministic value	Probability distribution	Source of data - comments
General characteristics of population			
Age of onset (years)	32	No distribution	Kessler 2005; Fernandez-Pujals 2015; committee's expert advice
Mean interval between episodes (years)	2	No distribution	Committee's expert advice
Number of previous episodes			
- medium risk of relapse	1	No distribution	Committee's expert advice
- high risk of relapse	3	No distribution	
Proportion of women	0.56	Beta: α=279; β=219	McManus 2016; weighted prevalence of depression 2.9% in men, 3.7% in women, survey sample N=7,546
Hazard ratios vs pill placebo – people at medium risk of relapse whose depression has responded to acute pharmacological treatment			
		Log-normal:	Guideline pairwise meta-analysis; distribution based on 10,000 iterations
Sertraline (SSRI)	0.46	95% CrI 0.38 to 0.54	
Venlafaxine (SNRI)	0.55	95% CrI 0.48 to 0.62	
Nortriptyline (TCA)	0.40	95% CrI 0.24 to 1.63	
Hazard ratios vs pill placebo – people at high risk of relapse whose depression has responded to acute pharmacological treatment			
		Log-normal	Guideline NMA; distribution based on 10,000 iterations
AD	0.50	95% CrI 0.44 to 0.55	
MBCT (AD tapering)	0.46	95% CrI 0.31 to 0.64	
MBCT + AD	0.34	95% CrI 0.19 to 0.55	
Group CT/CBT + AD	0.35	95% CrI 0.12 to 0.79	
Individual CT/CBT + AD	0.30	95% CrI 0.18 to 0.46	
Individual CT/CBT (AD tapering)	0.51	95% CrI 0.30 to 0.78	
Hazard ratios vs pill placebo – people at high risk of relapse whose depression has responded to acute pharmacological treatment: secondary analysis			
		Log-normal	Guideline NMA; distribution based on 10,000 iterations
AD	0.49	95% CrI 0.44 to 0.55	
MBCT (AD tapering)	0.46	95% CrI 0.32 to 0.63	
MBCT + AD	0.34	95% CrI 0.26 to 0.43	

Input parameter	Mean deterministic value	Probability distribution	Source of data - comments
Group CT/CBT + AD	0.37	95% CrI 0.24 to 0.54	
Individual CT/CBT + AD	0.30	95% CrI 0.18 to 0.46	
Individual CT/CBT (AD tapering)	0.50	95% CrI 0.29 to 0.79	
Individual psychoeducation + AD	0.40	95% CrI 0.18 to 0.76	
Self-help without/with minimal support + AD	0.45	95% CrI 0.32 to 0.61	
Self-help with support + AD	0.15	95% CrI 0.04 to 0.35	
Hazard ratios vs pill placebo – people at medium or high risk of relapse whose depression has responded to acute psychological treatment			
		Log-normal	Guideline NMA; distribution based on 10,000 iterations
Individual CT/CBT	0.67	95% CrI 0.31 to 1.26	
AD (fluoxetine)	0.81	95% CrI 0.43 to 1.37	
No treatment	1.28	95% CrI 0.45 to 2.95	
MBCT	0.89	95% CrI 0.29 to 2.14	
group CT/CBT	1.01	95% CrI 0.30 to 2.56	
Individual psychoeducation	0.92	95% CrI 0.29 to 2.20	
Self-help without/ith minimal support	1.17	95% CrI 0.37 to 2.85	
Self-help with support	0.40	95% CrI 0.07 to 1.33	
Baseline risk of relapse after a single (first) episode			
Weibull distribution – lambda	0.09	95% CI 0.07 to 0.12	Synthesis of data from Eaton 2008 & Mattisson 2007, using a Bayesian approach – fixed effects model; distribution based on 10,000 iterations using WinBUGS
Weibull distribution – gamma	0.63	95% CI 0.52 to 0.75	
Hazard ratio – new vs previous episode	1.15	Log-normal: 95% CI 1.11 to 1.18	Kessing 1999
Risk of recovery			Synthesis of data from Gonzales 1985; Holma 2008; Keller 1981, 1984 & 1992; Mueller 1996; and Skodol 2011, using a Bayesian approach – random effects model; distribution based on 10,000 iterations using WinBUGS
Weibull distribution – lambda	1.16	95% CI 1.08 to 1.24	
Weibull distribution – gamma	0.42	95% CI 0.37 to 0.47	
Proportion of people developing common side effects			Anderson 2012
– SSRIs	0.07	Beta: α=1,643; β=21,977	
– SNRIs	0.09	Beta: α=437; β=4,325	

Input parameter	Mean deterministic value	Probability distribution	Source of data - comments
– TCAs	0.07	Beta: α=52; β=724	
Duration of experiencing common side effects over the model time horizon – SSRIs (following acute AD treatment) – SNRIs (following acute AD treatment) – TCAs (following acute AD treatment) – SSRIs (following acute psych treatment)	 1.43 years 1.38 years 2.00 years 1.68 years	No distribution assumed	Anderson 2012
Mortality Risk ratio – depressed vs non-depressed Baseline mortality – non-depressed	 1.52 Age/sex spec	 Log-normal: 95% CI 1.45 to 1.59 No distribution	 Cuijpers 2014 Mortality statistics for the UK population (Office for National Statistics 2020)
Utility values Less severe depression More severe depression Remission/recovery Disutility due to side effects	 0.60 0.42 0.81 0.09	 Beta: α=182; β=122 Beta: α=54; β=75 Beta: α=531; β=125 Beta: α=6; β=59	Distributions determined using method of moments, based on data reported in Sobocki 2006 & 2007, Sullivan 2004 and further assumptions
Intervention costs – resource use Number of GP visits – drug treatment – 1st year – 2nd year – tapering Number of GP visits – GP care (pill placebo) – 1st year – 2nd year – tapering Number of GP visits - side effects (annual) Number of GP visits – psychological therapy Number of group MBCT sessions	 6 3 3 3 1 3 4 2 12	 0.70: 6, 0.20: 4-5, 0.10: 2-3 0.70: 3, 0.30: 1-2 0.70: 3, 0.30: 1-2 0.70: 3, 0.20: 1-2, 0.10: 0 0.70: 1, 0.30: 0 0.70: 3, 0.30: 1-2 No distribution in first year 0.70: 2; 0.30: 1 No distribution	 Probabilities assigned to numbers of sessions Number of visits based on the committee's expert opinion; probabilities based on assumption. If number of GP visits in 2nd year of maintenance pharmacological treatment equalled 1, only 50% of the 2nd year drug acquisition cost and 50% of the extra GP visit costs due to side effects were incurred

Input parameter	Mean deterministic value	Probability distribution	Source of data - comments
Number of group CT sessions	8		Participants missing one or more group sessions assumed not to be replaced by others; therefore no impact on total intervention cost
Number of individual CT/CBT sessions	10	0.60: 10, 0.20: 8-9, 0.15: 6-7, 0.05: 1-5	
Number of individual psychoeducation sessions	10		Number of visits based on the committee's expert opinion; probabilities based on assumption
Number of cCBT without support sessions	N/A		
Number of cCBT with support sessions	7	0.70: 7; 0.25: 5-6; 0.05: 1-4	
Intervention costs - unit costs			
Drug acquisition costs	Table 102	No distribution	National drug tariff, January 2017
Medication for management of side effects	£2.50	No distribution	Assumption – 3-month cost
cCBT provider, hardware & capital overheads	£53	No distribution	Committee's expert advice and Kaltenthaler 2006
GP unit cost	£39		Curtis 2020; distribution based on assumption
HI therapist Band 7 unit cost	£110		
Therapist Band 6 unit cost	£89	All health professional unit costs: Normal, SE=0.05*mean	See Table 103 for health professional unit costs; distribution based on assumption
HI MBCT therapist Band 7 unit cost	£112		
MBCT therapist Band 6 unit cost	£91		
PWP (Band 5) unit cost	£50		
Annual NHS health state cost			Based primarily on cost data reported in Byford 2011, supplemented by data from Curtis 2020; NHS England 2016 and Radhakrishnan 2013, expressed in 2020 prices using the HCHSI and NHSCII (Curtis 2020). For details see Table 110 and Table 111; distribution based on assumption
Relapse - remaining in state	£1,102	Gamma SE=0.20*mean	
Relapse - final year before remission	£1,449		
Remission	£528		
Remission – 1st year extra cost	£136		
Annual discount rate	0.035	No distribution	Applied to both costs and outcomes. NICE 2014

AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; HCHSI: hospital & community health services index; HI: high intensity; MBCT: mindfulness-based cognitive therapy; NSHCII: NHS cost inflation index; SE: standard error; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

A number of deterministic one- and n- way (combined) sensitivity analyses were undertaken to explore the impact of alternative hypotheses on the results. The following scenarios were explored alone or in combination, where appropriate:

- Change (increase) in the number of previous episodes, resulting in an increase in the risk of relapse; the number of previous episodes was increased from 1 to 2 in people at medium risk of relapse and from 3 to 5 in people at high risk of relapse
- Change in the severity of depressive episodes, as reflected in respective health state utility values for less severe depression and more severe depression; under this scenario, people at medium risk of relapse were assumed to experience more severe depression if they relapsed and people at high risk of relapse were assumed to experience less severe depression if they relapsed.
- Use of the hazard ratio of antidepressant vs pill placebo (GP care) estimated for people whose depression has responded to psychological treatment in people receiving antidepressant maintenance treatment following response to acute pharmacological treatment, to explore the impact of the withdrawal syndrome of people in the pill placebo arm on the results (as people whose depression has responded to psychological treatment who move onto pill placebo do not experience antidepressant tapering). This scenario was explored only in people at medium risk of relapse, as the results for people at high risk of relapse were informed by NMA and various network connections and therefore it was difficult to isolate effects impacted by the possible development of withdrawal syndrome.
- Use of utility values for less severe depression (0.65) and more severe depression (0.56) reported in Mann and colleagues (2009); use of the utility value for remission of 0.70 reported in Kolovos 2017
- Use of a probability of side effects of 0.40 throughout the period people under pharmacological antidepressant treatment received antidepressants.
- Reduction in the number of individual CBT/CT sessions down to 4 (from 10, which was the number used in base-case analysis), to reflect more closely routine UK clinical practice for maintenance treatment aiming at relapse prevention
- Reduction in the resource use associated with provision of MBCT and group CT/CBT from 2 therapists (1 high intensity leading therapist in AfC Band 7 an 1 supporting therapist in AfC Band 6) and 8 participants per group (as assumed in the base-case analysis) to 1 high intensity therapist (AfC Band 7) and 12 participants per group, to reflect the lower end of intervention cost of group interventions.
- Change in the cost associated with the state of relapse by ± 50%
- Assuming a shorter relapse preventive effect of psychological interventions, by applying the hazard ratios of psychological interventions onto the baseline risk of relapse over the first year of the economic analysis only (and not in the first and second year, as in the base-case analysis). Under this scenario, the relapse preventive effect of combination therapies in the second year of the economic analysis was assumed to equal the effect of their pharmacological intervention component. This scenario was explored because the evidence on the long term effects of psychological interventions in relapse prevention (i.e. beyond one year and closer to two years) is limited and some evidence suggests a reduction in this effect (Kuyken 2015).

Presentation of the results

Results are reported separately for each cohort examined in the economic model. In each analysis, total costs and QALYs are presented for each intervention, averaged across 10,000 iterations of the model. For each treatment option, the Net Monetary Benefit (NMB) has been estimated for each iteration and averaged across the 10,000 iterations, determined by the formula

$$NMB = E \bullet \lambda - C$$

where E and C are the effects (QALYs) and total costs, respectively, of each treatment option, and λ represents the moneterised value of each QALY, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE, 2014). The treatment with the highest NMB is the most cost-effective option (Fenwick 2001).

Incremental mean costs and effects (QALYs) of each maintenance intervention versus GP care (with antidepressant drug tapering if relevant) are also presented in the form of cost effectiveness planes.

The mean (95%CI) ranking by cost-effectiveness is reported for each treatment (out of 10,000 iterations), where a rank of 1 suggests that a treatment is the most cost-effective amongst all evaluated treatment options. The probability of each intervention being cost-effective at the NICE lower cost-effectiveness threshold has also been calculated. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds (λ), and the probability that this treatment is the most cost-effective among those assessed (Fenwick 2001). Although cost-effectiveness results (total costs, total QALYs and NMB) are shown for all treatments considered in the NMAs, only treatments tested on at least 50 people in the NMA that informed each sub-analysis were considered when estimating probabilities and ranking and when drawing the CEAF for each population, as this was deemed the minimum evidence base that was adequate to inform recommendations.

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a health economics sub-group formed by members of the committee. The validity of the model structure, assumptions and input parameters were confirmed by the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. Moreover, a number of parameters, such as efficacy (risk and odds ratios), intervention costs, and number of previous episodes (which differ between populations at medium and high risk of relapse) were set at the same value across interventions and analyses, to explore whether total costs and benefits across interventions and analyses became equal, as expected. The primary and secondary analysis results as well as the results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Economic modelling results

People at medium risk of relapse whose depression has responded to acute pharmacological treatment

The base-case results of the analysis are presented in Table 113. Maintenance treatment with SSRIs, SNRIs or TCAs was more cost-effective than GP care and antidepressant drug tapering in people at medium risk of relapse whose depression had responded to acute acute pharmacological treatment with SSRIs, SNRIs or TCAs, respectively.

