National Institute for Health and Care Excellence

Draft for consultation

Depression in adults

[D] Further-line treatment

NICE guideline CG90 (update)

Evidence review underpinning recommendations 1.9.1 to 1.9.9 and 1.13.1 to 1.13.9, and research recommendations in the NICE guideline

November 2021

Draft for consultation

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

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

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

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Contents **4**
Further-line treatment **7**
Review question 7
Introduction 7
Summary of the protocol 8
Methods and processes 13
Clinical evidence 13
Summary of studies included in the evidence review 13
Quality assessment of studies included in the evidence review 97
Economic evidence 97
Summary of studies included in the economic evidence review 98
Economic model 104
Evidence statements 105
The committee's discussion of the evidence 176
Recommendations supported by this evidence review 182
References 183
Appendices **199**
Appendix A – Review protocol 199
Review protocol for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 199
Appendix B – Literature search strategies 208
Literature search strategies for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 208
Appendix C – Clinical evidence study selection 217
Study selection for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 217
Appendix D – Clinical evidence tables 218
Evidence tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 218
Appendix E – Forest plots 219

Forest plots for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 219

Appendix F – GRADE tables 357

GRADE tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 357

Appendix G – Economic evidence study selection 430

Economic evidence study selection for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 430

Appendix H – Economic evidence tables 431

Economic evidence tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 431

Appendix I – Economic evidence profiles 446

Economic evidence profiles for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 446

Appendix J – Economic analysis 452

Economic analysis for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 452

Appendix K – Excluded studies 453

Excluded studies for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 453

Appendix L – Research recommendations 454

Research recommendations for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode? 454

Further-line treatment

Review question

What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Introduction

This review was concerned with further-line treatment for those with depression, and included people with coexisting personality disorders, psychotic depression, and chronic depression. The committee recognised that these were overlapping populations in the context of further-line treatment, and agreed that a broader evidence base would more accurately reflect the complexities that may be associated with non-response to initial treatment.

Further-line treatments for depression may be required when people with depression have not responded to first-line treatments or are unable to tolerate them, and an alternative treatment is required, or in cases where people have not responded to multiple treatments.

Failure or intolerance of first-line treatment

First-line treatments for depression do not lead to remission in approximately two-thirds of people and therefore the choice of further-line treatment is a common clinical dilemma for patients and professionals. In addition, there will be people who cannot tolerate the original choice of first-line treatment, and these people will also require selection of an appropriate second-line option.

Further-line treatment strategies can include switching to a different medication or psychological therapy, switching from medication to a psychological therapy, or vice versa, using dose escalation, or using combinations of treatments. In addition, choice of second-line therapy may be informed by personal preference, although patient characteristics including previous history of treatment response, type of depressive syndrome and comorbidities can be helpful in guiding the choice.

For the people who remain depressed despite second-line treatment, the terms ‘treatment resistance’ or ‘treatment resistant depression’ (TRD) are often used.

Treatment resistant depression

Treatment resistant depression (TRD) is usually defined as a failure to respond to 2 adequate courses of antidepressants within a specified episode of depression. There does not appear to be a similarly accepted definition of failure to 2 adequate courses of psychological therapy.

Recent models of TRD (such as the Massachusetts General Hospital and the Maudsley Staging Method) consider the duration of depression, the severity of the illness and the number and types of treatments. A systematic review of all of these approaches identified that the Maudsley Staging Method had the best predictive utility in assessing resistance. However, all of these staging methods remain limited through their focus on assessing resistance to treatments within the current episode.

Recent clinical trials and functional neuroimaging studies have suggested that some types of psychotherapy may have an important place in overcoming treatment resistance, and further

clarifying this role, particularly at later stages of treatment failure, may help in developing fuller models of treatment resistance and likelihood of future remission.

Alongside efforts to more clearly delineate treatment resistance there has been greater acknowledgement of so-called 'pseudo-resistance', where lack of response relates to misdiagnosis (for example, of bipolar depression) or under-treatment (for example, through inadequate dosage or length of treatment), rather than true treatment resistance. Understanding this problem of 'pseudo-resistance' (and avoiding incorrectly labelling an individual as genuinely treatment resistant) should remain a significant concern in day-to-day clinical practice in order to improve treatment outcomes.

Genuine treatment resistance has been linked to a number of demographic and illness characteristics, including: living alone; lower income; unemployment; male gender; lower education; higher complexity through associated physical or psychiatric disorder; and a longer, more severe current episode.

Several approaches to overcoming treatment resistant depression have been evaluated, including pharmacology, physical interventions and psychological therapy. Pharmacological next-step options include switching within a class of antidepressants (for example, different SSRIs); switching between different classes of antidepressants (for example, from an SSRI to a SNRI); combining different antidepressants together (for example, SSRI plus mirtazapine); or augmenting an antidepressant with an agent that is not antidepressant in its own right (for example, lithium). Given the lack of convincing superiority of one agent over another at group level, part of the therapeutic advantage of switching between antidepressants may come through 'pharmacogenomics', indicating the genetic factors that may make people differentially liable to the beneficial or adverse effects of particular pharmacological agents.

Evidence indicates that people continue to achieve remission when further treatment steps are used but that even with this approach around one third of people will remain treatment resistant at one year. After a period of treatment resistance there is some evidence that remission is less stable, associated with higher subsequent relapse and shorter average time to relapse, indicating over the longer term that those people who find it difficult to get well may also then find it more difficult to stay well.

The aim of this review is to identify the most effective interventions for people who have had no or limited response to previous treatment(s) for the current episode of depression, have not tolerated previous treatment(s) for the current episode of depression, or who have treatment-resistant depression.

Summary of the protocol

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

1 **Table 1: Summary of the protocol (PICO table)**

Population	• Adults in a depressive episode whose depression has not responded or there has been limited response to previous treatment(s) (for the current episode) according to DSM, ICD or similar criteria, or (residual) depressive symptoms as indicated by depression scale score, or who have not tolerated previous treatment (for the current episode), or who are defined as meeting criteria for treatment-resistant depression, and who have been randomised to the further-line interventions at the point at which they had no/inadequate/limited response If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review.

Intervention	**Psychological interventions:** • Behavioural therapies • Cognitive and cognitive behavioural therapies • Counselling • Interpersonal psychotherapy • Psychodynamic psychotherapies • Psychoeducational interventions • Self-help with or without support • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) **Psychosocial interventions**: • Peer support • Mindfulness, meditation or relaxation **Pharmacological interventions:** SSRIs, including: • Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline TCAs, including: • Amineptine • Amitriptyline • Clomipramine • Desipramine • Imipramine • Lofepramine • Nortriptyline TeCAs • Mianserin SNRIs, including: • Duloxetine • Venlafaxine Other antidepressant drugs • Bupropion • Mirtazapine Anticonvulsants, including: • Lamotrigine

	Antipsychotics, including: • Amisulpride • Aripiprazole • Olanzapine • Quetiapine • Risperidone • Ziprasidone Anxiolytics • Buspirone Stimulants • Methylphenidate Other agents • Lithium • Omega-3 fatty acids • Thyroid hormones **Physical interventions:** • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD) Interventions will be categorised into the following strategies: • Dose escalation strategies • Switching strategies • Augmentation strategies
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcome	**Critical:** • Depression symptomatology • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects **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; PTSD: post-traumatic stress disorder; SAD: seasonal affective disorder; SNRIs: serotonin noradrenaline reuptake inhibitor SSRIs: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant

For further details see the review protocol in appendix A.

Methods and processes

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

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

Clinical evidence

Included studies

125 RCTs were included in this review (Appelberg 2001; Baert 2010_study 2; Barbee 2011; Bauer 2009; Bauer 2013; Bauer 2019; Baumann 1996; Berman 2007; Berman 2009; Bose 2012; Carpenter 2002; Chan 2012; Cheon 2017; Chiesa 2015; Corya 2006; Dai 2019; Danielsson 2014; Doree 2007; Dornseif 1989; Dozois 2009; Dunn 1979; Dunner 2007; Durgam 2016; Earley 2018; Eisendrath 2016; El-Khalili 2010; Embling 2002; Fang 2010; Fang 2011; Fava 1994a; Fava 2002; Fava 2012/Mischoulon 2012 [1 study reported across 2 papers]; Fava 2018; Fava 2019; Ferreri 2001; Folkerts 1997; Fonagy 2015; Girlanda 2014; GlaxoSmithKline 2009; Gulrez 2012; Haghighi 2013; Ho 2014; Hobart 2018a; Hobart 2018b; Jahangard 2018; Joffe 1993; Kamijima 2013; Kamijima 2018; Kato 2018; Keitner 2009; Kennedy 2003; Kessler 2018a/2018b; Kim 2019; Kocsis 2009/Klein 2011 [1 study reported across 2 papers]; Kornstein 2008; Lavretsky 2011; Lenox-Smith 2008; Lenze 2015; Li 2009; Li 2013; Li 2015; Licht 2002; Lynch 2007_study 2; Mahmoud 2007; Mantani 2017; Marcus 2008; Mather 2002; McIntyre 2007; Mohamed 2017; Moica 2018; Mota-Pereira 2011; Mowla 2011; Mozaffari-Khosravi 2013; Murray 2010; Nakagawa 2017; Nakajima 2011; Nakao 2018; Nan 2017; Navarro 2019a; Navarro 2019b; Nemets 2002; Nierenberg 2003a; Nierenberg 2006; Ostacoli 2018; Otsuka Pharmaceutical 2015; Otsuka Pharmaceutical 2016; Papakostas 2015; Patkar 2006; Paykel 1999/Scott 2000 [1 study reported across 2 papers]; Peet 2002; Poirier 1999; Ravindran 2008a; Reeves 2008; Reynolds 2010; Rocca 2002b; Ruhe 2009; Rush 2006; Salehi 2016; Santos 2008; Schindler 2007; Schlogelhofer 2014; Schramm 2007; Schweizer 1990; Schweizer 2001; Sharma 2017; Shelton 2005; Song 2007; Souery 2011a; Souza 2016; Stein 1993; Strauss 2012; Thase 2007; Thase 2015a; Thase 2015b; Town 2017/2020; Trivedi 2006; Uebelacker 2017; Wang 2012a; Watkins 2011a; Wiles 2008; Wiles 2013/2016; Xiao 2020; Yang 2016; Yoshimura 2014; Zhang 2016). There was evidence for 67 comparisons.

The included studies are summarised in Table 2 to Table 68.

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 68.

Table 2: Summary of included studies. Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Chan 2012 RCT China	N=50 Mean age (years): 46.2 Gender (% female): 76 Ethnicity (% BME): NR Baseline severity: HAMD 11.91 (less severe)	CBT group + any antidepressant Intensity: 10x 90-min sessions	Waitlist + any antidepressant	Inadequate response: participants met inclusion criteria despite all receiving antidepressants at baseline	Treatment length (weeks): 10 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due to any reason
Chiesa 2015 RCT Italy	N=50 Mean age (years): 49.0 Gender (% female): 72 Ethnicity (% BME): NR Baseline severity: HAMD 16.4 (more severe)	Mindfulness-based cognitive therapy (MBCT) group + any antidepressant Intensity: 8x 2-hour weekly sessions	Attention-placebo (psychoeducational control group) + any antidepressant Intensity: 8x 2-hour weekly sessions	Inadequate response (failure to achieve remission, HAMD score≥8) to treatment with antidepressants at adequate dosages for at least 8 weeks before study beginning	Treatment length (weeks): 8 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 2-month follow-up ○ 4-month follow-up • Depression symptomatology change score • Discontinuation due to any reason
Dozois 2009 RCT Canada	N=48 Mean age (years): 46.5 Gender (% female): 74 Ethnicity (% BME): 2	CBT individual + any antidepressant Intensity: 15x 1-hour sessions	Waitlist + any antidepressant	Inadequate response: participants met inclusion criteria despite all receiving antidepressants at baseline	Treatment length (weeks): 15 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: HAMD 19.72 (more severe)				• Discontinuation due to any reason
Dunn 1979 RCT Canada	N=24 Mean age (years): NR Gender (% female): 70 Ethnicity (% BME): NR Baseline severity: BDI 22.5 (more severe)	CBT individual + TCA Intensity: 16x twice-weekly sessions	Waitlist + TCA	Inadequate response to current TCA treatment	Treatment length (weeks): 8 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 6-month follow-up • Depression symptomatology change score
Eisendrath 2016 RCT US	N=173 Mean age (years): 46.2 Gender (% female): 76 Ethnicity (% BME): 20 Baseline severity: HAMD 17.9 (more severe)	Mindfulness-based cognitive therapy (MBCT) group + any antidepressant Intensity: 8x 2.25-hour weekly sessions	Attention-placebo (health enhancement programme) + any AD antidepressant Intensity: 8x 2.25-hour weekly sessions	TRD: Inadequate response to 2 or more adequate trials prescribed during the current episode assessed with the Antidepressant Treatment History Form (ATHF)	Treatment length (weeks): 8 Outcomes: • Remission • Response • Discontinuation due to any reason
Embling 2002 RCT UK	N=38 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: BDI-	CBT group + any antidepressant Intensity: 12x 60-90 min sessions	Waitlist + any antidepressant	Inadequate response: participants met inclusion criteria despite taking antidepressants for at least 1 month prior to study entry	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	II 31 (more severe)				
Kocsis 2009/Klein 2011 RCT US	N=296 Mean age (years): 44.6 Gender (% female): 54 Ethnicity (% BME): 11 Baseline severity: HAMD 19.15 (more severe)	Cognitive behavioral analysis system of psychotherapy (CBASP) + any antidepressant Intensity: 16-20 sessions	Any antidepressant	Inadequate response (≥60% reduction in HAMD score, a HAMD total score<8, and no longer meeting DSM-IV criteria for MDD for 2 consecutive visits during weeks 6-12) to 12 weeks of antidepressant medication according to a pharmacotherapy algorithm	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Remission • Discontinuation due ato any reason • Functional impairment endpoint
Lynch 2007_study 2 RCT US	N=35 Mean age (years): 61.4 Gender (% female): 46 Ethnicity (% BME): 14 Baseline severity: HAMD 16.53 (more severe)	Dialectical behaviour therapy (DBT) + any antidepressant Intensity: 24x individual sessions + 24x group sessions	Any antidepressant	Inadequate response (HAMD score>10) to 8 weeks of prospective treatment with physician choice of SSRI	Treatment length (weeks): 24 Outcomes: • Depression symptomatology endpoint • Remission • Discontinuation due ato any reason
Nakagawa 2017 RCT Japan	N=80 Mean age (years): 40.6 Gender (% female): 36	CBT individual + any antidepressant Intensity: 16x 50-min sessions (+4 additional	Any antidepressant	Inadequate response: at least a minimal degree of treatment-resistant depression (Maudsley Staging	Treatment length (weeks): 16 Outcomes: • Depression symptomatology at: ○ Endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 20.9 (more severe)	sessions if appropriate)		Method for treatment-resistant depression score≥3) and HAMD score≥16 despite having received adequate therapeutic levels of antidepressant medication for at least 8 weeks as part of their routine care	○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up • Depression symptomatology change score • Remission at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up • Response at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up • Discontinuation due ato any reason • Quality of life physical component score at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up • Quality of life mental component score at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Nakao 2018 RCT Japan	N=40 Mean age (years): 40.2 Gender (% female): 50 Ethnicity (% BME): NR Baseline severity: HAMD 18.4 (more severe)	Blended computerised CBT and individual face-to-face CBT + any antidepressant Intensity: 12 online modules + 12x 45-min face-to-face sessions	Waitlist + any antidepressant	Inadequate response: HAMD score ≥14 despite having received adequate therapy with ≥1 antidepressant medications for at least 6 weeks as part of their routine care	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due ato any reason • Quality of life endpoint • Quality of life physical component score • Quality of life mental component score
Paykel 1999/Scott 2000 RCT UK	N=158 Mean age (years): 43.4 Gender (% female): 49 Ethnicity (% BME): NR Baseline severity: HAMD 12.2 (less severe)	CBT individual + any antidepressant Intensity: 16 sessions	Any antidepressant	Inadequate response (HAMD≥8 and BDI≥9) to antidepressant medication for at least the previous 8 weeks, with at least 4 weeks at an adequate dose	Treatment length (weeks): 20 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 6-month follow-up ○ 11-month follow-up • Depression symptomatology change score • Remission • Discontinuation due ato any reason • Functional impairment at: ○ Endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					○ 11-month follow-up
Strauss 2012 RCT UK	N=28 Mean age (years): 43 Gender (% female): 71 Ethnicity (% BME): NR Baseline severity: BDI-II 39.11 (more severe)	Person-based cognitive therapy (PBCT) group + any antidepressant Intensity: 12x 90-min sessions	Any antidepressant	Inadequate response: met inclusion criteria despite requirement to have been on stable antidepressant treatment for at least 3 months	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due ato any reason
Watkins 2011a RCT UK	N=42 Mean age (years): 44.2 Gender (% female): 57 Ethnicity (% BME): 5 Baseline severity: HAMD 12.7 (less severe)	Rumination-focused CBT + SSRI/SNRI Intensity: 12 sessions	SSRI/SNRI	Inadequate response (HAMD score≥8 and BDI-II score≥9) to antidepressant medication taken at a therapeutic dose as recommended by the BNF and/or equivalent to 125 mg of amitriptyline for at least 8 weeks continuously during the current episode and within the past 2 months	Treatment length (weeks): 26 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due ato any reason
Wiles 2008 RCT UK	N=25 Mean age (years): 45.3 Gender (% female): 84	CBT individual + SSRI Intensity: 12-20 sessions	SSRI	Inadequate response (BDI-II≥15) despite having taken antidepressant medication	Treatment length (weeks): 17 Outcomes: • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: BDI-II 29.21 (less severe)			for at least 6 weeks at recommended (BNF) doses	• Discontinuation due ato any reason
Wiles 2013/2016 RCT UK	N=469 Mean age (years): 49.6 Gender (% female): 72 Ethnicity (% BME): 2 Baseline severity: BDI-II 31.8 (more severe)	CBT individual + any antidepressant Intensity: 12x 50-60min sessions (+6 sessions if judged to be clinically appropriate)	Any antidepressant	Inadequate response (BDI-II≥14) to an adhered to, adequate dose of antidepressant medication (based on BNF and advice from psychopharmacology experts) for at least 6 weeks	Treatment length (weeks): 26 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 6-month follow-up ○ 40-month follow-up • Remission at: ○ Endpoint ○ 6-month follow-up ○ 40-month follow-up • Response at: ○ Endpoint ○ 6-month follow-up ○ 40-month follow-up • Discontinuation due ato any reason • Quality of life physical component score at: ○ Endpoint ○ 6-month follow-up ○ 40-month follow-up • Quality of life mental component score at: ○ Endpoint ○ 6-month follow-up

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					○ 40-month follow-up

BDI/BDI-II: Beck depression inventory; BME: black and minority ethnic; BNF: British national formulary; CBT: cognitive behavioural therapy; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TRD: treatment-resistant depression

Table 3: Summary of included studies. Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Kocsis 2009/Klein 2011 RCT US	N=395 Mean age (years): 45.8 Gender (% female): 57 Ethnicity (% BME): 10 Baseline severity: HAMD 19.48 (more severe)	Cognitive behavioral analysis system of psychotherapy (CBASP) + any antidepressant (algorithm-based) Intensity: 16-20 sessions	Brief Supportive Psychotherapy + any antidepressant (algorithm-based)	Inadequate response (≥60% reduction in HAMD score, a HAMD total score<8, and no longer meeting DSM-IV criteria for MDD for 2 consecutive visits during weeks 6-12) to 12 weeks of antidepressant medication according to a pharmacotherapy algorithm	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Remission • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment endpoint

BME: black and minority ethnic; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MDD: major depressive disorder; RCT: randomised controlled trial

Table 4: Summary of included studies. Comparison 3. Augmenting with counselling versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Kocsis 2009/Klein 2011 RCT US	N=291 Mean age (years): 45.3 Gender (% female): 55 Ethnicity (% BME): 12 Baseline severity: HAMD 19.08 (more severe)	Brief Supportive Psychotherapy + any antidepressant (algorithm-based) Intensity: 16-20 sessions	Any antidepressant (algorithm-based)	Inadequate response (≥60% reduction in HAMD score, a HAMD total score<8, and no longer meeting DSM-IV criteria for MDD for 2 consecutive visits during weeks 6-12) to 12 weeks of antidepressant medication according to a pharmacotherapy algorithm	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Remission • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment endpoint

BME: black and minority ethnic; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MDD: major depressive disorder; RCT: randomised controlled trial

Table 5: Summary of included studies. Comparison 4. Augmenting with IPT versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Murray 2010 RCT Canada	N=64 Mean age (years): 45.2 Gender (% female): 72 Ethnicity (% BME): NR	IPT group (Re-ChORD) + any antidepressant Intensity: 16x 90-min sessions	Any antidepressant	TRD: Mean 2.95 (SD=1.1) failed medication trials	Treatment length (weeks): 16 Outcomes: • Depression symptomatology change score • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (unclear severity)				• Discontinuation due to any reason
Reynolds 2010 RCT US	N=124 Mean age (years): 72.3 Gender (% female): 68 Ethnicity (% BME): 8 Baseline severity: HAMD 12.5 (less severe)	IPT individual + escitalopram (dose increase; 10-20mg/day) Intensity: IPT 16x 60-75 min sessions	Escitalopram (dose increase; 10-20mg/day)	Inadequate (partial) response (HAMD score=11-14) to 6 weeks prospective open-label treatment with escitalopram	Treatment length (weeks): 16 Outcomes: • Remission • Discontinuation due to any reason
Schramm 2007 RCT Germany	N=130 Mean age (years): 41.9 Gender (% female): 65 Ethnicity (% BME): NR Baseline severity: HAMD 23.53 (more severe)	IPT individual & group (modified for an inpatient setting) + SSRI/TCA (sertraline 50-250mg/day or amitriptyline 75-360mg/day) Intensity: 15x 50-min individual sessions	SSRI/TCA (sertraline 50-250mg/day or amitriptyline 75-360mg/day)	Inadequate response: met inclusion criteria despite 83% having received outpatient treatment before admission	Treatment length (weeks): 5 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 3-month follow-up ○ 12-month follow-up • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Global functioning at: ○ Endpoint ○ 3-month follow-up ○ 12-month follow-up
Souza 2016	N=40	IPT individual + any	Any antidepressant	Inadequate response to 1 trial of	Treatment length (weeks): 19

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
RCT Brazil	Mean age (years): 49.2 Gender (% female): 85 Ethnicity (% BME): NR Baseline severity: HAMD 19 (more severe)	antidepressant Intensity: 16x 40-min weekly sessions		antidepressant medication in adequate dose (defined as the equivalent of at least 75mg of amitriptyline) and duration (at least 4 weeks)	Outcomes: • Depression symptomatology at: ○ Endpoint ○ 1-month follow-up • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; IPT: interpersonal therapy; NR: not reported; RCT: randomised controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; TRD: treatment-resistant depression

Table 6: Summary of included studies. Comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Town 2017/2020 RCT Canada	N=60 Mean age (years): 41.6 Gender (% female): 63 Ethnicity (% BME): 3 Baseline severity: HAMD 23.77 (more severe)	Intensive short-term dynamic psychotherapy + any antidepressant Intensity: 20 sessions	Any antidepressant	Inadequate response to treatment (HAMD score ≥16) to at least 1 trial of antidepressants at the adequate recommended therapeutic dose. 34% 2 or more failed antidepressants for current episode	Treatment length (weeks): 26 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up ○ 12-month follow-up • Depression symptomatology change score • Remission at: ○ Endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					○ 12-month follow-up • Response • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; RCT: randomised controlled trial

Table 7: Summary of included studies. Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fonagy 2015 RCT UK	N=129 Mean age (years): 44.3 Gender (% female): 66 Ethnicity (% BME): NR Baseline severity: HAMD 20.1 (more severe)	Long-term psychodynamic psychotherapy (following manual by Taylor 2015) + any antidepressant Intensity: 60x 50-min weekly sessions	Any antidepressant	TRD: Inadequate response to least 2 different treatments (mean of 3.7 previously failed treatment attempts)	Treatment length (weeks): 78 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 6-month follow-up ○ 12-month follow-up ○ 24-month follow-up • Remission at: ○ Endpoint ○ 24-month follow-up • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 8: Summary of included studies. Comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/- attention-placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Baert 2010_study 2 RCT	N=44 Mean age (years): 42.3	Attentional bias training + any	Attention-placebo + any antidepressant	Inadequate response: met inclusion	Treatment length (weeks): 1.4

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Belgium & Netherlands	Gender (% female): 64 Ethnicity (% BME): NR Baseline severity: HAMD 23.19 (more severe)	antidepressant Intensity: 1x pre-training lab session, 10x training sessions at home, & 1 post-training lab session	Intensity: 1x pre-training lab session, 10x training sessions at home, & 1 post-training lab session	criteria despite all participants having received therapy and/or medication at study entry	Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score
Dai 2019 RCT China	N=40 Mean age (years): 38.7 Gender (% female): 45 Ethnicity (% BME): NR Baseline severity: HAMD 23.01 (more severe)	Attentional bias training + any antidepressant Intensity: 10 sessions (daily over 10 days)	Attention-placebo + any antidepressant Intensity: 10 sessions (daily over 10 days)	Inadequate response (HAMD score≥20) despite at least 6 weeks of adequate antidepressant treatment	Treatment length (weeks): 1.4 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 1-month follow-up • Depression symptomatology change score • Discontinuation due to any reason
Schlogelhofer 2014 RCT Austria	N=90 Mean age (years): 47.8 Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: HAMD 12.6 (less severe)	Cognitive bibliotherapy + any antidepressant Intensity: 1 monitoring session	Any antidepressant	Inadequate response (not achieving full remission, HAMD score 10-19) to at least 1 course of a recommended dose of an antidepressant medication for at least 4 weeks (the median treatment	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				duration with antidepressant medication before screening was 6 months)	

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 9: Summary of included studies. Comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Mantani 2017 RCT Japan	N=164 Mean age (years): 40.9 Gender (% female): 53 Ethnicity (% BME): NR Baseline severity: PHQ-9 13.2 (less severe)	Computerised CBT (CCBT) + switch to escitalopram 5-10 mg/day or sertraline 25-100 mg/day Intensity: 8 sessions	Switch to escitalopram 5-10 mg/day or sertraline 25-100 mg/day	Inadequate response (BDI-II≥10) after taking 1 or more antidepressants at an adequate dosage for at least 4 weeks	Treatment length (weeks): 9 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason

BDI-II: Beck depression inventory; BME: black and minority ethnic; NR: not reported; PHQ-9: patient health questionnaire-9 item; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitors

Table 10: Summary of included studies. Comparison 9. Augmenting with art therapy versus attention-placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Nan 2017 RCT China	N=106 Mean age (years): 45.1	Clay art therapy + any antidepressant	Attention-placebo (non-directive visual art control group)	Inadequate response (BDI-II≥10) after taking 1 or more	Treatment length (weeks): 6 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): 89 Ethnicity (% BME): NR Baseline severity: BDI-II 30.59 (more severe)	Intensity: 6x 2.5-hour sessions	+ any antidepressant Intensity: 6x 2.5-hour sessions	antidepressants at an adequate dosage for at least 4 weeks	• Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due to any reason

BDI-II: Beck depression inventory; BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial

Table 11: Summary of included studies. Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Ostacoli 2018 RCT Italy & Spain	N=82 Mean age (years): 47.9 Gender (% female): 84 Ethnicity (% BME): NR Baseline severity: NR (less severe)	Eye Movement Desensitization Reprocessing (EMDR), following the DeprEnd protocol (Hofmann et al. 2016) + any antidepressant Intensity: 12-18 sessions	CBT individual (Beck, 1979) + any antidepressant Intensity: 12-18 sessions	Inadequate response (BDI-II≥10) after taking 1 or more antidepressants at an adequate dosage for at least 4 weeks	Treatment length (weeks): 13-26 Outcomes: • Depression symptomatology endpoint • Remission at: ○ Endpoint ○ 6-month follow-up • Discontinuation due to any reason • Global functioning at: ○ Endpoint ○ 6-month follow-up

BDI-II: Beck depression index; BME: black and minority ethnic; CBT: cognitive behavioural therapy; NR: not reported; RCT: randomised controlled trial

Table 12: Summary of included studies. Comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Dornseif 1989 RCT US	N=371 Mean age (years): 43.4 Gender (% female): 66 Ethnicity (% BME): 6 Baseline severity: HAMD 26.7 (more severe)	Fluoxetine 60mg/day	Fluoxetine 20mg/day	Inadequate response (<50% reduction in HAMD) to 3 weeks of single-blind therapy with fluoxetine 20mg	Treatment length (weeks): 5 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Kim 2019 RCT Korea	N=50 Mean age (years): 39.5 Gender (% female): 76 Ethnicity (% BME): NR Baseline severity: MADRS 20.2 (less severe)	Escitalopram 30mg/day	Escitalopram 20mg/day	Inadequate response (non-remission defined by MADRS score > 10) after 4 weeks of open-label treatment with 10–20 mg of escitalopram per day	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Licht 2002 RCT Denmark & Iceland	N=197 Mean age (years): 40.0 Gender (% female): 59 Ethnicity (% BME): NR Baseline severity: NR (unclear severity)	Sertraline 200mg/day	Sertraline 100mg/day	Inadequate response (<50% improvement on HAMD) to 6 weeks of open-label treatment with sertraline (50-100mg/day)	Treatment length (weeks): 5 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Ruhe 2009 RCT Netherlands	N=60 Mean age (years): 42.4 Gender (% female): 67 Ethnicity (% BME): 40 Baseline severity: HAMD 20.6 (more severe)	Paroxetine 30-50mg/day	Paroxetine 20mg/day	Inadequate response (<50% improvement on HAMD) to 6 weeks, open-label paroxetine treatment (20 mg/day)	Treatment length (weeks): 6 Outcomes: • Depressionsymptomatology endpoint • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Qulity of life mental component score
Schweizer 1990 RCT US	N=77 Mean age (years): 45.1 Gender (% female): 56 Ethnicity (% BME): NR Baseline severity: HAMD 25 (more severe)	Fluoxetine 60mg/day	Fluoxetine 20mg/day	Inadequate response (<50% improvement on HAMD) to 3-week open-label prospective treatment with fluoxetine 20mg/day. 74% previous antidepressant prescribed	Treatment length (weeks): 5 Outcomes: • Response • Discontinuation due to any reason • Discontinuation due to side effects
Schweizer 2001 RCT US	N=75 Mean age (years): 40.0 Gender (% female): 54 Ethnicity (% BME): NR	Sertraline 150mg/day	Sertraline 50mg/day	Inadequate response (failure to achieve remission [HAMD>8]) to 3-week open-label prospective treatment phase with	Treatment length (weeks): 5 Outcomes: • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (unclear severity)			sertraline (50mg/day)	

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 13: Summary of included studies. Comparison 12. Increasing the dose of SSRI versus switching to SNRI

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Bose 2012 RCT US	N=484 Mean age (years): 42.3 Gender (% female): 59 Ethnicity (% BME): 22 Baseline severity: MADRS 34.8 (more severe)	Escitalopram (dose increase) 20mg/day	Duloxetine 60mg/day	Inadequate response (<50% improvement on MADRS) to 2 weeks of single-blind escitalopram (10mg/day)	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life endpoint

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 14: Summary of included studies. Comparison 13. Increasing the dose of SSRI versus augmenting with TCA

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fava 1994a RCT US	N=27 Mean age (years): NR	Fluoxetine 40-60mg/day	Desipramine 25-50mg/day + fluoxetine 20mg/day	Inadequate response (defined as failure to achieve a 50% or	Treatment length (weeks): 4 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 18.54 (more severe)			greater reduction in HAMD score and a HAMD score of ≥10) to 8 weeks of open-label treatment with fluoxetine (20mg/day)	• Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects
Fava 2002 RCT US	N=67 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 16.86 (more severe)	Fluoxetine 40-60mg/day	Desipramine 25-50mg/day + fluoxetine 20mg/day	Inadequate response (defined as failure to achieve a 50% or greater reduction in HAMD score and a HAMD score of ≥10) to 8 weeks of open-label treatment with fluoxetine (20mg/day)	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Table 15: Summary of included studies. Comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Rocca 2002b RCT Italy	N=60 Mean age (years): 40.8 Gender (% female): 68 Ethnicity (% BME): NR	Paroxetine (dose increase) 40mg/day	Amisulpride 50mg/day + paroxetine 20mg/day	Inadequate response to 3-month treatment with paroxetine 20 mg/day	Treatment length (weeks): 13 Outcomes: • Depression symptomatology endpoint • Depression symptomatolo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: HAMD 18.3 (more severe)				gy change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional remission • Global functioning endpoint

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 16: Summary of included studies. Comparison 15. Increasing the dose of SSRI versus augmenting with lithium

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fava 1994a RCT US	N=29 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 18.09 (more severe)	Fluoxetine 40-60mg/day	Lithium 300-600mg/day + fluoxetine 20mg/day	Inadequate response (defined as failure to achieve a 50% or greater reduction in HAMD score and a HAMD score of ≥10) to 8 weeks of open-label treatment with fluoxetine (20mg/day)	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects
Fava 2002 RCT US	N=67 Mean age (years): NR Gender (% female): NR	Fluoxetine 40-60mg/day	Lithium 300-600mg/day + fluoxetine 20mg/day	Inadequate response (defined as failure to achieve a 50% or greater reduction in	Treatment length (weeks): 4 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 16.1 (more severe)			HAMD score and a HAMD score of ≥10) to 8 weeks of open-label treatment with fluoxetine (20mg/day)	• Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 17: Summary of included studies. Comparison 16. Switching to SSRI versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=119 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Fluoxetine 25 or 50mg/day	Venlafaxine 75-375mg/day	TRD: Inadequate response to a SSRI after at least 6 weeks at a therapeutic dose at entry into the trial and inadequate response (<30% improvement in MADRS total score) to an open-label, 7-week lead-in phase of venlafaxine (75–375 mg/day according to the investigator's clinical judgment)	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Shelton 2005 RCT	N=210	Fluoxetine 25-50mg/day	Nortriptyline 25-175mg/day	TRD: History of at least 1 failure to	Treatment length (weeks): 8

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
US & Canada	Mean age (years): 41.6 Gender (% female): 71 Ethnicity (% BME): 10 Baseline severity: MADRS 28.53 (more severe)			respond to SSRI after at least 4 weeks at a therapeutic dose, and failure to respond (<30% improvement on MADRS) to nortriptyline (25-175mg/day; mean modal dose 104.6mg/day) during a 7-week open-label treatment phase	Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 18: Summary of included studies. Comparison 17. Switching to a different SSRI versus continuing same SSRI

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Nakajima 2011 RCT Japan	N=41 Mean age (years): 47.5 Gender (% female): 41 Ethnicity (% BME): NR Baseline severity: MADRS 30.49 (more severe)	Paroxetine 20-40mg/day	Sertraline 50-100mg/day	Inadequate response (HAMD score improvement <20%) after 2 weeks of treatment with sertraline	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 19: Summary of included studies. Comparison 18. Switching to SSRI versus antipsychotic

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=122 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Fluoxetine 25 or 50mg/day	Olanzapine 6 or 12mg/day	TRD: Inadequate response to a SSRI after at least 6 weeks at a therapeutic dose at entry into the trial and inadequate response (<30% improvement in MADRS total score) to an open-label, 7-week lead-in phase of venlafaxine (75–375 mg/day according to the investigator's clinical judgment)	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Shelton 2005 RCT US & Canada	N=286 Mean age (years): 42.6 Gender (% female): 69 Ethnicity (% BME): 13 Baseline severity: MADRS 28.4 (more severe)	Fluoxetine 25-50mg/day	Olanzapine 6-12mg/day	TRD: History of at least 1 failure to respond to SSRI after at least 4 weeks at a therapeutic dose, and failure to respond (<30% improvement on MADRS) to nortriptyline (25-175mg/day; mean modal dose 104.6mg/day) during a 7-week open-label	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				treatment phase	

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 20: Summary of included studies. Comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=305 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Fluoxetine 25 or 50mg/day + Olanzapine 6 or 12mg/day	Olanzapine 6 or 12mg/day	TRD: Inadequate response to a SSRI after at least 6 weeks at a therapeutic dose at entry into the trial and inadequate response (<30% improvement in MADRS total score) to an open-label, 7-week lead-in phase of venlafaxine (75–375 mg/day according to the investigator's clinical judgment)	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Shelton 2005 RCT US & Canada	N=290 Mean age (years): 43.0 Gender (% female): 66 Ethnicity (% BME): 13 Baseline severity:	Fluoxetine 25-50mg/day + Olanzapine 6-12mg/day	Olanzapine 6-12mg/day	TRD: History of at least 1 failure to respond to SSRI after at least 4 weeks at a therapeutic dose, and failure to respond (<30% improvement on	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	MADRS 28.45 (more severe)			MADRS) to nortriptyline (25-175mg/day; mean modal dose 104.6mg/day) during a 7-week open-label treatment phase	• Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 21: Summary of included studies. Comparison 20. Augmenting with SSRI versus augmenting with lithium

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Navarro 2019b RCT Spain	N=104 Mean age (years): 55.4 Gender (% female): 68 Ethnicity (% BME): NR Baseline severity: HAMD 28.52 (more severe)	Citalopram 30mg/day + imipramine target plasma level 175-300 ng/mL	Lithium target plasma level 0.6-0.8 mEq/L + imipramine target plasma level 175-300 ng/mL	Inadequate response (HAMD improved ≤50%) following 10-week open-label treatment with imipramine	Treatment length (weeks): 10 Outcomes: • Depression symptomatology change score • Remission

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 22: Summary of included studies. Comparison 21. Switching to TCA versus SSRI

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Souery 2011a RCT Austria, Belgium,	N=189 Mean age (years): 51.4	Desipramine minimum dose 150mg/day (mean final dose	Citalopram minimum dose 40mg/day (mean final dose 43.06mg/day)	Inadequate response to treatment with at least 1 antidepressant (except	Treatment length (weeks): 4 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
France & Israel	Gender (% female): 72 Ethnicity (% BME): 5 Baseline severity: MADRS 31.5 (more severe)	169.61mg/day)		citalopram and desipramine) given at an adequate dose for at least 4 weeks	• Depression symptomatology endpoint • Remission • Response • Discontinuation due to any reason

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Table 23: Summary of included studies. Comparison 22. Switching to TCA versus augmenting with mirtazapine

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Navarro 2019a RCT Spain	N=112 Mean age (years): 55.5 Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: HAMD 28.22 (more severe)	Imipramine target plasma level 175-300 ng/mL	Mirtazapine 30mg/day + Venlafaxine 225-300mg/day	Inadequate response (non-remission HAMD>7) to 10 weeks of treatment with venlafaxine	Treatment length (weeks): 10 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TCA: tricyclic antidepressant

Table 24: Summary of included studies. Comparison 23. Switching to mianserin versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Ferreri 2001 RCT France	N=72 Mean age (years): 46.4	Mianserin 60mg/day	Fluoxetine 20mg/day	Inadequate response to previous fluoxetine treatment after at least	Treatment length (weeks): 6 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): 72 Ethnicity (% BME): NR Baseline severity: HAMD 26.99 (more severe)			6 weeks of treatment with 20 mg/day	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 25: Summary of included studies. Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Ferreri 2001 RCT France	N=70 Mean age (years): 45.9 Gender (% female): 74 Ethnicity (% BME): NR Baseline severity: HAMD 27.27 (more severe)	Mianserin 60mg/day + Fluoxetine 20mg/day	Fluoxetine 20mg/day	Inadequate response to previous fluoxetine treatment after at least 6 weeks of treatment with 20 mg/day	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Licht 2002 RCT Denmark & Iceland	N=197 Mean age (years): 40.0 Gender (% female): 61 Ethnicity (% BME): NR	Mianserin 10-30mg/day + Sertraline 100mg/day	Sertraline 100mg/day + placebo	Inadequate response (<50% improvement on HAMD) to 6 weeks of open-label treatment with sertraline	Treatment length (weeks): 5 Outcomes: • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (unclear severity)			(50-100mg/day)	

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 26: Summary of included studies. Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Licht 2002 RCT Denmark & Iceland	N=196 Mean age (years): 41.0 Gender (% female): 65 Ethnicity (% BME): NR Baseline severity: NR (unclear severity)	Mianserin 10-30mg/day + Sertraline 100mg/day	Sertraline 200mg/day + placebo	Inadequate response (<50% improvement on HAMD) to 6 weeks of open-label treatment with sertraline (50-100mg/day)	Treatment length (weeks): 5 Outcomes: • Remission • Response • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 27: Summary of included studies. Comparison 26. Augmenting with mianserin versus switch to mianserin

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Ferreri 2001 RCT France	N=66 Mean age (years): 47.5 Gender (% female): 76	Mianserin 60mg/day + Fluoxetine 20mg/day	Mianserin 60mg/day	Inadequate response to previous fluoxetine treatment after at least 6 weeks of treatment with 20 mg/day	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 27.39 (more severe)				• Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 28: Summary of included studies. Comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Kornstein 2008 RCT US	N=255 Mean age (years): 45.5 Gender (% female): 61 Ethnicity (% BME): 19 Baseline severity: HAMD 14.3 (less severe)	Duloxetine 120mg/day	Duloxetine 60mg/day	Inadequate response (HAMD score >7) to 5-week prospective treatment with duloxetine 60mg/day	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors

Table 29: Summary of included studies. Comparison 28. Switching to SNRI versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2010 RCT China	N=95 Mean age (years): NR	Venlafaxine extended release 225mg/day	Paroxetine 20mg/day	TRD: Inadequate response to 2 or more adequate treatments	Treatment length (weeks): 8 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)			from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month duration) determined through medical records and/or prospective treatment	• Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score

BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors; TRD: treatment-resistant depression

Table 30: Summary of included studies. Comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Lenox-Smith 2008 RCT Europe & Australia	N=406 Mean age (years): 42.5 Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: MADRS 30.9 (more severe)	Venlafaxine extended release 75-300mg/day	Citalopram 20-60mg/day	Inadequate response following 8 weeks of monotherapy with an adequate dosing regimen of an SSRI other than citalopram	Treatment length (weeks): 12 Outcomes: • Remission • Discontinuation due to any reason • Discontinuation due to side effects
Poirier 1999 RCT France	N=123 Mean age (years): 43.3	Venlafaxine 65-300mg/day	Paroxetine 20-40mg/day	TRD: History of resistance to 2 previous successive	Treatment length (weeks): 4 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): 72 Ethnicity (% BME): NR Baseline severity: HAMD 24.6 (more severe)			antidepressant treatments for the current episode (except venlafaxine or paroxetine)	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Rush 2006 RCT US	N=488 Mean age (years): 41.8 Gender (% female): 60 Ethnicity (% BME): 24 Baseline severity: QIDS 13.2 (more severe)	Venlafaxine extended release 37.5-375mg/day	Sertraline 50-200mg/day	Inadequate response (not achieved remission or who were intolerant [56%]) to an initial prospective treatment with citalopram	Treatment length (weeks): ≤14 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 31: Summary of included studies. Comparison 30. Switching to SNRI versus switching to bupropion

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Rush 2006 RCT US	N=489 Mean age (years): 41.5 Gender (% female): 61 Ethnicity (% BME): 25	Venlafaxine extended release 37.5-375mg/day	Bupropion sustained release 150-400mg/day	Inadequate response (not achieved remission or who were intolerant [56%]) to an initial prospective treatment with citalopram	Treatment length (weeks): ≤14 Outcomes: • Depression symptomatology change score • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: QIDS 13.2 (more severe)				• Discontinuation due to side effects

BME: black and minority ethnic; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors

Table 32: Summary of included studies. Comparison 31. Switching to SNRI versus switching to mirtazapine

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2010 RCT China	N=105 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Venlafaxine extended release 225mg/day	Mirtazapine 45mg/day	TRD: Inadequate response to 2 or more adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month duration) determined through medical records and/or prospective treatment	Treatment length (weeks): 8 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score

BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors; TRD: treatment-resistant depression

Table 33: Summary of included studies. Comparison 32. Switching to bupropion versus placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
GlaxoSmithKline 2009 RCT Japan	N=325 Mean age (years): 36.4 Gender (% female): 45 Ethnicity (% BME): NR Baseline severity: HAMD 19.6 (more severe)	Bupropion hydrochloride sustained release 100-300mg/day	Placebo	Inadequate response to paroxetine (20-40 mg/day) for 4 weeks	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 34: Summary of included studies. Comparison 33. Switching to bupropion versus switching to another antidepressant from same class

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Rush 2006 RCT US	N=477 Mean age (years): 42.3 Gender (% female): 56 Ethnicity (% BME): 23 Baseline severity: QIDS 13.3 (more severe)	Bupropion sustained release 150-400mg/day	Sertraline 50-200mg/day	Inadequate response (not achieved remission or who were intolerant [56%]) to an initial prospective treatment with citalopram	Treatment length (weeks): ≤14 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to side effects

BME: black and minority ethnic; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial

Table 35: Summary of included studies. Comparison 34. Augmenting with bupropion versus placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Gulrez 2012 RCT India	N=60 Mean age (years): 41.2 Gender (% female): 52 Ethnicity (% BME): NR Baseline severity: HAMD 17.67 (more severe)	Bupropion sustained release 300mg/day (target dose, titrated upwards from 150mg in first week) + SSRI	Placebo + SSRI	Inadequate response (HAMD score ≥16) after 4 weeks of SSRI treatment	Treatment length (weeks): 4 Outcomes: • Remission

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 36: Summary of included studies. Comparison 35. Augmenting with bupropion versus switching to bupropion

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Mohamed 2017 RCT US	N=1017 Mean age (years): 54.5 Gender (% female): 15 Ethnicity (% BME): 30 Baseline severity: QIDS 16.6 (more severe)	Bupropion 150-400mg/day + SSRI/SNRI	Bupropion 150-400mg/day	Inadequate response (QIDS score ≥16 after ≥6 weeks of treatment or score≥11 after ≥8 weeks of treatment with the 3 most recent weeks at a stable "optimal" dose) to a treatment course with a SSRI, SNRI, or mirtazapine that met or exceeded minimal standards for dose	Treatment length (weeks): 12 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				and duration of treatment	

BME: black and minority ethnic; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 37: Summary of included studies. Comparison 36. Switching to mirtazapine versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2010 RCT China	N=100 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Mirtazapine 45mg/day	Paroxetine 20mg/day	TRD: Inadequate response to 2 or more adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month duration) determined through medical records and/or prospective treatment	Treatment length (weeks): 8 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score
Kato 2018 RCT Japan	N=1109 Mean age (years): 41.5 Gender (% female): 51 Ethnicity (% BME): NR	Mirtazapine 7.5-45mg/day	Sertraline 50mg/day or 100mg/day (mean final dose 71.7mg)	Inadequate response (non-remission as defined by PHQ-9 score>4) to 2 weeks of treatment with sertraline (50mg or 100mg)	Treatment length (weeks): 6 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 4-month follow-up • Remission

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: PHQ-9 12.8 (less severe)				• Response • Discontinuation due to any reason
Xiao 2020 RCT China	N=136 Mean age (years): 39.6 Gender (% female): 66 Ethnicity (% BME): NR Baseline severity: HAMD 21.9 (more severe)	Mirtazapine 30mg/day	Paroxetine 20mg/day	Inadequate response: early non-response (HAMD score improved by less than 20%) to prospective open-label treatment with paroxetine (10-20mg/day) for 2 weeks	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; PHQ-9: patient health questionnaire-9 item; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 38: Summary of included studies. Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Carpenter 2002 RCT US	N=26 Mean age (years): 46.3 Gender (% female): 62 Ethnicity (% BME): NR Baseline severity: HAMD 22.3 (more severe)	Mirtazapine (final dose: 31% 15mg/69% 30mg) + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response (HAMD total score>12) after at least 4 weeks of standard antidepressant monotherapy at maximum recommended or tolerated doses	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					• Discontinuation due to side effects • Global functioning endpoint
Kato 2018 RCT Japan	N=1088 Mean age (years): 41.8 Gender (% female): 53 Ethnicity (% BME): NR Baseline severity: PHQ-9 12.7 (less severe)	Mirtazapine 7.5-45mg/day + sertraline 50mg/day or 100mg/day	Sertraline 50mg/day or 100mg/day (mean final dose 71.7mg)	Inadequate response (non-remission as defined by PHQ-9 score>4) to 2 weeks of treatment with sertraline (50mg or 100mg)	Treatment length (weeks): 6 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 4-month follow-up • Remission at: ○ Endpoint ○ 4-month follow-up • Response at endpoint • Discontinuation due to any reason
Kessler 2018a/2018b RCT UK	N=480 Mean age (years): 50.2 Gender (% female): 69 Ethnicity (% BME): 3 Baseline severity: BDI-II 31.05 (more severe)	Mirtazapine 30mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response to an SSRI or SNRI antidepressant at an adequate dose for at least 6 weeks	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Remission • Response • Discontinuation due to any reason • Quality of life endpoint • Quality of life physical component score • Quality of life mental component score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Xiao 2020 RCT China	N=136 Mean age (years): 39.3 Gender (% female): 53 Ethnicity (% BME): NR Baseline severity: HAMD 20.95 (more severe)	Mirtazapine 30mg/day + paroxetine 20mg/day	Paroxetine 20mg/day	Inadequate response: early non-response (HAMD score improved by less than 20%) to prospective open-label treatment with paroxetine (10-20mg/day) for 2 weeks	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BDI-II: Beck depression inventory; BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; PHQ-9: patient health questionnaire-9 item; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 39: Summary of included studies. Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Kato 2018 RCT Japan	N=1095 Mean age (years): 41.7 Gender (% female): 52 Ethnicity (% BME): NR Baseline severity: PHQ-9 12.7 (less severe)	Mirtazapine 7.5-45mg/day + sertraline 50mg/day or 100mg/day	Mirtazapine 7.5-45mg/day	Inadequate response (non-remission as defined by PHQ-9 score>4) to 2 weeks of treatment with sertraline (50mg or 100mg)	Treatment length (weeks): 6 Outcomes: • Depression symptomatology at: ○ Endpoint ○ 4-month follow-up • Remission at: ○ Endpoint ○ 4-month follow-up • Response at endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					• Discontinuation due to any reason
Xiao 2020 RCT China	N=136 Mean age (years): 38.6 Gender (% female): 57 Ethnicity (% BME): NR Baseline severity: HAMD 21.74 (more severe)	Mirtazapine 30mg/day + paroxetine 20mg/day	Mirtazapine 30mg/day	Inadequate response: early non-response (HAMD score improved by less than 20%) to prospective open-label treatment with paroxetine (10-20mg/day) for 2 weeks	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; PHQ-9: patient health questionnaire-9 item; RCT: randomised controlled trial

Table 40: Summary of included studies. Comparison 39. Augmenting with trazodone versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2011 RCT China	N=92 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Trazodone 100mg/day + paroxetine 20mg/	Paroxetine 20mg/day	TRD: Inadequate response to 2 or more adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month	Treatment length (weeks): 8 Outcomes: • Remission • Response • Quality of life physical component score • Quality of life mental component score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				duration) determined through medical records and/or prospective treatment. 1 week paroxetine lead-in	

BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 41: Summary of included studies. Comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Barbee 2011 RCT US	N=96 Mean age (years): 45.2 Gender (% female): 69 Ethnicity (% BME): NR Baseline severity: MADRS 27 (more severe)	Lamotrigine 100-400mg/day + paroxetine/paroxetine CR	Placebo + paroxetine/paroxetine CR	TRD: History of failure of ≥1 adequate trial of a US FDA-approved antidepressant within the current episode of MDD, and failure to respond (HAMD≥15) to open-label prospective treatment with paroxetine or paroxetine CR (in flexible doses up to 50/62.5mg/day) after 8 weeks	Treatment length (weeks): 10 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response • Discontinuation due to any reason • Discontinuation due to side effects
Fang 2011 RCT	N=84	Sodium valproate 600mg/day +	Paroxetine 20mg/day	TRD: Inadequate response to ≥2	Treatment length (weeks): 8

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
China	Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	paroxetine 20mg/day		adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month duration) determined through medical records and/or prospective treatment	Outcomes: • Remission • Response • Quality of life physical component score • Quality of life mental component score
Li 2009 RCT China	N=98 Mean age (years): 67.0 Gender (% female): 56 Ethnicity (% BME): NR Baseline severity: HAMD 23.7 (more severe)	Lamotrigine 50-100mg/day + sertraline 100-150mg/day	Sertraline 100-150mg/day	TRD (failure to respond to at least 2 antidepressant treatment trials with adequate dose and duration)	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response
Li 2015 RCT China	N=115 Mean age (years): 33.8 Gender (% female): 44 Ethnicity (% BME): NR Baseline severity:	Lamotrigine 25-150mg/day + paroxetine 20-40mg/day	Paroxetine 20-40mg/day	TRD (failure to respond to at least 2 antidepressant treatment trials with adequate dose and duration)	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	HAMD 36.5 (more severe)				
Mowla 2011 RCT Iran	N=53 Mean age (years): 36.2 Gender (% female): 57 Ethnicity (% BME): NR Baseline severity: HAMD 21.79 (more severe)	Topiramate 100-200mg/day + SSRI	Placebo + SSRI	Inadequate response (HAMD≥18) to at least 8 weeks of treatment with an adequate and stable dose of one of the SSRIs (fluoxetine, citalopram or sertraline)	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due to any reason
Santos 2008 RCT Brazil	N=34 Mean age (years): 27.5 Gender (% female): 74 Ethnicity (% BME): NR Baseline severity: MADRS 30.4 (more severe)	Lamotrigine 50-200mg/day + any antidepressant	Placebo + any antidepressant	TRD: Inadequate response to treatment with at least 2 antidepressants of different classes at the maximum-tolerated dose for at least 6 weeks	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response • Discontinuation due to any reason • Discontinuation due to side effects
Wang 2012a RCT China	N=60 Mean age (years): 45.3 Gender (% female): 45 Ethnicity (% BME): NR Baseline severity: HAMD 22.75 (more severe)	Lamotrigine 100-200mg/day + venlafaxine 75-225mg/day	Venlafaxine 75-225mg/day	TRD: failed to achieve a response in at least 2 antidepressant treatment trials of adequate dose and duration	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Yang 2016 RCT China	N=66 Mean age (years): 38.2 Gender (% female): 52 Ethnicity (% BME): NR Baseline severity: HAMD 28.01 (more severe)	Lamotrigine 150mg/day + escitalopram 10-20mg/day	Escitalopram 10-20mg/day	TRD: failed to achieve a response in at least 2 antidepressant treatment trials of adequate dose and duration	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response
Zhang 2016 RCT China	N=88 Mean age (years): 47.3 Gender (% female): 72 Ethnicity (% BME): NR Baseline severity: HAMD 31.23 (more severe)	Lamotrigine 50-200mg/day + duloxetine 60mg/day	Duloxetine 60mg/day	TRD: failed to respond to at least 2 antidepressant treatment trials of adequate dose and duration	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response

BME: black and minority ethnic; CR: controlled release; FDA: food and drug administration; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 42: Summary of included studies. Comparison 41. Augmenting with anticonvulsant versus lithium

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Schindler 2007 RCT Germany	N=34 Mean age (years): 47.7 Gender (% female): 50	Lamotrigine 25-250mg/day (mean final dose 152.94 mg/day) + any antidepressant	Lithium target plasma level 0.6–0.8mmol/l (mean final plasma level 0.71mmol/l) + any antidepressant	TRD: Inadequate response (<50% reduction of initial HAMD) to at least 2 trials of different classes of	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 22.1 (More severe)			antidepressants for a duration of at least 6 weeks	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 43: Summary of included studies. Comparison 42. Switching to antipsychotic versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=121 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Olanzapine 6 or 12mg/day	Venlafaxine 75-375mg/day	TRD: Inadequate response to SSRI after ≥6 weeks at a therapeutic dose at entry into the trial and inadequate response (<30% improvement in MADRS score) to 7 weeks of venlafaxine 75–375mg/day	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Shelton 2005 RCT US & Canada	N=212 Mean age (years): 42.2 Gender (% female): 67 Ethnicity (% BME): 16	Olanzapine 6-12mg/day	Nortriptyline 25-175mg/day	TRD: History of ≥1 failure to respond to SSRI after ≥4 weeks of therapy at a therapeutic dose, and failure to respond (<30%	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: MADRS 28.53 (more severe)			improvement on MADRS) to 7 weeks of nortriptyline 25-175mg/day	• Discontinuation due to any reason • Discontinuation due to side effects
Thase 2007 RCT US & Canada	N=405 Mean age (years): 44.5 Gender (% female): 62 Ethnicity (% BME): 16 Baseline severity: MADRS 29.9 (more severe)	Olanzapine 6, 12 or 18mg/day	Fluoxetine 50mg/day	TRD: Documented history of failure to achieve a satisfactory response (based on investigator's clinical judgement) to an antidepressant (except fluoxetine) after ≥6 weeks of therapy at a therapeutic dose to 8 weeks of fluoxetine 25-50mg/day	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 44: Summary of included studies. Comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=302 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR	Olanzapine 6 or 12mg/day + fluoxetine 25 or 50mg/day	Venlafaxine 75-375mg/day	TRD: Inadequate response to SSRI after ≥6 weeks at a therapeutic dose at entry into the trial and inadequate	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (more severe)			response (<30% improvement in MADRS score) to 7 weeks of venlafaxine 75–375mg/day	• Response • Discontinuation due to any reason • Discontinuation due to side effects
Shelton 2005 RCT US & Canada	N=214 Mean age (years): 42.2 Gender (% female): 67 Ethnicity (% BME): 10 Baseline severity: MADRS 28.6 (more severe)	Olanzapine 6-12mg/day + fluoxetine 25-50mg/day	Nortriptyline 25-175mg/day	TRD: History of ≥1 failure to respond to SSRI after ≥4 weeks of therapy at a therapeutic dose, and failure to respond (<30% improvement on MADRS) to 7 weeks of nortriptyline 25-175mg/day	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 45: Summary of included studies. Comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Corya 2006 RCT 16 countries	N=303 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Olanzapine 6 or 12mg/day + fluoxetine 25 or 50mg/day	Fluoxetine 25 or 50mg/day	TRD: Inadequate response to SSRI after ≥6 weeks at a therapeutic dose at entry into the trial and inadequate response (<30% improvement in MADRS score) to 7 weeks of	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				venlafaxine 75–375mg/day	• Discontinuation due to side effects
Shelton 2005 RCT US & Canada	N=288 Mean age (years): 42.1 Gender (% female): 70 Ethnicity (% BME): 9 Baseline severity: MADRS 28.45 (more severe)	Olanzapine 6-12mg/day + fluoxetine 25-50mg/day	Fluoxetine 25-50mg/day	TRD: History of ≥1 failure to respond to SSRI after ≥4 weeks of therapy at a therapeutic dose, and failure to respond (<30% improvement on MADRS) to 7 weeks of nortriptyline 25-175mg/day	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 46: Summary of included studies. Comparison 45. Augmenting with antipsychotic versus antidepressant-only or antidepressant + placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Bauer 2009 RCT Australia, Canada, Europe & South Africa	N=493 Mean age (years): 45.4 Gender (% female): 68 Ethnicity (% BME): 2 Baseline severity: HAMD 24.6 (more severe)	Quetiapine 150mg/day or 300mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response during the current episode to amtitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine, which were given for ≥6 weeks at adequate doses	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				(minimum effective dose according to label and including at least 1 dose increase as permitted by label)	
Bauer 2019 RCT 16 countries in Asia, Europe, Latin America, & North America	N=886 Mean age (years): 46.8 Gender (% female): 69 Ethnicity (% BME): 4 Baseline severity: MADRS 25.85 (more severe)	Brexpiprazole 1-3mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Insufficient response to 1-3 adequate antidepressants (including the treatment a patient was taking at screening) for the current MDE; and insufficient response (defined as <50% improvement in MADRS; MADRS score ≥18; CGI-I score ≥3) to open-label antidepressants and double-blind augmentation during the 8 week prospective treatment phase	Treatment length (weeks): 24 Outcomes: • Remission • Discontinuation due to any reason • Discontinuation due to side effects • Functional remission
Berman 2007 RCT US	N=362 Mean age (years): 45.4 Gender (% female): 63	Aripiprazole 2-20mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Inadequate response to 1-3 adequate antidepressant trials (>6 weeks duration at adequate doses) at	Treatment length (weeks): 6 Outcomes: • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 10 Baseline severity: MADRS 26 (more severe)			entry into trial and inadequate response (failing to meet criteria of <50% reduction in symptoms, HAMD≥15 and CGI-I≥3) to prospective treatment phase (8-week treatment with escitalopram [10/20mg/day], fluoxetine [20/40mg/day], paroxetine CR [37.5/50mg/day], sertraline [100/150mg/day] or venlafaxine [150/225mg/day])	• Discontinuation due to any reason • Discontinuation due to side effects
Berman 2009 RCT US	N=349 Mean age (years): 45.4 Gender (% female): 73 Ethnicity (% BME): 13 Baseline severity: MADRS 26.9 (more severe)	Aripiprazole 2-20mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Inadequate response to a previous antidepressant (as defined by <50% reduction in severity of depressive symptoms-determined by the MGH ATRQ) in 1-3 antidepressant trials of at least 6 weeks duration at	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				entry into trial and inadequate response (failing to meet criteria of <50% reduction in HAMD from baseline, HAMD≥14 and CGI-I≥3) to prospective treatment phase (8-week treatment with escitalopram [10/20mg/day], fluoxetine [20/40mg/day], paroxetine CR [37.5/50mg/day; paroxetine 30/40m/day if paroxetine CR unavailable], sertraline [100/150mg/day] or venlafaxine [150/225mg/day])	• Functional impairment change score
Dunner 2007 RCT US	N=64 Mean age (years): 44.0 Gender (% female): 52 Ethnicity (% BME): 11 Baseline severity:	Ziprasidone 80mg/day or 160mg/day + sertraline 100-200mg/day	Sertraline 100-200mg/day	TRD: Failure to respond to ≥1 previous course of treatment of ≥4 weeks' duration with a clinically appropriate dose of an SSRI or non-SSRI antidepress	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	MADRS 29.95 (more severe)			ant (based on self-report), and failure to respond (<30% improvement in MADRS score and continued to have a CGI-S score ≥4 and meet DSM-IV criteria for MDD) to an initial 6-week open-label prospective treatment phase with sertraline	• Discontinuation due to any reason • Discontinuation due to side effects
Durgam 2016 RCT US & Europe	N=819 Mean age (years): 45.7 Gender (% female): 71 Ethnicity (% BME): 13 Baseline severity: MADRS 29.1 (more severe)	Cariprazine 1-2mg/day or 2-4.5mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response during the current episode to antidepressant treatment for at least 6 weeks at recommended doses	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment change score
Earley 2018 RCT US	N=527 Mean age (years): 44.0 Gender (% female): 65 Ethnicity (% BME): 28	Cariprazine 1.5-4.5mg/day + any antidepressant	Placebo + any antidepressant	TRD: previously failed to respond to 1 or 2 adequate antidepressant trials, and inadequate response	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: MADRS 25.3 (more severe)			(HAMD score improved <50%, HAMD score <15, or CGI-I score <3) to prospective open-label 8 week prospective antidepressant treatment	• Response • Discontinuation due to any reason • Discontinuation due to side effects
El-Khalili 2010 RCT US	N=446 Mean age (years): 45.5 Gender (% female): 72 Ethnicity (% BME): 10 Baseline severity: HAMD 24.1 (more severe)	Quetiapine 150mg/day or 300mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response (continuing depressive symptoms) during their current depressive episode to one of the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine for at least 6 weeks at adequate doses (minimum effective dose according to US label and including ≥1 dose increase as permitted by label)	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2011 RCT China	N=90 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Risperidone 2mg/day + paroxetine 20mg/day	Paroxetine 20mg/day	TRD: Inadequate response to ≥2 adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants for ≥3-month duration) determined through medical records and/or prospective treatment	Treatment length (weeks): 8 Outcomes: • Remission • Response • Quality of life physical component score • Quality of life mental component score
Fava 2012/ Mischoulon 2012 RCT US	N=225 Mean age (years): 45 Gender (% female): 68 Ethnicity (% BME): 19 Baseline severity: MADRS 31.1 (more severe)	Aripiprazole 2mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response (< 50% reduction in depressive symptom severity, as assessed by the MGH ATRQ) to 1-3 antidepressant trials with an adequate dose of SSRIs/ SNRIs during the current episode for ≥8 weeks	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Fava 2018 RCT US	N=231 Mean age (years): 45.4	Cariprazine 0.1–0.3mg/day or 1–2mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: failed to respond to 1-2 adequate trials of antidepress	Treatment length (weeks): 8 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Gender (% female): 71 Ethnicity (% BME): 81 Baseline severity: MADRS 26.4 (more severe)			ants (<50% reduction in depressive symptoms using the MGH ATRQ) and failed to respond (achieved <50% improvement in HAMD, HAMD score >14, or CGI-I score ≥3) to 8-week prospective open-label antidepressant treatment phase	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Fava 2019 RCT US	N=207 Mean age (years): NR Gender (% female): 73 Ethnicity (% BME): 28 Baseline severity: HAMD 22.23 (more severe)	Pimavanserin 34mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response to 1 or 2 antidepressant treatments (including SSRI/SNRI) during the current depression episode	Treatment length (weeks): 5 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score
Hobart 2018a RCT US, Germany, Poland, Slovakia, & Hungary	N=394 Mean age (years): 42.9 Gender (% female): 74	Brexpiprazole 2mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Inadequate response (<50% improved according to the MGH ATRQ) to 1-3 prior antidepress	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 15 Baseline severity: MADRS 26.64 (more severe)			ants (on a therapeutic dose for an adequate duration) during the current episode; and inadequate response (<50% improvement in HAMD and MADRS, HAMD score >14, and CGI-I score ≥3) to 8-week prospective open-label antidepressant treatment	• Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score
Hobart 2018b RCT US, Russia, Poland, France, Serbia, Germany, & Canada	N=503 Mean age (years): 43.1 Gender (% female): 68 Ethnicity (% BME): 10 Baseline severity: MADRS 25.44 (more severe)	Brexpiprazole 2-3mg/day or quetiapine 150-300mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Inadequate response (defined as <50% improved on the MGH ATRQ) during the current episode to 1-3 antidepressants at a therapeutic dose and for an adequate duration (>6 weeks); inadequate response (<50% reduction in MADRS total score between the start of prospective treatment	Treatment length (weeks): 6 Outcomes: • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				and each 2-weekly visit; CGI-I score>3 at each 2-weekly visit; and MADRS total score≥ 18) to open-label 8-10 week prospective antidepressant treatment phase	
Kamijima 2013 RCT Japan	N=586 Mean age (years): 38.7 Gender (% female): 42 Ethnicity (% BME): NR Baseline severity: MADRS 25.3 (more severe)	Aripiprazole fixed dose 3mg/day or flexible dose 3-15mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Previous inadequate response to 1–3 antidepressant trials of at least 6-weeks' duration (64% 1 trial; 27% 2 trials; 10% 3 trials); and inadequate response (<50% reduction in HAMD from baseline to the end of the screening phase; HAMD score≥14; or CGI-I score≥3) to an 8-week, single-blind, prospective treatment phase	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score
Kamijima 2018 RCT	N=412 Mean age (years): 38.9	Aripiprazole 3-12mg/day + sertraline 100mg/day	Placebo + sertraline 100mg/day	TRD: inadequate response to 1-3 previous antidepressant	Treatment length (weeks): 6 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Japan, Korea, Malaysia, Taiwan, & Australia	Gender (% female): 37 Ethnicity (% BME): 99 Baseline severity: MADRS 25.05 (more severe)			treatments (75% 1 previous adequate antidepressant treatments) and inadequate response (<50% reduction in HAMD from baseline to the end of the prospective treatment period; HAMD score≥14 at the end of the prospective treatment period; and a constant CGI-I score≥3 throughout the prospective treatment period) to 8-week prospective treatment phase with sertraline	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Global functioning change score
Keitner 2009 RCT US	N=97 Mean age (years): 45.2 Gender (% female): 59 Ethnicity (% BME): 10 Baseline severity: MADRS 25.7 (more severe)	Risperidone 0.5-3mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response to open-label treatment trial with antidepressant monotherapy (the particular antidepressant used was based on clinician choice) lasting for ≥5 weeks	Treatment length (weeks): 4 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Lenze 2015 RCT US & Canada	N=181 Mean age (years): 66.0 Gender (% female): 57 Ethnicity (% BME): 12 Baseline severity: MADRS 23 (more severe)	Aripiprazole 2-15mg/day + venlafaxine 300mg/day	Placebo + venlafaxine 300mg/day	Inadequate response (failure to remit; MADRS>10) to venlafaxine 150-300mg/day (for ≥12 weeks of treatment with ≥4 weeks at the highest tolerated dose). 74% previous history of at least 1 adequate antidepressant trial during the present episode	Treatment length (weeks): 12 Outcomes: • Remission • Discontinuation due to any reason
Li 2013 RCT China	N=95 Mean age (years): 42.2 Gender (% female): 52 Ethnicity (% BME): NR Baseline severity: HAMD 25.9 (more severe)	Quetiapine 200-400mg/day + venlafaxine 225mg/day (antidepressant switch)	Venlafaxine 225mg/day (antidepressant switch)	TRD: Inadequate response (<50% reduction of initial HAMD and HAMD score ≥20) to ≥2 different antidepressant therapies with clinically-appropriate dosage and time-course	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Mahmoud 2007 RCT US	N=274 Mean age (years): 46.1 Gender (% female): 74	Risperidone 0.25-2mg/day + any antidepressant	Placebo + any antidepressant	Inadequate response (defined as CGI-S score≥4 and a Carroll Depression Scale	Treatment length (weeks): 6 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 24 Baseline severity: HAMD 24.6 (more severe)			score≥20) to a 4-week prospective open-label run-in period with current antidepressant monotherapy at the dosages recommended in product labelling	• Depression symptomatology endpoint • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life endpoint • Functional impairment endpoint
Marcus 2008 RCT US	N=381 Mean age (years): 44.5 Gender (% female): 67 Ethnicity (% BME): 11 Baseline severity: MADRS 26.1 (more severe)	Aripiprazole 2-20mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: Inadequate response to 1-3 previous antidepressant trials of >6 weeks' duration (>3 weeks for combination treatments) at a minimum acceptable dose as determined by the MGH ATRQ and inadequate response (defined as failure to achieve ≥50% reduction in the HAMD total score from baseline to the end of the prospective treatment phase, a HAMD>14, or a CGI-I score >3) to	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				8-week single-blind prospective treatment phase with standard antidepressant in accordance with current product labelling	
McIntyre 2007 RCT Canada	N=58 Mean age (years): 44.5 Gender (% female): 62 Ethnicity (% BME): NR Baseline severity: HAMD 23.3 (more severe)	Quetiapine 50-600mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response to treatment for their current episode with a single SSRI/venlafaxine at a therapeutic dose for ≥6 weeks	Treatment length (weeks): 8 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Moica 2018 RCT Romania	N=72 Mean age (years): 39.8 Gender (% female): 75 Ethnicity (% BME): NR Baseline severity: HAMD 23.39 (more severe)	Quetiapine 150mg/day + duloxetine 60mg/day	Duloxetine 60mg/day	Inadequate response (HAMD≥14) to the antidepressant therapy (the use of minimal doses accepted as effective for a period of at least 4 - 6 weeks), for the current depressive episode	Treatment length (weeks): 8 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score
Otsuka Pharmaceutical 2015 RCT US	N=372 Mean age (years): 43.5 Gender (% female): 68	Brexpiprazole 1-3mg/day + any antidepressant	Placebo + any antidepressant	TRD: history for the current depressive episode of an inadequate response to 1-3 adequate	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: NR (unclear severity)			antidepressant treatments; incomplete response to prospective open-label treatment with commercially available antidepressant for 8 weeks at maximally tolerated doses	• Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment change score
Otsuka Pharmaceutical 2016 RCT US	N=429 Mean age (years): 43.7 Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: NR (unclear severity)	Brexpiprazole 1-4mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	TRD: report a history for the current depressive episode of an inadequate response to 1-3 adequate antidepressant treatments; incomplete response to prospective open-label treatment with a commercially available antidepressant for 8 weeks at maximally tolerated doses	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life change score • Functional impairment change score
Papakostas 2015 RCT US	N=139 Mean age (years): 44.5 Gender (% female): 71 Ethnicity (% BME): NR	Ziprasidone 40-160mg/day + escitalopram 10-30mg/day	Placebo + escitalopram 10-30mg/day	Inadequate response (continued to meet DSM-IV criteria and had a QIDS-SR score≥10) to 8-week open-label prospective	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: HAMD 20 (more severe)			phase of escitalopram treatment. Mean number of past unsuccessful trials of antidepressants during the current major depressive episode was 0.94 (SD=0.76)	• Response • Discontinuation due to any reason • Discontinuation due to side effects
Reeves 2008 RCT US	N=23 Mean age (years): 44.0 Gender (% female): 70 Ethnicity (% BME): NR Baseline severity: MADRS 35.5 (more severe)	Risperidone 0.25-2mg/day + any antidepressant	Placebo + any antidepressant	Inadequate response to 1-2 antidepressants for 3 or more weeks	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Response • Discontinuation due to any reason • Discontinuation due to side effects
Song 2007 RCT China	N=120 Mean age (years): 44.0 Gender (% female): 50 Ethnicity (% BME): NR Baseline severity: HAMD 28 (more severe)	Risperidone 0.5-2mg/day + venlafaxine 50-250mg/day	Venlafaxine 50-250mg/day	TRD: inadequate response to at least 2 antidepressants at adequate dose	Treatment length (weeks): 6 Outcomes: • Depression symptomatology endpoint
Thase 2007 RCT	N=406 Mean age (years): 44.5	Olanzapine 6, 12 or 18mg/day +	Fluoxetine 50mg/day	TRD: Documented history of failure to achieve a	Treatment length (weeks): 8

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
US & Canada	Gender (% female): 64 Ethnicity (% BME): 13 Baseline severity: MADRS 30 (more severe)	fluoxetine 50mg/day		satisfactory response (based on investigator's clinical judgement) to an antidepressant (except fluoxetine) after ≥6 weeks of therapy at a therapeutic dose, and failure to respond (<25% decrease in HAMD) to an 8-week, open-label prospective fluoxetine (25-50mg/day) therapy lead-in	Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score
Thase 2015a RCT US, Poland, France, & Slovakia	N=379 Mean age (years): 44.7 Gender (% female): 70 Ethnicity (% BME): 13 Baseline severity: MADRS 26.85 (more severe)	Brexpiprazole 0.5-2mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response during the current episode, defined as <50% reduction in symptoms via patient self-reports on the MGH ATRQ to an adequate trial of 1-3 antidepressants including the most recent drug treatment. During the current episode, 82% had 1 prior antidepressant failure	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Thase 2015b RCT US, Germany, Ukraine, Russia, Hungary, Canada, & Romania	N=677 Mean age (years): 45.6 Gender (% female): 68 Ethnicity (% BME): 13 Baseline severity: MADRS 26.47 (more severe)	Brexpiprazole 1mg/day or 3mg/day + SSRI/SNRI	Placebo + SSRI/SNRI	Inadequate response during the current episode, defined as <50% reduction in MGH ATRQ score to an adequate trial of 1-3 antidepressants. 78% 1 prior antidepressant treatment	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Functional impairment score

BME: black and minority ethnic; CGI-I: clinical global impression-improvement; CGI-S: clinical global impression-severity; CR: controlled release; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; MDE: major depressive episode; MGH ATRQ: Massachusetts General Hospital antidepressant treatment response questionnaire; NR: not reported; QIDS-SR: quick inventory of depressive symptomatology-self report; RCT: randomised controlled trial; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 47: Summary of included studies. Comparison 46. Augmenting with antipsychotic versus bupropion

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Cheon 2017 RCT Korea	N=103 Mean age (years): 45.6 Gender (% female): 65 Ethnicity (% BME): NR Baseline severity: MADRS 25.54 (more severe)	Aripiprazole 2.5-20mg/day + SSRI	Bupropion 150-300mg/day + SSRI	Inadequate response to 4 or more weeks with SSRIs	Treatment length (weeks): 6 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Mohamed 2017 RCT US	N=1011 Mean age (years): 54.3 Gender (% female): 16 Ethnicity (% BME): 30 Baseline severity: QIDS 16.75 (more severe)	Aripiprazole 2-15mg/day + SSRI/SNRI	Bupropion 150-400mg/day + SSRI/SNRI	Inadequate response (QIDS score ≥16 after ≥6 weeks of treatment or score≥11 after ≥8 weeks of treatment with the 3 most recent weeks at a stable "optimal" dose) to a treatment course with a SSRI, SNRI, or mirtazapine that met or exceeded minimal standards for dose and duration of treatment	Treatment length (weeks): 12 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 48: Summary of included studies. Comparison 47. Augmenting with antipsychotic versus lithium

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Bauer 2013 RCT Australia, Austria, Belgium, Bulgaria, Germany, Hungary, Italy, Portugal, Romania,	N=460 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR	Quetiapine extended-release (XR) 200-300mg/day + SSRI/SNRI	Lithium 450-900mg/day (target plasma level: 0.6–1.2mmol/L) + SSRI/SNRI	Stage I (failure to achieve remission after ≥1 adequate trial of 1 major class of AD) or stage II (failure of adequate trials of 2	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Slovakia, Spain & UK	Baseline severity: MADRS 33.05 (more severe)			different classes of AD) TRD, 50% in each category	• Discontinuation due to side effects
Doree 2007 RCT Canada	N=20 Mean age (years): 50.8 Gender (% female): 60 Ethnicity (% BME): NR Baseline severity: MADRS 37.95 (more severe)	Quetiapine 400-800mg/day + any antidepressant	Lithium 600mg/day (target plasma levels 0.8–1.2 mmol/L) + any antidepressant	Inadequate response after 4 weeks of treatment with an antidepressant at the maximal recommended dose	Treatment length (weeks): 8 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Yoshimura 2014 RCT Japan	N=30 Mean age (years): 40.3 Gender (% female): 60 Ethnicity (% BME): NR Baseline severity: HAMD 22.7 (more severe)	Olanzapine (mean dose 7mg/day) or Aripiprazole (mean dose 9mg/day) + paroxetine	Lithium (mean dose 458mg/day) + paroxetine	Inadequate response (<50% improvement from baseline on HAMD) to 8-week prospective treatment with paroxetine	Treatment length (weeks): 4 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 49: Summary of included studies. Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Bauer 2013 RCT	N=459 Mean age (years): NR	Quetiapine extended-release (XR) 200-300mg/day + SSRI/SNRI	Quetiapine monotherapy 200-300mg/day	Stage I (failure to achieve remission after ≥1 adequate	Treatment length (weeks): 6 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Australia, Austria, Belgium, Bulgaria, Germany, Hungary, Italy, Portugal, Romania, Slovakia, Spain & UK	Gender (% female): NR Ethnicity (% BME): NR Baseline severity: MADRS 33.45 (more severe)			trial of 1 major class of antidepressants) or stage II (failure of adequate trials of 2 different classes of antidepressants) TRD, 50% in each category	• Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Thase 2007 RCT US & Canada	N=399 Mean age (years): 44.3 Gender (% female): 64 Ethnicity (% BME): 15 Baseline severity: MADRS 30 (more severe)	Olanzapine 6, 12 or 18mg/day + fluoxetine 50mg/day	Olanzapine monotherapy 6, 12 or 18mg/day	TRD: Documented history of failure to achieve a satisfactory response (based on investigator's clinical judgement) to an antidepressant (except fluoxetine) after at least 6 weeks of therapy at a therapeutic dose, and failure to respond (<25% decrease in HAMD) to 8 weeks of fluoxetine 25-50mg/day	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects • Quality of life physical component score • Quality of life mental component score

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 50: Summary of included studies. Comparison 49. Augmenting with antipsychotic versus switch to bupropion

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Mohamed 2017 RCT US	N=1016 Mean age (years): 54.4 Gender (% female): 14 Ethnicity (% BME): 32 Baseline severity: QIDS 16.75 (more severe)	Aripiprazole 2-15mg/day + SSRI/SNRI	Bupropion monotherapy 150-400mg/day	Inadequate response (QIDS score ≥16 after ≥6 weeks of treatment or score≥11 after ≥8 weeks of treatment with the 3 most recent weeks at a stable "optimal" dose) to a treatment course with a SSRI, SNRI, or mirtazapine that met or exceeded minimal standards for dose and duration of treatment	Treatment length (weeks): 12 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 51: Summary of included studies. Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Appelberg 2001 RCT Finland	N=113 Mean age (years): 44 Gender (% female): 63 Ethnicity (% BME): NR	Buspirone 20-60mg/day + citalopram or fluoxetine	Placebo + citalopram or fluoxetine	Inadequate response (as judged by the psychiatrist in charge of treatment) to ≥ 6 weeks of treatment with fluoxetine (at a dose of	Treatment length (weeks): 6 Outcomes: • Response

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (more severe)			≥30mg/day for ≥4 weeks prior to inclusion) or citalopram (at a dose of ≥40mg/day for ≥4 weeks prior to inclusion)	
Fang 2011 RCT China	N=91 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Buspirone 30mg/day + paroxetine	Paroxetine 20mg/day	TRD: Inadequate response to ≥2 adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with at least 3-month duration) determined through medical records and/or prospective treatment	Treatment length (weeks): 8 Outcomes: • Remission • Response • Quality of life physical component score • Quality of life mental component score

BME: black and minority ethnic; NR: not reported; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 52: Summary of included studies. Comparison 51. Augmenting with buspirone versus bupropion

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Trivedi 2006	N=565	Buspirone 15-60mg/day (mean final	Bupropion sustained release 200-	Inadequate response (without	Treatment length (weeks): 6

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
RCT US	Mean age (years): 41.1 Gender (% female): 59 Ethnicity (% BME): 22 Baseline severity: HAMD 15.8 (less severe)	dose 40.9 mg/day) + citalopram	400mg/day (mean final dose 267.5 mg/day) + citalopram	remission [HAMD>7]) to a mean of 11.9 weeks of citalopram therapy (mean final dose 55mg/day)	Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; RCT: randomised controlled trial