Table 113: Results of base-case economic analysis: interventions for people at medium risk of relapse whose depression has responded to acute pharmacological treatment (mean values from probabilistic analysis)

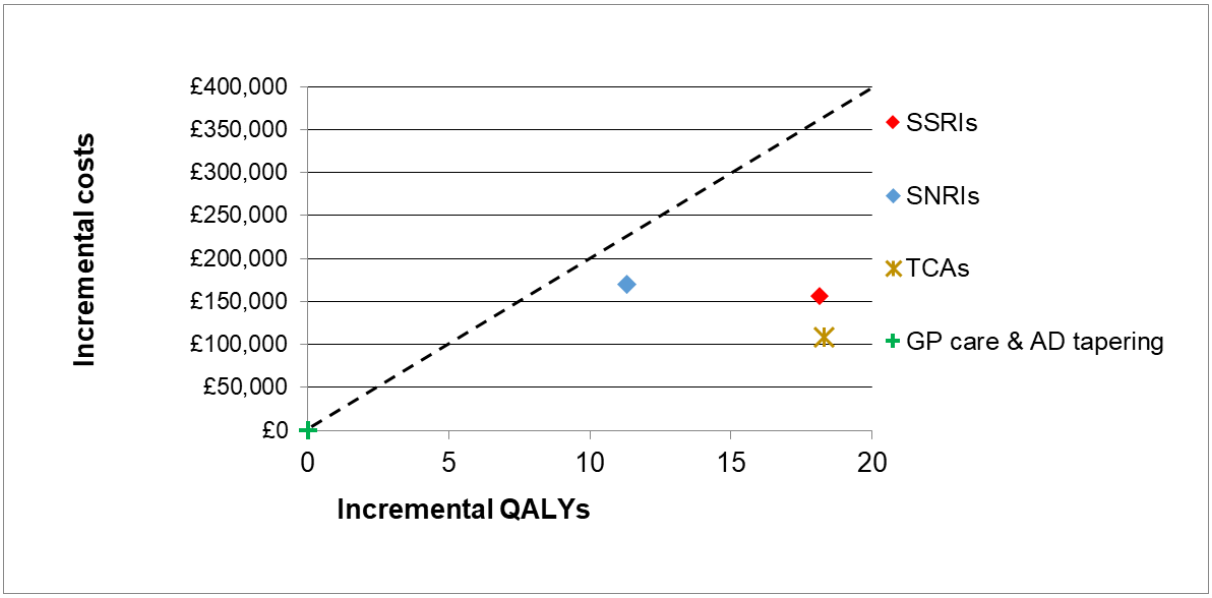
Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
People whose depression responded to acute SSRI treatment					
SSRI	6.854	£5,446	£131,636	0.88	1.12 (1 to 2)
GP care (SSRI tapering)	6.836	£5,290	£131,430	0.12	1.88 (1 to 2)
People whose depression responded to acute SNRI treatment					
SNRI	6.847	£5,458	£131,487	0.65	1.35 (1 to 2)
GP care (SNRI tapering)	6.836	£5,289	£131,431	0.35	1.65 (1 to 2)
People whose depression responded to acute TCA treatment					
TCA	6.854	£5,394	£131,691	0.88	1.12 (1 to 2)
GP care (TCA tapering)	6.836	£5,286	£131,433	0.12	1.88 (1 to 2)

[1] *At the NICE lower cost-effectiveness threshold of £20,000/QALY*

NMB: net monetary benefit; Prob: probability; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

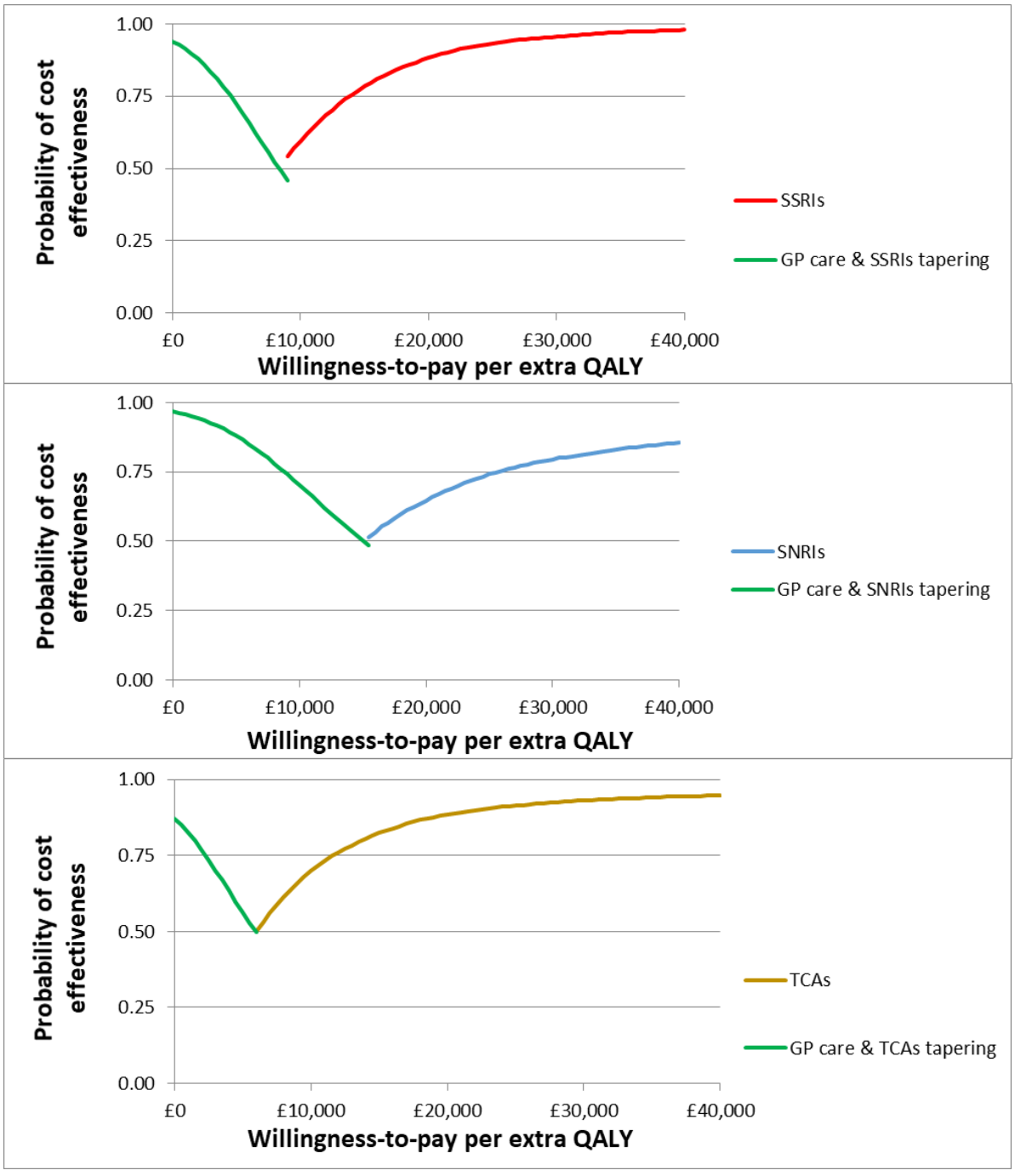
Figure 114 provides the cost effectiveness plane of the analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care and antidepressant drug tapering, which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that maintenance pharmacological treatment is cost-effective compared with GP care and antidepressant drug tapering for people at medium risk of relapse who remitted following acute pharmacological treatment (since all maintenance pharmacological treatments lie on the right side of the dotted line). It is noted that results for each maintenance pharmacological intervention versus GP care and antidepressant drug tapering refer to different study populations, depending on the acute pharmacological treatments they received, and therefore estimating the relative cost effectiveness between different maintenance pharmacological treatments is not relevant or appropriate.

Figure 114 Cost effectiveness plane of maintenance pharmacological interventions for people at medium risk of relapse whose depression had responded to acute pharmacological treatment – incremental costs and QALYs versus GP care and antidepressant drug tapering per 1,000 adults



The CEAFs for each sub-population at medium risk of relapse receiving either maintenance pharmacological treatment (SSRI, SNRI or TCA) or GP care and antidepressant drug tapering are shown in Figure 115. It can be seen that at the lower NICE cost-effectiveness threshold, all maintenance treatment drug classes are cost-effective. However, although, at this threshold, the probability of SSRIs and TCAs being cost-effective is high (88%), the probability of SNRIs being cost-effective is 65%.

Figure 115. Cost-effectiveness acceptability frontier of interventions for people at medium risk of relapse whose depression has responded to acute pharmacological treatment



In deterministic sensitivity analysis, increasing the number of previous episodes from 1 to 2, increasing the severity of depression following relapse from less to more severe, or

increasing the cost of relapse by 50% had no impact on the conclusions of the analysis. Reducing the cost of relapse by 50% resulted in GP care and SNRI tapering becoming more cost-effective than SNRI maintenance treatment.

Use of the (higher) hazard ratio of relapse of the antidepressants vs pill placebo (GP care) estimated for people whose depression has responded to psychological treatment (so as to minimise the impact of withdrawal syndrome in people who received GP care and antidepressant drug tapering) resulted in maintenance antidepressant treatment becoming less cost-effective than GP care and antidepressant drug tapering for all 3 antidepressant drug classes. Use of alternative utility values (reflecting lower utility gains associated with relapse prevention) also resulted in maintenance antidepressant treatment becoming less cost-effective than GP care and antidepressant drugs tapering. Finally, assuming a risk of 0.40 for side effects of antidepressant treatment over the whole duration of treatment also resulted in maintenance antidepressant treatment becoming less cost-effective than GP care and antidepressant drug tapering. Results of these 2 scenarios are shown in Table 114.

Table 114: Results of deterministic sensitivity analysis: interventions for people at medium risk of relapse whose depression has responded to acute pharmacological treatment

Base-case		Use of alternative HR		Use of alternative utility values		Risk of side effects 40%	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
People whose depression responded to acute SSRI treatment							
SSRI	£131,552	GP care	£131,352	GP care	£114,141	GP care	£131,352
GP care	£131,352	SSRI	£131,127	SSRI	£113,942	SSRI	£130,297
People whose depression responded to acute SNRI treatment							
SNRI	£131,404	GP care	£131,352	GP care	£114,142	GP care	£131,352
GP care	£131,352	SNRI	£131,088	SNRI	£113,862	SNRI	£130,211
People whose depression responded to acute TCA treatment							
TCA	£131,607	GP care	£131,355	GP care	£114,144	GP care	£131,355
GP care	£131,355	TCA	£131,115	TCA	£113,953	TCA	£130,405

In each scenario, interventions ordered from most to least cost-effective. NMB is estimated per person
HR: hazard ratio; NMB: net monetary benefit; Prob: probability; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

People at medium risk of relapse whose depression has responded to acute psychological treatment

The base-case results of this analysis are presented in Table 115. The most cost-effective maintenance treatment option for people at medium risk of whose depression had responded to acute psychological treatment was GP care, followed by no treatment. Maintenance individual CT/CBT was the most effective option but also the one with the highest cost and was the least cost-effective option following maintenance antidepressant treatment. The probability of GP care being the most cost-effective option was 0.47 at the lower NICE lower cost-effectiveness threshold of £20,000/QALY. Mean rankings (and wide confidence intervals) suggested uncertainty around the results. The order of interventions from most to least cost-effective was the same in deterministic analysis.

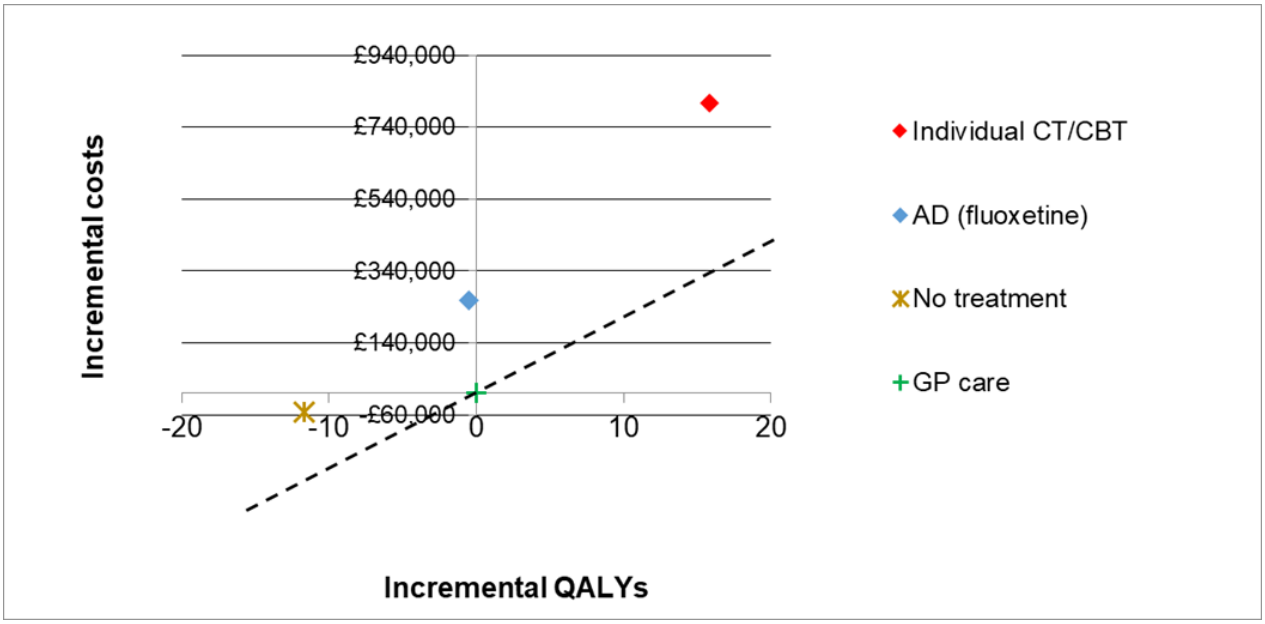
Table 115: Results of base-case economic analysis: interventions for people at medium risk of relapse whose depression has responded to acute psychological treatment (mean values from probabilistic analysis)

Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
GP care	6.836	5,194	£131,525	0.47	1.70 (1 to 3)
No treatment	6.824	5,140	£131,344	0.43	2.16 (1 to 4)
AD (fluoxetine)	6.835	5,450	£131,258	0.07	2.70 (1 to 4)
Individual CT/CBT	6.852	6,001	£131,034	0.03	3.44 (1 to 4)

[1] *At the NICE lower cost-effectiveness threshold of £20,000/QALY*
AD: antidepressant CBT: cognitive behavioural therapy; CT: cognitive therapy; NMB: net monetary benefit; *Prob: probability*

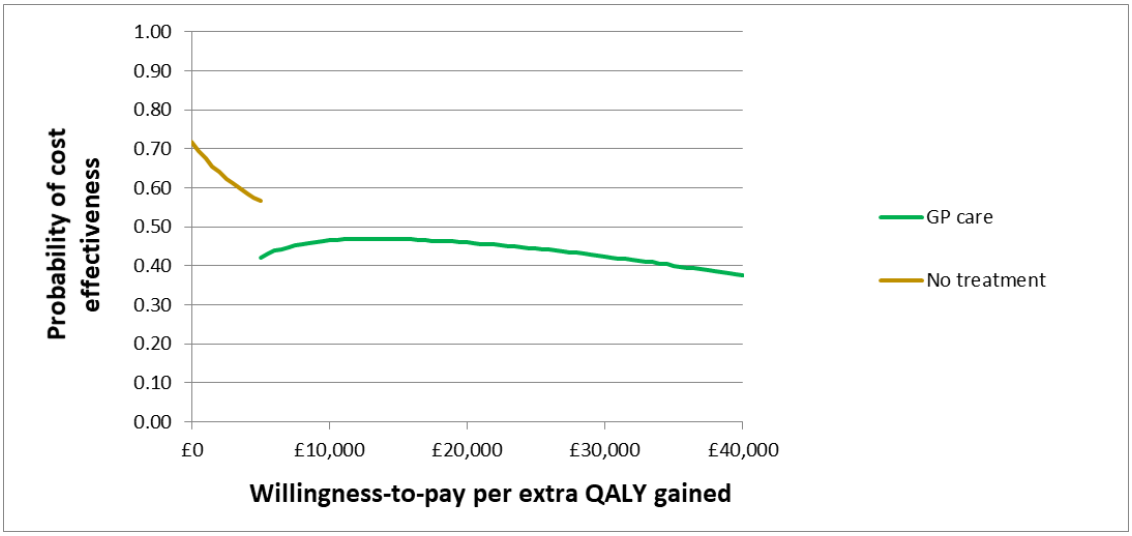
Figure 116 provides the cost effectiveness plane of the analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care, which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that maintenance treatments and no treatment are not cost-effective compared with GP care for people at medium risk of relapse who remitted following acute psychological treatment (since all options lie on the left side of the dotted line).

Figure 116 Cost effectiveness plane of maintenance treatment options for people at medium risk of relapse whose depression has responded to acute psychological treatment – incremental costs and QALYs versus GP care per 1,000 adults



The CEAF of this analysis showing the most cost-effective option at different cost-effectiveness thresholds is shown in Figure 117. GP care is the most cost-effective treatment option at the NICE lower cost-effectiveness threshold, with a probability that reaches 47%.

Figure 117 Cost-effectiveness acceptability frontier of interventions for people at medium risk of relapse whose depression has responded to acute psychological treatment



In deterministic sensitivity analysis, increasing the number of previous depressive episodes (and therefore the risk of future relapses) from 1 to 2 or changing the cost of the relapse state had no impact on the conclusions of the analysis and the ranking of interventions.

Assuming that future relapses led to more severe depression improved the ranking of maintenance antidepressant treatment and individual CT/CBT by one place; both became more cost-effective than no treatment.

Use of alternative utility values (assuming more conservative utility gains after relapse prevention) led to no treatment becoming the best treatment option.

Reducing the number of individual CT/CBT sessions down to 4 (from 10, which was the number used in base-case analysis) led to individual CT/CBT becoming the most cost-effective maintenance treatment option; when this scenario was combined with the assumption that the preventative effect of individual CT/CBT lasts only 1 year, individual CT/CBT became the second most cost-effective treatment option, below GP care.

Increasing the risk of side effects from antidepressants resulted in maintenance antidepressant treatment becoming the least cost-effective option.

Results of the scenarios that had an impact on base-case results are shown in Table 116.

Table 116: Results of deterministic sensitivity analysis: interventions for people at medium risk of relapse whose depression has responded to acute psychological treatment

Base-case		More severe depression		Alternative utility values	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
GP care	£131,469	GP care	£129,618	No treatment	£114,270
No treatment	£131,278	AD (fluoxetine)	£129,467	GP care	£114,259
AD (fluoxetine)	£131,172	Individual CT/CBT	£129,281	AD (fluoxetine)	£113,831
Individual CT/CBT	£130,868	No treatment	£129,199	Individual CT/CBT	£113,422
4 individual CT/CBT sessions		**4 individual CT/CBT sessions & 1 year effect**		**Increase in the risk of antidepressant side effects**	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**

Individual CT/CBT	£131,504	GP care	£131,469	GP care	£131,469
GP care	£131,469	Individual CT/CBT	£131,373	No treatment	£131,278
No treatment	£131,278	No treatment	£131,278	Individual CT/CBT	£130,868
AD (fluoxetine)	£131,172	AD (fluoxetine)	£131,172	AD (fluoxetine)	£129,988

In each scenario, interventions ordered from most to least cost-effective.
[1] per person
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; NMB: net monetary benefit

People at high risk of relapse whose depression has responded to acute pharmacological treatment

Primary analysis

The base-case results of the primary analysis are presented in Table 117. The most cost-effective maintenance treatment option for people at high risk of relapse whose depression had responded to acute pharmacological treatment was group CT/CBT combined with antidepressants, which, however, had been tested only in 22 people in the respective NMA that informed the economic analysis (hence mean ranking and probability of cost-effectiveness were not estimated for this option). Antidepressant maintenance treatment was the second most cost-effective intervention followed by other psychological interventions combined with either antidepressants or antidepressant tapering. The least cost-effective intervention was GP care and antidepressant tapering. Mean rankings (and their wide confidence intervals) suggested uncertainty around the results. In deterministic analysis, the order of interventions was the same, with the exception of individual CT/CBT and antidepressant tapering, which was the least cost-effective option, after GP care and antidepressant tapering.

Table 117: Results of base-case primary economic analysis: interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment (mean values from probabilistic analysis)

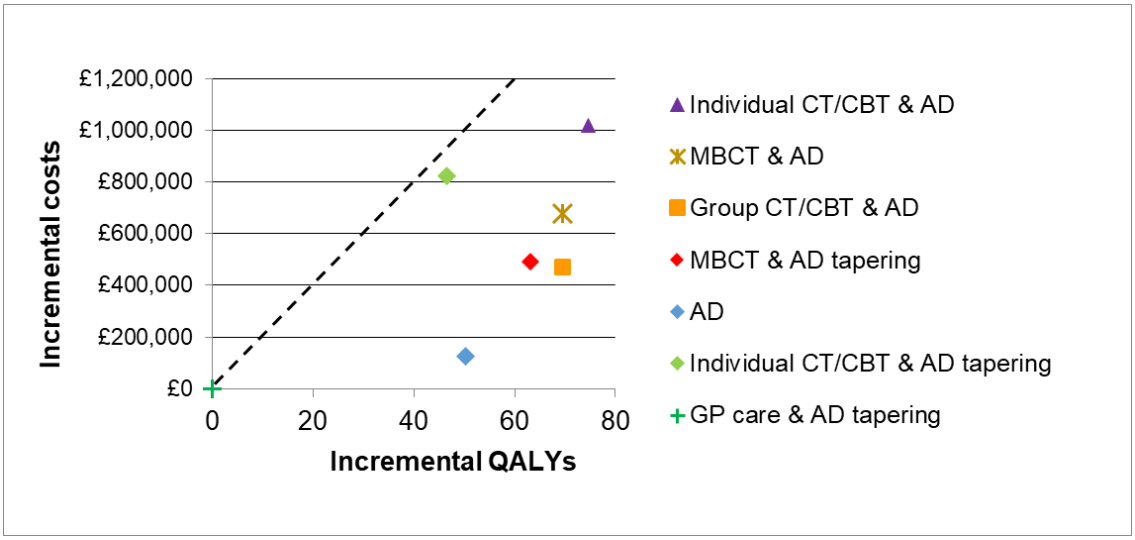
Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
group CT/CBT & AD	6.740	£5,921	£128,879	Not estimated (N=22)	
AD	6.721	£5,575	£128,838	0.39	1.90 (1 to 4)
MBCT & AD tapering	6.734	£5,941	£128,730	0.24	2.53 (1 to 5)
MBCT & AD	6.740	£6,126	£128,676	0.15	2.87 (1 to 5)
individual CT/CBT & AD	6.745	£6,468	£128,432	0.04	3.98 (1 to 6)
individual CT/CBT & AD tapering	6.717	£6,274	£128,065	0.18	4.35 (1 to 6)
GP care & AD tapering	6.671	£5,450	£127,960	0.00	5.37 (4 to 6)

[1] At the NICE lower cost-effectiveness threshold of £20,000/QALY
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; *Prob: probability*

Figure 118 provides the cost effectiveness plane of the primary analysis. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that all maintenance treatments assessed in the analysis are cost-effective compared with GP care and antidepressant drug tapering for people at high risk of relapse whose depression has responded to acute pharmacological treatment, as all treatments lie on the right side of the dotted line.

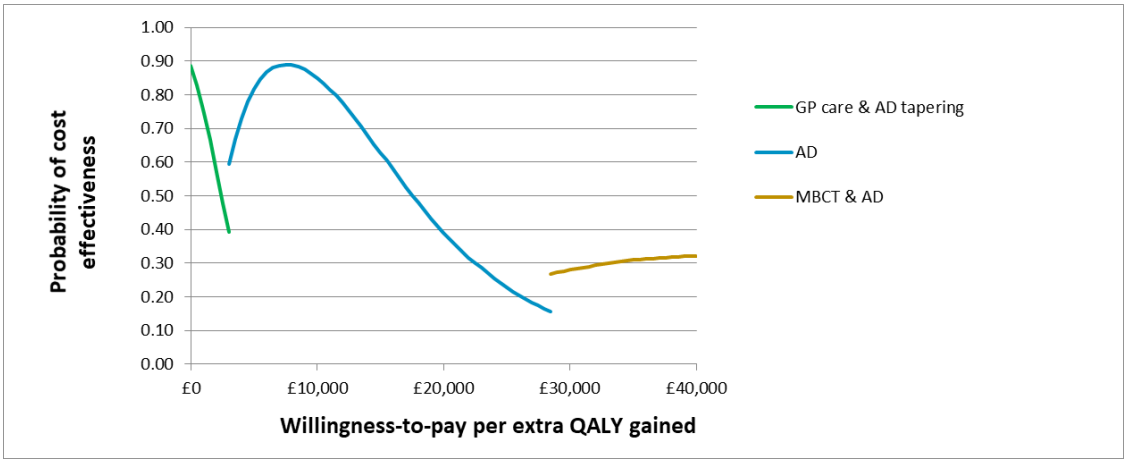
Figure 118 Cost effectiveness plane of maintenance interventions for people at high risk of relapse whose depression has responded to acute pharmacological

treatment – incremental costs and QALYs versus GP care and antidepressant drug tapering per 1,000 adults. Primary analysis



The CEAF of the analysis is shown in Figure 119. At the NICE lower cost-effectiveness threshold (£20,000/QALY), antidepressant treatment is the most cost-effective treatment option, with a low probability of being cost-effective, of only 0.39.

Figure 119. Cost-effectiveness acceptability frontier of interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment – primary analysis



In deterministic sensitivity analysis, increasing the number of previous depressive episodes (and therefore the risk of future relapses) from 2 to 5 had a small impact on the ranking of interventions. All other scenarios explored in sensitivity analysis had some impact on the results and conclusions of the analysis, as seen in Table 118. Reducing the resource use associated with provision of individual CT/CBT and/or group psychological interventions had a very strong impact, as it resulted in psychological interventions becoming the most cost-effective maintenance treatment options. Increasing the risk of side effects of antidepressants resulted in treatment options that involved antidepressant drug tapering becoming the most cost-effective options. Assuming people experienced less severe depression if they relapsed, or assuming smaller utility gains from relapse prevention led to significant improvement of the relative cost effectiveness of less intensive interventions, such as maintenance antidepressant treatment and GP care combined with antidepressant tapering.