Table 53: Summary of included studies. Comparison 52. Augmenting with methylphenidate versus placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Patkar 2006 RCT US	N=60 Mean age (years): 48.5 Gender (% female): 63 Ethnicity (% BME): 40 Baseline severity: HAMD 19.4 (more severe)	Methylphenidate extended release formulation 18-54mg/day + any antidepressant	Placebo + any antidepressant	Inadequate response to ≥1 antidepressant at study entry, defined as ≥ 6-week trial of an antidepressant at an acceptable therapeutic dose. 70% had failed multiple antidepressant trials for the current MDD episode	Treatment length (weeks): 4 Outcomes: • Remission • Response • Discontinuation due to side effects
Ravindran 2008a RCT Canada	N=145 Mean age (years): 43.8 Gender (% female): 65	Methylphenidate extended release formulation 18-54mg/day + any antidepressant	Placebo + any antidepressant	Inadequate response to 1-3 previous antidepressant monotherapies (including current AD	Treatment length (weeks): 5 Outcomes: • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 2 Baseline severity: MADRS 26.7 (more severe)			antidepressant of adequate dose and duration and at entry were taking an adequate dose of an antidepressant during the current depressive episode for ≥4 weeks	• Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; RCT: randomised controlled trial

Table 54: Summary of included studies. Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Baumann 1996 RCT Switzerland	N=25 Mean age (years): 41.8 Gender (% female): 71 Ethnicity (% BME): NR Baseline severity: NR (more severe)	Lithium 800mg/day (target plasma levels 0.5-0.8 mmol/L) + citalopram 20-60mg/day	Placebo + citalopram 20-60mg/day	Inadequate response (improvement<50% on HAMD) to 4-week prospective treatment phase with citalopram (20-60mg/day)	Treatment length (weeks): 1 Outcomes: • Response
Girlanda 2014 RCT Italy	N=56 Mean age (years): 46.5 Gender (% female): 63 Ethnicity (% BME): NR	Lithium (planned starting dose 150-300mg and target plasma levels from 0.4 to 1.0 mmol/L; actual mean dose 444 mg & mean blood level of 0.57 mEq/L) + any	Any antidepressant	TRD: Inadequate response to ≥2 antidepressants given sequentially at an adequate dose for an adequate time for the current	Treatment length (weeks): 52 Outcomes: • Depression symptomatology change score • Discontinuation due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: QIDS 18.3 (more severe)	antidepressant		depressive episode	
Joffe 1993 RCT Canada	N=33 Mean age (years): NR Gender (% female): 55 Ethnicity (% BME): NR Baseline severity: HAMD 19.47 (more severe)	Lithium 900-1200mg/day (target plasma level 0.55 nmol/L; mean dose 935.3mg/day) + desipramine/ imipramine	Placebo + desipramine/ imipramine	Inadequate response (HAMD score≥16) to a previous adequate trial of desipramine hydrochloride (90%) or imipramine hydrochloride (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects
Nierenberg 2003a RCT US	N=35 Mean age (years): 38.4 Gender (% female): 46 Ethnicity (% BME): NR Baseline severity: NR (unclear severity)	Lithium (dose NR) + nortriptyline	Placebo + nortriptyline	TRD: Inadequate response to 1-5 adequate trials of antidepressants during the current episode, and failure to respond to 6 weeks of nortriptyline	Treatment length (weeks): 6 Outcomes: • Response • Discontinuation due to any reason
Stein 1993 RCT UK	N=34 Mean age (years): 47.2 Gender (% female): 79 Ethnicity (% BME): NR Baseline severity:	Lithium 250mg/day + TCA	Placebo + TCA	Inadequate response (failure to show improvement) to treatment with ≥3 weeks of TCA at an adequate dose	Treatment length (weeks): 3 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	MADRS 29.9 (more severe)				• Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; TCA: tricyclic antidepressant; TRD: treatment-resistant depression

Table 55: Summary of included studies. Comparison 54. Augmenting with lithium versus switch to antipsychotic

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Bauer 2013 RCT Australia, Austria, Belgium, Bulgaria, Germany, Hungary, Italy, Portugal, Romania, Slovakia, Spain & UK	N=457 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: MADRS 33.3 (more severe)	Lithium 450-900mg/day (target plasma level: 0.6–1.2mmol/L) + SSRI/SNRI	Quetiapine monotherapy 200-300mg/day	Stage I (failure to achieve remission after ≥1 adequate trial of 1 major class of antidepressant) or stage II (failure of adequate trials of 2 different classes of antidepressant) TRD, 50% in each category	Treatment length (weeks): 6 Outcomes: • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TRD: treatment-resistant depression

Table 56: Summary of included studies. Comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Kennedy 2003 RCT	N=44 Mean age (years): 39.3	Lithium 600-900mg/day + SSRI/SNRI/ moclobemide	CBT individual 12 sessions + SSRI/SNRI/ moclobemide	Partial response (score of 8-15 on HAMD-D) to	Treatment length (weeks): 8 Outcomes:

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Canada	Gender (% female): 55 Ethnicity (% BME): NR Baseline severity: HAMD 11.9 (less severe)			1 of 4 standard antidepressant medications (moclobemide, paroxetine, sertraline, or venlafaxine) to maximum tolerated doses for 8-14 weeks	• Depression symptomatology at: ○ Endpoint ○ 1-month follow-up • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

Table 57: Summary of included studies. Comparison 56. Augmenting with lithium versus augmenting with TCA

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fava 1994a RCT US	N=26 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 19.01 (more severe)	Lithium 300-600mg/day + fluoxetine 20mg/day	Desipramine 25-50mg/day + fluoxetine 20mg/day	Inadequate response (<50% improvement in HAMD score and HAMD≥10) to 8 weeks of fluoxetine 20mg/day	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effect
Fava 2002 RCT	N=68 Mean age (years): NR	Lithium 300-600mg/day + fluoxetine 20mg/day	Desipramine 25-50mg/day + fluoxetine 20mg/day	Inadequate response (<50% improvemen	Treatment length (weeks): 4

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
US	Gender (% female): NR Ethnicity (% BME): NR Baseline severity: HAMD 16.75 (more severe)			t in HAMD score and HAMD≥10) to 8 weeks of fluoxetine 20mg/day	Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TCA: tricyclic antidepressant

Table 58: Summary of included studies. Comparison 57. Augmenting with omega-3 fatty acids versus placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Jahangard 2018 RCT Iran	N=50 Mean age (years): 42.5 Gender (% female): 68 Ethnicity (% BME): NR Baseline severity: MADRS 34.9 (more severe)	Omega-3 fatty acid 1000mg/day + sertraline 50-200mg/day	Placebo + sertraline 50-200mg/day	Inadequate response: met inclusion criteria despite receiving sertraline (50–200 mg/day) for 8 weeks	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Discontinuation due to any reason • Discontinuation due to side effects • Sleeping difficulties endpoint
Mozaffari-Khosravi 2013 RCT Iran	N=81 Mean age (years): 35.1 Gender (% female): 61	Eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) 1 g/day + any antidepressant	Placebo + any antidepressant	Inadequate response to current antidepressant treatment (met DSM-IV criteria for MDD	Treatment length (weeks): 12 Outcomes: • Depression symptomatology endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 15.7 (less severe)			and HAMD>7; mean length of antidepressant treatment: 3.9 months)	• Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects
Nemets 2002 RCT Israel	N=20 Mean age (years): 53.4 Gender (% female): 85 Ethnicity (% BME): NR Baseline severity: HAMD 23.15 (more severe)	Eicosapentaenoic acid (E-EPA) 2g/day + SSRI	Placebo + SSRI	Inadequate response: met inclusion criteria despite receiving current AD treatment for ≥3 months	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response • Discontinuation due to any reason • Discontinuation due to side effects
Peet 2002 RCT UK	N=70 Mean age (years): 44.7 Gender (% female): 84 Ethnicity (% BME): NR Baseline severity: MADRS 22.7 (more severe)	Ethyl-eicosapemtaenoate 1g/day, 2g/day or 4g/day + any antidepressant	Placebo + any antidepressant	Inadequate response (HAMD≥15) to ongoing treatment with antidepressant at an adequate dose	Treatment length (weeks): 12 Outcomes: • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MADRS: Montgomery-Asberg depression rating scale; MDD: major depressive disorder; NR: not reported; RCT: randomised controlled trial; SSRI: selective serotonin reuptake inhibitor

Table 59: Summary of included studies. Comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Fang 2011 RCT China	N=93 Mean age (years): NR Gender (% female): NR Ethnicity (% BME): NR Baseline severity: NR (more severe)	Thyroid hormone 80mg/day + paroxetine	Paroxetine 20mg/day	TRD: Inadequate response to ≥2 adequate treatments from different classes of antidepressants in the current depressive episode (adequate dosages of antidepressants with ≥3-month duration) determined through medical records and/or prospective treatment. Paroxetine 1-week lead-in	Treatment length (weeks): 8 Outcomes: • Remission • Response • Quality of life physical component score • Quality of life mental component score
Joffe 1993 RCT Canada	N=33 Mean age (years): NR Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: HAMD 18.75 (more severe)	Liothyronine sodium (triiodothyronine, T3) 37.5µg + desipramine/ imipramine	Placebo + desipramine/ imipramine	Inadequate response (HAMD≥16) to a previous adequate trial of desipramine hydrochloride (90%) or imipramine hydrochloride (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 60: Summary of included studies. Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Joffe 1993 RCT Canada	N=34 Mean age (years): NR Gender (% female): 59 Ethnicity (% BME): NR Baseline severity: HAMD 19.5 (more severe)	Liothyronine sodium (triiodothyronine, T3) 37.5µg + desipramine/ imipramine	Lithium 900-1200mg/day (target plasma level 0.55 nmol/L) + desipramine/ imipramine	Inadequate response (HAMD≥16) to a previous adequate trial of desipramine hydrochloride (90%) or imipramine hydrochloride (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Discontinuation due to any reason • Discontinuation due to side effects
Nierenberg 2006 RCT US	N=142 Mean age (years): 42.0 Gender (% female): 58 Ethnicity (% BME): 17 Baseline severity: QIDS 12.4 (more severe)	Thyroid hormone (T3) 25-50 µg/day + any antidepressant	Lithium 225-900mg/day + any antidepressant	TRD: Inadequate response (not achieved remission or who were intolerant) to an initial prospective treatment with citalopram and a second switch or augmentation trial	Treatment length (weeks): 14 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission • Response • Discontinuation due to side effects

BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; QIDS: quick inventory of depressive symptomatology; RCT: randomised controlled trial; TRD: treatment-resistant depression

Table 61: Summary of included studies. Comparison 60. Switching to ECT versus switching to paroxetine

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Folkerts 1997 RCT	N=40	6-9- ECT treatments	Paroxetine 20-50mg/day	TRD: Failure to respond to	Treatment length (weeks): 4

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Germany	Mean age (years): 49.8 Gender (% female): 54 Ethnicity (% BME): NR Baseline severity: HAMD 31.79 (more severe)			≥2 different antidepressants (including ≥1 TCA) over a total period of 8 weeks	Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Response • Discontinuation due to any reason • Discontinuation due to side effects

BME: black and minority ethnic; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial; TCA: tricyclic antidepressant; TRD: treatment-resistant depression

Table 62: Summary of included studies. Comparison 61. Augmenting with ECT versus continuing with antidepressant

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Haghighi 2013 RCT Iran	N=40 Mean age (years): 31.5 Gender (% female): 30 Ethnicity (% BME): NR Baseline severity: HAMD 37.2 (more severe)	12 ECT sessions + citalopram 40mg/day	Citalopram 40mg/day	Inadequate response to 2-weeks of citalopram (40mg/day) and ECT recommended by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score

BME: black and minority ethnic; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 63: Summary of included studies. Comparison 62. Augmenting with ECT versus augmenting with exercise

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Salehi 2016 RCT Iran	N=40 Mean age (years): 29.4 Gender (% female): 28 Ethnicity (% BME): NR Baseline severity: HAMD 41.23 (more severe)	12 ECT sessions + citalopram 40mg/day	12 exercise sessions + citalopram 40mg/day	Inadequate response to 2-weeks of citalopram (40mg/day) and ECT recommended by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission

BME: black and minority ethnic; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 64: Summary of included studies. Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Salehi 2016 RCT Iran	N=40 Mean age (years): 29.7 Gender (% female): 28 Ethnicity (% BME): NR Baseline severity: HAMD 42.5 (more severe)	12 ECT sessions + 12 exercise sessions + citalopram 40mg/day	12 exercise sessions + citalopram 40mg/day	Inadequate response to 2-weeks of citalopram (40mg/day) and ECT recommended by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission

BME: black and minority ethnic; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 65: Summary of included studies. Comparison 64. Augmenting with exercise versus TAU

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Danielsson 2014 RCT Sweden	N=42 Mean age (years): 45.5 Gender (% female): 76 Ethnicity (% BME): NR Baseline severity: MADRS 24 (more severe)	Aerobic exercise + SSRI/SNRI Intensity: 2 individual sessions + 16x twice-weekly 1-hour group training sessions	Enhanced TAU + SSRI/SNRI Intensity: 1 session	Inadequate response (retained diagnosis) to a course of antidepressants, of at least 6 weeks duration	Treatment length (weeks): 10 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason
Ho 2014 RCT China	N=52 Mean age (years): 46.2 Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: MADRS 19 (less severe)	Aerobic exercise group + any antidepressant Intensity: 15x thrice-weekly 40-min sessions	Any antidepressant	Inadequate response: met inclusion criteria despite being on antidepressant at baseline	Treatment length (weeks): 3 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission

BME: black and minority ethnic; MADRS: Montgomery-Asberg depression rating scale; NR: not reported; RCT: randomised controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual

Table 66: Summary of included studies. Comparison 65. Augmenting with exercise versus attention-placebo

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Lavretsky 2011 RCT US	N=73 Mean age (years): 70.6 Gender (% female): 62	Tai Chi + escitalopram 10-20mg/day Intensity: 10x 2-hour sessions	Attention-placebo (health education) + escitalopram 10-20mg/day	Inadequate response to 4 weeks prospective treatment with escitalopram	Treatment length (weeks): 10 Outcomes: • Depression symptomatology endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 9 (less severe)		Intensity: 10x 2-hour sessions		• Remission • Discontinuation due to any reason • Sleeping difficulties emdpoint
Mather 2002 RCT UK	N=86 Mean age (years): 65.0 Gender (% female): 69 Ethnicity (% BME): NR Baseline severity: HAMD 17.05 (more severe)	Weight training class + any antidepressant Intensity: 20x twice-weekly 45-min sessions	Attention-placebo (health education talks) + any antidepressant Intensity: 20x twice-weekly 30-40 min sessions	Inadequate response: all participants had been in receipt of a therapeutic dose of antidepressant therapy for at least 6 weeks without evidence of a sustained response prior to study entry	Treatment length (weeks): 10 Outcomes: • Response • Discontinuation due to any reason
Mota-Pereira 2011 RCT Portugal	N=33 Mean age (years): 47.5 Gender (% female): 66 Ethnicity (% BME): NR Baseline severity: HAMD 17 (more severe)	Aerobic exercise + any antidepressant Intensity: 60 sessions/12x 30-45min sessions supervised	Attention-placebo (social interaction with study staff and peers) + any antidepressant Intensity: 12x 30-45min sessions	Inadequate response (failure to show clinical remission, HAMD>7) to combined therapy in doses considered adequate for 9-15 months	Treatment length (weeks): 12 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason • Global functioning change score

1 *BME: black and minority ethnic; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised*
2 *controlled trial*

Table 67: Summary of included studies. Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Salehi 2016 RCT Iran	N=40 Mean age (years): 30.0 Gender (% female): 35 Ethnicity (% BME): NR Baseline severity: HAMD 43.38 (more severe)	Exercise + ECT + citalopram 40mg/day Intensity: Exercise: 12x thrice-weekly sessions; ECT: 12x thrice-weekly sessions	ECT + citalopram 40mg/day Intensity: 12x thrice-weekly exercise sessions	Inadequate response to 2-weeks of citalopram (40mg/day) and ECT recommended by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: • Depression symptomatology endpoint • Depression symptomatology change score • Remission

BME: black and minority ethnic; ECT: electroconvulsive therapy; HAMD: Hamilton depression scale; NR: not reported; RCT: randomised controlled trial

Table 68: Summary of included studies. Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Sharma 2017 RCT US	N=25 Mean age (years): 37.2 Gender (% female): 72 Ethnicity (% BME): 8 Baseline severity: HAMD 20.4 (more severe)	Sudarshan Kriya yoga (SKY) group + any antidepressant Intensity: 12 sessions	Waitlist + any antidepressant	Inadequate response: met inclusion criteria despite having received a stable dose of antidepressant treatment for at least 8 weeks	Treatment length (weeks): 8 Outcomes: • Depression symptomatology change score • Remission • Response • Discontinuation due to any reason
Uebelacker 2017 RCT US	N=122 Mean age (years): 46.5 Gender (% female): 84	Hatha yoga group + any antidepressant Intensity: 10-20x 80-min sessions	Attention-placebo (health living workshop) + any antidepressant	Inadequate response: met inclusion criteria despite currently taking an antidepressant at a	Treatment length (weeks): 10 Outcomes: • Remission at: ○ Endpoint ○ 3-month follow-up

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 16 Baseline severity: QIDS 12.87 (more severe)		Intensity: 10-20x 60-min sessions	dose with demonstrated effectiveness per American Psychiatric Association practice guidelines for at least 8 weeks	○ 6-month follow-up • Response at: ○ Endpoint ○ 3-month follow-up ○ 6-month follow-up • Discontinuation due to any reason

BME: black and minority ethnic; HAMD: Hamilton depression scale; QIDS: quick inventory of depressive symptomatology; 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).

The systematic search of the economic literature identified 3 UK studies that assessed the cost-effectiveness of psychological interventions (Hollinghurst 2014, Phillips 2014, Scott 2003), 3 UK studies that assessed the cost-effectiveness of pharmacological interventions (Benedict 2010, Edwards 2013, Kessler 2018a/2018b) and 1 UK study that assessed the cost-effectiveness of ECT (Greenhalgh 2005) for adults with depression showing an inadequate response to at least one previous intervention for the current episode. Following the hierarchy of inclusion criteria regarding country settings, one Canadian study (Town 2017/2020) that assessed the cost-effectiveness of short term psychodynamic psychotherapy, one Swedish study (Nordström 2010), one Finnish study (Soini 2017) and 6 US studies (Malone 2007, Taneja 2012, Olgiati 2013, Singh 2017, Sussman 2017, Yoon 2018) that assessed the cost effectiveness of pharmacological interventions, and 1 US study (Ross 2018) that assessed the cost-effectiveness of ECT in adults with depression that failed to respond to previous treatment were also included in the review, because they assessed interventions or made comparisons that had not been covered in UK studies.

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

Computerised cognitive behavioural therapy with support following inadequate response to antidepressants

Phillips 2014 undertook an economic analysis alongside a RCT (N=637; for the clinical analysis, completion was 56% at 6 weeks and 36% at 12 weeks; for the cost analysis, completion rates were not reported) to estimate the cost effectiveness of computerised CBT with support (the freely available package of MoodGYM) versus attention control in adults with depression, who were already under psychotropic medication, in the UK. The perspective of the analysis was that of the NHS. Costs included hospital services (inpatient and outpatient care), community services, staff time (GP, psychiatrist, district nurse, counsellor, occupational health providers, other providers) and medication. The outcome measures were the change in Work and Social Adjustment Scale (WSAS) scores and the QALY, estimated based on EQ-5D (UK tariff). The time horizon of the analysis was 12 weeks for the outcomes and 6 weeks for costs.

The time horizon of the analysis was very short and different for costs and outcomes, with very low completion rates for outcome data both at 6 and 12 weeks. Attention control was shown to be more costly and more effective than computerised CBT. The study is characterised by inadequate reporting of results; no incremental analysis was conducted (although it is possible to conduct from reported data) and no uncertainty results were presented. Finally, it is unclear if the intervention cost (in terms of equipment and overheads required) has been considered in the analysis. Therefore, although the study is directly applicable to the UK context, it is characterised by very serious limitations and therefore was not further considered when formulating recommendations.

Cognitive therapy or cognitive behavioural therapy in addition to antidepressants versus antidepressants alone

Scott 2003 conducted a cost effectiveness analysis alongside a RCT (Paykel1999/Scott 2000; N=158) that compared cognitive therapy in addition to antidepressant therapy and clinical management versus antidepressant therapy and clinical management alone, in adults who were in an episode of major depression within the past 18 months but not in the past 2 months, and who had residual symptoms over at least 8 weeks (HAMD ≥ 8 and BDI ≥ 9). The perspective of the analysis was that of the NHS and personal social services (PSS). Healthcare cost elements consisted of interventions (cognitive therapy, medication, clinical management), inpatient care, day hospital, staff time (GP, social worker, community psychiatric nurse, therapist/counsellor), group therapy and marital therapy. National and local inpatient unit costs were used. The outcome measure was the percentage of relapses prevented. The duration of the analysis was 17 months.

Cognitive therapy in addition to antidepressants and clinical management was significantly more effective and more costly than antidepressant therapy and clinical management alone, with an Incremental Cost Effectiveness Ratio (ICER) of £7,621/additional relapse prevented (2020 prices). This figure was higher depending on the method of imputation of missing data and reached £12,425 when a complete case analysis, using 65% of participants, was conducted. The probability of cognitive therapy in addition to antidepressant being cost-effective was 0.60 and 0.80 at a willingness to pay (WTP) of £10,500 and £15,000 per relapse prevented, respectively. This probability was sensitive to the method of missing data imputation. The study is partially applicable to the NICE decision-making context as it does not use the QALY as the measure of outcome and interpretation of the results requires

judgement as to whether the additional unit of benefit (prevention of one relapse) is worth the additional cost of £7,621. The study is characterised by minor limitations.

Hollinghurst 2014 conducted a cost consequence and cost-utility analysis alongside a RCT (Wiles 2013/2016; N=469) to assess the cost effectiveness of cognitive behavioural therapy (CBT) in addition to TAU versus TAU alone, in adults with major depression who had adhered to antidepressant medication for at least 6 weeks in primary care, but who continued to have significant depressive symptoms (BDI-II score ≥14 and ICD-10 diagnosis of depression), in the UK; TAU comprised GP care, including antidepressant treatment as judged appropriate by the person's GP or a referral, as required. The time horizon of the analysis was 12 months; 3-5 year follow up data were also reported. The perspective of the cost-utility analysis was that of the NHS and PSS, with cost elements comprising intervention (CBT), medication, primary and community mental and general health care, and specialist (secondary) mental health care. National unit costs were used. A number of outcomes were assessed, such as the change in BDI-II score, response and remission rates, and the SF-12 mental and physical subscales. QALYs were estimated using the EQ-5D (UK tariff), with SF-6D ratings being used for the estimation of QALYs in a sensitivity analysis.

CBT was found to be associated with a significant increase in total NHS and PSS costs and was also significantly better than control in a number of outcomes including response, the SF-12 mental sub-scale score and the QALY, both at 12 months and at the 3-5 year follow up. At 12 months, the ICER of CBT plus TAU versus TAU alone was £17,639/QALY (2020 prices). The probability of CBT being cost-effective was 0.74 and 0.91 at the NICE lower and upper cost effectiveness threshold of £20,000 and £30,000/QALY, respectively. Results were not sensitive to a change in psychologist unit costs and to the exclusion of hospitalisation costs; in contrast, results were sensitive to estimation of QALYs using the SF-6D instead of EQ-5D, with the ICER rising at £35,045/QALY. Analysis of participants with full complete data (instead of imputation of missing data) resulted in ICER of £21,720/QALY. At the 3-5 year follow up, the ICER of CBT versus TAU dropped at £5,943/QALY (2020 prices) with the probability of CBT being cost-effective rising at 0.92 and 0.95, at the NICE lower and upper cost effectiveness threshold of £20,000 and £30,000/QALY, respectively. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Intensive short-term psychodynamic psychotherapy

Town 2017/2020 assessed the cost-utility of intensive short-term psychodynamic psychotherapy versus secondary care TAU, comprising community mental health teams delivering pharmacotherapy and clinical management, supportive or structured activities focused around symptom management and in some cases individual or group psychotherapy, in adults with depression who were non-remitting following at least one antidepressant treatment course, over 18 months, in Canada. The study was undertaken alongside a RCT (Town 2017/2020, N=60) and adopted a mental health payer perspective. The study is partially applicable to the UK setting as it was conducted in Canada, and it was considered to have very serious limitations, as the authors reported that the intervention was dominant, yet in probabilistic analysis the intervention was cost-saving only in 2.5% of iterations and its probability of being cost-effective at a cost-effectiveness threshold of £15,000/QALY was 0.65. Therefore the study was not further considered when formulating recommendations.

Mirtazapine as an adjunct treatment to SSRIs or SNRIs

Kessler 2018a/2018b undertook a cost-utility analysis alongside a RCT (Kessler 2018a/2018b; N=480, with 75% of cost and effectiveness data available for the economic analysis) to assess the cost effectiveness of mirtazapine added to a SSRI or SNRs versus pill placebo added to a SSRI or SNRI, in adults with major depression who had used an SSRI or SNRI for at least six weeks but were still depressed, in the UK. The time horizon of

the analysis was 12 months. The perspective of the cost-utility analysis was that of the NHS and PSS. Costs included mirtazapine, other medication, hospital care related to depression or mental health (inpatient care, A&E attendances, outpatient care), primary and community care (e.g. GP or nurse contacts, CBT, counselling or other talking therapies, mental health clinic, prescribed exercise programmes, NHS Direct, NHS walk-in centres), personal social services (mental health nurse home visits, occupational therapy, social worker, day centre use, etc.) National unit costs were used. The primary measure of outcome was the QALY, estimating using the 5-level EQ-5D (UK tariff).

Mirtazapine was found to be more costly and more effective than pill placebo, with an incremental net monetary benefit (INMB) of £430 (-£987 to £1,846) [completer analysis] and £99 (-£115 to £313) [imputed data analysis] in 2020 prices. The probability of mirtazapine being cost-effective was 0.69 and 0.71 at the NICE lower and upper cost effectiveness threshold of £20,000 and £30,000/QALY, respectively. The study is partially applicable to the NICE decision-making context as it used the EQ-5D-5L (and not the 3-level one) and is characterised by minor limitations.

Continuation of current pharmacological treatment (citalopram) versus switching to another antidepressant (venlafaxine, sertraline) or augmentation with bupropion

Olgiati 2013 compared the cost-effectiveness of different strategies for adults with depression that did not remit following pharmacological treatment (citalopram), comprising continuation of current treatment (citalopram), switching to sertraline or venlafaxine, or augmentation of citalopram with bupropion in the US. The study reported that both switching and augmentation strategies were more cost-effective than continuation of current treatment with citalopram. However, efficacy data for the 3 strategies were taken from different studies without using a common comparator, thus breaking randomisation rules. The study is partially applicable to the UK context and is characterised by very serious limitations; therefore, it has not been considered further when formulating recommendations.

Sertraline versus venlafaxine versus bupropion following inadequate response to previous SSRI treatment

Soini 2017 assessed the relative cost-effectiveness of a number of antidepressants (sertraline, venlafaxine, bupriopion, as well as agomelatine and votrioxetine that were not part of this review question) for adults with depression that required further treatment after inadequate response to previous treatment with SSRIs. The study was based on decision-analytic modelling and was conducted from the perspective of the Finnish health service payer. Costs included medication, GP visits, psychiatrist, psychotherapist or counsellor's time, and hospital (psychiatric ward, outpatient visit). National unit costs were used. The source of efficacy data for the 3 interventions of interest was a RCT (Rush 2006; n=727 at level 2). The measure of outcome was the QALY, based on Finish EQ-5D ratings on the VAS scale. The time horizon of the analysis was 12 months.

According to the results, sertraline was dominated by both venlafaxine and bupropion. Bupropion was more effective and more costly than venlafaxine, with an ICER of £2,249/QALY in 2020 prices. The study is partially applicable to the UK as it was conducted in Finland, and is characterised by potentially serious limitations, including the bias introduced in the analysis, as it was funded by industry. Moreover, the analysis included two further interventions (agomelatine, vortioxertine) that were not part of the review question for this guideline (and thus were not of interest) and assessed uncertainty, in the form of probability of cost-effectiveness, after making pairwise comparisons (so that vortioxetine was compared with one intervention at a time); therefore, it was not possible to extract the uncertainty associated with the 3 interventions of interest (in terms of probability of cost-effectiveness of each intervention out of the 3) from the study.

Singh 2017 assessed the relative cost-effectiveness of sertraline, venlafaxine and bupriopion for adults with depression that required further treatment after inadequate response to previous treatment with SSRIs. The study was conducted alongside a RCT (Rush 2006; n=727) and was conducted from the perspective of the US government as a payer. Costs included medication, outpatient and A&E visits, as well as hospitalisation. National unit costs were used. Two measures of outcome were used: response and remission. The time horizon of the analysis was 9 weeks.

According to the results, there were no statistically significant differences in costs or in effects among the 3 interventions. At a cost-effectiveness threshold of £23,000 per unit of effectiveness, venlafaxine had the highest net health benefit in terms of response and a probability of being the most cost-effective option around 40%, while sertraline had the highest net health benefit in terms of remission and a probability of being the most cost-effective option of approximately 45%. The study is partially applicable to the NICE decision making-context as it was carried out in the US and did not use the QALY as the outcome measure and is characterised by potentially serious limitations, mainly due to its short time horizon.

Duloxetine versus venlafaxine versus mirtazapine following inadequate response to previous SSRI treatment

Benedict 2010 constructed an economic model to evaluate the cost effectiveness of duloxetine, venlafaxine and mirtazapine in adults with severe major depression who failed previous SSRI treatment and were referred to mental health specialists in secondary care in the UK. The duration of the analysis was 48 weeks. The analysis adopted the perspective of the Scottish NHS, with costs including medication, A&E visits, staff time (GPs, psychiatrists) and hospitalisation. Resource use estimates were based on expert opinion; national unit costs were used. The outcome measure was the QALY, based on EQ-5D ratings (UK tariff). Efficacy data were obtained from meta-analyses of RCTs, with randomisation rules possibly being broken. Duloxetine was found to dominate both venlafaxine and mirtazapine and to have a probability of being cost-effective of 0.80 at the NICE lower cost effectiveness threshold of £20,000/QALY. Although the study is directly applicable to the NICE decision-making context, it is characterised by potentially serious limitations, including the methods for meta-analysis and evidence synthesis (selective use of RCTs and synthesis that appears to have potentially broken randomisation) and the fact that it was funded by industry, which may have introduced bias in the analysis.

Escitalopram versus duloxetine versus venlafaxine following inadequate response to previous antidepressant treatment

Nordström 2010 developed an economic model to evaluate the cost effectiveness of escitalopram, duloxetine and venlafaxine in adults with major depression treated in primary care, who had had a history of treatment with another antidepressant within the previous 6 months, in Sweden. The time horizon of the analysis was 6 months. The analysis adopted a societal perspective but healthcare costs were reported separately and included medication, staff time (GP, psychiatrist, other doctors e.g. neurologist, cardiologist, psychotherapist, counsellor, psychologist, nurse), hospitalisation and treatment of side effects. Resource use estimates were based on a cohort study conducted in 56 primary care centres in Sweden over 6 months; national unit costs were used. The outcome measure was the probability of remission (defined as a MADRS total score ≤ 12) achieved after 8 weeks of treatment and sustained until the end of 6 months; and the QALY estimated based on EQ-5D ratings (UK tariff). Efficacy data were derived from pooled analysis of trial data, including only participants who had already received antidepressant therapy prior to randomisation; data for duloxetine and venlafaxine were pooled together. Considering only healthcare costs, escitalopram was found to dominate both duloxetine and venlafaxine and to have a probability of being cost-effective of more than 0.98 at the NICE lower cost effectiveness threshold of £20,000/QALY. The study is only partially applicable to the NICE decision-

making context and is characterised by potentially serious limitations, including the methods for evidence synthesis (selective use of RCTs and data pooling for two of the assessed interventions) and the fact that it was funded by industry, which may have introduced bias in the analysis.

Generic SSRIs (citalopram, fluoxetine, paroxetine) versus escitalopram versus paroxetine controlled release versus sertraline versus venlafaxine following inadequate response to previous SSRI treatment

Malone 2007 compared different SSRIs (including escitalopram, paroxetine controlled release, sertraline and venlafaxine) in adults with major depression who failed to achieve remission with previous treatment with SSRIs in the US. Efficacy estimates were based on a review of published trial data and further assumptions; evidence synthesis was done by naïve addition of efficacy data, leading to breaking of randomisation rules. Paroxetine controlled release and sertraline were found to be dominated by other SSRIs. Results for other SSRIs and ICERs are difficult to interpret, as the measure of outcome was the probability of response and not the QALY. The study was funded by industry, which may have introduced further bias to the analysis. The study is partially applicable to the UK context and is characterised by very serious limitations. Therefore, it has not been considered further when formulating recommendations.

Atypical antipsychotics adjunct to a SSRI versus lithium adjunct to a SSRI

Edwards 2013 developed an economic model to assess the cost-utility of atypical antipsychotics versus lithium, both as adjuncts to an SSRI, for the treatment of adults with treatment-resistant depression (defined as failure to respond to at least 2 previous antidepressants in the current episode of depression) in the UK. The study adopted a NHS and PSS perspective and considered medication costs, healthcare professional time (GP, community mental health teams, crisis resolution and home treatment teams), hospitalisation and monitoring (laboratory testing) costs. Efficacy data were taken from a systematic review and network meta-analysis that enabled an indirect comparison between the two interventions, using 6 RCTs comparing olanzapine plus fluoxetine versus fluoxetine alone in people with treatment-resistant depression and 1 RCT comparing lithium plus fluoxetine versus fluoxetine alone in people who had failed at least one antidepressant; a common class effect was assumed for SSRIs and also for antipsychotics. Data on lithium as adjunct to an SSRI were taken from a population that had failed to respond to one previous SSRI (and not from people with treatment-resistant depression) due to lack of more relevant data. In order to estimate the effect of each intervention, a fixed baseline MADRS score was assumed for both arms; the change in MADRS scores at endpoint was assumed to have a normal distribution, which was used to estimate proportions of people in the remission, response and no response states.

Resource use estimates were mainly based on clinical expert opinion, with the exception of the length of hospitalisation, which was based on national hospital episode statistics. In order to estimate medication costs in each arm of the model, it was assumed, based on expert advice, that antipsychotic use comprised 30% aripiprazole, 30% olanzapine, 20% quetiapine, and 20% risperidone; and SSRI use comprised 20% citalopram, 20% escitalopram, 30% fluoxetine, and 30% sertraline. The study utilised national unit costs. The outcome measure was the QALY estimated based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 12 months.

Augmentation of SSRIs with lithium was found to dominate augmentation of SSRIs with an atypical antipsychotic; the probability of lithium being dominant versus antipsychotics (both as adjuncts to an SSRI) was 1. Results were sensitive to the efficacy of augmentation strategies and discontinuation rates; they were robust under different assumptions regarding resource use, as well as under changes in remission and relapse risk at follow-up. The study is directly applicable to the UK context and is characterised by potentially serious limitations,

comprising mainly the source of efficacy data (i.e. the lack of evidence on treatment-resistant depression treated with lithium as an adjunct on a SSRI), the assumptions made around baseline and endpoint MADRS scores, and the fact that all resource use was based on expert opinion.

Aripiprazole adjunct to an antidepressant versus bupropion adjunct to antidepressant versus switching to bupropion

Yoon 2018 assessed the cost-effectiveness of aripiprazole adjunct to an antidepressant versus bupropion adjunct to an antidepressant versus switching to bupropion in adult veterans with treatment-resistant depression defined as failure to respond to at least 2 previous antidepressants in the current episode of depression. The economic study was conducted alongside a RCT (Mohamed 2017; N=1522, completers n=1131). The study used a healthcare perspective and included medication and mental health (inpatient, outpatient) costs. Unit costs were based on national sources. The outcome measures were remission, defined as QIDS-C score of ≤5 in 2 consecutive follow-up visits; and the QALY, estimated using EQ-5D. No further details on the use of EQ-5D were reported (e.g. whether the VAS value or a utility value was used; if the latter, which country's tariff was used). The time horizon of the analysis was 12 weeks.

Aripiprazole was found to be the most effective in terms of remission and the most costly among the 3 options; QALYs were very similar across the 3 options. Using the remission outcome, switching to bupropion was dominated by bupropion adjunct. The ICER of aripiprazole adjunct vs bupropion adjunct was £3,791/ remission (2020 prices). Using the QALY as the outcome, the ICER of aripiprazole adjunct vs bupropion switch was £348,428/QALY; the ICER of bupropion switch vs bupropion adjunct was £21,614/QALY. At a cost-effectiveness threshold of £15,000/remission, the probability of cost-effectiveness was 76% for aripiprazole adjunct, 23% for bupropion adjunct and only 1% for bupropion switch. The study is partially applicable to the UK context as it was conducted in the UK and is characterised by potentially serious limitations, including its short time horizon, the unclear method of estimation of QALYs from EQ-5D, and the potential conflicts of interest due to relations with pharmaceutical industry.

Various antipsychotics adjunct to antidepressants versus antidepressant treatment alone

Taneja 2012 compared the cost-effectiveness of different antipsychotics (aripiprazole, quetiapine and olanzapine) as adjuncts to antidepressants versus antidepressant treatment alone, in adults with major depression who had responded inadequately to previous antidepressant therapy in the US, from a healthcare perspective, using decision-analytic modellling. The measure of outcome was response. Efficacy data were derived from a meta-analysis of published phase III clinical trials and indirect comparison using placebo as baseline comparator. The time horizon was too short (only 6 weeks) to allow assessment of the cost effectiveness of interventions over the duration of the depressive episode; moreover, the study was funded by industry, which may have introduced additional bias in the analysis. The study is partially applicable to the UK context and is characterised by very serious limitations (as the time horizon was not adequate to measure effects) and was therefore not considered further.

Sussman 2017 also compared the cost-effectiveness of different antipsychotics (brexpiprazole, quetiapine 150 and 300mg/day, olanzapine/fluoxetine) as adjuncts to antidepressants versus antidepressant treatment alone, in adults with major depression who had responded inadequately to previous antidepressant therapy in the US, from a payer's perspective, using decision-analytic modelling. The measures of outcome were response and remission. Efficacy data were derived from various trials and meta-analyses, using indirect comparisons for evidence synthesis. The time horizon was 48 weeks. The study found that quetiapine was dominated by olanzapine/fluoxetine. Brexpiprazole was the most

effective and most costly intervention. Its ICER versus olanzapine/fluoxetine was £36,619/responder and £53,969/remitter. The ICER of olanzapine/fluoxetine versus antidepressants alone was £8,053/responder and £9,986/remitter (2020 prices). The study is partially applicable to the UK context and is characterised by potentially serious limitations, mainly that is was funded by industry, which may have introduced bias in the analysis.

ECT versus TCAs, SSRIs, SNRIs and lithium augmentation

Greenhalgh 2005 developed an economic model to assess the cost effectiveness of electroconvulsive therapy (ECT) compared with various pharmacological treatments such as TCAs, SSRIs, SNRIs and lithium augmentation in adults with major depressive disorder who require hospitalisation. The interventions assessed in the analysis were combined in 8 strategies of 3 lines of therapy and maintenance therapy following ECT, which mostly comprised SSRIs. Efficacy data were taken from a systematic literature review of RCTs and published meta-analyses, and further assumptions. No harms were modelled for any of the modelled interventions (in terms of costs or outcomes), although early treatment discontinuation (for any reason) was considered in the model structure (however, this was not assumed to have any effect on health-related quality of life).

The perspective of the analysis was that of the NHS. Costs included intervention (ECT, medication), hospitalisation, continued care for non-responders (nursing home placement with psychiatric provision), and maintenance treatment (laboratory testing, contacts with GP, psychiatrist and psychiatric nurse). Resource use data were based on published literature and expert opinion. The outcome measure was the QALY, estimated based on preferences for vignettes using the McSad health state classification system valued by service users with previous depression in Canada. The time horizon of the analysis was 12 months.

The most effective and cost-effective strategy appeared to be a sequence of ECT – SSRI – lithium augmentation, which had an ICER versus a sequence of SNRI – ECT – lithium augmentation of £10,082/QALY (2020 prices). All other strategies were dominated. Results were modestly sensitive to use of alternative utility values and robust to small changes in costs and suicide rates. The study is partially applicable to the NICE decision-making context as the method of generation of QALYs was not consistent with NICE recommendations and is characterised by potentially serious limitations, including the assumptions made in clinical and cost input parameters and the lack of consideration of any intervention harms.

Ross 2018 also constructed an economic model to assess the cost effectiveness of ECT being used as 1st-6th line treatment following 0-5 lines of pharmacological and/or psychological treatment, compared with no ECT (antidepressants and/or psychological treatment alone) in people with treatment-resistant depression in the UK. Efficacy data were taken from meta-analyses, RCTs, observational studies and further assumptions. No comparative data between ECT and pharmacotherapy/psychotherapy were utilised in the analysis and no evidence synthesis of available data was undertaken. The perspective of the analysis was that of the healthcare system. Costs included ECT, medication, outpatient and inpatient care, and laboratory testing. Resource use data were based on published literature. The outcome measure was the QALY, estimated using published utility data that had, in turn, been estimated using the EQ-5D (UK tariff). The time horizon of the analysis was 4 years. The study is partially applicable to the NICE decision-making context as the method of generation of QALYs was not consistent with NICE recommendations and is characterised by very serious limitations, as no comparative data between ECT and pharmacotherapy/ psychotherapy seem to have been utilised in the analysis and no evidence synthesis of available data was undertaken. Therefore this study was not considered further.

Economic model

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

Evidence statements

Clinical evidence statements

Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 13 RCTs (N=1224) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 10 RCTs (N=524) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 2 RCTs (N=123) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with attention-placebo, on depression symptomatology at 2-3 month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 5 RCTs (N=696) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, on depression symptomatology at 4-6 month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 2 RCTs (N=238) shows neither a clinically important nor statistically significant effect of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on depression symptomatology at 11-12 month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=248) shows a statistically significant but not clinically important benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on depression symptomatology at 40-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Moderate quality evidence from 8 RCTs (N=1293) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, on the rate of remission for adults with

depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

- Moderate quality evidence from 1 RCT (N=80) shows a clinically important but not statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of remission at 3-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 2 RCTs (N=549) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT relative to continuing with antidepressants-only on the rate of remission at 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=80) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of remission at 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=469) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of remission at 40-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Moderate quality evidence from 6 RCTs (N=829) shows a clinically important and statistically significant benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=80) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of response at 3-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 2 RCTs (N=549) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT relative to continuing with antidepressants-only on the rate of response at 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=80) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of response at 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=469) shows a clinically important and statistically significant benefit of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on the rate of response at 40-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Moderate quality evidence from 13 RCTs (N=1494) shows neither a clinically important nor statistically significant effect on the number of participants who discontinued for any reason of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or augmenting with waitlist or attention-placebo, for the further-line treatment of depression

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=296) shows lower discontinuation due to side effects for participants receiving combined cognitive behavioural analysis system of psychotherapy (CBASP) and antidepressant treatment relative to antidepressants-only for the further-line treatment of depression, however this effect is not statistically significant

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=40) shows neither a clinically important nor statistically significant effect of augmenting antidepressants with a blended computerised and face-to-face CBT intervention, relative to waitlist and antidepressants, on quality of life at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate to low quality evidence from 3 RCTs (N=530) shows neither clinically important nor statistically significant effects of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only or antidepressants and waitlist, on quality of life physical and mental component scores for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- High to moderate quality evidence from 1 RCT (N=80) shows neither clinically important nor statistically significant effects of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on quality of life physical and mental component scores at 3-month follow-up and 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 2 RCTs (N=469) shows neither clinically important nor statistically significant effects of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on quality of life physical and mental component scores at 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=242) shows neither a clinically important nor statistically significant effect of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on quality of life physical component score at 40-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=242) shows a statistically significant but not clinically important benefit of augmenting antidepressants with individual CBT,

relative to continuing with antidepressants-only, on quality of life mental component score at 40-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Personal, social, and occupational functioning

- Low quality evidence from 2 RCTs (N=405) shows a statistically significant but not clinically important benefit of augmenting antidepressants with cognitive and cognitive behavioural therapies, relative to continuing with antidepressants-only, on functional impairment for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

- Moderate quality evidence from 1 RCT (N=158) shows neither a clinically important nor statistically significant effect of augmenting antidepressants with individual CBT, relative to continuing with antidepressants-only, on functional impairment at 11-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

Critical outcomes:

Depression symptomatology

- High quality evidence from 1 RCT (N=342) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with cognitive behavioural analysis system of psychotherapy (CBASP) relative to brief supportive psychotherapy, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Moderate quality evidence from 1 RCT (N=395) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with cognitive behavioural analysis system of psychotherapy (CBASP), relative to brief supportive psychotherapy, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=395) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with cognitive behavioural analysis system of psychotherapy (CBASP) relative to brief supportive psychotherapy, on the rate of discontinuation for any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=395) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with brief supportive psychotherapy, relative to cognitive behavioural analysis system of psychotherapy (CBASP), on the rate of discontinuation due to side effects for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- High quality evidence from 1 RCT (N=334) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with cognitive behavioural analysis system of psychotherapy (CBASP) relative to brief supportive psychotherapy, on functional impairment for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 3. Augmenting with counselling versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- High quality evidence from 1 RCT (N=244) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with brief supportive psychotherapy, relative to continuing with antidepressants-only, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Moderate quality evidence from 1 RCT (N=291) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with brief supportive psychotherapy, relative to continuing with antidepressants-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=291) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with brief supportive psychotherapy, relative to continuing with antidepressants-only, on the rate of discontinuation due to any reason for adults with depression who have shown

an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=291) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with brief supportive psychotherapy, relative to continuing with antidepressants-only, on the rate of discontinuation due to side effects for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- High quality evidence from 1 RCT (N=237) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with brief supportive psychotherapy, relative to continuing with antidepressants-only, on functional impairment for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 4. Augmenting with IPT versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=158) shows a statistically significant but not clinically important benefit of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 3 RCTs (N=212) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 2 RCTs (N=131) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on depression symptomatology at 1-3 month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=97) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on depression symptomatology at 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Low quality evidence from 4 RCTs (N=358) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 3 RCTs (N=234) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 4 RCTs (N=358) shows higher discontinuation due to any reason with combined IPT and antidepressant treatment relative to continuing with antidepressants-only for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Low quality evidence from 1 RCT (N=124) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on global functioning for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=97) shows statistically significant but not clinically important benefits of augmenting antidepressant treatment with IPT, relative to continuing with antidepressants-only, on global functioning at 3-month and 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with intensive short-term dynamic psychotherapy, relative to continuing with antidepressants-only,

on depression symptomatology at endpoint, and on change from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

- Moderate quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with intensive short-term dynamic psychotherapy, relative to continuing with antidepressants-only, on depression symptomatology at 3-month, 6-month and 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- High quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with intensive short-term dynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=60) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with intensive short-term dynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of remission at 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 1 RCT (N=60) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with intensive short-term dynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of response at 12-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=60) shows higher discontinuation due to any reason with combined intensive short-term dynamic psychotherapy and antidepressant treatment relative to continuing with antidepressants-only for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=99) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode
- Very low quality evidence from 1 RCT (N=96-98) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on depression symptomatology at 6-month or 12-month follow-up for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode
- Very low quality evidence from 1 RCT (N=92) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on depression symptomatology at 2-year follow-up for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode

Remission

- Very low quality evidence from 1 RCT (N=129) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode
- Very low quality evidence from 1 RCT (N=129) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of remission at 2-year follow-up for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=129) shows neither a clinically important nor statistically significant effect of augmenting antidepressant treatment with long-term psychodynamic psychotherapy, relative to continuing with antidepressants-only, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 2 previous treatments for the current episode

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/- attention-placebo)

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 3 RCTs (N=157) shows neither a clinically important nor statistically significant effect of augmenting antidepressants with a self-help intervention, relative to continuing with antidepressants-only or augmenting with attention-placebo, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 3 RCTs (N=157) shows a statistically significant but not clinically important benefit of augmenting antidepressants with a self-help intervention, relative to continuing with antidepressants-only or augmenting with attention-placebo, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=32) shows a clinically important and statistically significant benefit of augmenting antidepressants with attentional bias training, relative to augmenting with attention-placebo, on depression symptomatology at 1-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=130) shows higher discontinuation due to any reason with combined self-help and antidepressant treatment, relative to continuing with antidepressants-only or combined attention-placebo and antidepressant treatment for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

Critical outcomes:

Depression symptomatology

- Low to very low quality evidence from 1 RCT (N=164) shows a clinically important and statistically significant benefit of switching to SSRI and augmenting with computerised CBT, relative to switching to SSRI-only, on depression symptomatology at endpoint, and change from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=164) shows a clinically important but not statistically significant benefit of switching to SSRI and augmenting with computerised CBT, relative to switching to SSRI-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=164) shows a clinically important and statistically significant benefit of switching to SSRI and augmenting with computerised CBT, relative to switching to SSRI-only, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=164) shows higher discontinuation due to any reason with combined SSRI switch and computerised CBT augmentation relative to switch to SSRI-only for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 9. Augmenting with art therapy versus attention-placebo

Critical outcomes:

Depression symptomatology

- Moderate to low quality evidence from 1 RCT (N=100) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with clay art therapy, relative to augmenting with attention-placebo, on depression symptomatology (at endpoint, and change from baseline to endpoint) for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=106) shows lower discontinuation due to any reason with combined clay art therapy and antidepressant treatment relative to attention-placebo augmentation for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=66) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with eye movement desensitization reprocessing (EMDR), relative to augmenting with individual CBT, on depression symptomatology at endpoint for adults with depression

who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=82) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with eye movement desensitization reprocessing (EMDR), relative to augmenting with individual CBT, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 1 RCT (N=82) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with eye movement desensitization reprocessing (EMDR) relative to individual CBT, on the rate of remission at 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=82) shows higher discontinuation due to any reason with combined eye movement desensitization reprocessing (EMDR) and antidepressant treatment relative to individual CBT augmentation for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Very low quality evidence from 1 RCT (N=66) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with eye movement desensitization reprocessing (EMDR) relative to individual CBT, on global functioning at endpoint and 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=57) shows a clinically important and statistically significant benefit of remaining on the same dose of paroxetine for an

additional 6 weeks, relative to an increased dose, on depression symptomatology at endpoint for adults with depression who have failed to respond to 6 weeks of treatment with paroxetine

- Very low quality evidence from 2 RCTs (N=416) shows neither a clinically important nor statistically significant difference between increasing the dose of the SSRI relative to continuing at the same dose for an additional 5-6 weeks, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to 3-4 weeks of treatment with a SSRI

Remission

- Very low quality evidence from 5 RCTs (N=753) shows neither a clinically important nor statistically significant difference between increasing the dose of the SSRI relative to continuing at the same dose for an additional 5-6 weeks, on the rate of remission for adults with depression who have failed to respond to 3-6 weeks of treatment with a SSRI

Response

- Very low quality evidence from 6 RCTs (N=830) shows neither a clinically important nor statistically significant difference between increasing the dose of the SSRI relative to continuing at the same dose for an additional 5-6 weeks, on the rate of response for adults with depression who have failed to respond to 3-6 weeks of treatment with a SSRI

Discontinuation due to any reason

- Very low quality evidence from 5 RCTs (N=753) shows lower discontinuation due to any reason with an increased dose of the SSRI relative to the same dose for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 4 RCTs (N=558) shows higher discontinuation due to side effects with an increased dose of the SSRI relative to the same dose for the further-line treatment of depression, however this effect is not statistically significant

Important outcomes:

Quality of life

- Moderate quality evidence from 1 RCT (N=57) shows a clinically important and statistically significant benefit of remaining on the same dose of paroxetine for an additional 6 weeks, relative to an increased dose, on quality of life physical component score for adults with depression who have failed to respond to 6 weeks of treatment with paroxetine
- High quality evidence from 1 RCT (N=57) shows a clinically important and statistically significant benefit of increasing the dose of paroxetine relative to continuing at the same dose for an additional 6 weeks, on quality of life mental component score for adults with depression who have failed to respond to 6 weeks of treatment with paroxetine

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 12. Increasing the dose of SSRI versus switching to SNRI

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=472) shows a statistically significant but not clinically important benefit of increasing the dose of escitalopram, relative to switching to duloxetine, on depression symptomatology at endpoint for adults with depression who have failed to respond to 2 weeks of treatment with escitalopram
- Low quality evidence from 1 RCT (N=472) shows neither a clinically important nor statistically significant difference between increasing the dose of escitalopram relative to switching to duloxetine on depression symptomatology change from baseline to endpoint, for adults who had failed to respond to 2 weeks of treatment with escitalopram

Remission

- Very low quality evidence from 1 RCT (N=484) shows a clinically important and statistically significant benefit of increasing the dose of escitalopram, relative to switching to duloxetine, on the rate of remission for adults with depression who have failed to respond to 2 weeks of treatment with escitalopram

Response

- Low quality evidence from 1 RCT (N=484) shows neither a clinically important nor statistically significant difference between increasing the dose of escitalopram relative to switching to duloxetine on the rate of response, for adults who had failed to respond to 2 weeks of treatment with escitalopram

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=484) shows neither a clinically important nor statistically significant difference between increasing the dose of escitalopram relative to switching to duloxetine on the rate of discontinuation for any reason, for adults who had failed to respond to 2 weeks of treatment with escitalopram

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=484) shows neither a clinically important nor statistically significant difference between increasing the dose of escitalopram relative to switching to duloxetine on the rate of discontinuation due to side effects, for adults who had failed to respond to 2 weeks of treatment with escitalopram

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=472) shows neither a clinically important nor statistically significant difference between increasing the dose of escitalopram relative to switching to duloxetine on quality of life, for adults who had failed to respond to 2 weeks of treatment with escitalopram

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 13. Increasing the dose of SSRI versus augmenting with TCA

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=94) shows a clinically important and statistically significant benefit of increasing the dose of fluoxetine, relative to augmenting the same dose of fluoxetine with desipramine, on depression symptomatology at endpoint for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine
- Low quality evidence from 2 RCTs (N=94) shows neither a clinically important nor statistically significant difference between increasing the dose of fluoxetine, relative to augmenting the same dose of fluoxetine with desipramine on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Remission

- Low quality evidence from 2 RCTs (N=94) shows a clinically important but not statistically significant benefit of increasing the dose of fluoxetine, relative to augmenting the same dose of fluoxetine with desipramine, on the rate of remission for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=94) shows lower discontinuation due to any reason with an increased dose of fluoxetine relative to augmenting the same dose of fluoxetine with desipramine for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=27) shows lower discontinuation due to side effects with an increased dose of fluoxetine relative to augmenting the same dose of fluoxetine with desipramine for the further-line treatment of depression, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=60) shows neither a clinically important nor statistically significant difference between increasing the dose of paroxetine, relative to augmenting the same dose of paroxetine with amisulpride on depression symptomatology at endpoint and change from baseline to endpoint, for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Remission

- Low quality evidence from 1 RCT (N=60) shows a clinically important but not statistically significant benefit of augmenting paroxetine with amisulpride, relative to increasing the dose of paroxetine, on the rate of remission for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Response

- Low quality evidence from 1 RCT (N=60) shows neither a clinically important nor statistically significant difference between increasing the dose of paroxetine, relative to augmenting the same dose of paroxetine with amisulpride, on the rate of response for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=60) shows neither a clinically important nor statistically significant difference between increasing the dose of paroxetine, relative to augmenting the same dose of paroxetine with amisulpride, on the rate of discontinuation for any reason for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=60) shows neither a clinically important nor statistically significant difference between increasing the dose of paroxetine, relative to augmenting the same dose of paroxetine with amisulpride, on the rate of discontinuation due to side effects for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Moderate quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting paroxetine with amisulpride, relative to increasing the dose of paroxetine, on the rate of functional remission for adults with depression who have failed to respond to 3 months of treatment with paroxetine

- Moderate quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting paroxetine with amisulpride, relative to increasing the dose of paroxetine, on global functioning for adults with depression who have failed to respond to 3 months of treatment with paroxetine

Comparison 15. Increasing the dose of SSRI versus augmenting with lithium

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=96) shows neither a clinically important nor statistically significant difference between increasing the dose of fluoxetine, relative to augmenting the same dose of fluoxetine with lithium on depression symptomatology at endpoint and change from baseline to endpoint, for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Remission

- Low quality evidence from 2 RCTs (N=96) shows a clinically important and statistically significant benefit of increasing the dose of fluoxetine, relative to augmenting the same dose of fluoxetine with lithium, on the rate of remission for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=96) shows lower discontinuation due to any reason with an increased dose of fluoxetine relative to augmenting the same dose of fluoxetine with lithium for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=29) shows lower discontinuation due to side effects with an increased dose of fluoxetine relative to augmenting the same dose of fluoxetine with lithium for the further-line treatment of depression, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 16. Switching to SSRI versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=324) shows neither a clinically important nor statistically significant difference between switching to a SSRI, relative to continuing with the antidepressant, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=329) shows a higher rate of remission for continuing with the antidepressant for an additional 8-12 weeks, relative to switching to a SSRI, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Response

- Very low quality evidence from 2 RCTs (N=329) shows a higher rate of response for continuing with the antidepressant for an additional 8-12 weeks, relative to switching to a SSRI, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=329) shows neither a clinically important nor statistically significant difference between switching to a SSRI relative to continuing with the antidepressant on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=329) shows a higher rate of discontinuation due to side effects for those switching to a SSRI relative to continuing with the antidepressant for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 17. Switching to a different SSRI versus continuing same SSRI

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=41) shows a clinically important and statistically significant benefit of switching to a different SSRI, relative to continuing with the same SSRI for an additional 6 weeks, on the rate of remission for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Response

- Very low quality evidence from 1 RCT (N=41) shows a clinically important and statistically significant benefit of switching to a different SSRI, relative to continuing with the same SSRI for an additional 6 weeks, on the rate of response for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=41) shows a lower rate of discontinuation due to any reason with a switch to a different SSRI relative to continuing with the same SSRI for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=41) shows neither a clinically important nor statistically significant difference between switching to a different SSRI relative to continuing with the same SSRI on the rate of discontinuation due to side effects, for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 18. Switching to SSRI versus antipsychotic

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=401) shows a statistically significant but not clinically important benefit of switching to a SSRI, relative to switching to an antipsychotic, on depression symptomatology change from baseline to endpoint for

adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=408) shows neither a clinically important nor statistically significant difference between switching to a SSRI relative to switching to an antipsychotic on the rate of remission, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=408) shows a clinically important and statistically significant benefit of switching to a SSRI, relative to switching to an antipsychotic, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=408) shows neither a clinically important nor statistically significant difference between switching to a SSRI relative to switching to an antipsychotic on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=408) shows significantly lower discontinuation due to side effects with switching to a SSRI, relative to switching to an antipsychotic, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=595) shows neither a clinically important nor statistically significant difference between switching to a combined SSRI and antipsychotic treatment, relative to switching to an antipsychotic-only, on depression symptomatology change from baseline to endpoint for adults with depression who

have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=595) shows a clinically important but not statistically significant benefit of switching to a combined SSRI and antipsychotic treatment, relative to switching to an antipsychotic-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=595) shows a clinically important and statistically significant benefit of switching to a combined SSRI and antipsychotic treatment, relative to switching to an antipsychotic-only, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=595) shows neither a clinically important nor statistically significant difference between switching to a combined SSRI and antipsychotic treatment, relative to switching to an antipsychotic-only, on discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=595) shows neither a clinically important nor statistically significant difference between switching to a combined SSRI and antipsychotic treatment, relative to switching to an antipsychotic-only, on discontinuation due to side effects for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 20. Augmenting with SSRI versus augmenting with lithium

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=104) shows a clinically important and statistically significant benefit of augmenting imipramine treatment with citalopram,

relative to augmenting with lithium, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to 10 weeks of treatment with imipramine

Remission

- Low quality evidence from 1 RCT (N=104) shows a clinically important and statistically significant benefit of augmenting imipramine treatment with citalopram, relative to augmenting with lithium, on the rate of remission for adults with depression who have failed to respond to 10 weeks of treatment with imipramine

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 21. Switching to TCA versus SSRI

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=152) shows neither a clinically important nor statistically significant difference between switching to desipramine relative to switching to citalopram on depression symptomatology, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=189) shows a clinically important but not statistically significant benefit of switching to desipramine relative to switching to citalopram on the rate of remission, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=189) shows neither a clinically important nor statistically significant difference between switching to desipramine relative to switching to citalopram on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=189) shows neither a clinically important nor statistically significant difference between switching to desipramine relative to switching to citalopram on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 22. Switching to TCA versus augmenting with mirtazapine

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=112) shows a clinically important and statistically significant benefit of switching to imipramine, relative to augmenting venlafaxine with mirtazapine, on depression symptomatology (at endpoint and change from baseline to endpoint) for adults with depression who have failed to respond to 10 weeks of treatment with venlafaxine

Remission

- Low quality evidence from 1 RCT (N=112) shows a clinically important and statistically significant benefit of switching to imipramine, relative to augmenting venlafaxine with mirtazapine, on the rate of remission for adults with depression who have failed to respond to 10 weeks of treatment with venlafaxine

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=112) shows a higher rate of discontinuation due to any reason with a switch to imipramine relative to augmenting venlafaxine with

mirtazapine for the further-line treatment of depression, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 23. Switching to mianserin versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=71) shows neither a clinically important nor statistically significant difference between switching to mianserin, relative to continuing with fluoxetine for an additional 6 weeks, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to 6 weeks of treatment with fluoxetine

Remission

- Very low quality evidence from 1 RCT (N=72) shows a clinically important but not statistically significant benefit of switching to mianserin, relative to continuing with fluoxetine for an additional 6 weeks, on the rate of remission for adults with depression who have failed to respond to 6 weeks of treatment with fluoxetine

Response

- Very low quality evidence from 1 RCT (N=72) shows a clinically important but not statistically significant benefit of switching to mianserin, relative to continuing with fluoxetine for an additional 6 weeks, on the rate of response for adults with depression who have failed to respond to 6 weeks of treatment with fluoxetine

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=72) shows higher discontinuation due to any reason associated with switching to mianserin relative to continuing with fluoxetine for an additional 6 weeks, for adults with depression who have failed to respond to 6 weeks of treatment with fluoxetine, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=72) shows significantly higher discontinuation due to side effects associated with switching to mianserin, relative to

continuing with fluoxetine for an additional 6 weeks, for adults with depression who have failed to respond to 6 weeks of treatment with fluoxetine

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=70) shows a clinically important and statistically significant benefit of augmenting fluoxetine with mianserin, relative to continuing with fluoxetine-only, on depression symptomatology change from baseline to endpoint for adults with depression who had failed to respond to at least 6 weeks of treatment with fluoxetine

Remission

- Very low quality evidence from 2 RCTs (N=267) shows a clinically important but not statistically significant benefit of augmenting a SSRI with mianserin, relative to continuing with SSRI-only, on the rate of remission for adults with depression who had failed to respond to at least 6 weeks of SSRI treatment

Response

- Very low quality evidence from 2 RCTs (N=267) shows neither a clinically important nor statistically significant difference between augmenting a SSRI with mianserin relative to continuing with SSRI-only, on the rate of response for adults with depression who had failed to respond to at least 6 weeks of SSRI treatment

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=267) shows higher discontinuation due to any reason associated with augmenting a SSRI with mianserin relative to continuing with SSRI-only, for adults with depression who have failed to respond to at least 6 weeks of SSRI treatment, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=70) shows higher discontinuation due to side effects associated with augmenting fluoxetine with mianserin relative to continuing with fluoxetine-only, for adults with depression who have failed to respond to at least 6 weeks of treatment with fluoxetine, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=196) shows a clinically important and statistically significant benefit of augmenting sertraline with mianserin, relative to increasing the dose of sertraline, on the rate of remission for adults with depression who have failed to respond to 6 weeks of treatment with sertraline

Response

- Very low quality evidence from 1 RCT (N=196) shows neither a clinically important nor statistically significant difference between augmenting sertraline with mianserin relative to increasing the dose of sertraline, on the rate of response for adults with depression who have failed to respond to 6 weeks of treatment with sertraline

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=196) shows neither a clinically important nor statistically significant difference between augmenting sertraline with mianserin relative to increasing the dose of sertraline, on the rate of discontinuation due to any reason for adults with depression who have failed to respond to 6 weeks of treatment with sertraline

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 26. Augmenting with mianserin versus switch to mianserin

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=65) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine with mianserin relative to switching to mianserin (and discontinuing fluoxetine), on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to at least 6 weeks of fluoxetine treatment

Remission

- Very low quality evidence from 1 RCT (N=66) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine with mianserin relative to switching to mianserin (and discontinuing fluoxetine), on the rate of remission, for adults with depression who have failed to respond to at least 6 weeks of fluoxetine treatment

Response

- Very low quality evidence from 1 RCT (N=66) shows a clinically important but not statistically significant benefit of augmenting fluoxetine with mianserin, relative to switching to mianserin (and discontinuing fluoxetine), on the rate of response for adults with depression who have failed to respond to at least 6 weeks of fluoxetine treatment

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=66) shows lower discontinuation due to any reason associated with augmenting fluoxetine with mianserin relative to switching to mianserin (and discontinuing fluoxetine), for adults with depression who have failed to respond to at least 6 weeks of treatment with fluoxetine, however this effect is not statistically significant

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=66) shows lower discontinuation due to side effects associated with augmenting fluoxetine with mianserin relative to switching to mianserin (and discontinuing fluoxetine), for adults with depression who have failed to respond to at least 6 weeks of treatment with fluoxetine, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=248) shows neither a clinically important nor statistically significant difference between increasing the dose and continuing on the same dose of duloxetine on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to 5 weeks of treatment with duloxetine

Remission

- Very low quality evidence from 1 RCT (N=255) shows neither a clinically important nor statistically significant difference between increasing the dose and continuing on the same dose of duloxetine on the rate of remission, for adults with depression who have failed to respond to 5 weeks of treatment with duloxetine

Response

- Very low quality evidence from 1 RCT (N=255) shows neither a clinically important nor statistically significant difference between increasing the dose and continuing on the same dose of duloxetine on the rate of response, for adults with depression who have failed to respond to 5 weeks of treatment with duloxetine

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=255) shows higher discontinuation due to any reason associated with increasing the dose of duloxetine relative to continuing on the same dose, for adults with depression who have failed to respond to at 5 weeks of treatment with duloxetine, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=255) shows neither a clinically important nor statistically significant difference between increasing the dose and continuing on the same dose of duloxetine on the rate of discontinuation due to side effects, for adults with depression who have failed to respond to 5 weeks of treatment with duloxetine

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 28. Switching to SNRI versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=95) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and continuing with paroxetine on the rate of remission, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=95) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and continuing with paroxetine on the rate of response, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=95) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and continuing with paroxetine on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=95) shows lower discontinuation due to side effects associated with switching to venlafaxine relative to continuing with paroxetine, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

- Low to very low quality evidence from 1 RCT (N=95) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and continuing with paroxetine on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 2 RCTs (N=595) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and a within-class switch to a SSRI, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 3 RCTs (N=1017) shows a clinically important but not statistically significant benefit of switching to venlafaxine, relative to a within-class switch to a SSRI, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 2 RCTs (N=611) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and a within-class switch to a SSRI, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=529) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and a within-class switch to a SSRI, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 3 RCTs (N=1017) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and a within-class switch to a SSRI, on the rate of discontinuation due to side effects for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 30. Switching to SNRI versus switching to bupropion

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=489) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to bupropion on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to treatment with citalopram

Remission

- Very low quality evidence from 1 RCT (N=489) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to bupropion on the rate of remission, for adults with depression who have failed to respond to treatment with citalopram

Response

- Very low quality evidence from 1 RCT (N=489) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to bupropion on the rate of response, for adults with depression who have failed to respond to treatment with citalopram

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=489) shows lower discontinuation due to side effects associated with switching to venlafaxine relative to switching to bupropion for adults with depression who have failed to respond to treatment with citalopram, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 31. Switching to SNRI versus switching to mirtazapine

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=105) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to mirtazapine on the rate of remission, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=105) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to mirtazapine on the rate of response, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=105) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to mirtazapine on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 1 RCT (N=105) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to mirtazapine on the rate of discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=105) shows neither a clinically important nor statistically significant difference between switching to venlafaxine and switching to mirtazapine on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 32. Switching to bupropion versus placebo

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=322) shows neither a clinically important nor statistically significant difference between switching to bupropion and placebo on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to 4 weeks of treatment with paroxetine

Remission

- Very low quality evidence from 1 RCT (N=325) shows neither a clinically important nor statistically significant difference between switching to bupropion and placebo on the rate of remission, for adults with depression who have failed to respond to 4 weeks of treatment with paroxetine

Response

- Very low quality evidence from 1 RCT (N=325) shows neither a clinically important nor statistically significant difference between switching to bupropion and placebo on the rate of response, for adults with depression who have failed to respond to 4 weeks of treatment with paroxetine

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=325) shows significantly higher discontinuation due to any reason with switching to bupropion relative to placebo, for adults with depression who have failed to respond to 4 weeks of treatment with paroxetine

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=325) shows neither a clinically important nor statistically significant difference between switching to bupropion and placebo on the rate of discontinuation due to side effects, for adults with depression who have failed to respond to 4 weeks of treatment with paroxetine

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 33. Switching to bupropion versus switching to another antidepressant from same class

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=477) shows neither a clinically important nor statistically significant difference between switching to bupropion and switching to sertraline on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to treatment with citalopram

Remission

- Very low quality evidence from 1 RCT (N=477) shows neither a clinically important nor statistically significant difference between switching to bupropion and switching to sertraline on the rate of remission, for adults with depression who have failed to respond to treatment with citalopram

Response

- Very low quality evidence from 1 RCT (N=477) shows neither a clinically important nor statistically significant difference between switching to bupropion and switching to sertraline on the rate of response, for adults with depression who have failed to respond to treatment with citalopram

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=477) shows higher discontinuation due to side effects with switching to bupropion relative to switching to sertraline for adults with depression who have failed to respond to treatment with citalopram, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 34. Augmenting with bupropion versus placebo

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Moderate quality evidence from 1 RCT (N=60) shows a clinically important and statistically significant benefit of augmenting with bupropion relative to placebo for adults with depression who have failed to respond to 4 weeks of SSRI treatment

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 35. Augmenting with bupropion versus switching to bupropion

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Moderate quality evidence from 1 RCT (N=1017) shows neither a clinically important nor statistically significant difference between augmenting with bupropion and switching to bupropion on the rate of remission, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- High quality evidence from 1 RCT (N=1017) shows neither a clinically important nor statistically significant difference between augmenting with bupropion and switching to bupropion on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Moderate quality evidence from 1 RCT (N=1017) shows neither a clinically important nor statistically significant difference between augmenting with bupropion and switching to bupropion on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 1 RCT (N=1017) shows higher discontinuation due to side effects with switching to bupropion relative to augmenting with bupropion for the further-line treatment of depression, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 36. Switching to mirtazapine versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=1223) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with the antidepressant on depression symptomatology at endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 1 RCT (N=136) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with paroxetine (for an additional 6 weeks) on depression symptomatology change from baseline to endpoint, for adults with depression who have failed to respond to 2 weeks of treatment with paroxetine
- High quality evidence from 1 RCT (N=1078) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with sertraline (for an additional 6 weeks) on depression symptomatology at 4-month follow-up, for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Remission

- Low quality evidence from 3 RCTs (N=1345) shows a statistically significant but not clinically important benefit of switching to mirtazapine relative to continuing with the antidepressant on the rate of remission, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- High quality evidence from 1 RCT (N=1109) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with sertraline (for an additional 6 weeks) on the rate of remission at 4-month follow-up, for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Response

- Moderate quality evidence from 3 RCTs (N=1345) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with the antidepressant on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 3 RCTs (N=1345) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with the antidepressant on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=236) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with the antidepressant on the rate of discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=100) shows neither a clinically important nor statistically significant difference between switching to mirtazapine and continuing with paroxetine on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

- Low quality evidence from 4 RCTs (N=1657) shows a statistically significant but not clinically important benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo or continuing with SSRI/SNRI-only, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 2 RCTs (N=162) shows a clinically important but not statistically significant benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- High quality evidence from 1 RCT (N=1058) shows neither a clinically important nor statistically significant difference between augmenting sertraline treatment with mirtazapine, relative to continuing with sertraline-only (for an additional 6 weeks), on depression symptomatology at 4-months follow-up for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Remission

- Low quality evidence from 4 RCTs (N=1730) shows a clinically important and statistically significant benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo or continuing with SSRI/SNRI-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

- Moderate quality evidence from 1 RCT (N=1088) shows neither a clinically important nor statistically significant difference between augmenting sertraline treatment with mirtazapine, relative to continuing with sertraline-only (for an additional 6 weeks), on the rate of remission at 4-months follow-up for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Response

- Low quality evidence from 4 RCTs (N=1730) shows a statistically significant but not clinically important benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo or continuing with SSRI/SNRI-only, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 4 RCTs (N=1730) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with mirtazapine and augmentation with placebo or continuing with SSRI/SNRI-only, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=162) shows higher discontinuation due to side effects with mirtazapine augmentation of SSRI/SNRI treatment relative to augmentation with placebo for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=429) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo, on quality of life for adults with depression who have failed to respond to 6 weeks of treatment with a SSRI/SNRI
- Low quality evidence from 1 RCT (N=418) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo, on quality of life physical component score for adults with depression who have failed to respond to 6 weeks of treatment with a SSRI/SNRI
- Low quality evidence from 1 RCT (N=418) shows a statistically significant but not clinically important benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo, on quality of life mental component score for adults with depression who have failed to respond to 6 weeks of treatment with a SSRI/SNRI

Personal, social, and occupational functioning

- Very low quality evidence from 1 RCT (N=26) shows a clinically important and statistically significant benefit of augmenting SSRI/SNRI treatment with mirtazapine, relative to augmentation with placebo, on global functioning for adults with depression

who have failed to respond to at least 4 weeks of standard antidepressant monotherapy

Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

Critical outcomes:

Depression symptomatology

- High quality evidence from 2 RCTs (N=1213) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with mirtazapine, relative to switching to mirtazapine, on depression symptomatology at endpoint for adults with depression who have failed to respond to 2 weeks of SSRI treatment
- Very low quality evidence from 1 RCT (N=136) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with mirtazapine, relative to switching to mirtazapine, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to 2 weeks of treatment with paroxetine
- High quality evidence from 1 RCT (N=1060) shows neither a clinically important nor statistically significant difference between augmenting sertraline with mirtazapine, relative to switching to mirtazapine, on depression symptomatology at 4-month follow-up for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Remission

- Moderate quality evidence from 2 RCTs (N=1213) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with mirtazapine, relative to switching to mirtazapine, on the rate of remission for adults with depression who have failed to respond to 2 weeks of SSRI treatment
- High quality evidence from 1 RCT (N=1095) shows neither a clinically important nor statistically significant difference between augmenting sertraline with mirtazapine, relative to switching to mirtazapine, on the rate of remission at 4-month follow-up for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

Response

- High quality evidence from 2 RCTs (N=1213) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with mirtazapine, relative to switching to mirtazapine, on the rate of response for adults with depression who have failed to respond to 2 weeks of SSRI treatment

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=1213) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with mirtazapine, relative to switching to mirtazapine, on the rate of discontinuation due to any reason for adults with depression who have failed to respond to 2 weeks of SSRI treatment

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=136) shows higher discontinuation due to side effects associated with switching to mirtazapine relative to augmenting

paroxetine with mirtazapine for adults with depression who have failed to respond to 2 weeks of treatment with paroxetine, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 39. Augmenting with trazodone versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with trazodone and continuing with paroxetine-only on the rate of remission, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with trazodone and continuing with paroxetine-only on the rate of response, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with trazodone and continuing with paroxetine-only on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 8 RCTs (N=599) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with lamotrigine or topiramate, relative to continuing with antidepressant-only or augmentation with placebo, on depression symptomatology (at endpoint and change from baseline to endpoint) for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=84) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with sodium valproate and continuing with paroxetine-only on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 8 RCTs (N=641) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with lamotrigine or sodium valproate, relative to continuing with antidepressant-only or augmentation with placebo, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 3 RCTs (N=183) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lamotrigine or topiramate, relative to augmentation with placebo, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=130) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lamotrigine and augmentation with placebo on the rate of discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=84) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with lamotrigine and continuing with paroxetine-only on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 41. Augmenting with anticonvulsant versus lithium

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=34) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lamotrigine and augmenting with lithium on depression symptomatology at endpoint, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=34) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with lamotrigine, relative to augmenting with lithium, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=34) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with lamotrigine, relative to augmenting with lithium, on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=34) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with lamotrigine, relative to augmenting with lithium, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=34) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lamotrigine and augmenting with lithium on discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- High quality evidence from 1 RCT (N=34) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lamotrigine and augmenting with lithium on discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 42. Switching to antipsychotic versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 3 RCTs (N=729) shows neither a clinically important nor statistically significant difference between switching to olanzapine and continuing with antidepressant treatment on depression symptomatology at endpoint, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 3 RCTs (N=738) shows a higher rate of remission associated with continuing with antidepressant treatment relative to switching to olanzapine for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Response

- Very low quality evidence from 3 RCTs (N=738) shows a significantly higher rate of response associated with continuing with antidepressant treatment relative to switching to olanzapine for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Moderate quality evidence from 3 RCTs (N=738) shows a significantly higher rate of discontinuation due to any reason with switching to olanzapine, relative to continuing with antidepressant treatment, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 3 RCTs (N=738) shows a significantly higher rate of discontinuation due to side effects with switching to olanzapine, relative to continuing with antidepressant treatment, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Low quality evidence from 1 RCT (N=400) shows neither a clinically important nor statistically significant difference between switching to olanzapine and continuing with fluoxetine on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=502) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and fluoxetine, and continuing with venlafaxine or nortriptyline, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=516) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and fluoxetine, and continuing with venlafaxine or nortriptyline, on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=516) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and fluoxetine, and continuing with venlafaxine or nortriptyline, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=516) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and

fluoxetine, and continuing with venlafaxine or nortriptyline, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=516) shows a significantly higher rate of discontinuation due to side effects associated with switching to combined olanzapine and fluoxetine, relative to continuing with venlafaxine or nortriptyline, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=574) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and fluoxetine, and switching to fluoxetine-only, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=591) shows a clinically important but not statistically significant benefit of switching to combined olanzapine and fluoxetine, relative to switching to fluoxetine-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=591) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and fluoxetine, and switching to fluoxetine-only, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=591) shows neither a clinically important nor statistically significant difference between switching to combined olanzapine and

fluoxetine, and switching to fluoxetine-only, on the rate of discontinuation due to any reason for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=591) shows a significantly higher rate of discontinuation due to side effects associated with switching to combined olanzapine and fluoxetine, relative to switching to fluoxetine-only, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 45. Augmenting with antipsychotic versus antidepressant-only or antidepressant + placebo

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 5 RCTs (N=706) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with antidepressant-only, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 20 RCTs (N=6716) shows a statistically significant but not clinically important benefit of augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with antidepressant-only, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 28 RCTs (N=10,078) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with antidepressant-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 28 RCTs (N=9154) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with

antidepressant-only, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 28 RCTs (N=10,012) shows a significantly higher rate of discontinuation due to any reason associated with augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with antidepressant-only, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 27 RCTs (N=9989) shows a significantly higher rate of discontinuation due to side effects associated with augmenting antidepressant treatment with an antipsychotic, relative to augmentation with placebo or continuing with antidepressant-only, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=202) shows a statistically significant but not clinically important benefit of augmenting SSRI/SNRI treatment with risperidone, relative to augmentation with placebo, on quality of life at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 2 RCTs (N=727) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with an antipsychotic and augmentation with placebo on quality of life change from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode
- Low to very low quality evidence from 2 RCTs (N=491) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with an antipsychotic and continuing with the SSRI-only on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

- Low quality evidence from 1 RCT (N=313) shows a clinically important and statistically significant benefit of augmenting sertraline with aripiprazole, relative to augmentation with placebo, on global functioning change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode
- Very low quality evidence from 1 RCT (N=886) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with brexpiprazole and placebo augmentation on functional remission, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

- Very low quality evidence from 1 RCT (N=201) shows a clinically important and statistically significant benefit of augmenting SSRI/SNRI treatment with risperidone, relative to placebo augmentation, on functional impairment at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 10 RCTs (N=4554) shows a statistically significant but not clinically important benefit of augmenting antidepressant treatment with an antipsychotic, relative to placebo augmentation, on functional impairment change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Comparison 46. Augmenting with antipsychotic versus bupropion

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=103) shows a statistically significant but not clinically important benefit of augmenting SSRI treatment with aripiprazole, relative to bupropion augmentation, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 4 weeks of SSRI treatment

Remission

- Low quality evidence from 2 RCTs (N=1114) shows a clinically important but not statistically significant benefit of augmenting SSRI/SNRI treatment with aripiprazole, relative to bupropion augmentation, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Moderate quality evidence from 2 RCTs (N=1114) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with aripiprazole and augmentation with bupropion on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Moderate quality evidence from 2 RCTs (N=1114) shows neither a clinically important nor statistically significant difference between augmenting SSRI/SNRI treatment with aripiprazole and augmentation with bupropion on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 2 RCTs (N=1114) shows a higher rate of discontinuation due to side effects associated with augmenting SSRI/SNRI treatment with bupropion relative to augmentation with aripiprazole for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 47. Augmenting with antipsychotic versus lithium

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Low quality evidence from 3 RCTs (N=510) shows a higher rate of remission associated with augmenting antidepressant treatment with an antipsychotic relative to augmentation with lithium for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Response

- Low quality evidence from 3 RCTs (N=510) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with an antipsychotic and lithium augmentation on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 3 RCTs (N=510) shows a higher rate of discontinuation due to any reason associated with augmenting antidepressant treatment with lithium relative to augmentation with an antipsychotic for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 3 RCTs (N=510) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with an antipsychotic and lithium augmentation on the rate of discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=395) shows a statistically significant but not clinically important benefit of augmenting fluoxetine treatment with olanzapine, relative to switching to olanzapine monotherapy, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

- Low quality evidence from 2 RCTs (N=858) shows a clinically important and statistically significant benefit of augmenting SSRI/venlafaxine treatment with an antipsychotic, relative to switching to antipsychotic monotherapy, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=858) shows a higher rate of response associated with augmenting SSRI/venlafaxine treatment with an antipsychotic, relative to switching to antipsychotic monotherapy for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=858) shows a significantly higher rate of discontinuation due to any reason associated with switching to antipsychotic monotherapy, relative to augmenting SSRI/venlafaxine treatment with an antipsychotic, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=858) shows neither a clinically important nor statistically significant difference between augmenting SSRI/venlafaxine treatment with an antipsychotic and switching to antipsychotic monotherapy on the rate of discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

- Very low quality evidence from 1 RCT (N=395) shows a statistically significant but not clinically important benefit of augmenting fluoxetine treatment with olanzapine,

relative to switching to olanzapine monotherapy, on quality of life physical component score for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

- Low quality evidence from 1 RCT (N=395) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine treatment with olanzapine and switching to olanzapine monotherapy on quality of life mental component score, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 49. Augmenting with antipsychotic versus switch to bupropion

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Moderate quality evidence from 1 RCT (N=1016) shows a clinically important and statistically significant benefit of augmenting SSRI/SNRI treatment with aripiprazole, relative to switching to bupropion monotherapy, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Moderate quality evidence from 1 RCT (N=1016) shows a statistically significant but not clinically important benefit of augmenting SSRI/SNRI treatment with aripiprazole, relative to switching to bupropion monotherapy, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- High quality evidence from 1 RCT (N=1016) shows a significantly higher rate of discontinuation due to any reason associated with switching to bupropion monotherapy, relative to augmenting SSRI/SNRI treatment with aripiprazole, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Moderate quality evidence from 1 RCT (N=1016) shows a significantly higher rate of discontinuation due to side effects associated with switching to bupropion monotherapy, relative to augmenting SSRI/SNRI treatment with aripiprazole, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Low quality evidence from 1 RCT (N=91) shows a higher rate of remission associated with continuing paroxetine-only treatment relative to augmenting paroxetine with buspirone on the rate of remission for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Response

- Low quality evidence from 2 RCTs (N=193) shows neither a clinically important nor statistically significant difference between augmenting SSRI treatment with buspirone, relative to placebo augmentation or continuing with the SSRI-only, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

- Moderate quality evidence from 1 RCT (N=91) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with buspirone, relative to continuing with paroxetine-only, on quality of life physical and mental component scores for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 51. Augmenting with buspirone versus bupropion

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=565) shows a statistically significant but not clinically important benefit of augmenting citalopram with bupropion, relative to buspirone augmentation, on depression symptomatology (at endpoint, and change from baseline to endpoint) for adults with depression who have failed to respond to citalopram monotherapy

Remission

- Low quality evidence from 1 RCT (N=565) shows neither a clinically important nor statistically significant difference between bupropion and buspirone augmentation of citalopram on the rate of remission, for adults with depression who have failed to respond to citalopram monotherapy

Response

- Moderate quality evidence from 1 RCT (N=565) shows neither a clinically important nor statistically significant difference between bupropion and buspirone augmentation of citalopram on the rate of response, for adults with depression who have failed to respond to citalopram monotherapy

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

- Moderate quality evidence from 1 RCT (N=565) shows a higher rate of discontinuation due to side effects associated with buspirone augmentation of citalopram, relative to bupropion augmentation, for adults with depression who have failed to respond to citalopram monotherapy

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 52. Augmenting with methylphenidate versus placebo

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=144) shows neither a clinically important nor statistically significant difference between augmentation of antidepressant treatment with methylphenidate or placebo on depression symptomatology change

from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=60) shows a clinically important but not statistically significant benefit of augmentation of antidepressant treatment with methylphenidate, relative to placebo augmentation, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=205) shows neither a clinically important nor statistically significant difference between augmentation of antidepressant treatment with methylphenidate or placebo on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=145) shows higher discontinuation due to any reason associated with augmentation of antidepressant treatment with methylphenidate relative to placebo for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to side effects

- Very low quality evidence from 2 RCTs (N=205) shows higher discontinuation due to side effects associated with augmentation of antidepressant treatment with methylphenidate relative to placebo for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=67) shows neither a clinically important nor statistically significant difference between augmentation of TCA treatment with lithium

or placebo on depression symptomatology at endpoint, for adults with depression who have failed to respond to TCA monotherapy

- Low quality evidence from 3 RCTs (N=116) shows neither a clinically important nor statistically significant difference between augmentation of antidepressant treatment with lithium or placebo on depression symptomatology change from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Low quality evidence from 1 RCT (N=34) shows a clinically important but not statistically significant benefit of augmenting TCA treatment with lithium, relative to placebo augmentation, on the rate of remission for adults with depression who have failed to respond to TCA monotherapy

Response

- Very low quality evidence from 2 RCTs (N=59) shows a clinically important but not statistically significant benefit of augmenting SSRI/TCA treatment with lithium, relative to placebo augmentation, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 4 RCTs (N=159) shows a lower rate of discontinuation due to any reason associated with augmenting antidepressant treatment with lithium relative to placebo augmentation for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to side effects

- Low quality evidence from 2 RCTs (N=68) shows a higher rate of discontinuation due to side effects associated with augmenting TCA treatment with lithium relative to placebo augmentation for adults with depression who have failed to respond to TCA monotherapy, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 54. Augmenting with lithium versus switch to antipsychotic

Critical outcomes:

Depression symptomatology

No evidence was identified for this outcome.