Table 118: Results of deterministic sensitivity analysis: interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment – primary analysis

Base-case		Increase in number of previous episodes		Less severe depression		Alternative utility values	
Intervention	NMB[1]	Intervention	NMB[1]	Intervention	NMB[1]	Intervention	NMB[1]
group CT/CBT & AD	£128,778	group CT/CBT & AD	£127,120	AD	£130,629	AD	£112,538
AD	£128,748	AD	£126,960	group CT/CBT & AD	£130,485	GP care & AD tapering	£112,409
MBCT & AD tapering	£128,632	MBCT & AD	£126,928	MBCT & AD tapering	£130,470	MBCT & AD tapering	£112,363
MBCT & AD	£128,582	MBCT & AD tapering	£126,872	GP care & AD tapering	£130,290	group CT/CBT & AD	£112,327
individual CT/CBT & AD	£128,212	individual CT/CBT & AD	£126,596	MBCT & AD	£130,286	MBCT & AD	£112,125
GP care & AD tapering	£127,877	individual CT/CBT & AD tapering	£125,991	individual CT/CBT & AD	£129,870	individual CT/CBT & AD	£111,691
individual CT/CBT & AD tapering	£127,836	GP care & AD tapering	£125,716	individual CT/CBT & AD tapering	£129,671	individual CT/CBT & AD tapering	£111,609
Increase in the risk of side effects of antidepressants (40%)		**4 individual CT/CBT sessions**		**Group delivery: 1 therapist / 12 participants**		**4 individual CT/CBT sessions & Group delivery: 1 therapist / 12 participants**	
Intervention	NMB[1]	Intervention	NMB[1]	Intervention	NMB[1]	Intervention	NMB[1]
MBCT & AD tapering	£128,632	individual CT/CBT & AD	£128,857	group CT/CBT & AD	£129,024	group CT/CBT & AD	£129,024
GP care & AD tapering	£127,877	group CT/CBT & AD	£128,778	MBCT & AD tapering	£129,004	MBCT & AD tapering	£129,004
individual CT/CBT & AD tapering	£127,836	AD	£128,748	MBCT & AD	£128,957	MBCT & AD	£128,957
group CT/CBT & AD	£127,523	MBCT & AD tapering	£128,632	AD	£128,748	individual CT/CBT & AD	£128,857
AD	£127,517	MBCT & AD	£128,582	individual CT/CBT & AD	£128,212	AD	£128,748
MBCT & AD	£127,326	individual CT/CBT & AD tapering	£128,472	GP care & AD tapering	£127,877	individual CT/CBT & AD tapering	£128,472
individual CT/CBT & AD	£126,950	GP care & AD tapering	£127,877	individual CT/CBT & AD tapering	£127,836	GP care & AD tapering	£127,877

4 individual CT/CBT sessions & Group delivery: 1 therapist / 12 participants & 1-year effect		Reduction in the cost of relapse by 50%		Increase in the cost of relapse by 50%	
Intervention	NMB[1]	Intervention	NMB[1]	Intervention	NMB[1]
group CT/CBT & AD	£128,882	AD	£129,196	group CT/CBT & AD	£128,371
MBCT & AD	£128,813	group CT/CBT & AD	£129,185	AD	£128,300
AD	£128,748	MBCT & AD tapering	£129,070	MBCT & AD tapering	£128,193
individual CT/CBT & AD	£128,674	MBCT & AD	£128,988	MBCT & AD	£128,175
MBCT & AD tapering	£128,518	individual CT/CBT & AD	£128,607	individual CT/CBT & AD	£127,816
individual CT/CBT & AD tapering	£127,988	GP care & AD tapering	£128,450	individual CT/CBT & AD tapering	£127,398
GP care & AD tapering	£127,877	individual CT/CBT & AD tapering	£128,273	GP care & AD tapering	£127,305

In each scenario, interventions ordered from most to least cost-effective.
[1] per person
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit

Secondary analysis

Results of the secondary analysis, which considered a wider range of interventions, are provided in Table 119. The most cost-effective maintenance treatment option appeared to be cCBT with support combined with antidepressants, which, however, had been tested only in 42 people in the respective NMA that informed the economic analysis (hence mean ranking and probability of cost-effectiveness were not estimated for this option). Individual psychoeducation combined with antidepressants was the second most cost-effective intervention followed by cCBT without or with minimal support combined with antidepressants. Antidepressant maintenance treatment was the fourth most cost-effective intervention followed by other psychological interventions combined with either antidepressants or antidepressant tapering. The least cost-effective intervention was GP care and antidepressant tapering. The mean rankings (and their wide confidence intervals) suggest uncertainty around the results. Results of deterministic analysis were very similar.

Table 119: Results of base-case secondary economic analysis: interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment – secondary analysis (mean values from probabilistic analysis)

Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
cCBT with support & AD	6.765	£5,632	£129,663	Not estimated (N=44)	
individual psychoeducation & AD	6.733	£5,689	£128,971	0.51	2.69 (1 to 8)
cCBT without support & AD	6.726	£5,638	£128,892	0.22	2.96 (1 to 7)
AD	6.721	£5,575	£128,842	0.05	3.32 (1 to 6)
Group CT/CBT & AD	6.736	£5,929	£128,793	0.11	3.9 (1 to 8)
MBCT & AD tapering	6.734	£5,941	£128,732	0.08	4.43 (1 to 8)
MBCT & AD	6.740	£6,125	£128,681	0.01	5.2 (2 to 8)
individual CT/CBT & AD	6.745	£6,468	£128,434	0.01	6.64 (2 to 9)
individual CT/CBT & AD tapering	6.728	£6,301	£128,260	0.02	7.3 (2 to 9)
GP care & AD tapering	6.671	£5,450	£127,960	0.00	8.56 (7 to 9)

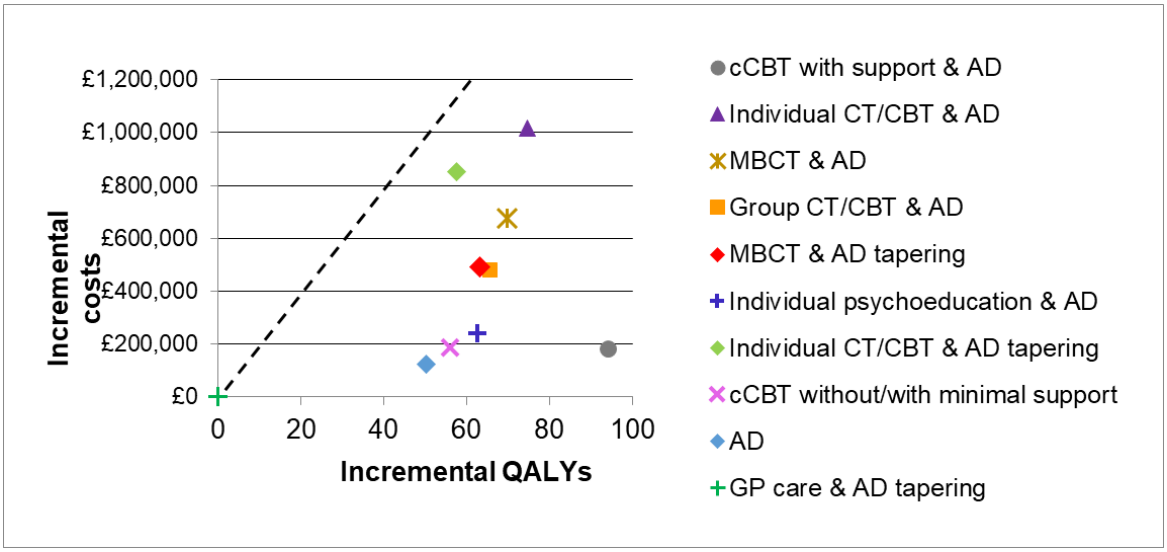
[1] *At the NICE lower cost-effectiveness threshold of £20,000/QALY*

AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; *Prob: probability*

The cost-effectiveness plane of the secondary analysis is shown in Figure 120. All interventions are cost-effective compared with GP care and antidepressant drug tapering for people at high risk of relapse whose depression has responded to acute pharmacological treatment, since all maintenance treatments lie on the right side of the dotted line.

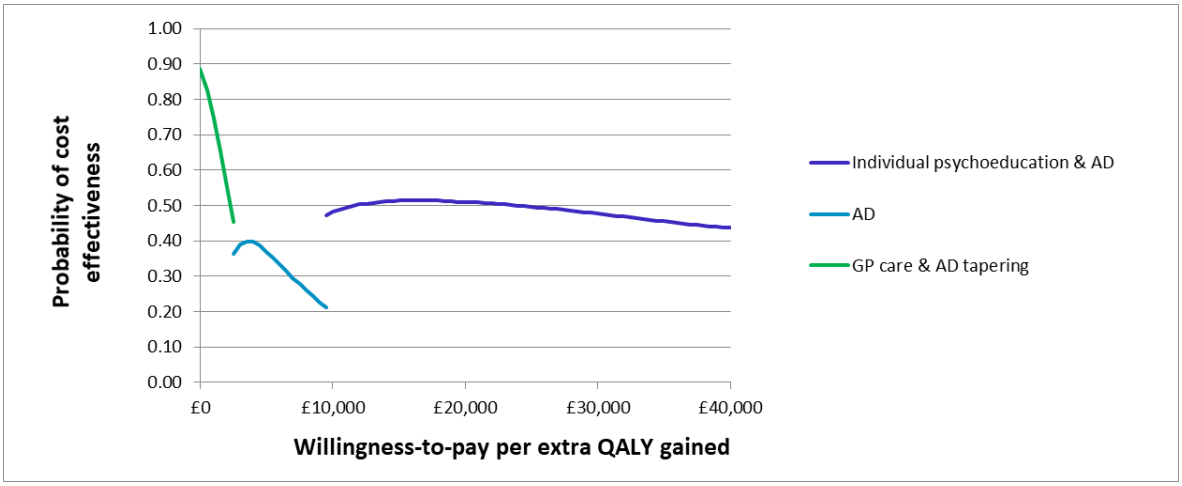
Figure 120 Cost effectiveness plane of maintenance interventions for people at high risk of relapse whose depression has responded to acute pharmacological

treatment – incremental costs and QALYs versus GP care and antidepressant drug tapering per 1,000 adults. Secondary analysis



The CEAF of the analysis is shown in Figure 121. At the NICE lower cost-effectiveness threshold (£20,000/QALY), individual psychoeducation is the most cost-effective treatment option, with a 0.51 probability of being cost-effective.

Figure 121 Cost-effectiveness acceptability frontier of interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment – secondary analysis



In deterministic sensitivity analysis, changing the cost of the relapse state by ±50% had practically no impact on the ranking of interventions. All other scenarios explored in sensitivity analysis had some impact on the results and conclusions of the analysis, as seen in Table 120. As with primary analysis, reducing the resource use associated with provision of individual CT/CBT and/or group psychological interventions had a very strong impact, as it resulted in psychological interventions becoming the most cost-effective maintenance treatment options. Increasing the risk of side effects of antidepressants resulted in treatment options that involved antidepressant drug tapering becoming the most cost-effective options. Assuming people experienced less severe depression if they relapsed, or assuming smaller utility gains from relapse prevention led to significant improvement of the relative cost effectiveness of less intensive interventions, such as maintenance antidepressant treatment and GP care combined with antidepressant tapering.

Table 120: Results of deterministic sensitivity analysis: interventions for people at high risk of relapse whose depression has responded to acute pharmacological treatment – secondary analysis

Base-case		Increase in number of previous episodes		Less severe depression		Alternative utility values	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
cCBT with support & AD	£129,560	cCBT with support & AD	£128,078	cCBT with support & AD	£131,038	cCBT with support & AD	£112,788
Individual psychoeducation & AD	£128,855	Individual psychoeducation & AD	£127,149	AD	£130,631	AD	£112,539
cCBT & AD	£128,800	cCBT & AD	£127,051	cCBT & AD	£130,628	cCBT & AD	£112,516
AD	£128,751	group CT/CBT & AD	£127,017	Individual psychoeducation & AD	£130,625	Individual psychoeducation & AD	£112,490
group CT/CBT & AD	£128,700	AD	£126,964	MBCT & AD tapering	£130,472	GP care & AD tapering	£112,409
MBCT & AD tapering	£128,634	MBCT & AD	£126,939	group CT/CBT & AD	£130,440	MBCT & AD tapering	£112,364
MBCT & AD	£128,590	MBCT & AD tapering	£126,875	MBCT & AD	£130,290	group CT/CBT & AD	£112,294
individual CT/CBT & AD	£128,213	individual CT/CBT & AD	£126,598	GP care & AD tapering	£130,290	MBCT & AD	£112,129
individual CT/CBT & AD tapering	£128,034	individual CT/CBT & AD tapering	£126,242	individual CT/CBT & AD tapering	£129,924	individual CT/CBT & AD tapering	£111,837
GP care & AD tapering	£127,877	GP care & AD tapering	£125,716	individual CT/CBT & AD	£129,871	individual CT/CBT & AD	£111,692
4 individual CT/CBT sessions		**Group delivery: 1 therapist / 12 participants**		**4 individual CT/CBT sessions & group delivery: 1 therapist / 12 participants**		**Increase in the risk of side effects of antidepressants (40%)**	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
cCBT with support & AD	£129,597	cCBT with support & AD	£129,560	cCBT with support & AD	£129,597	MBCT & AD tapering	£128,634
individual CT/CBT & AD	£128,858	MBCT & AD tapering	£129,007	MBCT & AD tapering	£129,007	cCBT with support & AD	£128,273
Individual psychoeducation & AD	£128,855	MBCT & AD	£128,965	MBCT & AD	£128,965	individual CT/CBT & AD tapering	£128,034
cCBT & AD	£128,800	group CT/CBT & AD	£128,945	group CT/CBT & AD	£128,945	GP care & AD tapering	£127,877
AD	£128,751	individual Psychoeducation & AD	£128,855	individual CT/CBT & AD	£128,858	Individual psychoeducation & AD	£127,608
group CT/CBT & AD	£128,700	cCBT & AD	£128,800	Individual psychoeducation & AD	£128,855	cCBT & AD	£127,562
individual CT/CBT & AD tapering	£128,670	AD	£128,751	cCBT & AD	£128,800	AD	£127,520
MBCT & AD tapering	£128,634	individual CT/CBT & AD	£128,213	AD	£128,751	group CT/CBT & AD	£127,449
MBCT & AD	£128,590	individual CT/CBT & AD tapering	£128,034	individual CT/CBT & AD tapering	£128,670	MBCT & AD	£127,334
GP care & AD tapering	£127,877	GP care & AD tapering	£127,877	GP care & AD tapering	£127,877	individual CT/CBT & AD	£126,951

In each scenario, interventions ordered from most to least cost-effective.
[1] per person
AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit

People at high risk of relapse whose depression has responded to acute psychological treatment

Primary analysis

The base-case results of the primary analysis are presented in Table 121. The most cost-effective maintenance treatment option for people at high risk of relapse whose depression had responded to acute psychological treatment was GP care. Individual CT/CBT was the most effective option but third most cost-effective one due to its high cost. Maintenance antidepressant treatment was the second most cost-effective option. The least cost-effective treatment option was no treatment. The particularly similar mean rankings of interventions and their wide confidence intervals suggest very high uncertainty in the results. The relative cost-effectiveness of interventions was the same in deterministic analysis.

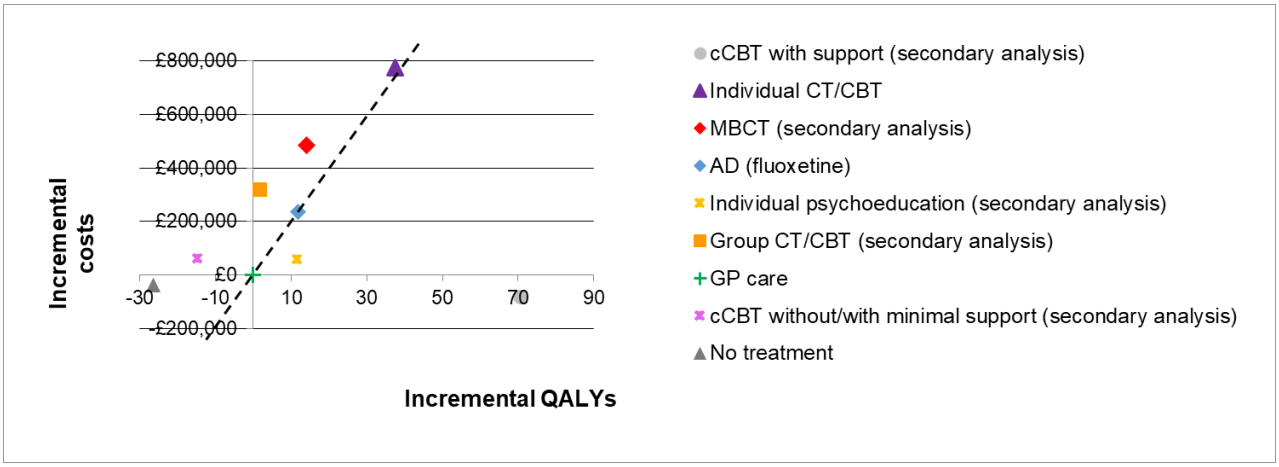
Table 121: Results of base-case primary economic analysis: interventions for people at high risk of relapse whose depression has responded to acute psychological treatment (mean values from probabilistic analysis)

Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
GP care	6.671	£5,355	£128,055	0.25	2.46 (1 to 4)
Antidepressant (fluoxetine)	6.682	£5,591	£128,054	0.28	2.35 (1 to 4)
Individual CT/CBT	6.708	£6,131	£128,031	0.20	2.39 (1 to 4)
No treatment	6.644	£5,317	£127,564	0.27	2.81 (1 to 4)

[1] *At the NICE lower cost-effectiveness threshold of £20,000/QALY*
CBT: cognitive behavioural therapy; CT: cognitive therapy; NMB: net monetary benefit; *Prob: probability*

Figure 122 shows the cost effectiveness plane of both the primary and secondary analysis. The slope of the dotted line (NICE lower cost effectiveness threshold) suggests that all options included in primary analysis are less cost-effective than GP care, although individual CT/CBT and maintenance antidepressant treatment are only marginally so.

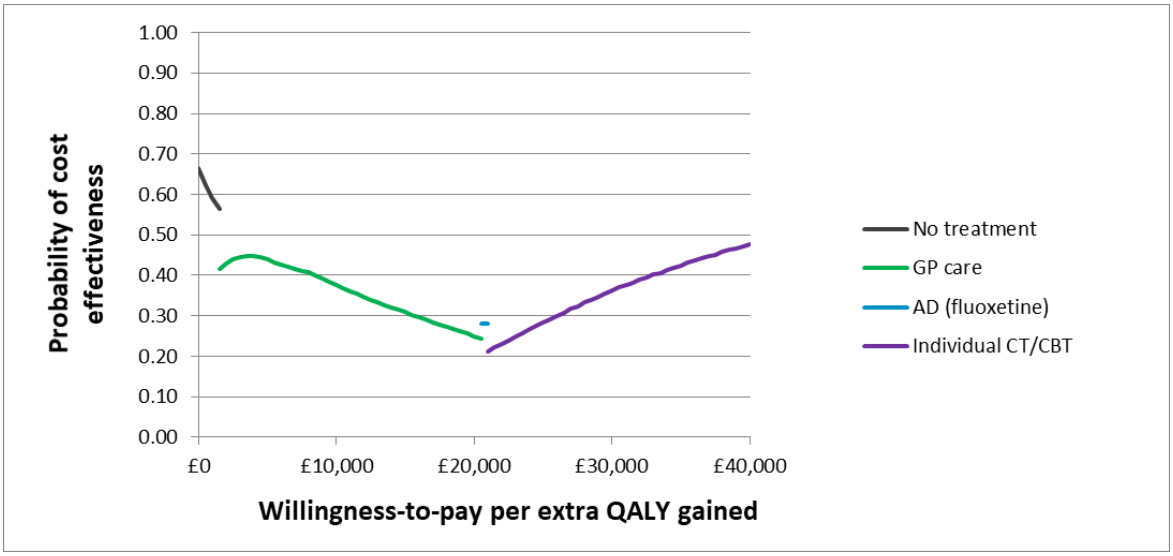
Figure 122 Cost effectiveness plane of maintenance interventions for people at high risk of relapse whose depression has responded to acute psychological treatment – incremental costs and QALYs versus GP care per 1,000 adults. Primary and secondary analysis



The CEAF of the analysis is shown in Figure 123. At the NICE lower cost-effectiveness threshold (£20,000/QALY), GP care is the most cost-effective option with a probability of 0.25. Maintenance antidepressant treatment becomes the most cost-effective option at a threshold of £20,500/QALY and a probability of 0.28, and individual CT/CBT becomes the

most cost-effective option at a threshold of £21,000/QALY and a probability of only 0.21. These findings suggest high uncertainty around the relative cost-effectiveness of maintenance treatment options in people at high risk of relapse whose depression has responded to acute psychological treatment.

Figure 123. Cost-effectiveness acceptability frontier of interventions for people at high risk of relapse whose depression has responded to acute psychological treatment – primary analysis



Deterministic sensitivity analysis revealed that findings were sensitive to all alternative scenarios tested, with the exception of a 50% reduction in the cost of relapse, which is not surprising given the underlying uncertainty characterising the results.

Results of the scenarios tested in deterministic sensitivity analysis are shown in Table 122.

Table 122: Results of deterministic sensitivity analysis: interventions for people at high risk of relapse whose depression has responded to acute psychological treatment – primary analysis

Base-case		5 previous episodes		Less severe depression	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
GP care	£127,993	AD (fluoxetine)	£125,926	GP care	£130,406
AD (fluoxetine)	£127,954	individual CT/CBT	£125,923	AD (fluoxetine)	£130,181
individual CT/CBT	£127,849	GP care	£125,830	No treatment	£130,122
No treatment	£127,424	No treatment	£125,084	individual CT/CBT	£129,926
Alternative utility values		**4 individual CT/CBT sessions**		**50% increase in cost of relapse**	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
GP care	£112,525	individual CT/CBT	£128,478	AD (fluoxetine)	£127,425
No treatment	£112,353	GP care	£127,993	GP care	£127,421
AD (fluoxetine)	£112,227	AD (fluoxetine)	£127,954	individual CT/CBT	£127,355
individual CT/CBT	£111,912	No treatment	£127,424	No treatment	£126,785

4 individual CT/CBT sessions & 1 year effect		Increase in risk of antidepressant side effects	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**
individual CT/CBT	£128,198	GP care	£127,993
GP care (pill placebo)	£127,993	individual CT/CBT	£127,849
AD (fluoxetine)	£127,954	No treatment	£127,424

No treatment high	£127,424	AD (fluoxetine)	£126,798

In each scenario, interventions ordered from most to least cost-effective.
[1] per person
AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; NMB: net monetary benefit

Secondary analysis including additional interventions

The base-case results of the secondary analysis are shown in Table 123. The most cost-effective maintenance treatment option appeared to be cCBT with support, which, however, had been tested only in 42 people in the respective NMA that informed the economic analysis (hence mean ranking and probability of cost-effectiveness were not estimated for this option). Individual psychoeducation was the second most cost-effective intervention followed by GP care. Antidepressant maintenance treatment was the fourth most cost-effective intervention followed by other psychological interventions. No treatment was the least cost-effective option. Mean rankings and wide confidence intervals suggested uncertainty around the results. Order of interventions from most to least cost-effective was the same in deterministic analysis.

Table 123: Results of base-case secondary economic analysis: interventions for people at high risk of relapse whose depression has responded to acute psychological treatment (mean values from probabilistic analysis)

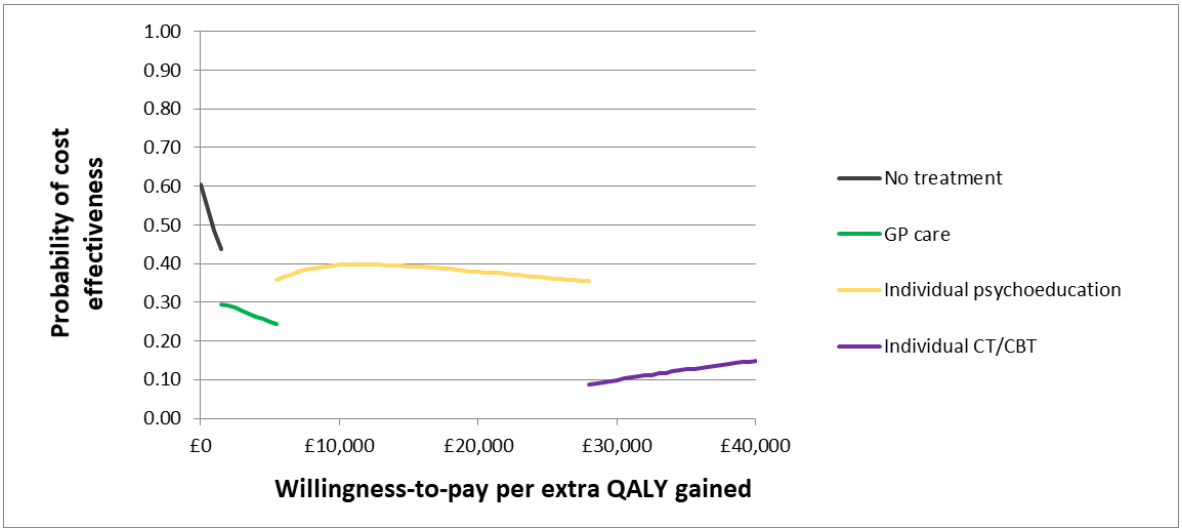
Maintenance treatment option	Mean /person			Prob best[1]	Mean ranking
	QALY	Cost	NMB		
cCBT with support	6.741	£5,271	£129,557	Not estimated	
Individual psychoeducation	6.682	£5,412	£128,230	0.38	3.34 (1 to 8)
GP care	6.671	£5,355	£128,055	0.13	4.56 (1 to 8)
Antidepressant (fluoxetine)	6.682	£5,591	£128,054	0.13	4.39 (1 to 8)
Individual CT/CBT	6.708	£6,131	£128,031	0.05	4.47 (1 to 8)
MBCT	6.685	£5,842	£127,854	0.04	4.49 (1 to 8)
group CT/CBT	6.672	£5,674	£127,775	0.12	4.55 (1 to 8)
cCBT without support	6.656	£5,418	£127,697	0.11	4.75 (1 to 8)
No treatment	6.644	£5,317	£127,564	0.04	5.45 (1 to 8)

[1] At the NICE lower cost-effectiveness threshold of £20,000/QALY
CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; Prob: probability

The cost-effectiveness plane in Figure 122 shows the additional interventions considered in secondary analysis. Of these, only cCBT with support and individual psychoeducation are cost-effective compared with GP care and are thus placed on the right side of the dotted line (NICE lower cost-effectiveness threshold).

The CEAF of the secondary analysis is shown in Figure 124. Individual psychoeducation is the most cost-effective intervention at the NICE lower cost-effectiveness threshold with a probability of 0.38.

Figure 124. Cost-effectiveness acceptability frontier of interventions for people at high risk of relapse whose depression has responded to acute psychological treatment – secondary analysis



Results were moderately or strongly affected by alternative scenarios tested in deterministic sensitivity analysis, as shown in

Table **124**. The only scenario with no impact on the base-case results was the 50% reduction in the cost of relapse.