Remission

- Very low quality evidence from 1 RCT (N=457) shows neither a clinically important nor statistically significant difference between augmenting SSRI/venlafaxine treatment with lithium and switching to quetiapine monotherapy on the rate of remission, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=457) shows neither a clinically important nor statistically significant difference between augmenting SSRI/venlafaxine treatment with lithium and switching to quetiapine monotherapy on the rate of response, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 1 RCT (N=457) shows neither a clinically important nor statistically significant difference between augmenting SSRI/venlafaxine treatment with lithium and switching to quetiapine monotherapy on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=457) shows a higher rate of discontinuation due to side effects associated with switching to quetiapine monotherapy relative to augmenting SSRI/venlafaxine treatment with lithium for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=39) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lithium and augmenting with individual CBT on depression symptomatology (at endpoint, and change from baseline to endpoint), for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment

- Moderate quality evidence from 1 RCT (N=39) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with lithium, relative to augmenting with individual CBT, on depression symptomatology at 1-month follow-up for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment

Remission

- Low quality evidence from 1 RCT (N=44) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with lithium, relative to augmenting with individual CBT, on the rate of remission for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=44) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with lithium and augmenting with individual CBT on discontinuation due to any reason, for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment

Discontinuation due to side effects

- Low quality evidence from 1 RCT (N=44) shows a higher rate of discontinuation due to side effects associated with augmenting antidepressant treatment with lithium relative to augmenting with individual CBT for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 56. Augmenting with lithium versus augmenting with TCA

Critical outcomes:

Depression symptomatology

- Low quality evidence from 2 RCTs (N=94) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine with lithium or desipramine on depression symptomatology (at endpoint, and change from baseline to endpoint), for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Remission

- Very low quality evidence from 2 RCTs (N=94) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine with lithium or desipramine on the rate of remission, for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=94) shows neither a clinically important nor statistically significant difference between augmenting fluoxetine with lithium or desipramine on the rate of discontinuation due to any reason, for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine

Discontinuation due to side effects

- Very low quality evidence from 1 RCT (N=26) shows a higher rate of discontinuation due to side effects associated with augmenting fluoxetine with desipramine relative to lithium for adults with depression who have failed to respond to 8 weeks of treatment with fluoxetine, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 57. Augmenting with omega-3 fatty acids versus placebo

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 3 RCTs (N=132) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with omega-3 fatty acids, relative to placebo augmentation, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Very low quality evidence from 3 RCTs (N=132) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with omega-3 fatty acids, relative to placebo augmentation, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 1 RCT (N=81) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with omega-3 fatty acids, relative to placebo augmentation, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 3 RCTs (N=170) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with omega-3 fatty acids, relative to placebo augmentation, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 4 RCTs (N=221) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with omega-3 fatty acids and placebo augmentation on discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

- Low quality evidence from 4 RCTs (N=221) shows a lower rate of discontinuation due to side effects associated with augmenting antidepressant treatment with omega-3 fatty acids relative to placebo augmentation for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- High quality evidence from 1 RCT (N=50) shows a clinically important and statistically significant benefit of augmenting sertraline with omega-3 fatty acids, relative to placebo augmentation, on sleeping difficulties at endpoint for adults with depression who have failed to respond to 8 weeks of treatment with sertraline

Comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=33) shows a clinically important but not statistically significant benefit of augmenting desipramine or imipramine with triiodothyronine (T3), relative to placebo augmentation, on depression

symptomatology at endpoint for adults with depression who have failed to respond to at least 5 weeks of treatment with desipramine/imipramine

- Moderate quality evidence from 1 RCT (N=33) shows a clinically important and statistically significant benefit of augmenting desipramine or imipramine with triiodothyronine (T3), relative to placebo augmentation, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to at least 5 weeks of treatment with desipramine/imipramine

Remission

- Very low quality evidence from 2 RCTs (N=126) shows a clinically important but not statistically significant benefit of augmenting SSRI/TCA treatment with thyroid hormone, relative to placebo augmentation or continuing with the antidepressant-only, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 1 RCT (N=93) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with thyroid hormone and continuing with paroxetine-only, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- High quality evidence from 1 RCT (N=33) shows neither a clinically important nor statistically significant difference between augmenting desipramine or imipramine with triiodothyronine (T3) and placebo augmentation on the rate of discontinuation due to any reason, for adults with depression who have failed to respond to at least 5 weeks of treatment with desipramine/imipramine

Discontinuation due to side effects

- High quality evidence from 1 RCT (N=33) shows neither a clinically important nor statistically significant difference between augmenting desipramine or imipramine with triiodothyronine (T3) and placebo augmentation on the rate of discontinuation due to side effects, for adults with depression who have failed to respond to at least 5 weeks of treatment with desipramine/imipramine

Important outcomes:

Quality of life

- Moderate to low quality evidence from 1 RCT (N=93) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with thyroid hormone and continuing with paroxetine-only on quality of life physical and mental component scores, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 2 RCTs (N=176) shows a statistically significant but not clinically important benefit of augmenting antidepressant treatment with triiodothyronine (T3), relative to lithium augmentation, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 2 RCTs (N=176) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with thyroid hormone and augmenting with lithium on depression symptomatology change from baseline to endpoint, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Very low quality evidence from 2 RCTs (N=177) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with triiodothyronine (T3), relative to lithium augmentation, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 1 RCT (N=142) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with triiodothyronine (T3), relative to lithium augmentation, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=142) shows a higher rate of discontinuation due to any reason associated with augmenting desipramine or imipramine with lithium relative to triiodothyronine (T3) augmentation for adults with depression who have failed to respond to at least 5 weeks of treatment with desipramine/imipramine, however this effect is not statistically significant

Discontinuation due to side effects

- Low quality evidence from 2 RCT (N=177) shows a significantly higher rate of discontinuation due to side effects associated with augmenting antidepressant treatment with lithium, relative to triiodothyronine (T3) augmentation, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 60. Switching to ECT versus switching to paroxetine

Critical outcomes:

Depression symptomatology

- Low quality evidence from 1 RCT (N=39) shows a clinically important and statistically significant benefit of switching to ECT, relative switching to paroxetine, on depression symptomatology (at endpoint, and change from baseline to endpoint) for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Remission

No evidence was identified for this outcome.

Response

- Very low quality evidence from 1 RCT (N=40) shows a clinically important and statistically significant benefit of switching to ECT, relative switching to paroxetine, on the rate of response for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 1 RCT (N=40) shows a higher rate of discontinuation due to any reason associated with switching to paroxetine relative to switching to ECT for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to side effects

- High quality evidence from 1 RCT (N=40) shows neither a clinically important nor statistically significant difference between switching to ECT and switching to paroxetine on discontinuation due to side effects, for adults with depression who have shown an inadequate response to at least 2 previous courses of antidepressant treatment for the current episode

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 61. Augmenting with ECT versus continuing with antidepressant

Critical outcomes:

Depression symptomatology

- Very low quality evidence from 1 RCT (N=40) shows neither a clinically important nor statistically significant difference between augmenting citalopram with ECT and continuing with citalopram-only on depression symptomatology at endpoint, for adults with depression who have failed to respond to 2 weeks of treatment with citalopram
- Low quality evidence from 1 RCT (N=40) shows a clinically important but not statistically significant benefit of augmenting citalopram with ECT, relative to continuing with citalopram-only, on depression symptomatology change from baseline to endpoint for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Remission

No evidence was identified for this outcome.

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 62. Augmenting with ECT versus augmenting with exercise

Critical outcomes:

Depression symptomatology

- Moderate to low quality evidence from 1 RCT (N=40) shows neither a clinically important nor statistically significant difference between augmenting citalopram with ECT and augmenting with exercise on depression symptomatology (at endpoint, and change from baseline to endpoint), for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Remission

- Low quality evidence from 1 RCT (N=40) shows neither a clinically important nor statistically significant difference between augmenting citalopram with ECT and augmenting with exercise on the rate of remission, for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Critical outcomes:

Depression symptomatology

- High to moderate quality evidence from 1 RCT (N=40) shows a clinically important and statistically significant benefit of augmenting citalopram with both ECT and exercise, relative to augmenting with exercise-only, on depression symptomatology (at endpoint, and change from baseline to endpoint) for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Remission

- High quality evidence from 1 RCT (N=40) shows a clinically important and statistically significant benefit of augmenting citalopram with both ECT and exercise, relative to augmenting with exercise-only, on the rate of remission for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 64. Augmenting with exercise versus TAU

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=52) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with aerobic exercise, relative to continuing with antidepressant treatment, on depression symptomatology at endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 2 RCTs (N=94) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with aerobic exercise, relative to continuing with antidepressant treatment, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Moderate quality evidence from 2 RCTs (N=94) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with aerobic exercise, relative to continuing with antidepressant treatment, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 1 RCT (N=42) shows a clinically important but not statistically significant benefit of augmenting SSRI/SNRI treatment with aerobic exercise, relative to enhanced TAU and continuing with SSRI/SNRI treatment, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 2 RCTs (N=94) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with aerobic exercise and continuing with antidepressant treatment on discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 65. Augmenting with exercise versus attention-placebo

Critical outcomes:

Depression symptomatology

- Moderate quality evidence from 1 RCT (N=68) shows neither a clinically important nor statistically significant difference between augmenting escitalopram with a Tai Chi group and augmenting with attention-placebo on depression symptomatology at endpoint, for adults with depression who have failed to respond to 4 weeks of treatment with escitalopram
- Low quality evidence from 1 RCT (N=29) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with aerobic exercise, relative to augmenting with attention-placebo, on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Low quality evidence from 2 RCTs (N=106) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with exercise, relative to augmenting with attention-placebo, on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Low quality evidence from 2 RCTs (N=119) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with exercise, relative to augmenting with attention-placebo, on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Low quality evidence from 3 RCTs (N=192) shows a higher rate of discontinuation due to any reason associated with augmenting antidepressant treatment with exercise relative to augmenting with attention-placebo for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode, however this effect is not statistically significant

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

- Low quality evidence from 1 RCT (N=29) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with aerobic exercise, relative to augmenting with attention-placebo, on global functioning change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Moderate quality evidence from 1 RCT (N=68) shows neither a clinically important nor statistically significant difference between augmenting escitalopram with a Tai Chi group and augmenting with attention-placebo on sleeping difficulties at endpoint, for adults with depression who have failed to respond to 4 weeks of treatment with escitalopram

Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Critical outcomes:

Depression symptomatology

- High to moderate quality evidence from 1 RCT (N=40) shows a clinically important and statistically significant benefit of augmenting citalopram with both exercise and ECT, relative to augmenting with ECT-only, on depression symptomatology (at endpoint, and change from baseline to endpoint) for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Remission

- High quality evidence from 1 RCT (N=40) shows a clinically important and statistically significant benefit of augmenting citalopram with both exercise and ECT, relative to augmenting with ECT-only, on the rate of remission for adults with depression who have failed to respond to 2 weeks of treatment with citalopram

Response

No evidence was identified for this outcome.

Discontinuation due to any reason

No evidence was identified for this outcome.

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

Critical outcomes:

Depression symptomatology

- High quality evidence from 1 RCT (N=25) shows a clinically important and statistically significant benefit of augmenting antidepressant treatment with a yoga group intervention, relative to continuing with antidepressant treatment (and being placed on a waitlist for yoga), on depression symptomatology change from baseline to endpoint for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Remission

- Low quality evidence from 2 RCTs (N=147) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with a yoga group intervention, relative to continuing with antidepressant treatment (in addition to attention-placebo or waitlist), on the rate of remission for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low to very low quality evidence from 1 RCT (N=122) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with a yoga group intervention, relative to augmenting with attention-placebo, on the rate of remission at 3-month and 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Response

- Very low quality evidence from 2 RCTs (N=147) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with a yoga group intervention, relative to continuing with antidepressant treatment (in addition to attention-placebo or waitlist), on the rate of response for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode
- Low quality evidence from 1 RCT (N=122) shows a clinically important but not statistically significant benefit of augmenting antidepressant treatment with a yoga group intervention, relative to augmenting with attention-placebo, on the rate of response at 3-month and 6-month follow-up for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to any reason

- Very low quality evidence from 2 RCTs (N=147) shows neither a clinically important nor statistically significant difference between augmenting antidepressant treatment with a yoga group intervention and continuing with antidepressant treatment (in addition to attention-placebo or waitlist) on the rate of discontinuation due to any reason, for adults with depression who have shown an inadequate response to at least 1 previous course of antidepressant treatment for the current episode

Discontinuation due to side effects

No evidence was identified for this outcome.

Important outcomes:

Quality of life

No evidence was identified for this outcome.

Personal, social, and occupational functioning

No evidence was identified for this outcome.

Economic evidence statements

- Evidence from 1 single UK study conducted alongside a RCT (N=637) indicates that computerised CBT with support is unlikely to be cost-effective compared with attention control in people with depression that have had limited response to previous pharmacological treatment. The evidence is directly applicable to the UK context but is characterised by very serious limitations and therefore was not considered further.
- Evidence from 1 single UK study conducted alongside a RCT (N=158) is inconclusive regarding the cost effectiveness of cognitive therapy added to treatment as usual in people with depression who have responded inadequately to previous treatment and have residual depressive symptoms, 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. This evidence, although it was conducted in the UK, is only partially applicable to the NICE decision-making context (due to lack of QALY estimation) and it characterised by minor limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N = 469) suggests that CBT added to treatment as usual is a cost-effective treatment option in people with depression who have responded inadequately to previous treatment. This evidence is directly applicable to the NICE decision-making context and is characterised by minor limitations.
- Evidence from 1 single Canadian study conducted alongside a RCT (N=60) is inconclusive as to whether intensive short-term psychodynamic psychotherapy is cost-effective compared with TAU in people with depression who have responded inadequately to previous treatment. The evidence is partially applicable to the UK context and is characterised by very serious limitations and therefore was not considered further.
- Evidence from 1 single UK study conducted alongside a RCT (N=480) suggests that mirtazapine may be cost-effective when added to a SSRI or SNRI in people who have responded inadequately to previous treatment with a SSRI or SNRI. This evidence, although it was conducted in the UK, is only partially applicable to the NICE decision-making context (due to EQ-5D-5L being used for the estimation of QALYs) and it characterised by minor limitations.

- Evidence from 1 US model-based economic study suggests that switching (to venlafaxine or sertraline) or augmentation (with bupropion) pharmacological strategies are more cost-effective than continuation of current antidepressant treatment (citalopram) in adults with major depression that failed to respond to previous treatment. The study is partially applicable to the UK context and is characterised by very serious limitations.
- Evidence from 1 US model-based economic study suggests that switching (to venlafaxine or sertraline) or augmentation (with bupropion) pharmacological strategies are more cost-effective than continuation of current antidepressant treatment (citalopram) in adults with major depression that failed to respond to previous treatment with a SSRI. The study is partially applicable to the UK context and is characterised by very serious limitations.
- Evidence from 1 Finnish model-based economic study suggests that switching to bupropion is more cost-effective that switching to venlafaxine or sertraline in adults with depression that failed to respond to previous treatment with a SSRI. The study is partially applicable to the UK context and is characterised by potentially serious limitations. Evidence from 1 US study that made the same comparison was difficult to interpret, as the study did not use the QALY as the measure of outcome; nevertheless, the study suggested that the relative cost-effectiveness of the 3 treatment options was characterised by uncertainty. The US study is partially applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 UK model-based economic study suggests that duloxetine is more cost-effective than venlafaxine and mirtazapine in people with depression who have responded inadequately to previous antidepressant treatment with SSRIs. The study is directly applicable to the UK context but is characterised by potentially serious limitations.
- Evidence from 1 Swedish model-based economic study suggests that escitalopram is more cost-effective than duloxetine and venlafaxine in adults with major depression treated in primary care, who had had a history of treatment with another antidepressant within the previous 6 months. The study is partially applicable to the UK context and is characterised by potentially serious limitations.
- Evidence from 1 US model-based economic study suggests that paroxetine controlled release and sertraline are less cost-effective compared with other SSRIs in adults with major depression who failed to achieve remission with previous treatment with SSRIs. The study is partially applicable to the UK context and is characterised by very serious limitations.
- Evidence from 1 UK model-based study suggests that lithium dominates antipsychotics as an adjunct to SSRIs in the treatment of adults with treatment-resistant depression. The study is directly applicable to the NICE decision-making context and is characterised by potentially serious limitations.
- Evidence from 1 US study conducted alongside a RCT (N=1522) is inconclusive regarding the cost-effectiveness of aripiprazole adjunct to antidepressants versus bupropion adjunct to antidepressants versus switching to bupropion in adults with treatment-resistant depression. The study is partially applicable to the UK and is characterised by potentially serious limitations.
- Evidence from 2 US model-based economic study was inconclusive as to whether antipsychotics used as adjuncts to antidepressant therapy were cost-effective compared with antidepressant therapy alone in adults with major depression who had responded inadequately to previous antidepressant therapy, as the studies did not use the QALY as the measure of outcome. The studies are partially applicable to the UK context; one is characterised by very serious limitations and the other by potentially serious limitations.
- Evidence from 1 model-based UK study suggests that ECT may be cost-effective as part of a sequence of treatments that includes ECT – SSRI – lithium augmentation in adults with major depression that requires hospitalisation. The evidence is partially applicable to the NICE decision-making context and is characterised by potentially serious limitations.

- Evidence from 1 model-based US study suggests that ECT may be cost-effective as part of a sequence of antidepressant, psychological and ECT treatments. The evidence is partially applicable to the UK and is characterised by very serious limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the most effective treatments for depression that has not responded to previous therapies, so the committee prioritised depression symptomatology, remission and response as critical outcomes. As a treatment can only be effective if it is utilised by the person with depression, discontinuation due to any reason, and due to side effects, were also prioritised by the committee as critical outcomes.

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

The quality of the evidence

The quality of evidence was assessed using GRADE and was generally rated as low to very low, reflecting the high risk of bias associated with the studies. This included high risk of bias associated with randomisation method (as reflected by significant group differences at baseline), and lack of (or unclear) blinding of outcome assessment. There were also a limited number of studies for each comparator, small numbers of participants in most trials and imprecision in most of the results.

Benefits and harms

In developing recommendations for people with depression that has not responded or where there has been a limited response to treatment, the committee drew on their knowledge and experience that a significant number of people with depression may not adhere to the prescribed treatment regimen and their personal or social factors could have a significant impact on their response to treatment, and so should be identified and addressed if possible. They therefore agreed that a review of these factors should be considered before initiating any additional treatment options. Based on the expert opinion of the committee, it was noted that coexisting conditions or alternative diagnoses could also limit response to treatment, and it was agreed that the diagnosis should be reviewed if adherence and lifestyle factors had been addressed and a limited response continued.

The committee recognised that people with depression may experience a loss of confidence when the initial treatment has not worked, and may need reassurance that alternative or additional treatments can be tried, and that this can include a discussion about the rationale for switching to an alternative approach, acknowledging that some treatments have not worked and providing some explanation about how the further-line treatment works differently.

When developing the recommendations for further-line treatment, the committee considered a number of factors including the relative strength of the evidence, the preference that service users may have for medication or psychological interventions and the adverse effects of medication, in particular when combinations of medications are used. The committee were aware, from established data on response curves to antidepressant treatment that most people who respond to pharmacological interventions will have have shown some response

within 4 weeks of initiation of treatment. Response curves are similar for psychological interventions but response to psychological interventions may initially be slower than to medication with people typically responding to treatment within 4 to 6 weeks.

In developing their recommendations, the committee considered three main scenarios: first where a person had not responded to initial psychological therapy, secondly where a person had not responded to initial antidepressant medication, and thirdly where a person had not responded to initial treatment with a combination of antidepressant medication and psychological therapy.

Where there was limited or no response to initial psychological therapy, the committee drew on their expert knowledge, and evidence for other review questions in this guideline, as there was no evidence identified that was specific to this population. Based on this limited evidence base, the committee also made a research recommendation. The committee agreed that switching to an alternative psychological intervention may align with clinical needs and preferences, particularly for people who may not want to take antidepressant medication, and that this option should be discussed and considered. The committee also recommended a combination of a psychological intervention with antidepressant medication (adding an SSRI or mirtazapine) as an option for those who have shown a limited response to initial psychological therapy alone and who were willing to try an antidepressant. In developing this recommendation, the committee drew on the evidence for first-line treatments particularly in more severe depression where combination treatment was more clinically and cost-effective than medication alone. The committee also recognised that those who had shown limited response to an initial psychological intervention may wish to switch to an antidepressant treatment and so, drawing on their expert knowledge and experience and the data on first-line treatments developed a recommendation that a person should have the option of switching to an SSRI or mirtazapine alone.

Where there was limited or no response to an initial antidepressant monotherapy the committee recommended that, based on the evidence, either a group exercise programme or a psychological therapy should be used to augment the antidepressant. Alternatively, individuals could switch to a psychological intervention, or antidepressant medication could be continued but with an alternative drug or an increased dose. There was some evidence from randomised controlled trials for clinical benefits associated with augmenting antidepressant treatment with group exercise programmes, in particular aerobic exercise groups, and the committee agreed that this option should be discussed with the person and offered. However, the committee took into account that this option may not suit everyone, and may be difficult for some people to engage with. There was evidence from multiple trials in the review of the benefit of augmenting antidepressant medication with cognitive-behavioural therapies. The committee were also aware of a number of important, often pragmatic, trials of cognitive-behavioural therapies (including CBASP and rumination-focused CBT) as further-line treatment or treatment for residual depression, which replicated the findings in the meta-analysis but were excluded, typically because patients were not randomised at the point of non-response (including Clarke 2002; Fava 1994; Hollon 2014; Hvenegaard 2020; Moore and Blackburn 1997; Segal 2020; Teissman 2014). The committee agreed that an alternative further-line treatment option for those who have not responded to initial antidepressant treatment could be switching to a psychological intervention. There was no evidence that specifically examined switching to a psychological intervention for those who have not responded to initial antidepressant treatment, however, the committee drew on the evidence for first-line treatments in more severe depression. The committee agreed that the psychological interventions that had been identified as effective and cost-effective for first-line treatment of more severe depression could be used for people who had not responded to antidepressants and wished to try a psychological therapy instead. The committee also considered options for continuing antidepressant treatment. The committee were aware that currently, a common approach to a limited or non-response to pharmacological interventions is to either increase the dose or switch to an alternative medication. The committee noted that the evidence reviewed in this guideline did not

provide significant support for either of these two strategies as being effective. However, the committee were aware that in a number of the trials which were reviewed, the absence of benefit may have been due to improvement in the continued antidepressant/dose arm. The committee were also aware that some people would not want to try an exercise programme or a psychological intervention, nor be willing to accept the increased side effect burden of combined drug treatment. Given this, the committee agreed to make a recommendation for switching to another antidepressant or increasing the dose. However, the committee were concerned about the limited evidence for these strategies and so also recommended close monitoring and a review of the treatment strategy. They also recommended that discussion of other treatment options should take place and consideration be given to referral for specialist advice.

Where there was limited or no response to combined antidepressant medication and psychological therapy, the committee considered that the options used in those who had failed to respond to psychological intervention alone or antidepressant medication monotherapy, namely switching to another psychological therapy and/or continuing with antidepressant medication using an alternative drug or increased dose, should be used. Combinations with an antidepressant of a different class, antipsychotics (aripiprazole, risperidone, quetiapine, olanzapine) and lithium were all identified in the reviews undertaken for this guideline as effective: there was evidence for improved depression symptomatology and higher rates of remission or response in the treatment of people with no or limited response to initial antidepressant treatment and so the committee decided to recommend these options. There was also some evidence for clinical benefits associated with augmenting antidepressant treatment with ECT, lamotrigine or triiodothyronine, however, the committee agreed that these further-line treatment strategies may require increased monitoring, and that use of all combination medications would require advice from specialist mental health services. There was also some evidence for the use of augmentation with omega-3 but the committee noted that the studies used a number of different preparations and that there was uncertainty about the dose and preparation and so they did not recommend this combination. The committee were aware that for all combinations of medication, there was a risk of a significant increase in side effect burden and therefore recommended that people should be informed about this so that they can decide if this increased burden is acceptable to them.

The committee were aware that there was already NICE guidance on the use of vortioxetine in people who had had no or limited response to at least 2 previous antidepressants and so they included a reference to this as part of their recommendations.

There was some very limited evidence that ECT may be beneficial as a further-line treatment, either alone or in combination with exercise. The committee used this evidence to recommend that ECT may be considered for use as further-line treatment when other treatments have been unsuccessful. However, the committee were aware that there may be other situations where ECT could be considered: when a rapid response is needed (and the committee provided an example of when this might be the case), or if a person with severe depression had received successful ECT in the past and expressed a preference for it. The committee discussed the care and considerations that needed to be taken into account when delivering ECT, such as informing people of the risks and benefits, obtaining consent, monitoring cognitive function and stopping ECT. The committee amended the existing recommendations on these topics but agreed that there are now recognised up to date standards produced by the Royal College of Psychiatrists which provide guidance on how a sefae and effective ECT service should be delivered. This is in the contect of an ECT accreditation service (ECTAS), and so the committee added a recommendation to advise that clinics providing ECT should be accredited, and Trusts should ensure compliance with ECTAS standards.

r.

The committee were aware that, since the publication of the previous guideline, there had been much further research into refining the administration of ECT, comparing different modalities of ECT treatment, comparing ECT with other neuromodulatory therapies, and into possible adverse effects. However the remit of the original review of ECT for the guideline had a focus on sham-controlled randomised trials and so had not taken account of this wider evidence base. The committee was also aware of the PRIDE study of continuation ECT in depression in older people (Kellner 2016) which had reported a positive finding based on odds ratios.

The committee considered the short-term and long-term harms associated with medication, for example, side effects associated with SSRIs include drowsiness, nausea, insomnia, agitation, restlessness and sexual problems. For the TCAs there is the potential for cardiotoxicity and associated increased risk in overdose, although this is much greater for some TCAs such as amitriptyline and dosulepin and so the committee included a warning about this. They also added, based on their knowledge and the BNF guidance that 'lofepramine has a lower incidence of side-effects and is less dangerous in overdose [than other tricyclic antidepressants]' the fact that lofepramine has the best safety profile.. For lithium there were concerns about renal toxicity and thyroid and parathyroid function. For the antipsychotics concerns with weight gain and hyperlipidaemia and raised blood glucose were also considered. The committee took these factors into consideration and in particular the increased burden of harms that may arise with the use of a combination of medications. In developing the recommendations, the committee were mindful of the negative consequences of prolonged depressive episodes including not only the impact on the mental health of the individual and their family but also on an individual's physical health (depression is associated with poorer physical health outcomes) and the impact on employment. The committee agreed that the benefits of improving the outcome of a depressive episode outweighed the potential harms. The committee were also aware that a number of prescribers, including GPs, would not feel competent to initiate such combination treatment and therefore also recommended that combination therapy should be initiated in specialist settings or after consulting a specialist.

Longer-term follow-up

The committee noted that very few studies of further-line treatment reported any follow-up data, and this data was particularly sparse for the pharmacological trials. A small number of studies could be combined in meta-analyses for outcomes up to 6 months after endpoint, however, beyond this point it was predominantly single-study analyses. The committee considered this limited evidence, and noted that a small number of studies showed evidence for sustained benefits on depression outcomes associated with augmenting antidepressants with CBT (up to 40 months), IPT (up to 12 months), short-term psychodynamic psychotherapy (up to 12 months), and long-term psychodynamic psychotherapy (up to 2 years). The committee agreed that the effects on depression outcomes at follow-up were generally in line with the effects observed at endpoint, and this strengthened their confidence in the recommendations.

Quality of life and functioning outcomes

The committee also noted that there was very little data for quality of life or functioning outcomes. The committee considered the evidence for clinically important and statistically significant effects, and noted single-study analyses showing equivocal benefits on quality of life associated with increasing the dose of an SSRI (versus same dose), some evidence for a benefit on global functioning or functional impairment of antipsychotic augmentation (relative to increasing SSRI dose, or continuing with the antidepressant at the same dose) or augmenting antidepressants with exercise, and of omega-3 augmentation on sleeping difficulties. However, 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 committee considered the high healthcare costs and outcomes to the person associated with depression showing an inadequate response to treatment, and expressed the view that successful treatment, as expressed by full response to treatment and eventual remission, would lead to the optimal outcome to the person but also considerable cost-savings to the healthcare system.

The committee considered the available economic evidence on treatments for people with depression who have responded inadequately to previous treatment. They noted that UK evidence suggests that CBT may be a cost-effective treatment option in this population when added to TAU (including pharmacological treatment) compared with TAU alone. Regarding drugs, evidence from the UK suggests that mirtazapine is likely to be cost-effective when added to a SSRI or SNRI in people who have responded inadequately to previous treatment with a SSRI or SNRI; other UK evidence suggests that duloxetine is more cost-effective than venlafaxine and mirtazapine in people with depression that has responded inadequately to previous treatment with SSRIs. Evidence from Sweden suggests that escitalopram is more cost-effective than duloxetine and venlafaxine in people whose depression responded inadequately to previous antidepressant treatment. Evidence from Finland suggests that switching to bupropion is more cost-effective that switching to venlafaxine or sertraline in adults with depression that failed to respond to previous treatment with a SSRI. Other evidence from the UK suggests that lithium dominates antipsychotics as an adjunct to SSRIs in the treatment of adults with depression that has not responded to treatment. The committee noted that economic evidence on psychological interventions is overall characterised by minor limitations, whereas evidence on pharmacological interventions is characterised by minor to potentially serious limitations. Other available non-UK evidence was not considered as it was characterised by very serious limitations and/or high uncertainty. Finally, there was some UK evidence that ECT may be cost-effective as part of a sequence of treatments that includes ECT – SSRI – lithium augmentation in adults with major depression that requires hospitalisation. The committee considered this evidence when formulating separate ECT recommendations in the guideline.

The committee acknowledged that the economic evidence in this area is rather sparse and has limitations, and decided to draw additional information from the economic analysis of treatments of a new depressive episode that was undertaken for the guideline (See Evidence report B, Appendix J). According to the guideline economic analysis, group psychological therapies (such as group CBT and group behavioural activation), pharmacological treatment, and other low-intensity psychological and physical interventions were the most cost-effective options for the treatment of new episodes of less severe depression in adults. For populations with more severe depression, the combination of individual CBT with an antidepressant was likely to be the most cost-effective option for the treatment of new episodes, followed by pharmacological treatments, group exercise and individual psychological interventions (such as CBT, IPT or STPP). All these options were found to be more cost-effective than GP care.

Considering the available economic evidence, the committee decided to recommend further-line treatment options among those that were found to be cost-effective versus TAU (which might include GP care, referral to specialist care, and/or active pharmacological treatment), according to the type of treatment to which there was no or inadequate response, following a shared decision and based on the person's clinical need and preferences. They therefore recommended, as one cost-effective option, the combination of medication and psychological treatment for people who have responded inadequately to medication alone or to psychological intervention alone, and the possibility of changing the components of

combination therapy in people who are already on a combination of medication and a psychological therapy.

The committee considered that offering an SSRI or mirtazapine as an alternative or as an adjunct to psychological treatment to people whose symptoms have not adequately responded to an initial psychological intervention would have minor resource implications as the intervention cost of providing antidepressant treatment is overall lower than that of an individual psychological intervention. Moreover, the committee noted that switching from a psychological therapy that led to inadequate response to a different type of psychological therapy or a different type of treatment, such as pharmacological or combined therapy, would potentially result in better outcomes for the person and, therefore, anticipated reduction in further care costs.

The committee considered that increasing the dose of a well-tolerated drug, switching between antidepressants within the same or different class, or adding an antidepressant to existing medication (for example, adding a SSRI or mirtazapine) would have negligible resource implications in terms of the drug acquisition cost, as these drugs are available in generic form, although there are costs associated with the necessary clinical review of dose escalations or switching. Switching from a drug that is causing side effects to another drug of the same or different class may lead to cost-savings and better outcomes for the person, if the new drug is better tolerated.

The committee noted that, according to existing evidence, offering psychological therapy to people who have limited response to previous pharmacological treatment may be cost-effective. They also considered that adding a group exercise intervention to people with inadequate response to previous antidepressant treatment has been shown to be beneficial to the person and is likely to have minor resource implications.

The committee acknowledged the additional costs associated with combined medication therapy, for example combined antidepressant treatment or provision of lithium or antipsychotics in addition to antidepressant treatment, which should take place in specialist settings or after consultation with a specialist. These costs relate to specialist staff time but also to monitoring costs and costs associated with side effects. The committee considered the available UK evidence according to which adding mirtazapine to SSRI treatment is cost-effective. They also noted that lithium dominates antipsychotics as an adjunct to SSRIs in the treatment of adults with depression that has not responded to treatment, but noted that this evidence was characterised by potentially serious limitations. Based on the above considerations, the committee recommended combining different antidepressants (for example mirtazapine with a SSRI) or combining antidepressants with an antipsychotic or lithium in specialist settings, or after consultation with a specialist, as an option if a person has had no response or a limited response to antidepressant medication, does not want to try a psychological therapy, and wants to try a combination of medications and is willing to accept the possibility of an increased side-effect burden. In this population, alternative effective treatment options are limited and the committee expressed the view that the benefits of combined medication treatment are likely to outweigh costs associated with its provision to this group.

Other factors the committee took into account

When reviewing the evidence for further line treatment the committee had originally decided to separately examine the evidence base for treatment resistant depression (usually defined as no or limited response to two adequate courses of an antidepressant) from no or limited response to treatment. However, after carefully reviewing the trial populations and the variation in the criteria used to identify both no or limited response and treatment resistance the committee came to the view that there were considerable similarities and overlaps between the two populations and therefore decided to use the same data sets for both questions to inform the development of recommendations for no or limited response.

The review of further-line treatment included those with chronic depression, but the committee also took into consideration the evidence base for the first-line treatment of chronic depression that was reviewed in Evidence report E. When reviewing the evidence for further-line treatment, the committee were aware that a number of pragmatic trials were excluded, typically because they recruited in usual clinical settings and participants were not randomised at the point of no/inadequate/limited response. The committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.9.1 to 1.9.9, 1.13.1 to 1.3.9 and research recommendations in the NICE guideline.

References

Appelberg 2001

Appelberg BG, Syvälahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH (2001) Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. Journal of Clinical Psychiatry 62(6): 448-452.

Baert 2010_study 2

Baert S, De Raedt R, Schacht R, Koster EH (2010) Attentional bias training in depression: therapeutic effects depend on depression severity. Journal of Behavior Therapy and Experimental Psychiatry 41(3): 265-274.

Barbee 2011

Barbee JG, Thompson TR, Jamhour NJ, Stewart JW, Conrad EJ, Reimherr FW, Thompson PM, Shelton RC (2011) A double-blind placebo-controlled trial of lamotrigine as an antidepressant augmentation agent in treatment-refractory unipolar depression. Journal of Clinical Psychiatry 72(10): 1405-1412.

Bauer 2009

Bauer M, Pretorius HW, Constant EL, Earley WR, Szamosi J, Brecher M (2009) Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. Journal of Clinical Psychiatry 70(4): 540-549.

Bauer 2013

Bauer M, Dell'Osso L, Kasper S, Pitchot W, Vansvik ED, Köhler J, Jørgensen L, Montgomery SA (2013) Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder. Journal of Affective Disorders 151(1): 209-219.

Bauer 2019

Bauer M, Hefting N, Lindsten A, Josiassen MK, Hobart M (2019) A randomised, placebo-controlled 24-week study evaluating adjunctive brexpiprazole in patients with major depressive disorder. Acta Neuropsychiatrica 31(1): 27-35.