Table 124: Results of deterministic sensitivity analysis: interventions for people at high risk of relapse whose depression has responded to acute psychological treatment – secondary analysis

Base-case		5 previous episodes		Less severe depression		Alternative utility values	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
cCBT with support	£129,460	cCBT with support	£127,732	cCBT with support	£131,246	cCBT with support	£113,118
Individual psychoeducation	£128,105	Individual psychoeducation	£125,994	Individual psychoeducation	£130,438	Individual psychoeducation	£112,525
GP care	£127,993	AD (fluoxetine)	£125,926	GP care	£130,406	GP care	£112,525
AD (fluoxetine)	£127,954	individual CT/CBT	£125,923	AD (fluoxetine)	£130,181	No treatment	£112,353
individual CT/CBT	£127,849	GP care	£125,830	cCBT without support	£130,133	cCBT without support	£112,323
MBCT	£127,745	MBCT	£125,656	No treatment	£130,122	AD (fluoxerine)	£112,227
group CT/CBT	£127,627	group CT/CBT	£125,453	group CT/CBT	£130,065	group CT/CBT	£112,194
cCBT without support	£127,539	cCBT without support	£125,264	MBCT	£130,055	MBCT	£112,133
No treatment	£127,424	No treatment	£125,084	individual CT/CBT	£129,926	individual CT/CBT	£111,912
4 individual CT/CBT sessions		**Group delivery: 1 therapist / 12 participants**		**4 individual CT/CBT sessions & group delivery: 1 therapist / 12 participants**		**4 individual CT/CBT sessions & group delivery: 1 therapist / 12 participants & 1-year effect**	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**	**Intervention**	**NMB[1]**
cCBT with support	£129,496	cCBT with support	£129,460	cCBT with support	£129,496	cCBT with support	£128,963
individual CT/CBT	£128,478	MBCT	£128,107	individual CT/CBT	£128,478	individual CT/CBT	£128,198
Individual psychoeducation	£128,105	Individual psychoeducation	£128,105	MBCT	£128,107	Individual psychoeducation	£128,040
GP care	£127,993	GP care	£127,993	Individual psychoeducation	£128,105	MBCT	£128,022
AD (fluoxetine)	£127,954	AD (fluoxetine)	£127,954	GP care	£127,993	GP care	£127,993
MBCT	£127,745	group CT/CBT	£127,862	AD (fluoxetine)	£127,954	AD (fluoxetine)	£127,954
group CT/CBT	£127,627	individual CT/CBT	£127,849	group CT/CBT	£127,862	group CT/CBT	£127,883
cCBT without support	£127,539	cCBT without support	£127,539	cCBT without support	£127,539	cCBT without support	£127,685
No treatment	£127,424	No treatment	£127,424	No treatment	£127,424	No treatment	£127,424

Increase in cost of relapse by 50%		Increase in the risk of antidepressant side effects	
Intervention	**NMB[1]**	**Intervention**	**NMB[1]**
cCBT with support	£129,034	cCBT with support	£129,460
Individual psychoeducation	£127,551	Individual psychoeducation	£128,105
AD (fluoxetine)	£127,425	GP care	£127,993
GP care	£127,421	individual CT/CBT	£127,849

individual CT/CBT	£127,355	MBCT	£127,745
MBCT	£127,196	group CT/CBT	£127,627
group CT/CBT	£127,049	cCBT without support	£127,539
cCBT without support	£126,924	No treatment	£127,424
No treatment	£126,785	AD (fluoxetine)	£126,798

In each scenario, interventions ordered from most to least cost-effective.
[1] per person
AD: antidepressant; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit

Discussion – conclusions, strengths and limitations of economic analysis

The guideline economic analysis assessed the cost effectiveness of a range of pharmacological and psychological interventions for the maintenance treatment of adults whose depression has responded to acute treatment predominantly in primary care. The analysis considered appropriate interventions for adults with depression according to the acute treatment their most recent depressive episode responded to, and also according to their risk for future relapses, as determined by their number of previous depressive episodes. Conclusions from the guideline economic analysis may be relevant to people in secondary care, especially given that clinical evidence was derived mainly from studies conducted in secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

In people at medium risk of relapse whose depression has responded to pharmacological treatment (SSRIs, SNRIs or TCAs), maintenance pharmacological treatment appears to be cost-effective compared with GP care plus antidepressant drug tapering, with a probability of cost-effectiveness ranging from 0.65 for SNRIs to 0.88 for SSRIs and TCAs at the NICE lower cost-effectiveness threshold of £20,000/QALY. However, it is possible that the effect of maintenance antidepressant treatment has been overestimated in the literature due to the development of withdrawal syndrome. Using a lower treatment effect of antidepressant drugs versus pill placebo, obtained from people who were not already receiving antidepressants for the treatment of their depressive episode (and thus development of withdrawal syndrome was not relevant), results in GP care plus antidepressant drug tapering becoming more cost-effective than continuation of antidepressants as maintenance treatment option. Moreover, using a higher risk of side effects results in GP care and antidepressant drug tapering becoming more cost-effective than maintenance antidepressant drug treatment.

In people at medium risk of relapse whose depression has responded to psychological treatment, GP care appears to be the most cost-effective intervention (with a probability of 0.47 at the NICE lower cost-effectiveness threshold of £20,000/QALY), followed by no treatment. Maintenance psychological treatment (individual CT/CBT) consisting of 10 individual hourly sessions appears to be the least cost-effective option among those assessed in this analysis. However, if the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions so that its intervention cost is greatly reduced, then individual CT/CBT appears to become the most cost-effective maintenance treatment option among those assessed in this population, provided that its relapse preventive effect lasts two years. If its effect lasts one year, it becomes the second most cost-effective intervention after GP care. Results are driven by the uncertainty characterising the clinical efficacy model input parameters, the relatively high intervention cost of individual CT/CBT and the relatively low risk of relapse characterising the study population.

In people at high risk of relapse whose depression has responded to pharmacological treatment, antidepressant treatment appears to be the most cost-effective maintenance treatment option with a rather low probability of 0.39 at the NICE lower cost-effectiveness threshold of £20,000/QALY, although there is some evidence from a secondary analysis of somewhat lower applicability that low intensity psychological interventions (cCBT with support [based on limited evidence] or cCBT without support and individual psychoeducation) combined with maintenance antidepressant treatment may be more cost-effective than maintenance antidepressant treatment alone. Other high intensity interventions, such as individual CT/CBT, group CT/CBT and MBCT, either alone (following antidepressant drug tapering) or combined with maintenance antidepressant treatment appear to be more cost-effective than GP care and antidepressant drug tapering, but less cost-effective than maintenance antidepressant treatment alone, due to their high intervention costs. However, if the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions (instead of 10 assumed in base-case analysis) so that its intervention cost is greatly reduced, then individual CT/CBT combined with maintenance antidepressant

treatment becomes the most cost-effective maintenance treatment option for this population, among treatment options with adequate clinical evidence (i.e. N≥50 across RCTs included in the NMA informing the economic analysis). If group interventions can be delivered with lower resources (i.e. with 1 therapist and 12 participants per group instead of 2 therapists and 8 participants per group assumed in base-case analysis) so their intervention cost is reduced, then group CT/CBT combined with antidepressant drug treatment is the most cost-effective option. MBCT combined with antidepressant treatment or antidepressant drug tapering become also more cost-effective than maintenance antidepressant treatment alone. When lower resource intensity is assumed for both individual and group interventions, then MBCT with antidepressant drug tapering appears to be the most cost-effective treatment option in this population, among treatment options with adequate clinical evidence. However, when this scenario is combined with the assumption that the psychological treatment effect lasts one year only, then both group CT/CBT and MBCT combined with maintenance antidepressant treatment become the most cost-effective options, because of the retained antidepressant treatment effect over 2 years. Results are driven by the high effectiveness of psychological interventions but also by their high intervention cost, especially of individual CT/CBT. Using a higher risk of side effects results in treatment options that involve antidepressant drug tapering becoming more cost-effective than options that include maintenance antidepressant drug treatment.

In people at high risk of relapse whose depression has responded to psychological treatment, GP care appears to be the most cost-effective option but with a probability of only 0.25 at the NICE lower cost-effectiveness threshold of £20,000/QALY. Maintenance antidepressant treatment is the most cost-effective option at a slightly higher threshold of £20,500/QALY and a probability of 0.28, and individual CT/CBT becomes the most cost-effective option at a threshold of £21,000/QALY and a probability of 0.21. These findings suggest particularly high uncertainty in the results. According to a secondary analysis of somewhat lower applicability, cCBT with support (based on limited evidence) and individual psychoeducation appear to be more cost-effective than GP care, and other psychological interventions (individual CT/CBT, MBCT, group CT/CBT, cCBT without support) appear to be less cost-effective than GP care and antidepressant treatment but more cost-effective than no treatment. If the preventive effect of individual CT/CBT can be achieved with 4 hourly sessions, then individual CT/CBT becomes the most cost-effective option among treatment options with adequate clinical evidence (i.e. N≥50 across RCTs included in the NMA informing the economic analysis), even if its relapse preventive effect lasts only one year. If group interventions can be delivered with lower resources (i.e. with 1 therapist and 12 participants per group instead of 2 therapists and 8 participants per group assumed in base-case analysis) so their intervention cost is reduced, then MBCT becomes the most cost-effective treatment option among those with adequate clinical evidence. When lower resource intensity is assumed for both individual and group interventions, then individual CT/CBT becomes the most cost-effective treatment option among those with adequate clinical evidence, even if its effect is expected to last 1 year. Results are driven by the uncertainty characterising the clinical efficacy model input parameters and the relatively high cost of individual and group psychological interventions.

In general, assuming lower severity of depression in case of relapse, lower utility gains from relapse prevention, lower risks of relapse (as reflected in lower number of previous episodes) and lower costs of relapse favours less costly interventions such as GP care and antidepressant treatment. Assuming higher severity of depression in case of relapse, higher risks of relapse (as reflected in higher number of previous episodes) and higher costs of relapse favours more effective but also costlier interventions such as individual or group psychological interventions alone or combined with maintenance antidepressant treatment. Assuming lower resource intensity in the delivery of individual and group psychological interventions, provided that their relapse preventive effect was retained, greatly improves their cost-effectiveness. Lower intensity psychological interventions such as cCBT with or without support and individual psychoeducation, alone or combined with maintenance antidepressant treatment, as relevant, are not considerably affected by alternative scenarios,

as they combine low costs with high effectiveness, although the latter is based on more limited and somewhat less applicable evidence.

The economic analysis enabled estimation of the cost effectiveness of appropriate interventions for adults at medium risk of relapse (1-2 previous depressive episodes) to less severe depression and those at high risk of relapse (3+ previous depressive episodes) to more severe depression and allowed exploration of changes in the relative cost effectiveness of interventions with increasing number of previous depressive episodes, thus with increasing risk of relapse. The analysis also allowed consideration of cost effectiveness of interventions depending on the type of acute treatment (i.e. pharmacological or psychological) people had received and responded to when they experienced their most recent depressive episode.

Most available efficacy data were not specific to the risk of relapse of the study population, as determined by the number of previous depressive episodes. However, most studies reported some indicator of the number of previous episodes experienced by the study participants, such as mean or median number of previous episodes or the minimum number of previous episodes required as an inclusion criterion. This allowed categorisation of the study participants in each study as being at low, moderate or high risk of relapse. Some interventions considered in the guideline systematic review were tested exclusively on high risk populations, so the respective evidence was utilised only in populations at high risk of relapse in the economic analysis. Also, available evidence did not focus on the severity of depression; therefore distinguishing future episodes of depression into less and more severe in the economic model was exclusively determined by the utility value attached to future depressive episodes (all of which, in each cohort examined, had to be either less severe or more severe).

The analysis utilised clinical effectiveness parameters derived from NMAs conducted separately for each population of interest. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Caldwell 2005; Lu 2004). However, due to limited relevant data from primary care settings, efficacy data were mostly derived from RCTs conducted in secondary care and thus may not be directly relevant to the study population. Furthermore, the quality and limitations of RCTs considered in the NMAs have unavoidably impacted on the quality of the economic model clinical input parameters. For example, economic results may be have been affected by reporting and publication bias.

A number of RCTs included in the guideline systematic review compared psychological interventions versus TAU, and were thus not possible to include in the main networks constructed for each population. Nevertheless, after identifying what constituted TAU in each cohort, these studies were possible to include in NMA and economic secondary analyses and to consider as additional treatment options for relevant populations.

The pairwise meta-analysis and NMAs conducted to inform the economic analysis estimated hazard ratios for each intervention versus the baseline comparator (pill placebo), which was the most appropriate output given the underlying Weibull distribution characterising the risk of relapse. These hazard ratios were subsequently applied onto the baseline risk of relapse over the first 2 years of the analysis, in order to calculate the specific risk of relapse associated with each intervention and each population assessed in the economic analysis.

The relapse preventive effect of all interventions assessed in the model (pharmacological, psychological and combined) was assumed to last over 2 years from initiation of maintenance treatment in the base-case analysis. However, evidence on the longer-term effects of maintenance psychological interventions is limited and suggests that the effect of psychological interventions may actually diminish over time. Nevertheless, a scenario under which the effect of psychological interventions lasted only over the first year form initiation of maintenance therapy was tested in sensitivity analysis.

The baseline risk of relapse and the probability of recovery over time were estimated based on a review of naturalistic studies. Available data suggested that both parameters were characterised by a Weibull distribution, in which the event rates are proportional to a power of time. The economic analysis incorporated Weibull distribution characteristics for both input parameters, derived from available evidence, thus enabling a better representation of the course of depression over time. The increase in the risk of future relapses imposed by each additional depressive episode experienced by people with depression was also factored in the economic analysis by the means of a hazard ratio of relapse with every additional depressive episode.

The time horizon of the analysis was 10 years, which was considered by the committee adequate to capture longer-term benefits and costs (including cost-savings) associated with the preventive effect of interventions assessed.

Utility data used in the economic model were derived from a systematic review of studies reporting utility data for depression-related health states that were generated using the EQ-5D and the UK population tariff, as recommended by NICE.

NHS and PSS costs incurred by adults with depression that is in remission or in a depressive episode were derived from a large (N=88,935) naturalistic study that aimed to estimate health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database (Byford 2011). The study utilised data collected between 2001 and 2006 and, although not recent, was considered the best source of cost information for the study population as it provided detailed data of healthcare resource use relating to the primary care treatment of adults with depression in the UK. Resource estimates and unit costs were updated with 2020 cost data and supplemented with further evidence according to the committee's expert advice, where appropriate, to reflect current routine practice in the UK NHS.

Maintenance treatment early discontinuation has not been explicitly considered in the model structure. However, the clinical efficacy data utilised in the analysis have implicitly accounted for discontinuation, as an intension-to-treat approach was adopted in the guideline data extraction. Moreover, the probabilistic model did assume that a percentage of people in the cohort might have not completed treatment or they might have had less than perfect compliance, so a less than full intervention cost has been assumed for these people.