Baumann 1996

Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M (1996) A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. Journal of Clinical Psychopharmacology 16(4): 307-314.

Benedict 2010

Benedict A, Arellano J, De Cock E, Baird J (2010) Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland. Journal of Affective Disorders 120: 94-104.

Berman 2007

Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A (2007) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive

disorder: a multicenter, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry 68(6): 843-853.

Berman 2009

Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, Carson WH, Adson D, Taylor L, Hazel J, Marcus RN (2009) Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectrums 14(04): 197-206.

Bose 2012

Bose A, Tsai J, Li D (2012) Early non-response in patients with severe depression. Clinical Drug Investigation 32(6): 373-385.

Carpenter 2002

Carpenter LL, Yasmin S, Price LH (2002) A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biological Psychiatry 51(2):183-188.

Chan 2012

Chan AS, Wong QY, Sze SL, Kwong PP, Han YM, Cheung MC (2012) A Chinese Chan-based mind–body intervention for patients with depression. Journal of Affective Disorders 142(1-3): 283-289.

Cheon 2017

Cheon EJ, Lee KH, Park YW, Lee JH, Koo BH, Lee SJ, Sung HM (2017) Comparison of the efficacy and safety of aripiprazole versus bupropion augmentation in patients with major depressive disorder unresponsive to selective serotonin reuptake inhibitors: a randomized, prospective, open-label study. Journal of Clinical Psychopharmacology 37(2): 193-199.

Chiesa 2015

Chiesa A, Castagner V, Andrisano C, Serretti A, Mandelli L, Porcelli S, Giommi F (2015) Mindfulness-based cognitive therapy vs. psycho-education for patients with major depression who did not achieve remission following antidepressant treatment. Psychiatry Research 226(2): 474-483.

Corya 2006

Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G (2006) A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depression and Anxiety 23(6): 364-372.

Dai 2019

Dai Q, Hu L, Feng Z (2019) Attentional bias modification reduces clinical depression and enhances attention toward happiness. Journal of Psychiatric Research 109: 145-155.

Danielsson 2014

Danielsson L, Papoulias I, Petersson EL, Carlsson J, Waern M (2014) Exercise or basic body awareness therapy as add-on treatment for major depression: a controlled study. Journal of Affective Disorders 168: 98-106.

Doree 2007

Dorée JP, Rosiers JD, Lew V, Gendron A, Elie R, Stip E, Valérie Tourjman S (2007) Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. Current Medical Research and Opinion 23(2): 333-341.

Dornseif 1989

Dornseif BE, Dunlop SR, Potvin JH, Wernicke JF (1989) Effect of dose escalation after low-dose fluoxetine therapy. Psychopharmacology Bulletin 25(1): 71-79.

Dozois 2009

Dozois DJ, Bieling PJ, Patelis-Siotis I, Hoar L, Chudzik S, McCabe K, Westra HA (2009) Changes in self-schema structure in cognitive therapy for major depressive disorder: a randomized clinical trial. Journal of Consulting and Clinical Psychology 77(6): 1078-1088.

Dunn 1979

Dunn RJ (1979) Cognitive modification with depression-prone psychiatric patients. Cognitive Therapy and Research 3(3): 307-317.

Dunner 2007

Dunner DL, Amsterdam JD, Shelton RC, Loebel A, Romano SJ (2007) Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. Journal of Clinical Psychiatry 68(7): 1071-1077.

Durgam 2016

Durgam S, Earley W, Guo H, Li D, Németh G, Laszlovszky I, Fava M, Montgomery SA (2016) Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. Journal of Clinical Psychiatry 77(3): 371-378.

Earley 2018

Earley WR, Guo H, Németh G, Harsányi J, Thase ME (2018) Cariprazine augmentation to antidepressant therapy in major depressive disorder: results of a randomized, double-blind, placebo-controlled trial. Psychopharmacology Bulletin 48(4): 62-80.

Edwards 2013

Edwards S, Hamilton V, Nherera L, Trevor N (2013) Lithium or an atypical antipsychotic drug in the management of treatment resistant depression: a systematic review and economic evaluation. Health Technology Assessment 17(54).

Eisendrath 2016

Eisendrath SJ, Gillung E, Delucchi KL, Segal ZV, Nelson JC, McInnes LA, Mathalon DH, Feldman MD (2016) A randomized controlled trial of mindfulness-based cognitive therapy for treatment-resistant depression. Psychotherapy and Psychosomatics 85(2): 99-110.

El-Khalili 2010

El-Khalili N, Joyce M, Atkinson S, Buynak RJ, Datto C, Lindgren P, Eriksson H (2010) Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. International Journal of Neuropsychopharmacology 13(7): 917-932.

Embling 2002

Embling S (2002) The effectiveness of cognitive behavioural therapy in depression. Nursing Standard 17(14/15): 33-41.

Fang 2010

Fang Y, Yuan C, Xu Y, Chen J, Wu Z, Cao L, Yi Z, Hong W, Wang Y, Jiang K, Gao K (2010) Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: a double-blind, randomized pilot study in a Chinese population. Journal of Clinical Psychopharmacology 30(4): 357-364.

Fang 2011

Fang Y, Yuan C, Xu Y, Chen J, Wu Z, Cao L, Yi Z, Hong W, Wang Y, Jiang K, Cui X (2011) A pilot study of the efficacy and safety of paroxetine augmented with risperidone, valproate, buspirone, trazodone, or thyroid hormone in adult Chinese patients with treatment-resistant major depression. Journal of Clinical Psychopharmacology 31(5): 638-642.

Fava 1994a

Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM (1994) Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. American Journal of Psychiatry 151(9): 1372-1374.

Fava 2002

Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, Worthington J, Baer L, Rosenbaum JF (2002) Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. Journal of Clinical Psychopharmacology 22(4): 379-387.

Fava 2012/Mischoulon 2012

Fava M, Mischoulon D, Iosifescu D, Witte J, Pencina M, Flynn M, Harper L, Levy M, Rickels K, Pollack M (2012) A double-blind, placebo-controlled study of aripiprazole adjunctive to antidepressant therapy among depressed outpatients with inadequate response to prior antidepressant therapy (ADAPT-A Study). Psychotherapy and Psychosomatics 81(2): 87-97.

Mischoulon D, Witte J, Levy M, Papakostas GI, Pet LR, Hsieh WH, Pencina MJ, Ward S, Pollack MH, Fava M (2012) Efficacy of dose increase among nonresponders to low-dose aripiprazole augmentation in patients with inadequate response to antidepressant treatment: a randomized, double-blind, placebo-controlled, efficacy trial. Journal of Clinical Psychiatry 73(3): 353-357.

Fava 2018

Fava M, Durgam S, Earley W, Lu K, Hayes R, Laszlovszky I, Németh G (2018) Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial. International Clinical Psychopharmacology 33(6): 312-321.

Fava 2019

Fava M, Dirks B, Freeman MP, Papakostas GI, Shelton RC, Thase ME, Trivedi MH, Liu K, Stankovic S (2019) A phase 2, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in patients with major depressive disorder and an inadequate response to therapy (CLARITY). Journal of Clinical Psychiatry 80(6): 19m12928.

Ferreri 2001

Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ (2001) Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatrica Scandinavica 103(1): 66-72.

Folkerts 1997

Folkerts HW, Michael N, Tölle R, Schonauer K, Mücke S, Schulze-Mönking H (1997) Electroconvulsive therapy vs. paroxetine in treatment-resistant depression - a randomized study. Acta Psychiatrica Scandinavica 96(5): 334-342.

Fonagy 2015

Fonagy P, Rost F, Carlyle JA, McPherson S, Thomas R, Pasco Fearon RM, Goldberg D, Taylor D (2015) Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). World Psychiatry 14(3): 312-321.

Girlanda 2014

Girlanda F, Cipriani A, Agrimi E, Appino MG, Barichello A, Beneduce R, Bighelli I, Bisoffi G, Bisogno A, Bortolaso P, Boso M (2014) Effectiveness of lithium in subjects with treatment-resistant depression and suicide risk: results and lessons of an underpowered randomised clinical trial. BMC Research Notes 7(1): 731.

GlaxoSmithKline 2009

GlaxoSmithKline (2009) Clinical evaluation of 323U66 SR in patients With depression - placebo-controlled, double-blind, comparative study in patients With depression who did not respond sufficiently to selective serotonin re-uptake inhibitors. Available from: https://www.clinicaltrials.gov/ct2/show/results/NCT00296517 [accessed 31.01.17].

Greenhalgh 2005

Greenhalgh J, Knight C, Hind D, Beverley C, Walters S (2005) Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: Systematic reviews and economic modelling studies. Health Technology Assessment 9(9).

Gulrez 2012

Gulrez G, Badyal DK, Deswal RS, Sharma A (2012) Bupropion as an augmenting agent in patients of depression with partial response. Basic & Clinical Pharmacology & Toxicology 110(3): 227-230.

Haghighi 2013

Haghighi M, Salehi I, Erfani P, Jahangard L, Bajoghli H, Holsboer-Trachsler E, Brand S (2013) Additional ECT increases BDNF-levels in patients suffering from major depressive disorders compared to patients treated with citalopram only. Journal of Psychiatric Research 47(7): 908-915.

Ho 2014

Ho CW, Chan SC, Wong JS, Cheung WT, Chung DW, Lau TF (2014) Effect of aerobic exercise training on Chinese population with mild to moderate depression in Hong Kong. Rehabilitation Research and Practice 2014: 627376.

Hobart 2018a

Hobart M, Skuban A, Zhang P, Augustine C, Brewer C, Hefting N, Sanchez R, McQuade RD (2018) A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. Journal of Clinical Psychiatry 79(4): 17m12058.

Hobart 2018b

Hobart M, Skuban A, Zhang P, Josiassen MK, Hefting N, Augustine C, Brewer C, Sanchez R, McQuade RD (2018) Efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of major depressive disorder: a randomized, active-referenced, placebo-controlled study. Current Medical Research and Opinion 34(4): 633-642.

Jahangard 2018

Jahangard L, Sadeghi A, Ahmadpanah M, Holsboer-Trachsler E, Bahmani DS, Haghighi M, Brand S (2018) Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders-Results from a double-blind, randomized and placebo-controlled clinical trial. Journal of Psychiatric Research 107: 48-56.

Joffe 1993

Joffe RT, Singer W, Levitt AJ, MacDonald C (1993) A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Archives of General Psychiatry 50(5): 387-393.

Kamijima 2013

Kamijima K, Higuchi T, Ishigooka J, Ohmori T, Ozaki N, Kanba S, Kinoshita T, Koyama T, ADMIRE Study Group (2013) Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). Journal of Affective Disorders 151(3): 899-905.

Kamijima 2018

Kamijima K, Kimura M, Kuwahara K, Kitayama Y, Tadori Y (2018) Randomized, double-blind comparison of aripiprazole/sertraline combination and placebo/sertraline combination in patients with major depressive disorder. Psychiatry and Clinical Neurosciences 72(8): 591-601.

Kato 2018

Kato T, Furukawa TA, Mantani A, Kurata KI, Kubouchi H, Hirota S, Sato H, Sugishita K, Chino B, Itoh K, Ikeda Y (2018) Optimising first-and second-line treatment strategies for untreated major depressive disorder—the SUN☺ D study: a pragmatic, multi-centre, assessor-blinded randomised controlled trial. BMC Medicine 16(1): 1-6.

Keitner 2009

Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, Keller MB (2009) A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. Journal of Psychiatric Research 43(3): 205-214.

Kennedy 2003

Kennedy SH, Segal ZV, Cohen NL, Levitan RD, Gemar M, Bagby RM (2003) Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: an exploratory trial. Journal of Clinical Psychiatry 64(4): 439-444.

Kessler 2018a/2018b

Kessler DS, MacNeill SJ, Tallon D, Lewis G, Peters TJ, Hollingworth W, Shepherd T (2018) Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial (MIR). BMJ 363: k4218.

Kessler D, Burns A, Tallon D, Lewis G, MacNeill S, Round J, Dickens C (2018) Combining mirtazapine with SSRIs or SNRIs for treatment-resistant depression: the MIR RCT. Health Technology Assessment: 1-136.

Kim 2019

Kim EY, Kim SH, Lee HJ, Lee NY, Kim HY, Park CHK, Ahn YM (2019) A randomized, double-blind, 6-week prospective pilot study on the efficacy and safety of dose escalation in non-remitters in comparison to those of the standard dose of escitalopram for major depressive disorder. Journal of Affective Disorders 259: 91-97.

Kocsis 2009/Klein 2011

Kocsis JH, Gelenberg AJ, Rothbaum BO, Klein DN, Trivedi MH, Manber R, Keller MB, Leon AC, Wisniewski SR, Arnow BA, Markowitz JC (2009) Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: the REVAMP Trial. Archives of General Psychiatry 66(11): 1178-1188.

Klein DN, Leon AC, Li C, D'Zurilla TJ, Black SR, Vivian D, Dowling F, Arnow BA, Manber R, Markowitz JC, Kocsis JH (2011) Social problem solving and depressive symptoms over time: a randomized clinical trial of cognitive-behavioral analysis system of psychotherapy, brief supportive psychotherapy, and pharmacotherapy. Journal of Consulting and Clinical Psychology 79(3): 342-352.

Kornstein 2008

Kornstein SG, Dunner DL, Meyers AL, Whitmyer VG, Mallinckrodt CH, Wohlreich MM, Detke MJ, Hollandbeck MS, Greist JH (2008) A randomized, double-blind study of increasing or maintaining duloxetine dose in patients without remission of major depressive disorder after initial duloxetine therapy. Journal of Clinical Psychiatry 69(9): 1383-1392.

Lavretsky 2011

Lavretsky H, Alstein LL, Olmstead RE, Ercoli LM, Riparetti-Brown M, Cyr NS, Irwin MR (2011) Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. American Journal of Geriatric Psychiatry 19(10): 839-850.

Lenox-Smith 2008

Lenox-Smith AJ, Jiang Q (2008) Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. International Clinical Psychopharmacology 23: 113-119.

Lenze 2015

Lenze EJ, Mulsant BH, Blumberger DM, Karp JF, Newcomer JW, Anderson SJ, Dew MA, Butters MA, Stack JA, Begley AE, Reynolds CF (2015) Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. The Lancet 386(10011): 2404-2412.

Li 2009

Li C, Chui G, Song Z (2009) Clinical observation of lamotrigine augmentation with sertraline on the geriatric treatment-resistant depression. Chinese Journal of Gerontology 29: 96–97 [in Chinese].

Li 2013

Li X, Xing B, Yu E, Chen W, Wu H (2013) The combined treatment of venlafaxine and quetiapine for treatment-resistant depression: a clinical study. Journal of Neuropsychiatry and Clinical Neurosciences 25(2): 157-160.

Li 2015

Li Q, Hu C, Ma H (2015) A control study of lamotrigine combined with paroxetine for the treatment of refractory depression. Jounral of Psychiatry (China) 28: 284-286 [in Chinese].

Licht 2002

Licht RW, Qvitzau S (2002) Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology 161(2): 143-151.

Lynch 2007_study 2

Lynch TR, Cheavens JS, Cukrowicz KC, Thorp SR, Bronner L, Beyer J (2007) Treatment of older adults with co-morbid personality disorder and depression: a dialectical behavior therapy approach. International Journal of Geriatric Psychiatry 22(2): 131-143.

Mahmoud 2007

Mahmoud RA, Pandina GJ, Turkoz I, Kosik-Gonzalez C, Canuso CM, Kujawa MJ, Gharabawi-Garibaldi GM (2007) Risperidone for treatment-refractory major depressive disorder: a randomized trial. Annals of Internal Medicine 147(9): 593-602.

Malone 2007

Malone DC (2007) A budget-impact and cost-effectiveness model for second-line treatment of major depression. Journal of Managed Care Pharmacy 13: S8-S18.

Mantani 2017

Mantani A, Kato T, Furukawa TA, Horikoshi M, Imai H, Hiroe T, Chino B, Funayama T, Yonemoto N, Zhou Q, Kawanishi N (2017) Smartphone cognitive behavioral therapy as an adjunct to pharmacotherapy for refractory depression: randomized controlled trial. Journal of Medical Internet Research 19(11): e373.

Marcus 2008

Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM (2008) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. Journal of Clinical Psychopharmacology 28(2): 156-165.

Mather 2002

Mather AS, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo ME (2002) Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. British Journal of Psychiatry 180(5): 411-415.

McIntyre 2007

McIntyre A, Gendron A, McIntyre A (2007) Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. Depression and Anxiety 24(7): 487-494.

Mohamed 2017 / Yoon 2018

Mohamed S, Johnson GR, Chen P, Hicks PB, Davis LL, Yoon J, Scrymgeour A (2017) Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: the VAST-D randomized clinical trial. JAMA 318(2): 132-145.

Yoon J, Zisook S, Park A, Johnson GR, Scrymgeour A, Mohamed S (2018) Comparing cost-effectiveness of aripiprazole augmentation with other "next-step" depression treatment strategies: a randomized clinical trial. Journal of Clinical Psychiatry 80: 18.

Moica 2018

Moica T, Grecu IG, Sabău D, Szasz S, Grecu MG, Moica S, Grosan A, Buicu F (2018) The efficacy of quetiapine XR as an adjunctive therapy to duloxetine in depressed patients with inadequate response to monotherapy. Farmacia 66(2): 354-357.

Mota-Pereira 2011

Mota-Pereira J, Silverio J, Carvalho S, Ribeiro JC, Fonte D, Ramos J (2011) Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. Journal of Psychiatric Research 45(8): 1005-1011.

Mowla 2011

Mowla A, Kardeh E (2011) Topiramate augmentation in patients with resistant major depressive disorder: a double-blind placebo-controlled clinical trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35(4): 970-973.

Mozaffari-Khosravi 2013

Mozaffari-Khosravi H, Yassini-Ardakani M, Karamati M, Shariati-Bafghi SE (2013) Eicosapentaenoic acid versus docosahexaenoic acid in mild-to-moderate depression: a randomized, double-blind, placebo-controlled trial. European Neuropsychopharmacology 23(7): 636-644.

Murray 2010

Murray G, Michalak EE, Axler A, Yaxley D, Hayashi B, Westrin Å, Ogrodniczuk JS, Tam EM, Yatham LN, Lam RW (2010) Relief of chronic or resistant depression (Re-ChORD): a pragmatic, randomized, open-treatment trial of an integrative program intervention for chronic depression. Journal of Affective Disorders 123(1): 243-248.

Nakagawa 2017

Nakagawa A, Mitsuda D, Sado M, Abe T, Fujisawa D, Kikuchi T, Iwashita S, Mimura M, Ono Y (2017) Effectiveness of supplementary cognitive-behavioral therapy for pharmacotherapy-resistant depression: a randomized controlled trial. Journal of Clinical Psychiatry 78(8): 1126-1135.

Nakajima 2011

Nakajima S, Uchida H, Suzuki T, Watanabe K, Hirano J, Yagihashi T, Takeuchi H, Abe T, Kashima H, Mimura M (2011) Is switching antidepressants following early nonresponse more beneficial in acute-phase treatment of depression?: a randomized open-label trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35(8): 1983-1989.

Nakao 2018

Nakao S, Nakagawa A, Oguchi Y, Mitsuda D, Kato N, Nakagawa Y, Tamura N, Kudo Y, Abe T, Hiyama M, Iwashita S (2018) Web-based cognitive behavioral therapy blended with face-to-face sessions for major depression: randomized controlled trial. Journal of Medical Internet Research 20(9): e10743.

Nan 2017

Nan JKM, Ho RTH (2017) Effects of clay art therapy on adults outpatients with major depressive disorder: a randomized controlled trial. Journal of Affective Disorders 217: 237-245.

Navarro 2019a

Navarro V, Boulahfa I, Obach A, Jerez D, Diaz-Ricart M, Gastó C, Guarch J (2019) Switching to imipramine versus add-on mirtazapine in venlafaxine-resistant major depression: a 10-week randomized open study. Journal of Clinical Psychopharmacology 39(1): 63-66.

Navarro 2019b

Navarro V, Boulahfa I, Obach A, Jerez D, Diaz-Ricart M, Gastó C, Guarch J (2019) Lithium augmentation versus citalopram combination in imipramine-resistant major depression: a 10-week randomized open-label study. Journal of Clinical Psychopharmacology 39(3): 254-257.

Nemets 2002

Nemets B, Stahl Z, Belmaker RH (2002) Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. American Journal of Psychiatry 159(3): 477-479.

Nierenberg 2003a

Nierenberg AA, Papakostas GI, Petersen T, Montoya HD, Worthington JJ, Tedlow J, Alpert JE, Fava M (2003) Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. Journal of Clinical Psychopharmacology 23(1): 92-95.

Nierenberg 2006

Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, Alpert JE, Warden D, Luther JF, Niederehe G, Lebowitz B (2006) A comparison of lithium and T 3 augmentation following two failed medication treatments for depression: a STAR* D report. American journal of Psychiatry 163(9): 1519-1530.

Nordstrom 2010

Nordstrom G, Despiegel N, Marteau F, Danchenko N, Maman K (2010) Cost effectiveness of escitalopram versus SNRIs in second-step treatment of major depressive disorder in Sweden. Journal of Medical Economics 13: 516-526.

Olgiati 2013

Olgiati P, Bajo E, Bigelli M, Montgomery S, Serretti A, group CEAP (2013) Challenging sequential approach to treatment resistant depression: cost-utility analysis based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. European Neuropsychopharmacology 23: 1739-1746.

Ostacoli 2018

Ostacoli L, Carletto S, Cavallo M, Baldomir-Gago P, Di Lorenzo G, Fernandez I, Hase M, Justo-Alonso A, Lehnung M, Migliaretti G, Oliva F (2018) Comparison of eye movement desensitization reprocessing and cognitive behavioral therapy as adjunctive treatments for recurrent depression: the European depression EMDR network (EDEN) randomized controlled trial. Frontiers in Psychology 9: 74.

Otsuka Pharmaceutical 2015

Otsuka Pharmaceutical Development & Commercialization, Inc. (2015) Study of the safety and efficacy of OPC-34712 as adjunctive therapy in the treatment of adults with major depressive disorder (STEP-D222). Last updated 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT01052077 [accessed November 2019].

Otsuka Pharmaceutical 2016

Otsuka Pharmaceutical Development & Commercialization, Inc. (2016) Study of the safety and efficacy of OPC-34712 as adjunctive therapy in the treatment of patients with major depressive disorder. Last updated 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT00797966 [accessed November 2019].

Papakostas 2015

Papakostas GI, Fava M, Baer L, Swee MB, Jaeger A, Bobo WV, Shelton RC (2015) Ziprasidone augmentation of escitalopram for major depressive disorder: efficacy results from a randomized, double-blind, placebo-controlled study. American Journal of Psychiatry 172(12): 1251-1258.

Patkar 2006

Patkar AA, Masand PS, Pae CU, Peindl K, Hooper-Wood C, Mannelli P, Ciccone P (2006) A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. Journal of Clinical Psychopharmacology 26(6): 653-656.

Paykel 1999/Scott 2000 / Scott 2003

Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, Jenaway A, Cornwall PL, Hayhurst H, Abbott R, Pope M (1999) Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Archives of General Psychiatry 56(9): 829-835.

Scott J, Teasdale JD, Paykel ES, Johnson AL, Abbott R, Hayhurst H, Moore R, Garland A (2000) Effects of cognitive therapy on psychological symptoms and social functioning in residual depression. British Journal of Psychiatry 177(5): 440-446.

Scott J, Palmer S, Paykel E, Teasdale J, Hayhurst H (2003) Use of cognitive therapy for relapse prevention in chronic depression: Cost-effectiveness study. British Journal of Psychiatry 182: 221-227.

Peet 2002

Peet M, Horrobin DF (2002) A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Archives of General Psychiatry 59(10): 913-919.

Phillips 2014

Phillips R, Schneider J, Molosankwe I, Leese M, Foroushani PS, Grime P, et al. Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. Psychological Medicine 2014; 44: 741-52.

Poirier 1999

Poirier MF, Boyer P (1999) Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. British Journal of Psychiatry 175(1): 12-16.

Ravindran 2008a

Ravindran AV, Kennedy SH, O'Donovan MC, Fallu A, Camacho F, Binder CE (2008) Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: results of a double-blind, randomized, placebo-controlled trial. Journal of Clinical Psychiatry 69(1): 87-94.

Reeves 2008

Reeves H, Batra S, May RS, Zhang R, Dahl DC, Li X (2008) Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Journal of Clinical Psychiatry 69(8): 1228-1236.

Reynolds 2010

Reynolds III CF, Dew MA, Martire LM, Miller MD, Cyranowski JM, Lenze E, Whyte EM, Mulsant BH, Pollock BG, Karp JF, Gildengers A (2010) Treating depression to remission in older adults: a controlled evaluation of combined escitalopram with interpersonal psychotherapy versus escitalopram with depression care management. International Journal of Geriatric Psychiatry 25(11): 1134-1141.

Rocca 2002b

Rocca P, Marchiaro L, Rasetti R, Rivoira E, Bogetto F (2002) A comparison of paroxetine versus paroxetine plus amisulpride in the treatment of dysthymic disorder: efficacy and psychosocial outcomes. Psychiatry Research 112(2): 145-152.

Ross 2018

Ross EL, Zivin K, Maixner DF (2018) Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA Psychiatry 75: 713-722.

Ruhe 2009

Ruhé HG, Booij J, v Weert HC, Reitsma JB, Fransen EJ, Michel MC, Schene AH (2009) Evidence why paroxetine dose escalation is not effective in major depressive disorder: a randomized controlled trial with assessment of serotonin transporter occupancy. Neuropsychopharmacology 34(4): 999-1010.

Rush 2006 / Singh 2017

Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K (2006) Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. New England Journal of Medicine 354(12): 1231-1242.

Singh A, Brooks MM, Voorhees RE, Potter MA, Roberts MS, Luther JF, Wisniewski SR (2017) Cost-effective drug switch options after unsuccessful treatment with an SSRI for depression. Psychiatric Services 68: 81-87.

Salehi 2016

Salehi I, Hosseini SM, Haghighi M, Jahangard L, Bajoghli H, Gerber M, Pühse U, Holsboer-Trachsler E, Brand S (2016) Electroconvulsive therapy (ECT) and aerobic exercise training (AET) increased plasma BDNF and ameliorated depressive symptoms in patients suffering from major depressive disorder. Journal of Psychiatric Research 76: 1-8.

Santos 2008

Santos MA, Rocha FL, Hara C (2008) Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: a randomized, placebo-

controlled, double-blind study. Primary Care Companion to the Journal of Clinical Psychiatry 10(3): 187.

Schindler 2007

Schindler F, Anghelescu IG (2007) Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. International Clinical Psychopharmacology 22(3): 179-182.

Schlogelhofer 2014

Schlögelhofer M, Willinger U, Wiesegger G, Eder H, Priesch M, Itzlinger U, Bailer U, Schosser A, Leisch F, Aschauer H (2014) Clinical study results from a randomized controlled trial of cognitive behavioural guided self-help in patients with partially remitted depressive disorder. Psychology and Psychotherapy: Theory, Research and Practice 87(2): 178-190.

Schramm 2007

Schramm E, van Calker D, Dykierek P, Lieb K, Kech D Clin Psych S, Zobel D Clin Psych I, Leonhart D Clin Psych R, Berger M (2007) An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. American Journal of Psychiatry 164(5): 768-777.

Schweizer 1990

Schweizer E, Rickels K, Amsterdam JD, Fox I, Puzzuoli G, Weise C (1990) What constitutes an adequate antidepressant trial for fluoxetine? Journal of Clinical Psychiatry 51: 8-11.

Schweizer 2001

Schweizer E, Rynn M, Mandos LA, Demartinis N, Garcia-Espana F, Rickels K (2001) The antidepressant effect of sertraline is not enhanced by dose titration: results from an outpatient clinical trial. International Clinical Psychopharmacology 16(3): 137-143.

Sharma 2017

Sharma A, Barrett MS, Cucchiara AJ, Gooneratne NS, Thase ME (2017) A breathing-based meditation intervention for patients with major depressive disorder following inadequate response to antidepressants: a randomized pilot study. Journal of Clinical Psychiatry 78: e59.

Shelton 2005

Shelton RC, Williamson DJ, Corya SA, Sanger TM, Van Campen LE, Case M, Briggs SD, Tollefson GD (2005) Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. Journal of Clinical Psychiatry 66(10): 1289-1297.

Soini 2017

Soini E, Hallinen T, Brignone M, Campbell R, Diamand F, Cure S, Aalto-Setala 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 Review of Pharmacoeconomics and Outcomes Research 17: 293-302.

Song 2007

Song ZW, Liu XB, Li YD (2007) Venlafaxine combined with low-dose risperidone for treatment-resistant depression. Journal of Clinical Rehabilitative Tissue Engineering Research 11 [in Chinese].

Souery 2011a

Souery D, Serretti A, Calati R, Oswald P, Massat I, Konstantinidis A, Linotte S, Kasper S, Montgomery S, Zohar J, Mendlewicz J (2011) Citalopram versus desipramine in treatment resistant depression: Effect of continuation or switching strategies. A randomized open study. World Journal of Biological Psychiatry 12(5): 364-375.

Souza 2016

Souza LH, Salum GA, Mosqueiro BP, Caldieraro MA, Guerra TA, Fleck MP (2016) Interpersonal psychotherapy as add-on for treatment-resistant depression: a pragmatic randomized controlled trial. Journal of Affective Disorders 193: 373-380.

Stein 1993

Stein G, Bernadt MO (1993) Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. British Journal of Psychiatry 162(5): 634-640.

Strauss 2012

Strauss C, Hayward M, Chadwick P (2012) Group person-based cognitive therapy for chronic depression: A pilot randomized controlled trial. British Journal of Clinical Psychology 51(3): 345-350.

Sussman 2017

Sussman M, Yu J, Kamat SA, Hartry A, Legacy S, Duffy R, Aigbogun MS (2017) Cost-effectiveness of brexpiprazole adjunctive treatment for major depressive disorder. Journal of Affective Disorders 207: 54-62.

Taneja 2012

Taneja C, Papakostas GI, Jing Y, Baker RA, Forbes RA, Oster G (2012) Cost-effectiveness of adjunctive therapy with atypical antipsychotics for acute treatment of major depressive disorder. Annals of Pharmacotherapy 46: 642-649.

Thase 2007

Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, Watson SB, Dubé S (2007) A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. Journal of Clinical Psychiatry 68(2): 224-236.

Thase 2015a

Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, McQuade RD, Carson WH, Nyilas M, Sanchez R (2015) Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. Journal of Clinical Psychiatry 76(9): 1224-1231.

Thase 2015b

Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H (2015) Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. Journal of Clinical Psychiatry 76(9): 1232-1240.

Town 2017/2020

Town JM, Abbass A, Stride C, Bernier D (2017) A randomised controlled trial of Intensive short-term dynamic psychotherapy for treatment resistant depression: the Halifax depression study. Journal of Affective Disorders 214: 15–25.

Town JM, Abbass A, Stride C, Nunes A, Bernier D, Berrigan P (2020) Efficacy and cost-effectiveness of intensive short-term dynamic psychotherapy for treatment resistant depression: 18-Month follow-up of the Halifax depression trial. Journal of Affective Disorders 273: 194-202.

Trivedi 2006

Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, Ritz L, Nierenberg AA, Lebowitz BD, Biggs MM, Luther JF (2006) Medication augmentation after the failure of SSRIs for depression. New England Journal of Medicine 354(12): 1243-1252.

Uebelacker 2017

Uebelacker LA, Tremont G, Gillette LT, Epstein-Lubow G, Strong DR, Abrantes AM, Tyrka AR, Tran T, Gaudiano BA, Miller IW (2017) Adjunctive yoga v. health education for persistent major depression: a randomized controlled trial. Psychological Medicine 47(12): 2130-2142.

Wang 2012a

Wang L (2012) Clinical study of lamotrigine amalgamation of venlafaxine on the treatment-resistant depression. Tianjin Pharmacy 24: 9–11 [in Chinese].

Watkins 2011a

Watkins ER, Mullan E, Wingrove J, Rimes K, Steiner H, Bathurst N, Eastman R, Scott J (2011) Rumination-focused cognitive-behavioural therapy for residual depression: phase II randomised controlled trial. British Journal of Psychiatry 199(4): 317-322.

Wiles 2008

Wiles NJ, Hollinghurst S, Mason V, Musa M, Burt V, Hyde J, Jerrom B, Lewis G, Kessler D (2008) A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: a pilot study. Behavioural and Cognitive Psychotherapy 36(1): 21-33.

Wiles 2013/2016 / Hollinghurst 2014

Wiles N, Thomas L, Abel A, Ridgway N, Turner N, Campbell J, Garland A, Hollinghurst S, Jerrom B, Kessler D, Kuyken W (2013) Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. The Lancet 381(9864): 375-384.

Wiles NJ, Thomas L, Turner N, Garfield K, Kounali D, Campbell J, Kessler D, Kuyken W, Lewis G, Morrison J, Williams C (2016) Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBalT randomised controlled trial. The Lancet Psychiatry 3(2):137-144.

Wiles N, Thomas L, Abel A, Barnes M, Carroll F, Ridgway N, Sherlock S, Turner N, Button K, Odondi L, Metcalfe C, Owen-Smith A, Campbell J, Garland A, Hollinghurst S, Jerrom B, Kessler D, Kuyken W, Morrison J, Turner K, Williams C, Peters T, Lewis G (2014) Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: The CoBalT randomised controlled trial. Health Technology Assessment 18(31).

Hollinghurst S, Carroll FE, Abel A, Campbell J, Garland A, Jerrom B, Kessler D, Kuyken W, Morrison J, Ridgway N, Thomas L, Turner K, Williams C, Peters TJ, Lewis G, Wiles N (2014)

Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: Economic evaluation of the CoBalT Trial. British Journal of Psychiatry 204: 69-76.

Xiao 2020

Xiao L, Zhu X, Gillespie A, Feng Y, Zhou J, Chen X, Gao Y, Wang X, Ma X, Gao C, Xie Y (2020) Effectiveness of mirtazapine as add-on to paroxetine v. paroxetine or mirtazapine monotherapy in patients with major depressive disorder with early non-response to paroxetine: a two-phase, multicentre, randomized, double-blind clinical trial. Psychological Medicine 51(7): 1166-1174.

Yang 2016

Yang CH, Yang HZ, Gao X, et al. (2016) Comparative study of lamotrigine combined with escitalopram in the treatment of MECT-resistant patients with depressive disorder. Sichuan Mental Health 29: 406–409 [in Chinese].

Yoshimura 2014

Yoshimura R, Hori H, Umene-Nakano W, Ikenouchi-Sugita A, Katsuki A, Atake K, Nakamura J (2014) Comparison of lithium, aripiprazole and olanzapine as augmentation to paroxetine for inpatients with major depressive disorder. Therapeutic Advances in Psychopharmacology 4(3): 123-129.

Zhang 2016

Zhang F, Tian B (2016) A comparative study of duloxetine combined with lamotrigine in the treatment of patients with treatment-resistant depression. Journal of Psychiatry (China) 29: 335–338 [in Chinese].

Appendices

Appendix A – Review protocol

Review protocol for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 69: Review protocol

Field (based on PRISMA-P)	Content
Review question	What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?
Type of review question	Intervention review
Objective of the review	To identify the most effective interventions for people who have had no or limited response to previous treatment(s) (for the current episode), have not tolerated previous treatment(s) (for the current episode), or have treatment-resistant depression
Population	• Adults in a depressive episode whose depression has not responded or there has been limited response to previous treatment(s) (for the current episode) according to DSM, ICD or similar criteria, or (residual) depressive symptoms as indicated by depression scale score, or who have not tolerated previous treatment (for the current episode), or who are defined as meeting criteria for treatment-resistant depression, and who have been randomised to the further-line interventions at the point at which they had no/inadequate/limited response If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review.
Exclude	• Trials of women with antenatal or postnatal depression • Trials of children and young people (mean age under 18 years) • Trials of people with learning disabilities • Trials of people with bipolar disorder • Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) • Trials that specifically recruit participants with a physical health condition in addition to depression (e.g. depression in people with diabetes)
Intervention	Interventions listed below are examples of interventions which may be included either alone or in combination:

Field (based on PRISMA-P)	Content
	Psychological interventions • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) • Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT], third-wave cognitive therapies, Mindfulness-based Cognitive Therapy [MBCT] and Cognitive Behavioural Analysis System of Psychotherapy [CBASP]) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Interpersonal psychotherapy (IPT) • Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Psychoeducational interventions (including psychoeducational group programmes) • 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) **Psychosocial interventions:** • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR]) **Pharmacological interventions** Antidepressants SSRIs • Citalopram • Escitalopram • Fluvoxamine • Fluoxetine • Paroxetine • Sertraline TCAs

Field (based on PRISMA-P)	Content
	• Amineptine[1] • Amitriptyline • Clomipramine • Desipramine[2] • Imipramine • Lofepramine • Nortriptyline TeCAs • Mianserin SNRIs • Duloxetine • Venlafaxine Other antidepressant drugs • Bupropion[3] • Mirtazepine Anticonvulsants • Lamotrigine[3] Antipsychotics • Amisulpride[3] • Aripiprazole[3] • Olanzapine[3] • Quetiapine • Risperidone[3] • Ziprasidone[2] Anxiolytics • Buspirone

Field (based on PRISMA-P)	Content
	Stimulants • Methylphenidate[3] Other agents • Lithium • Omega-3 fatty acids • Thyroid hormone[3] **Physical interventions** • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD) Interventions will be categorised into the following strategies: • Dose escalation strategies • Switching strategies (including switching to another antidepressant of the same class, switching to another antidepressant of a different class, and switching to a non-antidepressant treatment) • Augmentation strategies (including augmenting the antidepressant with another antidepressant, augmenting the antidepressant with a non-antidepressant agent and augmenting the antidepressant with a psychological/psychosocial/physical intervention)
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo In addition to placebo and head-to-head comparators, comparator treatment strategies include: • Continuing with the antidepressant at the same dose • Continuing with the antidepressant-only
Outcomes	**Critical outcomes:**

Field (based on PRISMA-P)	Content
	Efficacy • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) The following depression scales will be included in the following hierarchy: • MADRS • HAMD • QIDS • PHQ • CGI (for dichotomous outcomes only) • CES-D • BDI • HADS-D (depression subscale) • HADS (full scale) Acceptability/tolerability • Discontinuation due to any reason (including side effects) • Discontinuation due to side effects (for pharmacological trials) **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])

Field (based on PRISMA-P)	Content
	○ Sleeping difficulties (as assessed with a validated scale, including Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI]) ○ Employment (for instance, % unemployed) ○ Interpersonal problems (as assessed with a validated scale, including Inventory of Interpersonal Problems [IIP]) Outcomes will be assessed at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, and >2 years).
Study design	RCTs Systematic reviews of 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** A meta-analysis using a random-effects model will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible.

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: • Psychotic depression • Depression with coexisting personality disorder • Chronic depression
Data management (software)	Endnote was used to sift through the references identified by the search, and for data extraction 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	If trials specifically recruited populations with chronic depressive symptoms they would be included in this review (as opposed to RQ 2.6) if the treatment was further-line and if they reported a critical outcome. A Cochrane review of psychological therapies for treatment-resistant depression in adults was identified (Ijaz et al., 2018) which was used a source of studies for the review of psychological interventions. 1. Amineptine is not available to prescribe as a medicine (although it falls under Class C of the Misuse of Drugs Act 1971, and listed as Schedule 2 under the Controlled Drugs Regulations 2001). However, this drug is included in this review in order to assess the class effect of pharmacological interventions for depression 2. Desipramine and ziprasidone are not available in the UK to prescribe. However, these drugs are included in this review in order to assess the class effect of pharmacological interventions for depression

Field (based on PRISMA-P)	Content
	3. None of these drugs are licensed for use in depression. However, they are included in the review in order to assess harms and efficacy for off-label use and to assess the class effect of pharmacological interventions for depression
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.

Field (based on PRISMA-P)	Content
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	CRD42019151342

BDI: Beck depression inventory;(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; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: Diagnostic and statistical manual; ECT: electroconvulsive therapy; EFT: emotion-focused therapy; EMDR: eye movement desensitization and reprocessing; EQ-5D: European quality of life 5 dimensions; GAF: global assessment of functioning; GAS: global assessment scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HADS-D: hospital anxiety and depression scale – depression; HAMD: Hamilton Depression Rating Scale; ICD: International classification of diseases; IIP: inventory of interpersonal problems; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–Åsberg Depression Rating Scale; MBSR: Mindfulness-based stress reduction; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PHQ-9: patient health questionnaire-9; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depressive symptomatology; QLDS: quality of life depression scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire QOLI: quality of life inventory RCT: randomised controlled trial; REBT: rational emotive behaviour therapy; RoB: risk of bias; SAD: seasonal affective disorder; SAS: social adjustment scale; SDS: Sheehan disability scale; SMD: standardised mean difference; SNRI: serotonin-noradrenaline reuptake inhibitor; SOFAS: social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant; WHOQOL-BRIEF: World health organization quality of life assessment (brief); WHO-5: world health organization 5-item wellbeing index; WSAS: work and social adjustment scale

Appendix B – Literature search strategies

Literature search strategies for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Clinical search

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

Date of Search: 16/05/2019

Search updated: 04/06/2020

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

#	Searches
28	Antidepressive Agents, Tricyclic/ use ppez
29	tricyclic antidepressant drugs/ use psyh
30	monoamine oxidase inhibitor/ use oemezd,emcr
31	monoamine oxidase inhibitors/ use ppez,psyh
32	tetracyclic antidepressive agent/ use oemezd,emcr
33	amfebutamone/ or amineptine/ or amitriptyline/ or bupropion/ or clomipramine/ or chlorimipramine/ or citalopram/ or desipramine/ or duloxetine/ or Duloxetine Hydrochloride/ or escitalopram/ or fluvoxamine/ or fluoxetine/ or imipramine/ or lofepramine/ or mianserin/ or mirtazapine/ or moclobemide/ or nefazadone/ or nortriptyline/ or paroxetine/ or phenelzine/ or sertraline/ or venlafaxine/ or Venlafaxine Hydrochloride/
34	(antidepress* or amfebutamone or amineptin* or amitr?ptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mianserin or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or phenelzin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or TeCA* or tetracyclic or tricyclic or ((monoamine or serotonin) adj2 inhibitor*)).tw.
35	or/16-34
36	(anticonvulsive agent/ or anticonvulsant therapy/) use oemezd,emcr
37	Anticonvulsants/ use ppez
38	anticonvulsive drugs/ use psyh
39	lamotrigine/ or (lamotrigine or anticonvul* or anti-convul*).tw.
40	or/38-39
41	neuroleptic agent/ use oemezd,emcr
42	Antipsychotic Agents/ use ppez
43	neuroleptic drugs/ use psyh
44	amisulpride/ or aripiprazole/ or olanzapine/ or quetiapine/ or Quetiapine Fumarate/ or risperidone/ or ziprasidone/
45	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone).tw.
46	or/41-45
47	anxiolytic agent/ use oemezd,emcr
48	Anti-Anxiety Agents/ use ppez
49	tranquilizing drugs/ use psyh
50	buspirone/
51	(anxiolytic* or antianxiet* or anti-anxiet* or tranquili* or buspirone).tw.
52	or/47-51
53	central stimulant agent/ use oemezd,emcr
54	Central Nervous System Stimulants/ use ppez
55	CNS stimulating drugs/ use psyh
56	methylphenidate/ or (methylphenidate or ritalin).tw.
57	or/53-56
58	lithium/ or lithium.tw.
59	omega 3 fatty acid/ use oemezd,emcr
60	Fatty Acids, Omega-3/ use ppez
61	fatty acids/ use psyh
62	(omega adj ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)).tw.
63	thyroid hormone/ use oemezd,emcr
64	Thyroid Hormones/ use ppez
65	exp thyroid hormones/ use psyh
66	(thyroid hormone* or calcitonin or dextrothyroxine or diiodotyrosine or monoiodotyrosine or thyronines or thyroxine).tw.
67	or/58-66
68	acupuncture/ or acupuncture.tw.
69	electroconvulsive therapy/ use oemezd,emcr,ppez
70	electroconvulsive shock therapy/ use psyh
71	(ECT or ((electroconvuls* or electro-convuls*) adj2 (therap* or treatment*)) or electroshock* or (shock adj (therap* or treatment*))).tw.
72	exp exercise/
73	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Swimming/ or Walking/) use ppez
74	(exp kinesiotherapy/ or exp physical activity/ or fitness/ or exp sport/) use oemezd,emcr
75	(exp physical fitness/ or exp sports/) use psyh
76	yoga/
77	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking).tw.
78	or/68-77
79	peer group/ or mentoring/
80	peer relations/ use psyh
81	friendship/
82	Friends/ use ppez
83	(befriend* or friend* or mentor* or peer group* or peer support or (communit* adj (navigat* or support*))).tw.
84	or/79-83
85	or/15,35,40,46,52,57,67,78,84

#	Searches
86	6 and 85
87	Letter/ use ppez
88	letter.pt. or letter/ use oemezd,emcr
89	note.pt.
90	editorial.pt.
91	Editorial/ use ppez
92	News/ use ppez
93	exp Historical Article/ use ppez
94	Anecdotes as Topic/ use ppez
95	Comment/ use ppez
96	Case Report/
97	case study/ use oemezd,emcr
98	(letter or comment*).ti.
99	or/87-98
100	randomized controlled trial/
101	random*.ti,ab.
102	100 or 101
103	99 not 102
104	(animals/ not humans/) use ppez
105	(animal/ not human/) use oemezd,emcr
106	nonhuman/ use oemezd,emcr
107	exp animals/ use psyh
108	"primates (nonhuman)"/ use psyh
109	exp Animals, Laboratory/ use ppez
110	exp Animal Experimentation/ use ppez
111	exp animal experiment/ use oemezd,emcr
112	exp experimental animal/ use oemezd,emcr
113	exp Models, Animal/ use ppez
114	animal model/ use oemezd,emcr
115	animal models/ use psyh
116	animal research/ use psyh
117	exp Rodentia/ use ppez
118	exp rodent/ use oemezd,emcr
119	exp rodents/ use psyh
120	(rat or rats or mouse or mice).ti.
121	or/103-120
122	86 not 121
123	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
124	123 use ppez
125	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
126	125 use ppez
127	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
128	127 use oemezd,emcr
129	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
130	129 use psyh
131	124 or 126
132	128 or 130 or 131
133	Meta-Analysis/
134	exp Meta-Analysis as Topic/
135	systematic review/
136	meta-analysis/
137	(meta analy* or metanaly* or metaanaly*).ti,ab.
138	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
139	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
140	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
141	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
142	(search* adj4 literature).ab.
143	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
144	cochrane.jw.
145	((pool* or combined) adj2 (data or trials or studies or results)).ab.
146	(or/133-135,137,139-144) use ppez
147	(or/135-138,140-145) use oemezd,emcr
148	(or/133,137,139-144) use psyh
149	or/146-148

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

1

2 The Cochrane Library, issue 5 of 12, May 2019

3 Date of Search: 21/05/2019

4 Search updated: 05/06/2020

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

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

1

1 Health Economics search

2 Database(s): Embase 1974 to 2019 Week 08, Ovid MEDLINE(R) and Epub Ahead of Print,
3 In-Process & Other Non-Indexed Citations and Daily 1946 to February 26, 2019, PsycINFO
4 1806 to February Week 1 2019

5 Date of search: 27/02/2019

6 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"

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

3 Date of search: 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

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

3 Date of search: 26/02/2019

4 Search updated: 02/03/2020

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

#	Query	Limiters/Expanders
S1	(MH "Depression+") OR (MH "Premenstrual Dysphoric Disorder") OR (MH "Seasonal Affective Disorder")	Search modes - Boolean/Phrase

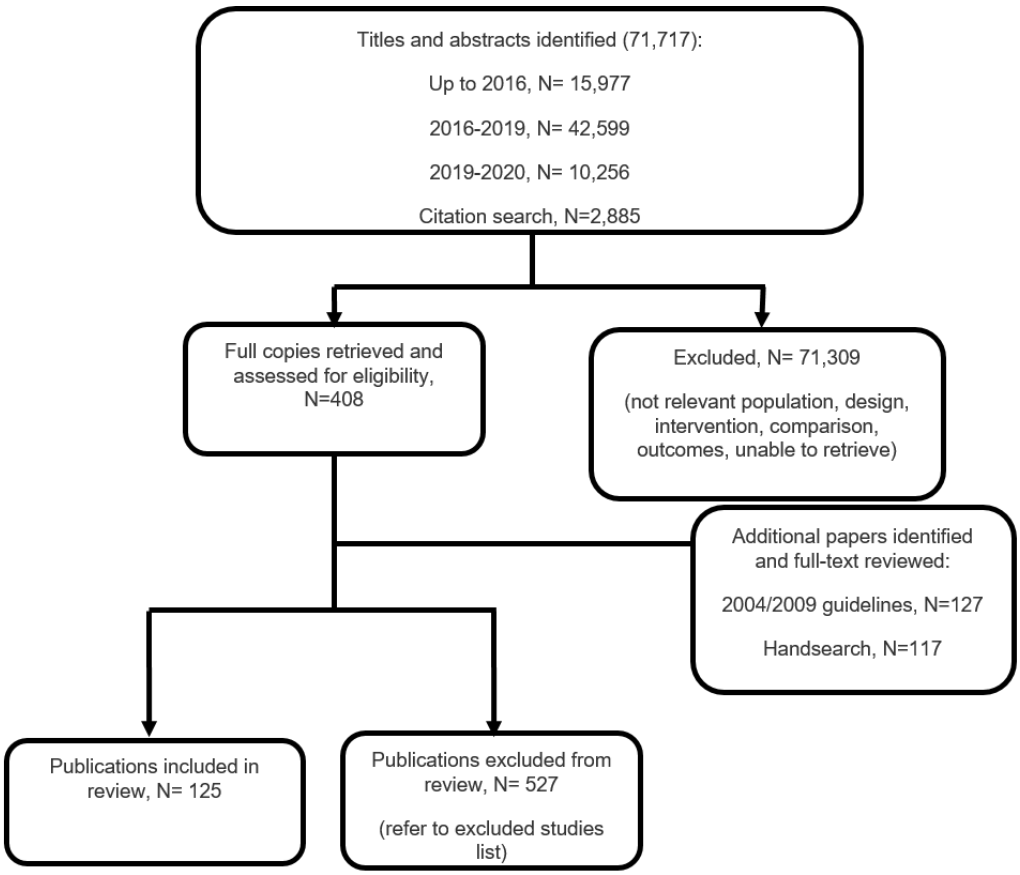
1

2

Appendix C – Clinical evidence study selection

Study selection for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Please refer to the clinical evidence tables in supplement D – Clinical evidence tables for Evidence review D Further-line treatment.

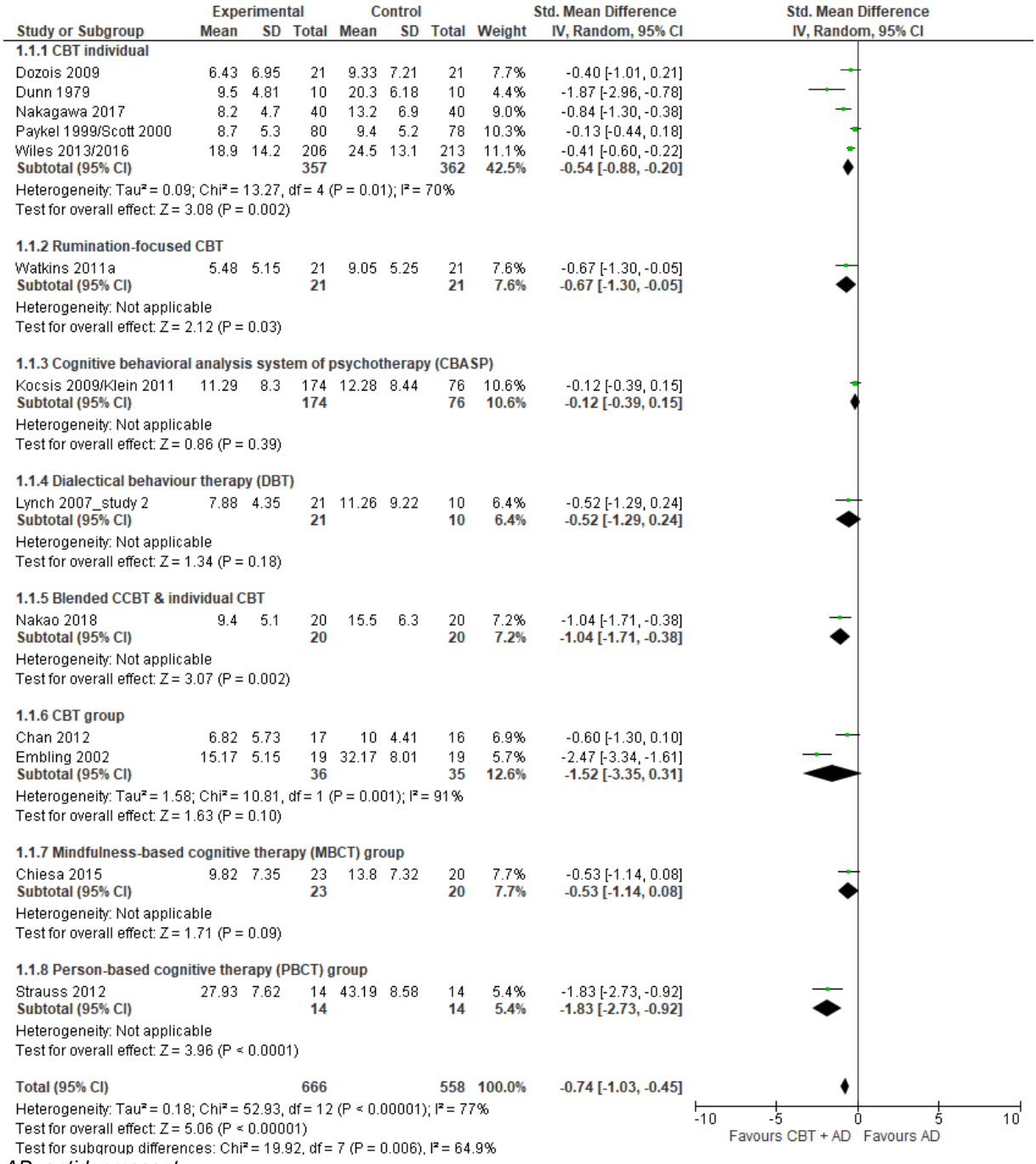
Appendix E – Forest plots

Forest plots for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an

inadequate response to at least one previous intervention for the current episode?

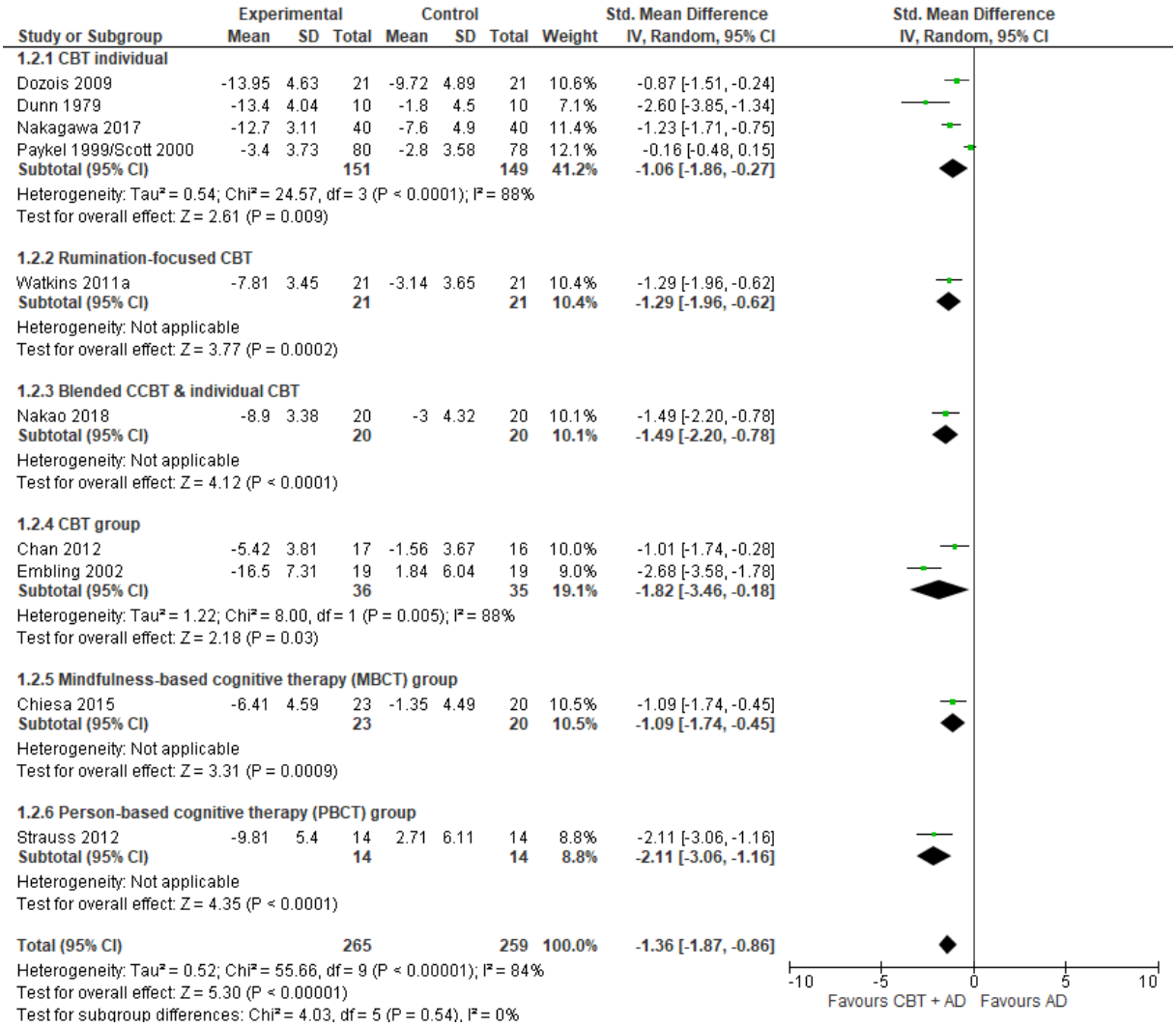
Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Figure 2: Depression symptomatology endpoint



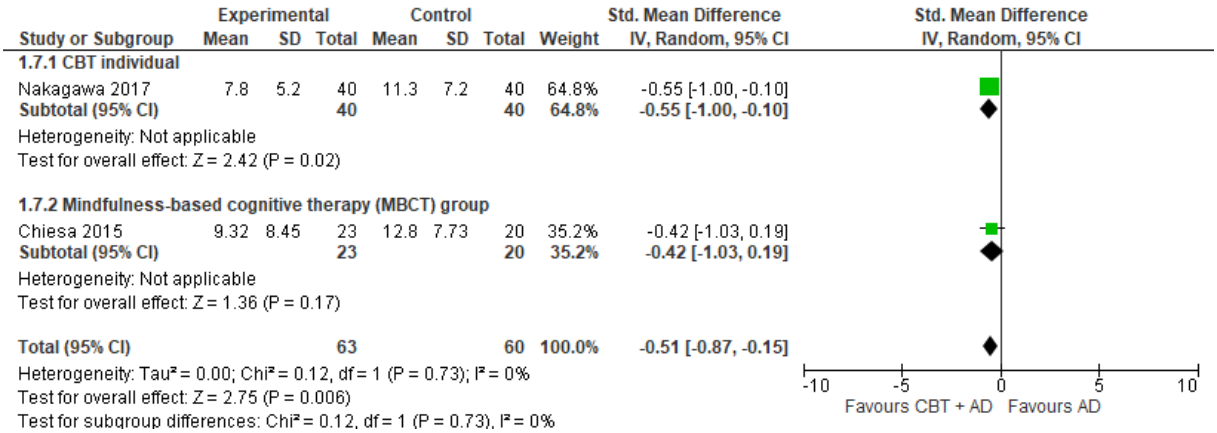
AD: antidepressant

Figure 3: Depression symptomatology change score



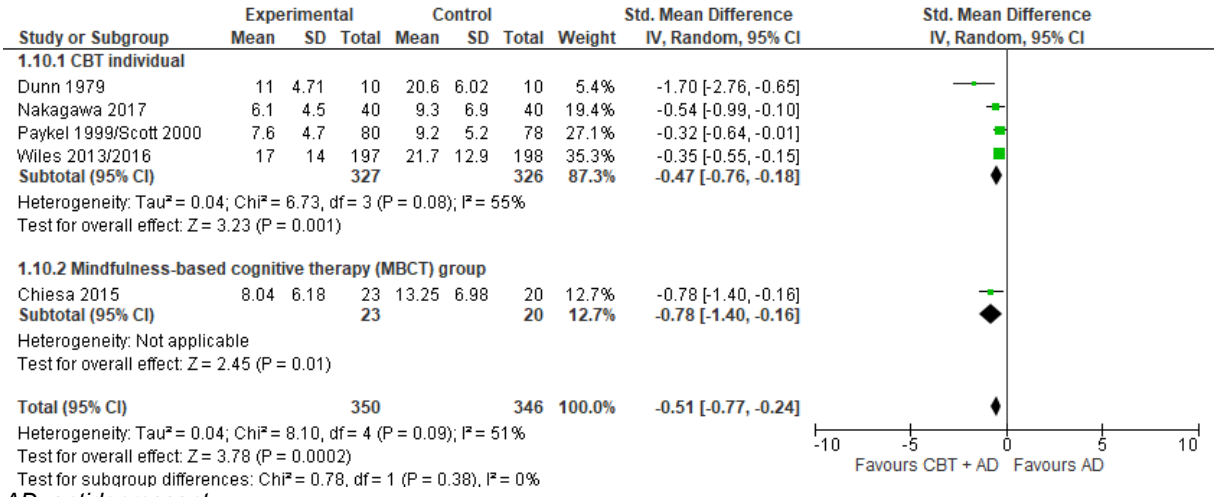
AD: antidepressant

Figure 4: Depression symptomatology at 2-3 month follow-up



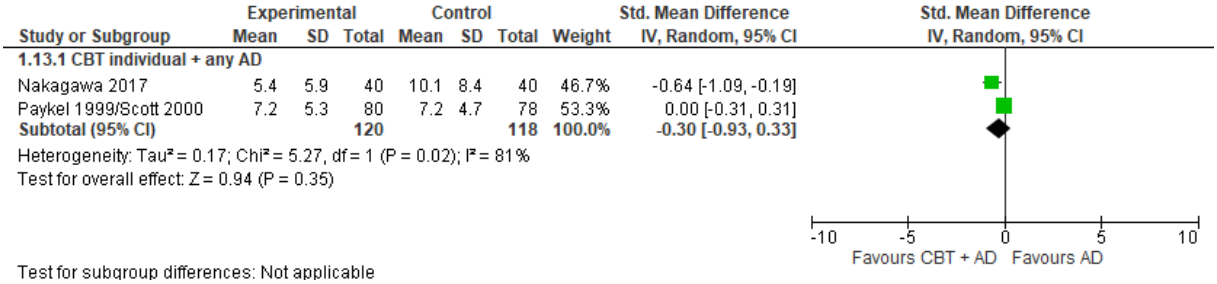
AD: antidepressant

Figure 5: Depression symptomatology at 4-6 month follow-up



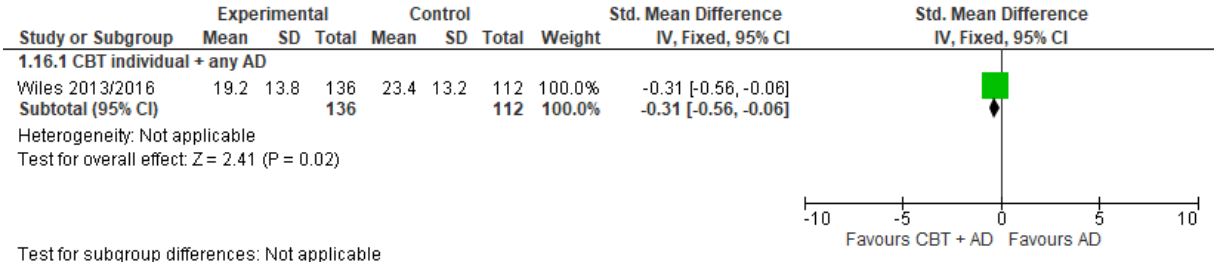
AD: antidepressant

Figure 6: Depression symptomatology at 11-12 month follow-up



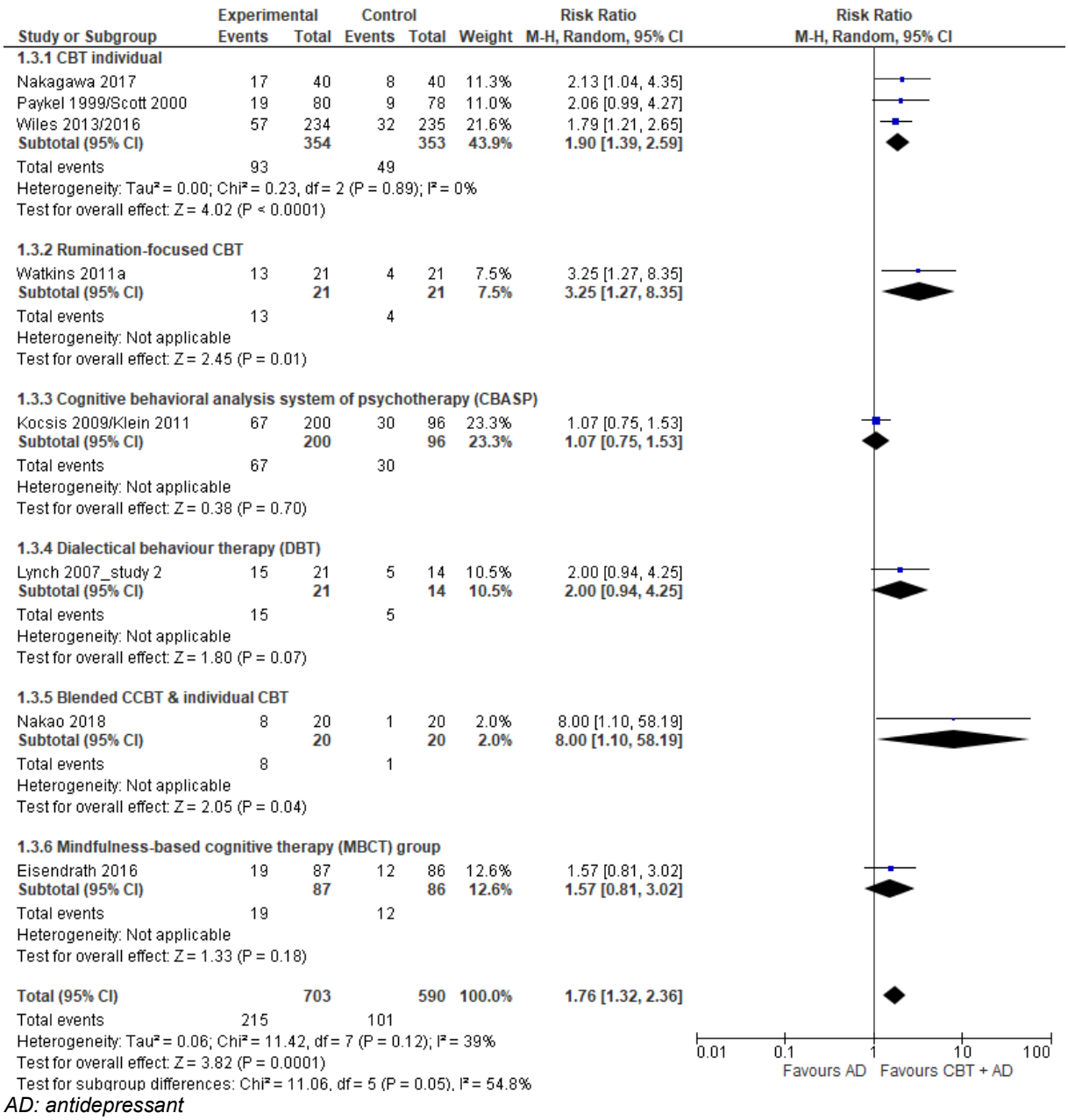
AD: antidepressant

Figure 7: Depression symptomatology at 40-month follow-up



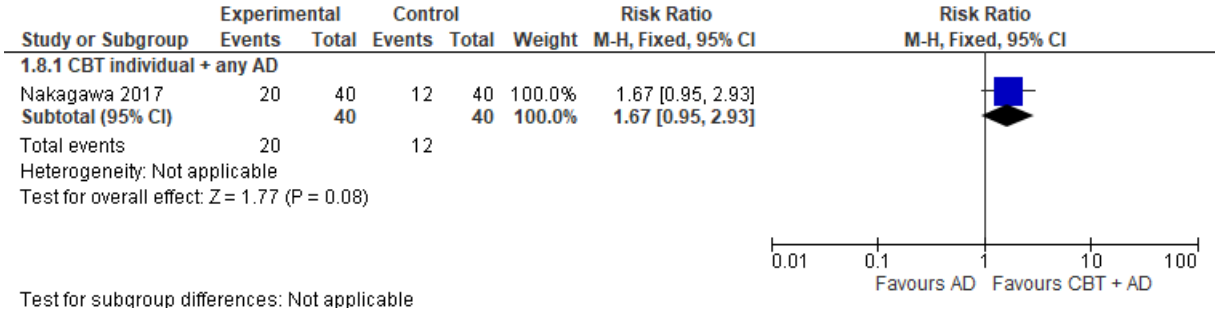
AD: antidepressant

Figure 8: Remission (ITT)



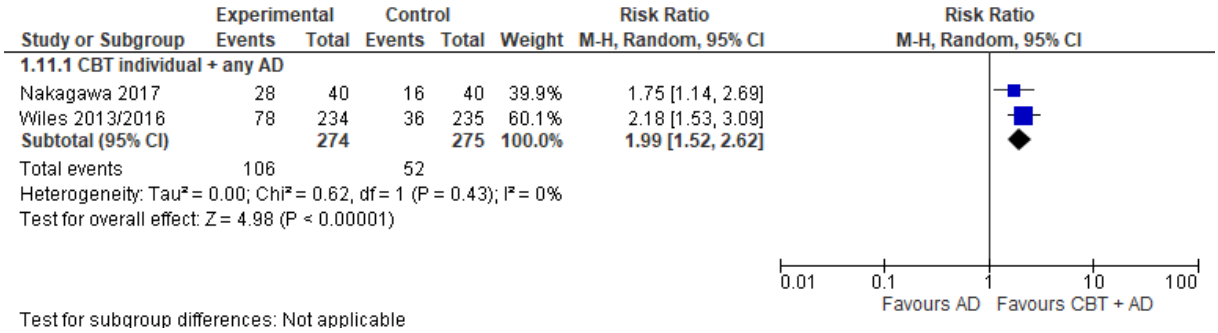
AD: antidepressant

Figure 9: Remission (ITT) at 3-month follow-up



AD: antidepressant

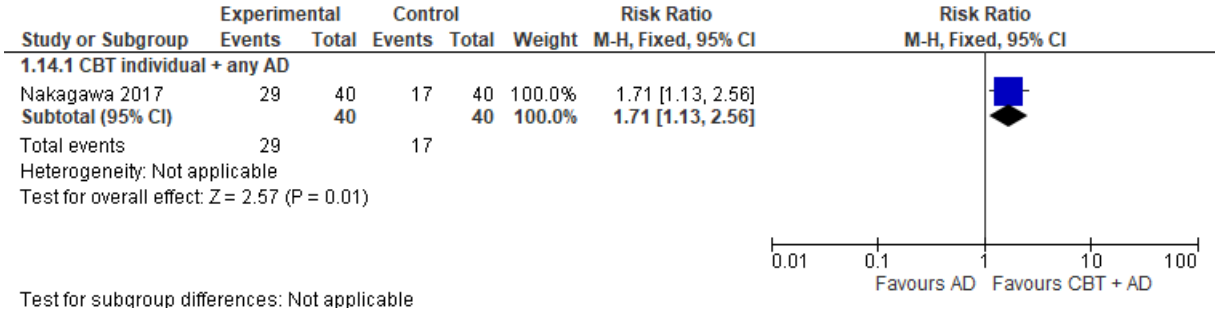
Figure 10: Remission (ITT) at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

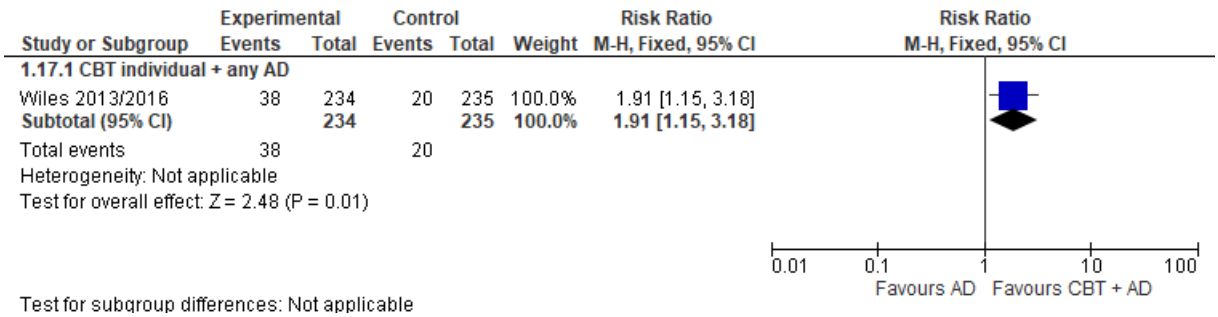
Figure 11: Remission (ITT) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

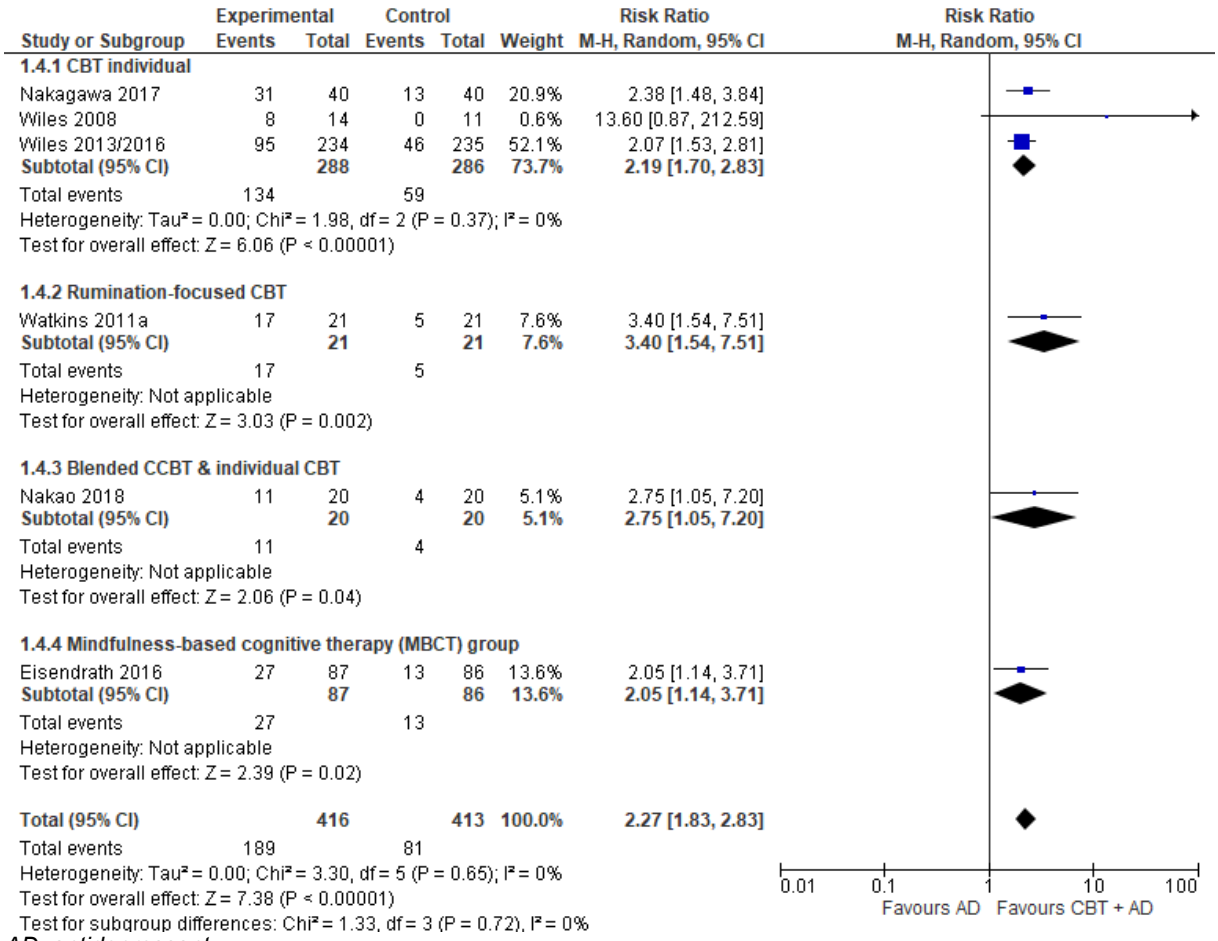
Figure 12: Remission (ITT) at 40-month follow-up



Test for subgroup differences: Not applicable

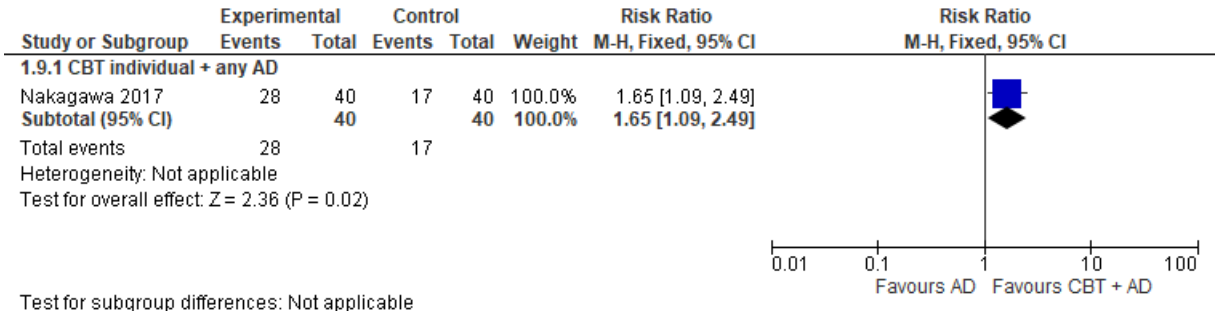
AD: antidepressant

Figure 13: Response (ITT)



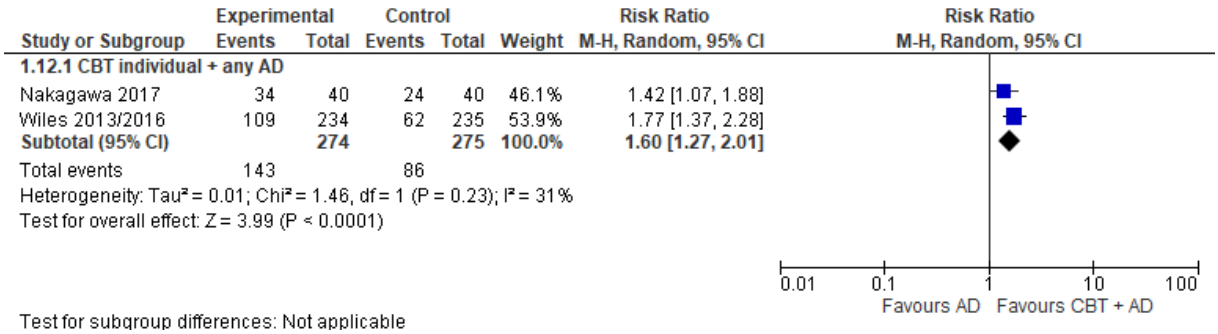
AD: antidepressant

Figure 14: Response (ITT) at 3-month follow-up



AD: antidepressant

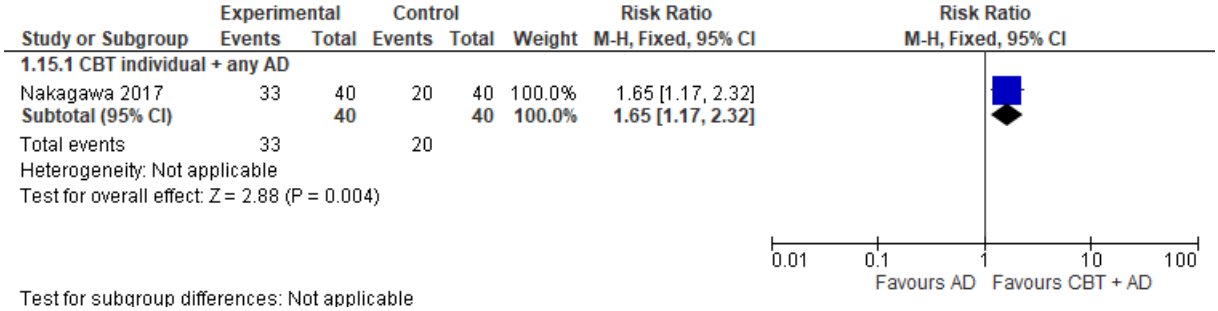
Figure 15: Response (ITT) at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

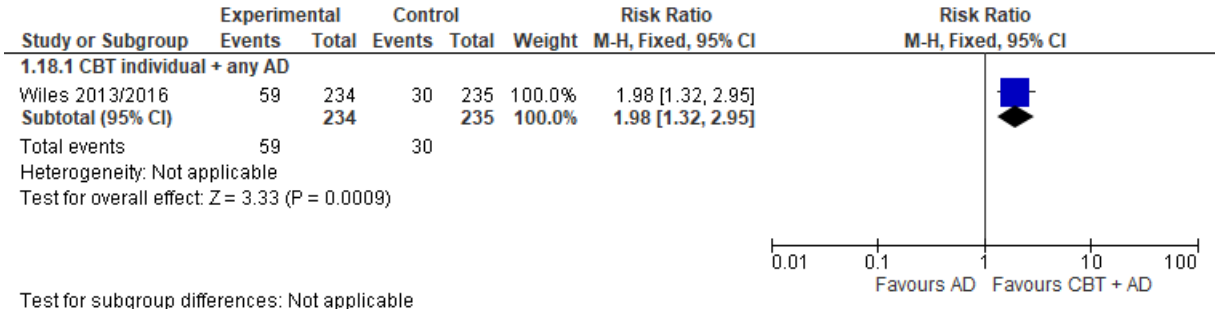
Figure 16: Response (ITT) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