The impact of common side effects from maintenance antidepressant treatment alone or in combination on HRQoL and costs associated with their management was incorporated in the economic analysis. The analysis utilised data from a large large US managed care claims database. The committee acknowledged that surveys of self-reported side effects in people receiving antidepressant medication report much higher prevalence of side effects, however, evidence suggests that only a proportion of those impact on HRQoL and management costs. The committee pointed out that the focus of the economic analysis was the prevalence of side effects with a measurable impact on HRQoL and healthcare resource use and this was more likely to be reflected in side effects recorded through patient claims. Nevertheless, a sensitivity analysis was conducted, which tested a higher prevalence of side effects from antidepressant treatment, to explore its impact on cost-effectiveness results. No side effects were considered for people receiving non-pharmacological interventions; however, people receiving non-pharmacological treatments for depression are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Therefore, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness. On the other hand, other less common side effects associated with treatment with antidepressants (such as upper gastrointestinal bleeds and falls) were not considered in the economic model. Such side effects result in considerable reduction in HRQoL and high costs for their management; nevertheless, they are relatively rare and therefore their omission is unlikely to have significantly impacted on the model results, although it is acknowledged as a limitation

that has potentially overestimated the cost effectiveness of antidepressants alone or combined with a psychological intervention relative to other maintenance treatments.

Overall conclusions from the guideline economic analysis

In people at medium risk of relapse whose depression has responded to pharmacological treatment (SSRIs, SNRIs or TCAs), maintenance pharmacological treatment appears to be cost-effective compared with GP care plus antidepressant drug tapering. However, after removing potential exaggeration of maintenance antidepressant treatment effects associated with the devlepoment of withdrawal syndrome, GP care plus antidepressant drug tapering appears to be more cost-effective than maintenance antidepressant treatment.

In people at medium risk of relapse whose depression has responded to psychological treatment, GP care appears to be the most cost-effective intervention, followed by no treatment. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions, then it appears to become the most cost-effective maintenance treatment option, provided that its relapse preventive effect is retained over two years.

In people at high risk of relapse whose depression has responded to pharmacological treatment, maintenance antidepressant treatment appears to be the most cost-effective maintenance treatment option, although somewhat less applicable evidence (to this population) suggests that low intensity psychological interventions (cCBT with support, based on more limited evidence, cCBT without support and individual psychoeducation) combined with maintenance antidepressant treatment may be more cost-effective than maintenance antidepressant treatment alone. GP care and antidepressant drug tapering appears to be the least cost-effective option. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (i.e. with 1 therapist and 12 participants per group), then their combinations with maintenance antidepressant treatment become more cost-effective than antidepressant treatment alone, while MBCT with antidepressant drug tapering becomes the second most cost-effective treatment option as long as its effect is retained over two years.

In people at high risk of relapse whose depression has responded to psychological treatment, GP care appears to be marginally more cost-effective than both maintenance antidepressant treatment and individual CT/CBT. Additional evidence, which is somewhat less applicable to this population, suggests that low intensity psychological interventions (cCBT with support, based on more limited evidence, and individual psychoeducation) may be more cost-effective than GP care and that other psychological interventions (MBCT, group CT/CBT, cCBT without support) are likely to be less cost-effective than GP care but more cost-effective than no treatment. If the preventive effect of individual CT/CBT can be achieved in 4 hourly sessions and if group psychological interventions (MBCT, group CT/CBT) can be delivered with lower resources (i.e. with 1 therapist and 12 participants per group), then they become more cost-effective than GP care, with individual CT/CBT becoming the most cost-effective option, even if its effect is expected to last 1 year.

In general, assuming lower severity of depression in case of relapse, lower utility gains from relapse prevention, lower risks of relapse (as reflected in lower number of previous episodes) and lower costs of relapse favours less costly interventions such as GP care and antidepressant treatment. Assuming higher severity of depression in case of relapse, higher risks of relapse (as reflected in higher number of previous episodes) and higher costs of relapse favours more effective but also costlier interventions such as individual or group psychological interventions alone or combined with maintenance antidepressant treatment. Assuming lower resource intensity in the delivery of individual and group psychological interventions, provided that their relapse preventive effect is retained, greatly improves their cost-effectiveness. Lower intensity psychological interventions such as cCBT with or without support and individual psychoeducation, alone or combined with maintenance antidepressant treatment, as relevant, are not considerably affected by alternative scenarios, as they

combine low costs with high effectiveness, although the latter is based on more limited and somewhat less applicable evidence. Assuming a higher risk of side effects from antidepressant treatment increases the cost-effectiveness of options that include antidepressant drug tapering relative to options that include antidepressants alone or combined with psychological interventions.

Conclusions from the guideline economic analysis refer mainly to people with depression who are predominantly managed in primary care; however, they may be relevant to people in secondary care as well, especially given that clinical evidence was derived almost exclusively from studies conducted in secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

References

Anderson HD, Pace WD, Libby AM, West DR, Valuck RJ (2012). Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. Clin Ther, 34(1), 113-123.

Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, Vollebergh W, Dragomirecka E, Kohn R, Keller M, Kessler RC, Kawakami N, Kiliç C, Offord D, Ustun TB, Wittchen HU (2003). The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res, 12(1), 3-21. Erratum in: Int J Methods Psychiatr Res (2003), 12(3), 165.

Bet PM, Hugtenburg JG, Penninx BW, Hoogendijk WJ (2013). Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol, 23(11), 1443-51.

Bockting CL, Spinhoven P, Koeter MW, Wouters LF, Schene AH, Depression Evaluation Longitudinal Therapy Assessment Study Group (2006). Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. J Clin Psychiatry, 67(5), 747-755.

Briggs A, Sculpher M, Claxton K (2006) Decision Modelling for Health Economic Evaluation. New York, NY: Oxford University Press

British Association for Behavioural & Cognitive Psychotherapies (2016). Criteria and Guidelines for re-accreditation as a Behavioural and/or Cognitive Psychotherapist. British Association for Behavioural & Cognitive Psychotherapies.

British National Formulary (June 2021). London: BMJ Group and the Royal Pharmaceutical Society of Great Britain. https://bnf.nice.org.uk [Accessed 7 June 2021]

Bukh JD, Andersen PK, Kessing LV (2016). Rates and predictors of remission, recurrence and conversion to bipolar disorder after the first lifetime episode of depression--a prospective 5-year follow-up study. Psychol Med, 46(6), 1151-1161.

Byford S, Barrett B, Despiégel N, Wade A (2011). Impact of treatment success on health service use and cost in depression. PharmacoEconomics, 29(2), 157-170.

Caldwell DM, Ades AE, Higgins JP (2005) Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331(7521), 897-900

Comijs HC, Nieuwesteeg J, Kok R, van Marwijk HW, van der Mast RC, Naarding P, Voshaar RC, Verhaak P, de Waal MW, Stek ML (2015). The two-year course of late-life depression; results from the Netherlands study of depression in older persons. BMC Psychiatry, 15, 20.

Coryell W, Endicott J, Keller MB (1991). Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry, 148(10), 1353-1358.

Cascade E, Kalali AH, Kennedy SH (2009). Real-World Data on SSRI Antidepressant Side Effects. Psychiatry (Edgmont), 6(2), 16-8.

Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J (2011). Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ, 343, d4551.

Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J (2018). Antidepressant use and risk of adverse outcomes in people aged 20-64 years: cohort study using a primary care database. BMC Med, 16(1), 36.

Curtis L, Burns A (2020) Unit Costs of Health & Social Care 2020. Canterbury: PSSRU, University of Kent.

Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW (2014). Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am J Psychiatry, 171(4), 453-62.

Daly C, Downing BC, Welton NJ (2021). A Practical Guide to Inconsistency Checks in Bayesian Network Meta-Analysis. Available from http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/mpes/nice/tsu-reports/ [accessed 28 May 2021]

Dias S, Welton NJ, Caldwell DM, Ades AE (2010). Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine, 29, 932–944.

Dias S, Welton NJ, Sutton AJ, Ades AE (2011a, last updated 2016). NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Available from http://nicedsu.org.uk/technical-support-documents/technical-support-documents/ [accessed 28 May 2021]

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE (2011b, last updated 2014). NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials. Available from http://nicedsu.org.uk/technical-support-documents/technical-support-documents/ [accessed 28 May 2021]

Eaton WW, Shao H, Nestadt G, Lee HB, Bienvenu OJ, Zandi P (2008). Population-based study of first onset and chronicity in major depressive disorder. Arch Gen Psychiatry, 65(5), 513-520.

Fenwick E, Claxton K, Sculpher M (2001) Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 10(8), 779-87.

Fernandez-Pujals AM, Adams MJ, Thomson P, McKechanie AG, Blackwood DH, Smith BH, Dominiczak AF, Morris AD, Matthews K, Campbell A, Linksted P, Haley CS, Deary IJ, Porteous DJ, MacIntyre DJ, McIntosh AM (2015). Epidemiology and Heritability of Major Depressive Disorder, Stratified by Age of Onset, Sex, and Illness Course in Generation Scotland: Scottish Family Health Study (GS:SFHS). PLoS One, 10(11), e0142197.

Gilbody S, Richards D, Barkham M (2007a). Diagnosing depression in primary care using self-completed instruments: UK validation of PHQ-9 and CORE-OM. Br J Gen Pract, 57(541), 650-652.

Gilbody S, Richards D, Brealey S, Hewitt C (2007b). Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med, 22(11), 1596-1602.

Gonzales LR, Lewinsohn PM, Clarke GN (1985). Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. J Consult Clin Psychol, 53(4), 461-469.

Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand, 122(3), 184-191.

Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman AT (2013). Recurrence of major depressive disorder and its predictors in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Psychol Med, 43(1), 39-48.

Holma KM, Holma IA, Melartin TK, Rytsala HJ, Isometsa ET (2008). Long-term outcome of major depressive disorder in psychiatric patients is variable. J Clin Psychiatry, 69(2), 196-205.

Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, Leth-Moller K, Iversen M, Banke MB, Petersen IJ, Klingenberg SL, Krogh J, Ebert SE, Timm A, Lindschou J, Gluud C (2017). Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. BMC Psychiatry, 17(1), 58.

Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, Parry G, Rooney G, Sutcliffe P (2006). Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. Health Technol Assess, 10(33).

Kanai T, Takeuchi H, Furukawa TA, Yoshimura R, Imaizumi T, Kitamura T, Takahashi K (2003). Time to recurrence after recovery from major depressive episodes and its predictors. Psychol Med, 33(5), 839-845.

Keller MB, Klerman GL, Lavori PW, Coryell W, Endicott J, Taylor J (1984). Long-term outcome of episodes of major depression. Clinical and public health significance. JAMA, 252(6), 788-792.

Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RM, Shea T (1992). Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry, 49(10), 809-816.

Keller MB, Shapiro RW (1981). Major depressive disorder. Initial results from a one-year prospective naturalistic follow-up study. J Nerv Ment Dis, 169(12), 761-768.

Kennedy N, Abbott R, Paykel ES (2003). Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. Psychol Med, 33(5), 827-838.

Kessing LV, Andersen PK (1999). The effect of episodes on recurrence in affective disorder: a case register study. J Affect Disord, 53(3), 225-231.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry, 62(6), 593-602.

Kiloh LG, Andrews G, Neilson M (1988). The long-term outcome of depressive illness. Br J Psychiatry, 153, 752-757.

Kind P, Hardman G, Macran S (1999). UK population norms for EQ-5D. Centre for Health Economics, University of York.

Koeser L, Donisi V, Goldberg DP, McCrone P (2015). Modelling the cost-effectiveness of pharmacotherapy compared with cognitive-behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK. Psychological Medicine, 45, 3019-3031.

Kolovos S, Bosmans JE, van Dongen JM, van Esveld B, Magai D, van Straten A, van der Feltz-Cornelis C, van Steenbergen-Weijenburg KM, Huijbregts KM, van Marwijk H, Riper H,

van Tulder MW (2017). Utility scores for different health states related to depression: individual participant data analysis. Qual Life Res, 26(7), 1649-1658.

Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD (2008). Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol, 76(6), 966-78.

Lee AS, Murray RM (1988). The long-term outcome of Maudsley depressives. Br J Psychiatry, 153, 741-751.

Lehmann HE, Fenton FR, Deutsch M, Feldman S, Engelsmann F (1988). An 11-year follow-up study of 110 depressed patients. Acta Psychiatr Scand, 78(1), 57-65.

Lu G, Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine 23(20), 3105-24.

Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000). WinBUGS-A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing 10, 325-337.

Magnil M, Janmarker L, Gunnarsson R, Björkelund C (2013). Course, risk factors, and prognostic factors in elderly primary care patients with mild depression: a two-year observational study. Scand J Prim Health Care, 31(1), 20-5.

Maj M, Veltro F, Pirozzi R, Lobrace S, Magliano L (1992). Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry, 149(6), 795-800.

Mann R, Gilbody S, Richards D (2009). Putting the 'Q' in depression QALYs: A comparison of utility measurement using EQ-5D and SF-6D health related quality of life measures. Social psychiatry and psychiatric epidemiology, 44(7), 569-578.

Mattisson C, Bogren M, Horstmann V, Munk-Jörgensen P, Nettelbladt P (2007). The long-term course of depressive disorders in the Lundby Study. Psychol Med, 37(6), 883-91.

Mavridis D, Giannatsi M, Cipriani A, Salanti G (2015). A primer on network meta-analysis with emphasis on mental health. Evidence Based Mental Health, 18, 40–46.

Maund E, Stuart B, Moore M, Dowrick C, Geraghty A, Dawson S, Kendrick T (2019). Managing antidepressant discontinuation: a systematic review. Annals of Family Medicine, 17(1), 52-60.

McManus S, Bebbington P, Jenkins R, Brugha T (eds) (2016). Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. Leeds: NHS Digital.

Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Sokero TP, Isometsa ET (2004). Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. J Clin Psychiatry, 65(6), 810-819.

Montgomery SA, Nielsen RZ, Poulsen LH, Häggström L (2014). A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum Psychopharmacol, 29(5), 470-82.

Mueller TI, Keller MB, Leon AC, Solomon DA, Shea MT, Coryell W, Endicott J (1996). Recovery after 5 years of unremitting major depressive disorder. Arch Gen Psychiatry, 53(9), 794-799.

Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry, 156(7), 1000-1006.

National Institute for Health and Care Excellence (2013) Guide to the Methods of Technology Appraisal 2013 (PMG 9). Available from: www.nice.org.uk/pmg9

National Institute for Health and Care Excellence (2014, last updated October 2020) Developing NICE guidelines: the manual (PMG 20). Available from: www.nice.org.uk/process/pmg20

Netten A, Knight J, Dennett J, Cooley R, Slight A (1998). Development of a ready reckoner for staff costs in the NHS, Vols 1 & 2. Canterbury: PSSRU, University of Kent.

NHS Business Services Authority (2020) Prescription Cost Analysis - England 2019. NHS Business Services Authority. Available from: https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-2019 [Accessed 20 January 2021]

NHS Business Services Authority, NHS Prescription Services (2021). NHS England and Wales. Electronic Drug Tariff. Issue: June 2021. Compiled on the behalf of the Department of Health and Social Care. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff [Accessed 11 June 2021]

NHS England and Health Education England (2016a). 2015 Adult IAPT workforce census report. NHS England and Health Education England.

NHS England and Health Education England (2016b). National College for Teaching and Leadership. Review of clinical and educational psychology training arrangements. NHS England and Health Education England.

NHS England (18 September 2016). More people than ever receiving psychological therapies and recovering. Available from: https://www.england.nhs.uk/2016/07/psychological-therapies/ [Accessed 3 February 2021]

NHS Improvement (2020). National Schedule of NHS costs - Year 2018-19 - NHS trusts and NHS foundation trusts. Available from: https://improvement.nhs.uk/resources/national-cost-collection/

Ntzoufras I (2009). Bayesian modeling using WinBUGS. Chapter 7: Introduction to Generalized Linear Models: Binomial and Poisson Data. Hoboken, NJ: Wiley.

Nuggerud-Galeas S, Sáez-Benito Suescun L, Berenguer Torrijo N, Sáez-Benito Suescun A, Aguilar-Latorre A, Magallón Botaya R, Oliván Blázquez B (2020). Analysis of depressive episodes, their recurrence and pharmacologic treatment in primary care patients: A retrospective descriptive study. PLoS One, 15(5).

Office for National Statistics (2020). National life tables – life expectancy in the UK: 2017 to 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2017to2019 [accessed 15 January 2021]

Ormel J, Oldehinkel T, Brilman E, vanden Brink, W. (1993). Outcome of depression and anxiety in primary care. A three-wave 3 1/2-year study of psychopathology and disability. Arch Gen Psychiatry, 50(10), 759-766

Richards A, Barkham M, Cahill J, Richards D, Williams C, Heywood P (2003). PHASE: a randomised, controlled trial of supervised self-help cognitive behavioural therapy in primary care. Br J Gen Pract, 53(495), 764-770.

Radhakrishnan M, Hammond G, Jones PB, Watson A, McMillan-Shields F, Lafortune L (2013). Cost of improving Access to Psychological Therapies (IAPT) programme: an analysis of cost of session, treatment and recovery in selected Primary Care Trusts in the East of England region. Behav Res Ther, 51(1), 37-45.

Richards DA, Lovell K, Gilbody S, Gask L, Torgerson D, Barkham M, Bland M, Bower P, Lankshear AJ, Simpson A, Fletcher J, Escott D, Hennessy S, Richardson R (2008). Collaborative care for depression in UK primary care: a randomized controlled trial. Psychol Med, 38(2), 279-87.

Riihimaki KA, Vuorilehto MS, Melartin TK, Isometsa ET (2014). Five-year outcome of major depressive disorder in primary health care. Psychol Med, 44(7), 1369-1379.

Sapin C, Fantino B, Nowicki ML, Kind P (2004). Usefulness of EQ-5D in assessing health status in primary care patients with major depressive disorder. Health and Quality of Life Outcomes, 2(20).

Skodol AE, Grilo CM, Keyes KM, Geier T, Grant BF, Hasin DS (2011). Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. Am J Psychiatry, 168(3), 257-264.

Sobocki P, Ekman M, Agren H, Krakau I, Runeson B, Martensson B, Jonsson B (2007). Health-related quality of life measured with EQ-5D in patients treated for depression in primary care. Value in Health, 10(2), 153-160.

Sobocki P, Ekman M, Agren H, Runeson B, Jonsson B (2006). The mission is remission: Health economic consequences of achieving full remission with antidepressant treatment for depression. International Journal of Clinical Practice, 60(7), 791-798.

Soini E, Hallinen T, Brignone M, Campbell R, Diamand F, Cure S, Aalto-Setälä M, Danchenko N, Koponen H, Kolasa K (2017). Cost-utility analysis of vortioxetine versus agomelatine, bupropion SR, sertraline and venlafaxine XR after treatment switch in major depressive disorder in Finland. Expert Rev Pharmacoecon Outcomes Res, 17(3), 293-302.

Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, Coryell W, Warshaw M, Turvey C, Maser JD, Endicott J (2000). Multiple recurrences of major depressive disorder. Am J Psychiatry, 157(2), 229-33.

Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A (2002). Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society B, 64, 583-616

Spiegelhalter D, Thomas A, Best N, Lunn DJ (2003). WinBUGS user manual: Version 1.4. Cambridge: MRC Biostatistics Unit.

Spijker J, de Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA (2002). Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry, 181, 208-213.

Stegenga BT, Kamphuis MH, King M, Nazareth I, Geerlings MI (2012). The natural course and outcome of major depressive disorder in primary care: the PREDICT-NL study. Soc Psychiatry Psychiatr Epidemiol, 47(1), 87-95.

Steinert C, Hofmann M, Kruse J, Leichsenring F (2014). Relapse rates after psychotherapy for depression - Stable long-term effects? A meta-analysis. J Affect Disord, 168, 107-118.

Sullivan PW, Valuck R, Saseen J, MacFall HM (2004). A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. CNS Drugs, 18, 911-932.

Uher R, Farmer A, Henigsberg N, Rietschel M, Mors O, Maier W, Kozel D, Hauser J, Souery D, Placentino A, Strohmaier J, Perroud N, Zobel A, Rajewska-Rager A, Dernovsek MZ, Larsen ER, Kalember P, Giovannini C, Barreto M, McGuffin P, Aitchison KJ (2009). Adverse reactions to antidepressants. Br J Psychiatry, 195(3), 202-10.

Van Leeuwen E, van Driel ML, Horowitz MA, Kendrick T, Donald M, De Sutter AI, Robertson L, Christiaens T (2021). Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database Systematic Reviews, 4(4).

van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG, (2000). Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. J Fam Pract, 49(12), 1113-20.

van Valkenhoef G, Dias S, Ades AE, Welton NJ (2016a). Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Research Synthesis Methods, 7, 80–93.

van Valkenhoef G, Kuiper J (2016b). gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. Available from: https://CRAN.R-project.org/package=gemtc [accessed 28 May 2021]

van Weel-Baumgarten E, van den Bosch W, van den Hoogen H, Zitman FG (1998). Ten year follow-up of depression after diagnosis in general practice. Br J Gen Pract, 48(435), 1643-6.

Yiend J, Paykel E, Merritt R, Lester K, Doll H, Burns T (2009). Long term outcome of primary care depression. J Affect Disord, 118(1-3), 79-86.

Appendix K – Excluded studies

Excluded studies for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Clinical studies

Please refer to the clinical evidence tables in supplement C – Clinical evidence tables for Evidence Review C Relapse prevention

Economic studies

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

Appendix L - Research recommendations

Research recommendations for review question: For adults whose depression has responded to treatment, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions for preventing relapse (including maintenance treatment)?

Research question

What is the effectiveness and cost-effectiveness of brief courses of psychological treatment in preventing relapse for people who have had a successful course of treatment with antidepressants or psychological therapies but remain at high risk for relapse?

Why this is important

The rate of relapse in depression may be up to 50% after a first episode, rising to 80% in people who have had three or more episodes of depression. However, despite evidence that a course of psychological therapy (such as CBT) to treat an acute episode of depression can have an acute prophylactic effect to prevent relapse, it is not known whether the addition of brief (4 to 6 sessions) individual or group psychological therapy (such as CBT) with a specific relapse prevention focus and including guided self-help, results in lower incidence of relapse following successful treatment with antidepressant or another psychological therapy.

Table 125: Research recommendation rationale

Research question	**What is the effectiveness and cost-effectiveness of brief courses of psychological treatment (CBT) in preventing relapse for people who have had a successful course of treatment with antidepressants or psychological therapies but remain at high risk for relapse?**
Why this is needed	
Importance to 'patients' or the population	Relapse is a frequent occurrence with implications for the wellbeing and quality of life for individuals with depression. Antidepressants can be effective in preventing relapse but not all people with depression can tolerate them or wish to take them long-term.
Relevance to NICE guidance	The guidelines currently make recommendations for the prevention of relapse but there is uncertainty whether, in adults in remission from depression following either antidepressant medication or psychological therapies, brief (e.g., 4 sessions) of individual or group psychological therapy with a relapse focus group results in lower incidence of depressive relapse.
Relevance to the NHS	Preventing relapse of depression would reduce costs to the NHS of treating further episodes of acute depression.
National priorities	The NHS Long Term plan makes access to effective mental health services a key national priority
Current evidence base	Course of psychological interventions (primarily CBT) (typically 10-16 sessions) have been shown to have relapse prevention effects when provided for the acute episode that last beyond the end of

Research question	What is the effectiveness and cost-effectiveness of brief courses of psychological treatment (CBT) in preventing relapse for people who have had a successful course of treatment with antidepressants or psychological therapies but remain at high risk for relapse?
	acute treatment. Similarly, in people at high risk of relapse whose depression has responded to psychological treatment, c. 10 sessions of maintenance individual CT/CBT was found to be effective at relapse prevention but not cost-effective relative to GP care in health economic analyses, whereas if still effective, shorter interventions (4 hourly sessions) would be cost-effective. Two group based psychological interventions (group CBT and MBCT) have been developed and shown to be effective in trials when compared to treatment as usual and antidepressant medication. However, the use of a relatively brief psychological intervention (4 sessions and including lower intensity interventions within IAPT) after successful recovery from antidepressants or other psychological interventions has not been tested. The committee's review of the evidence indicated that there was an absence of evidence for the use of relatively brief but potentially cost-effective psychological interventions post-recovery.
Equality	NA - No equality issues
Feasibility	Numbers of people treated for depression make this study feasible. It is likely that brief relapse prevention therapy could be provided within IAPT.
Other comments	NA

NA: not applicable

Table 126: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults whose depression has responded to treatment with either antidepressant treatment or psychological therapies, and who are at a higher risk of relapse (indicated by residual symptoms, repeated prior episodes of depression; elevated avoidance and rumination) who are randomised to a relapse prevention psychological intervention while in full or partial remission.
Intervention	A brief psychological intervention (c. 4 sessions) in individual or group format (e.g., CBT), including low-intensity IAPT interventions, focussed on relapse prevention.
Comparator	Treatment as usual; ongoing antidepressant medication
Outcomes	• Relapse • Quality of life • Adverse events • Discontinuation • Cost-effectiveness

Criterion	Explanation
Study design	Randomised controlled trial
Timeframe	Minimum follow-up 2 years
Additional information	The randomised controlled trial should be designed to identify both moderators and mediators of treatment effect, and to test for both equivalence and superiority, and ideally to compare tapering and maintenance of antidepressant medication, where relevant.

NA: not applicable

Research question

Is maintenance electronconvulsive therapy (ECT) effective and safe for relapse prevention in people with severe and recurring depression whose depression has remitted on ECT?

Why this is important

A small number of people do not benefit in any significant way from pharmacological or psychological interventions but do respond to ECT. However, many of these people relapse and need repeated treatment with ECT. This results in considerable suffering to them and it is also costly, because ECT often necessitates inpatient care. A small number of studies suggest possible benefits from maintenance ECT but it is used little in the NHS and further research is needed.

Table 127: Research recommendation rationale

Research question	Is maintenance ECT effective and safe for relapse prevention in people with severe and recurring depression whose depression has remitted on ECT?
Why this is needed	
Importance to 'patients' or the population	Relapse is a frequent occurrence with implications for the wellbeing and quality of life for individuals with depression. If ECT has been effective for the treatment of a person's depression,maintenance ECT may be a possible option to prevent relapse.
Relevance to NICE guidance	The guidelines currently make recommendations for the prevention of relapse but the separate recommendations on ECT currently suggest that ECT should be stopped when remission has been achieved and that antidepressants or psychological therapies should be started to prevent relapse.
Relevance to the NHS	Preventing relapse of depression would reduce costs to the NHS of treating further episodes of acute depression.
National priorities	The NHS Long Term plan makes access to effective mental health services a key national priority
Current evidence base	There is some limited evidence on the use of ECT for relapse prevention in older people but not in the wider population.
Equality	NA - No equality issues

Research question	Is maintenance ECT effective and safe for relapse prevention in people with severe and recurring depression whose depression has remitted on ECT?
Feasibility	Numbers of people treated for depression make this study feasible.
Other comments	NA

Table 128: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults whose depression has responded to treatment with ECT, and who are at a higher risk of relapse (indicated by residual symptoms, repeated prior episodes of depression; elevated avoidance and rumination).
Intervention	Maintenance ECT
Comparator	• Sham ECT • Antidepressant medication • Psychological therapies for relapse prevention
Outcomes	• Relapse • Quality of life • Adverse events, including impact on cognitive function • Discontinuation • Cost-effectiveness
Study design	Mirror image or non-randomised study
Timeframe	Minimum follow-up 2 years
Additional information	The characteristics of people who are likely to be considered for maintenance ECT makes a randomised controlled trial unfeasible.