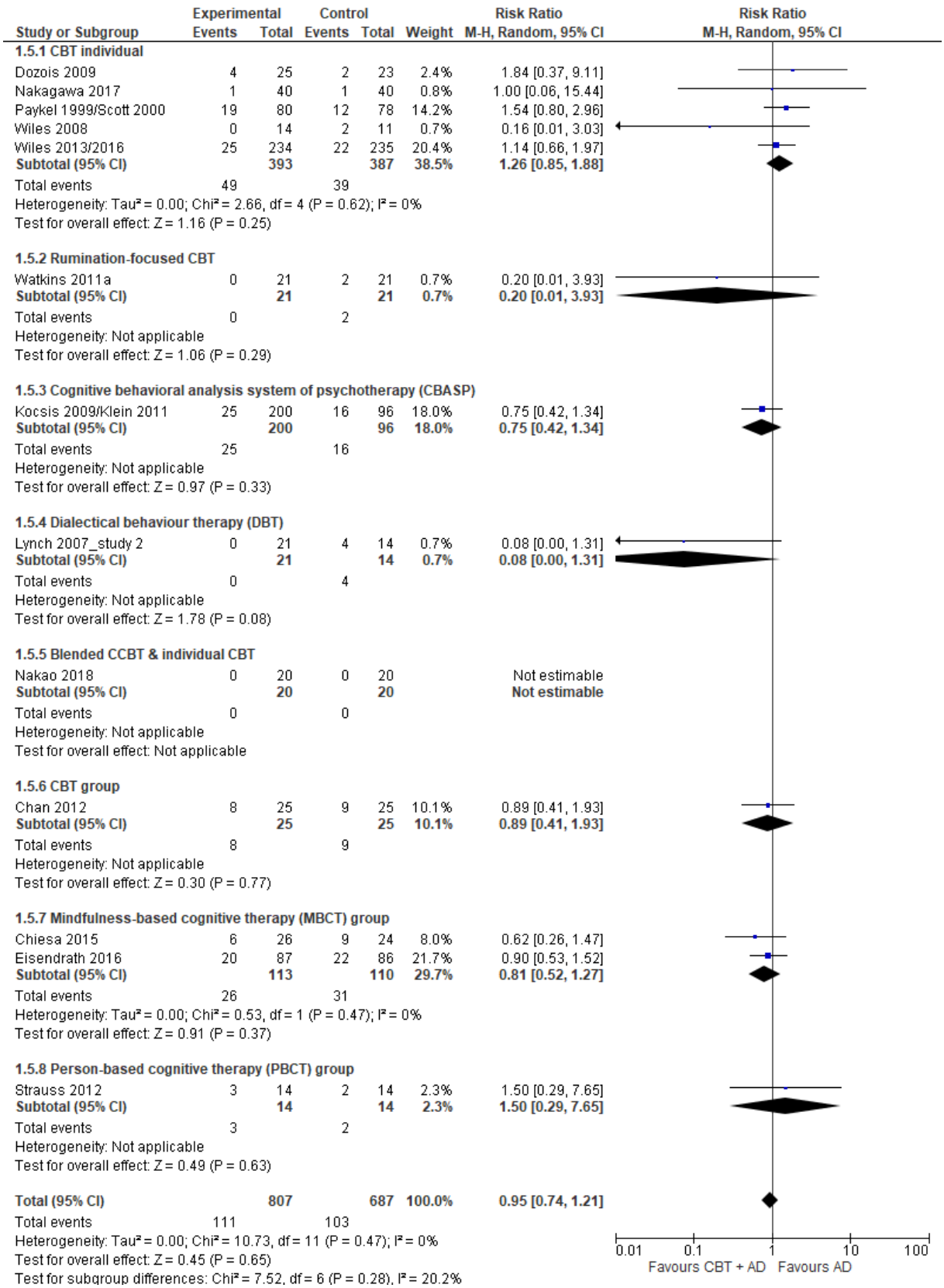
Figure 17: Response (ITT) at 40-month follow-up



Test for subgroup differences: Not applicable

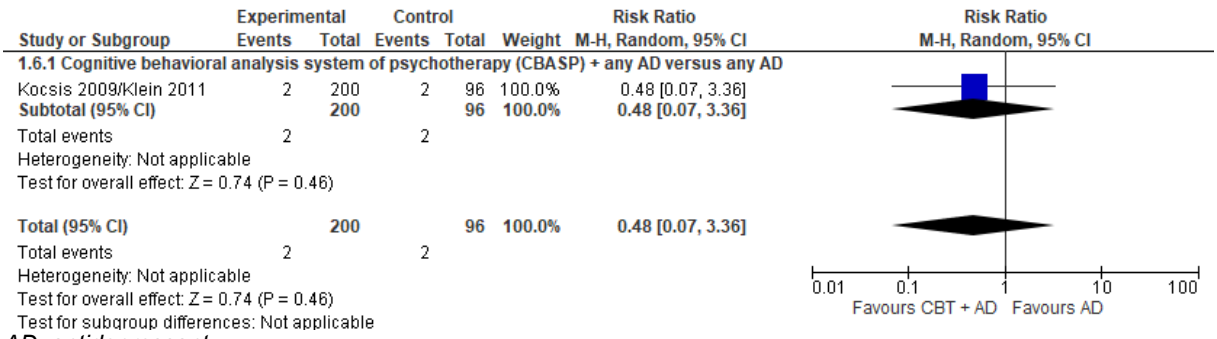
AD: antidepressant

Figure 18: Discontinuation due to any reason



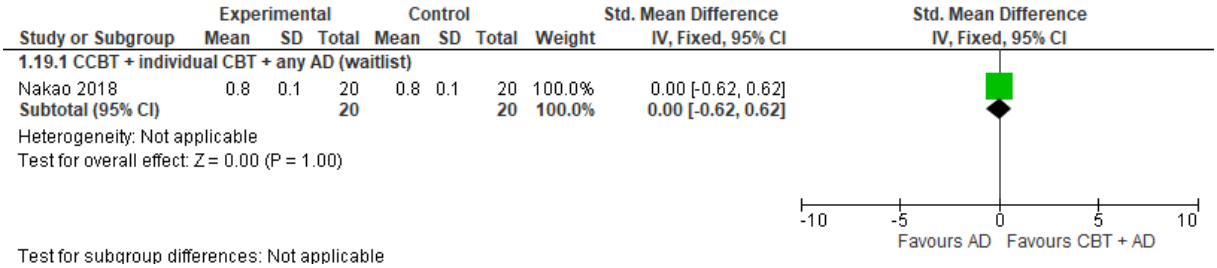
AD: antidepressant

Figure 19: Discontinuation due to side effects



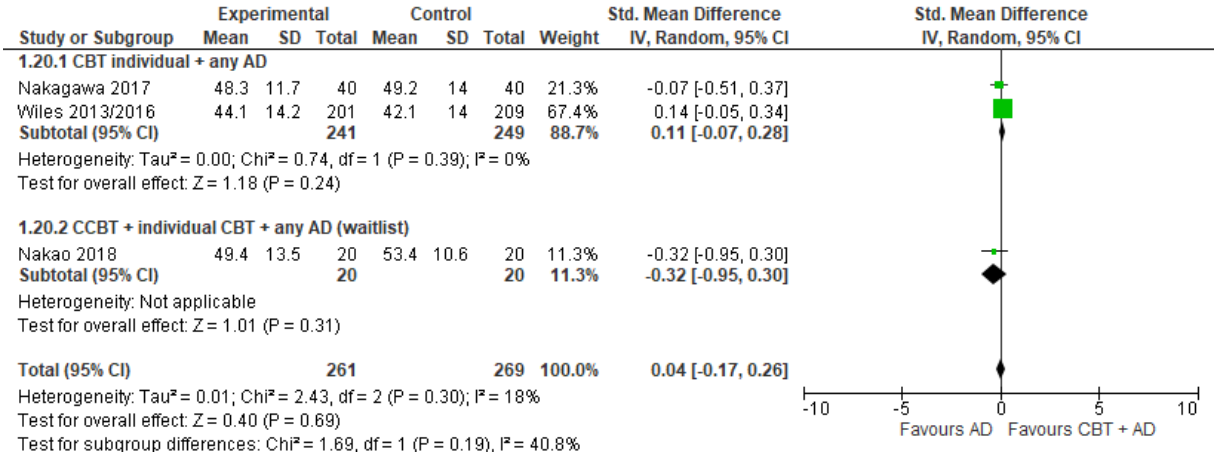
AD: antidepressant

Figure 20: Quality of life endpoint



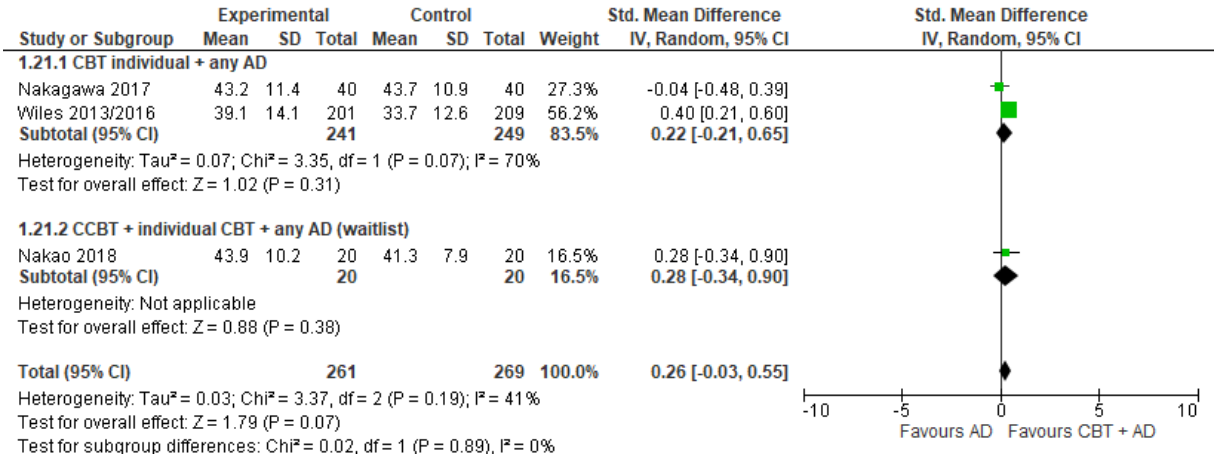
AD: antidepressant

Figure 21: Quality of life physical component score (PCS) endpoint



AD: antidepressant

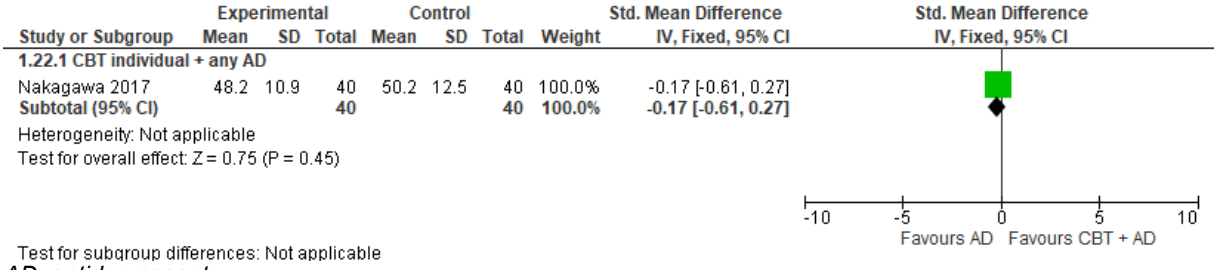
98 **Figure 22: Quality of life mental component score (MCS) endpoint**



99
100 *AD: antidepressant*

101

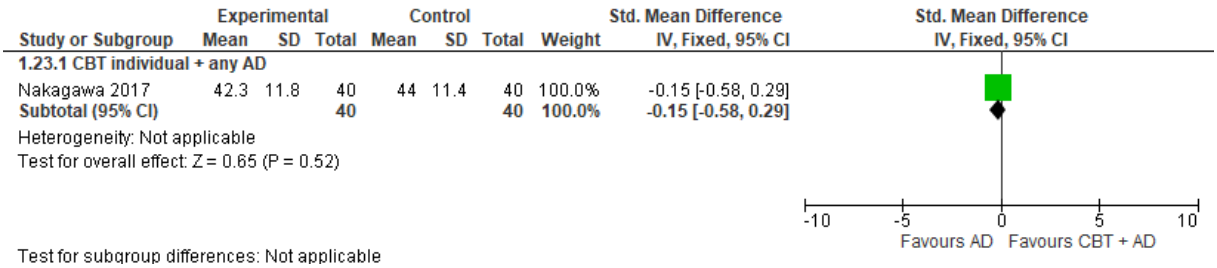
102 **Figure 23: Quality of life physical component score (PCS) at 3-month follow-up**



103 Test for subgroup differences: Not applicable
104 *AD: antidepressant*

105

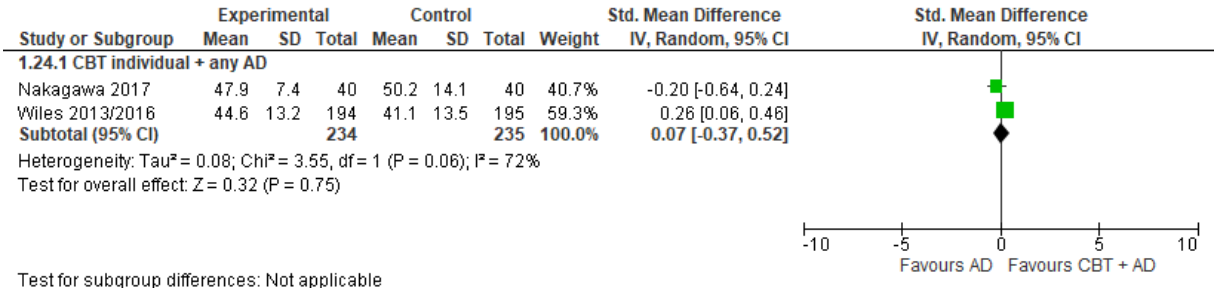
106 **Figure 24: Quality of life mental component score (MCS) at 3-month follow-up**



107 Test for subgroup differences: Not applicable
108 *AD: antidepressant*

109

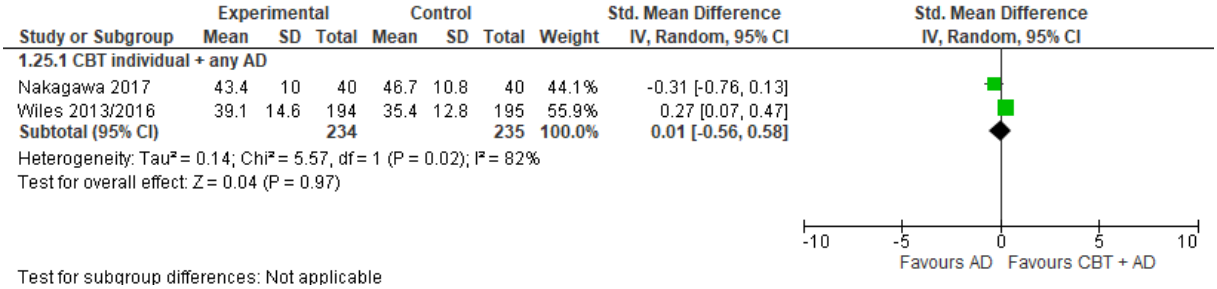
Figure 25: Quality of life physical component score (PCS) at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

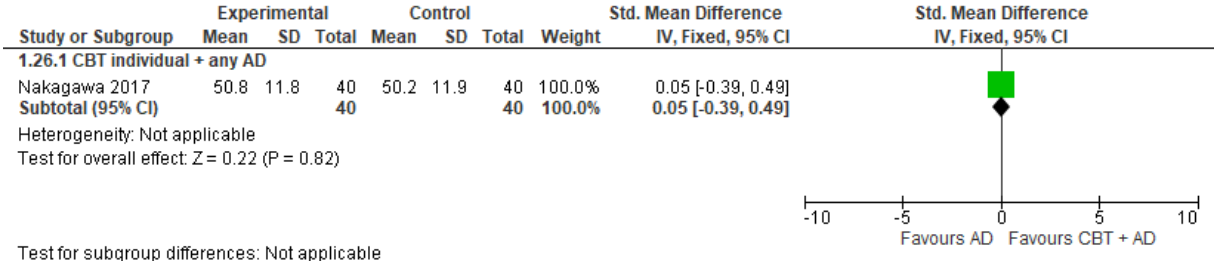
Figure 26: Quality of life mental component score (MCS) at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

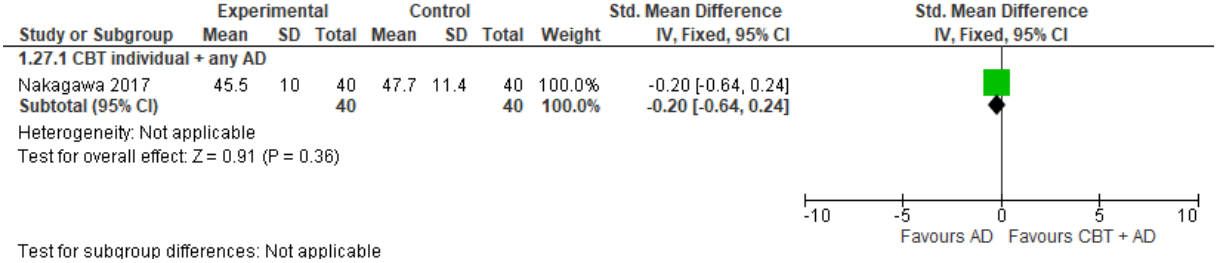
Figure 27: Quality of life physical component score (PCS) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

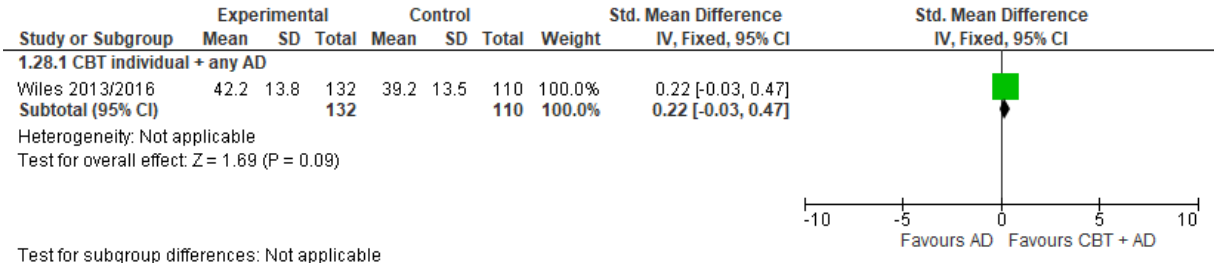
Figure 28: Quality of life mental component score (MCS) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

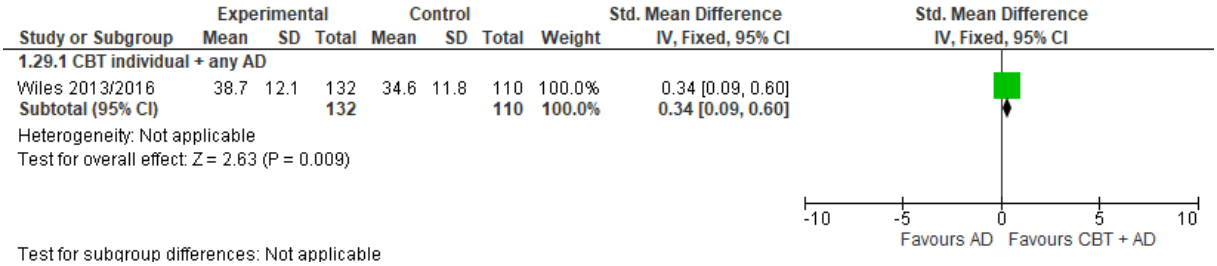
Figure 29: Quality of life physical component score (PCS) at 40-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

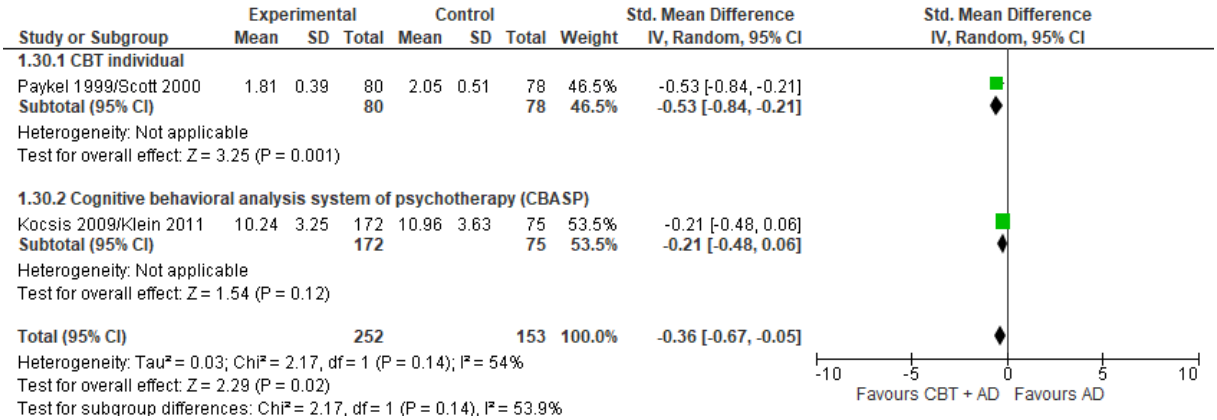
Figure 30: Quality of life mental component score (MCS) at 40-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

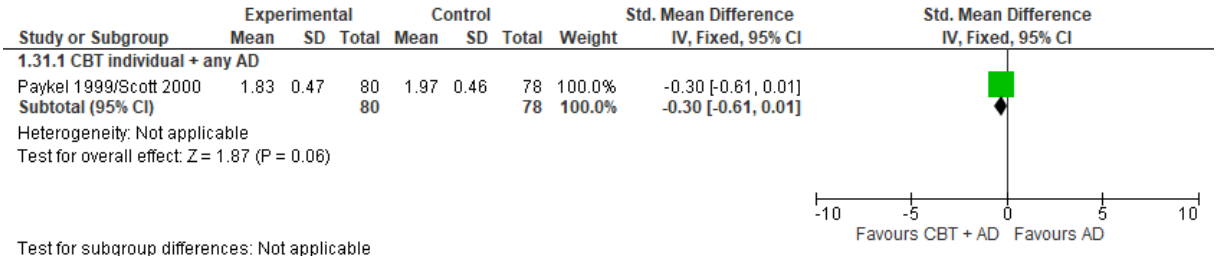
Figure 31: Functional impairment endpoint



Test for subgroup differences: Chi² = 2.17, df = 1 (P = 0.14), I² = 53.9%

AD: antidepressant

Figure 32: Functional impairment at 11-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

Figure 33: Depression symptomatology endpoint

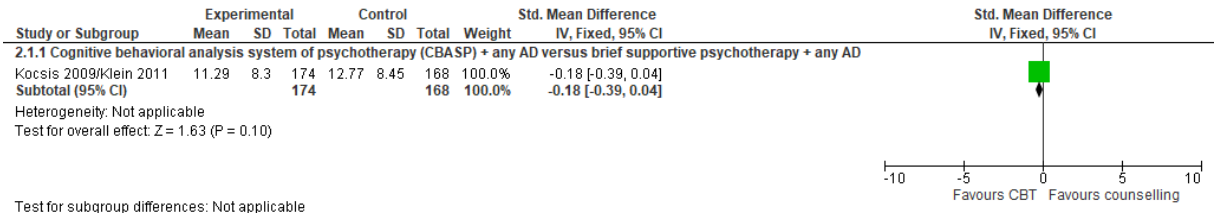


Figure 34: Remission (ITT)

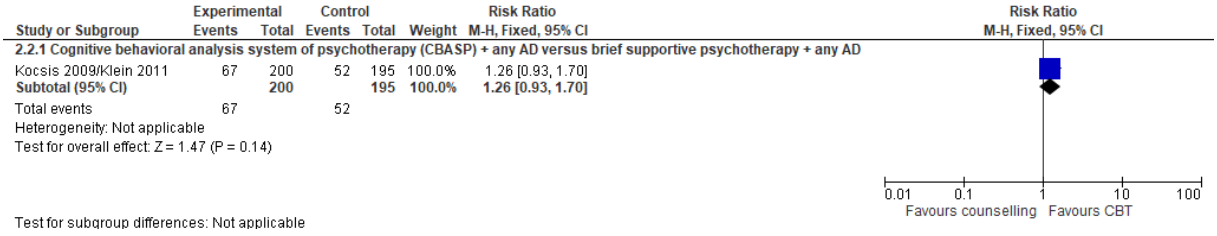


Figure 35: Discontinuation due to any reason

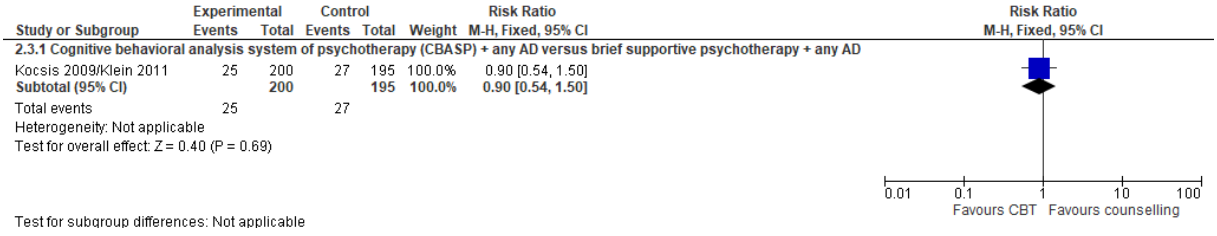
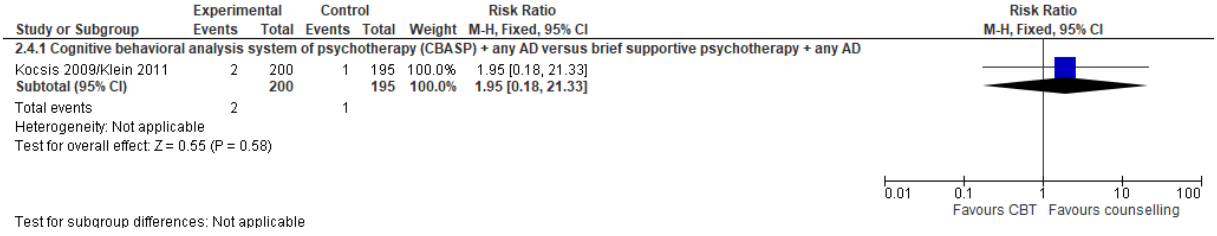
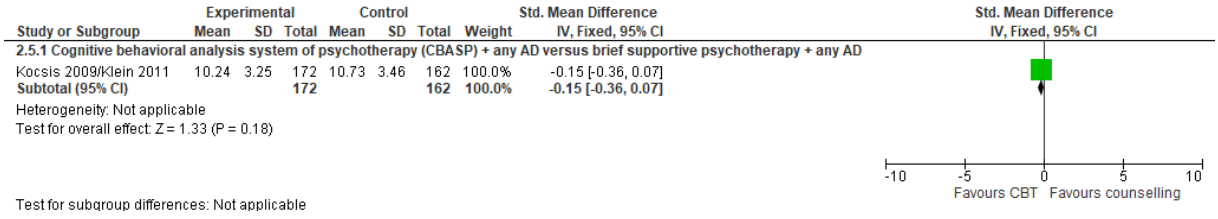


Figure 36: Discontinuation due to side effects



158 **Figure 37: Functional impairment endpoint**

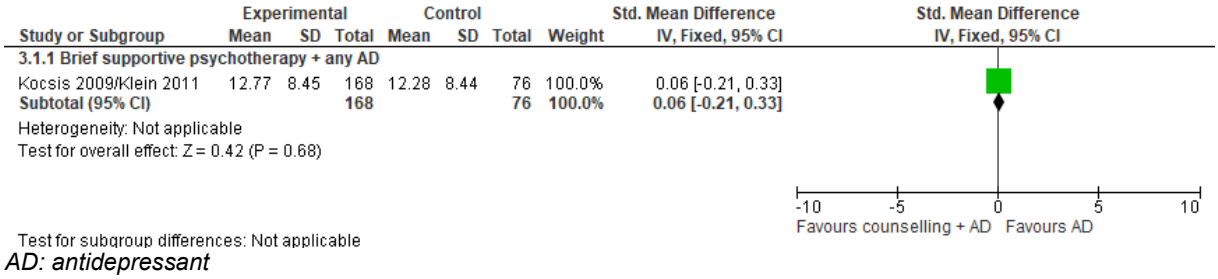


159

160

161 ***Comparison 3. Augmenting with counselling versus continuing with antidepressant***

162 **Figure 38: Depression symptomatology endpoint**

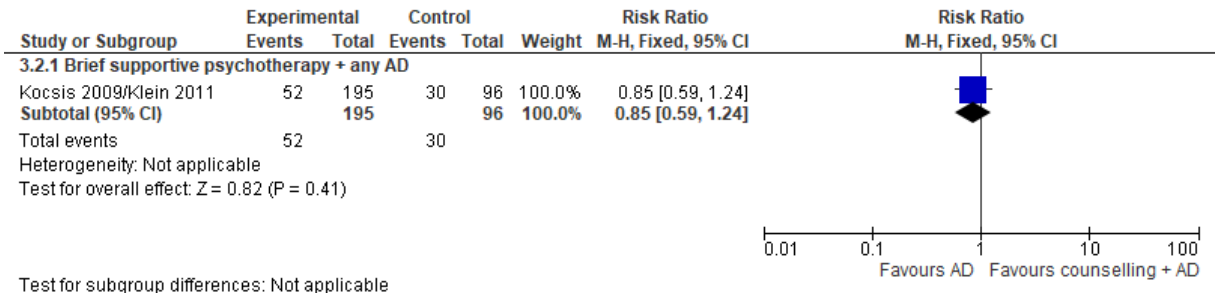


163

164 *AD: antidepressant*

165

166 **Figure 39: Remission (ITT)**

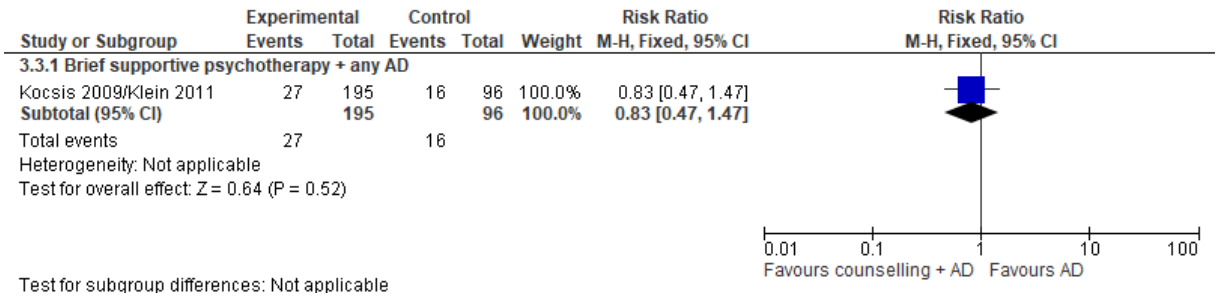


167

168 *AD: antidepressant*

169

170 **Figure 40: Discontinuation due to any reason**

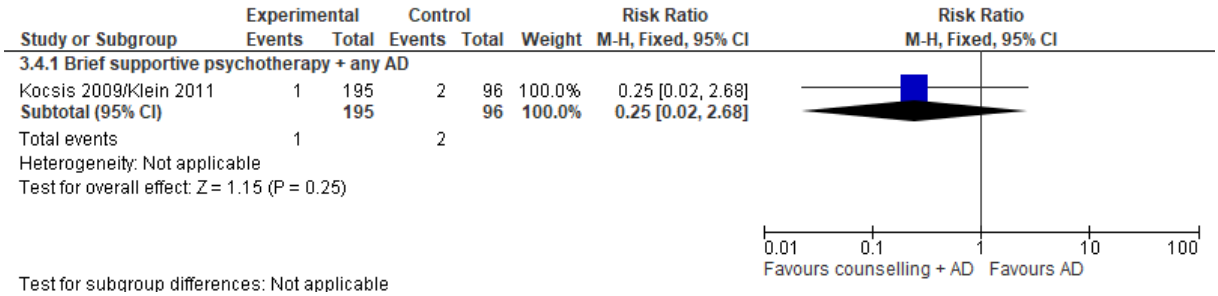


171

172 *AD: antidepressant*

173

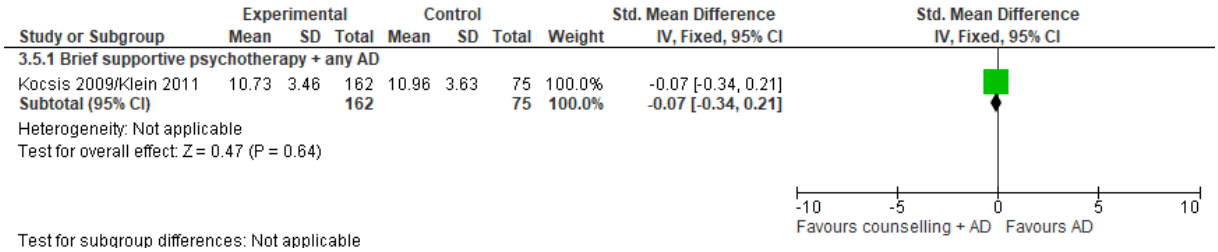
Figure 41: Discontinuation due to side effects



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 42: Functional impairment endpoint

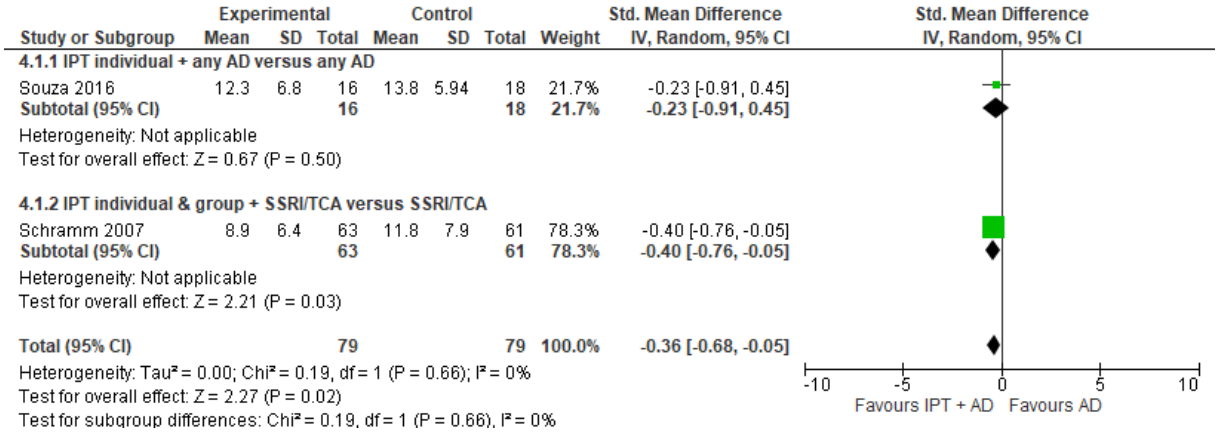


Test for subgroup differences: Not applicable

AD: antidepressant

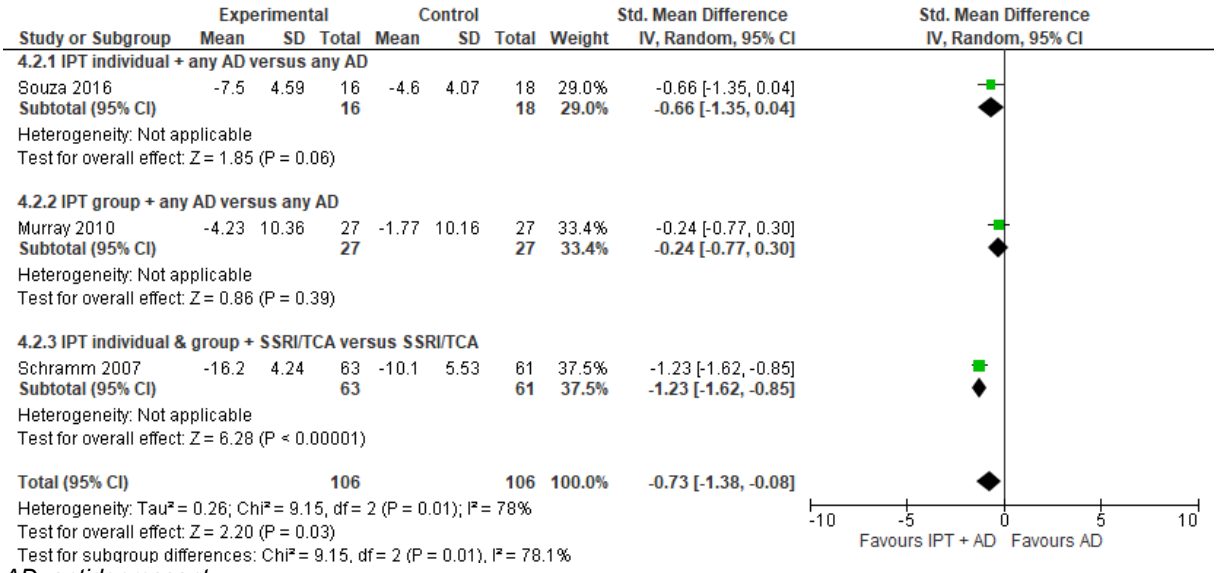
Comparison 4. Augmenting with IPT versus continuing with antidepressant

Figure 43: Depression symptomatology endpoint



AD: antidepressant

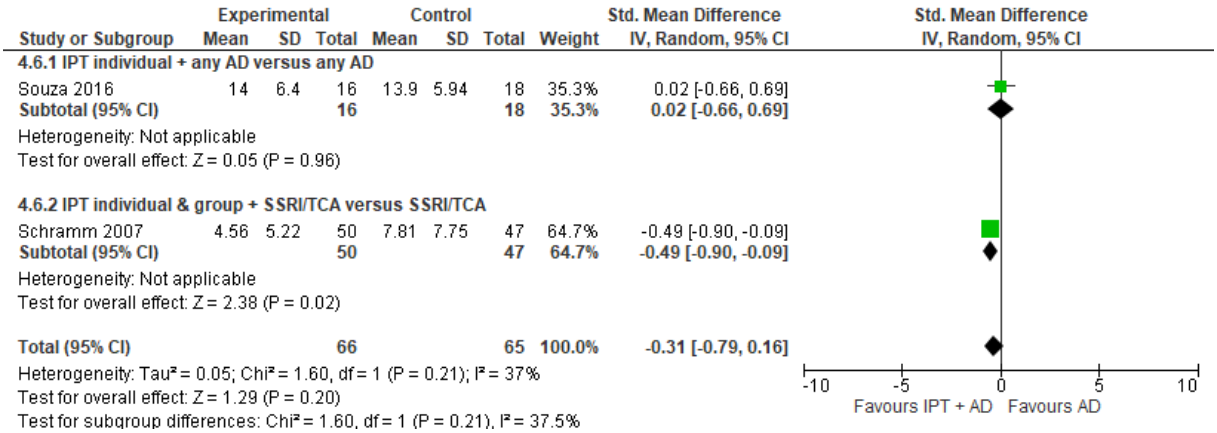
187 **Figure 44: Depression symptomatology change score**



188
189 *AD: antidepressant*

190

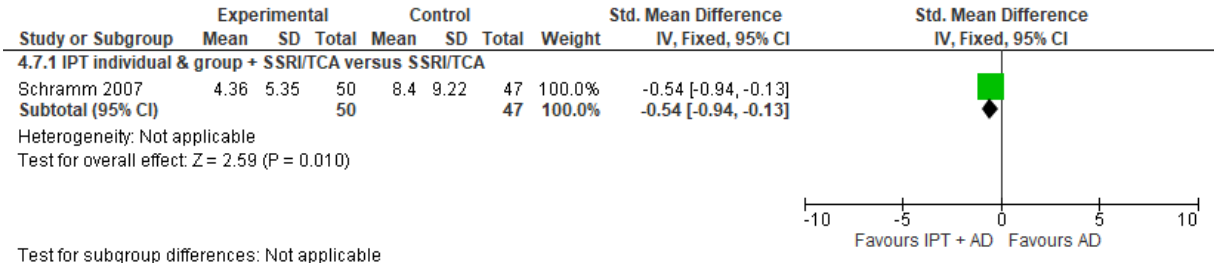
191 **Figure 45: Depression symptomatology at 1-3 month follow-up**



192
193 *AD: antidepressant*

194

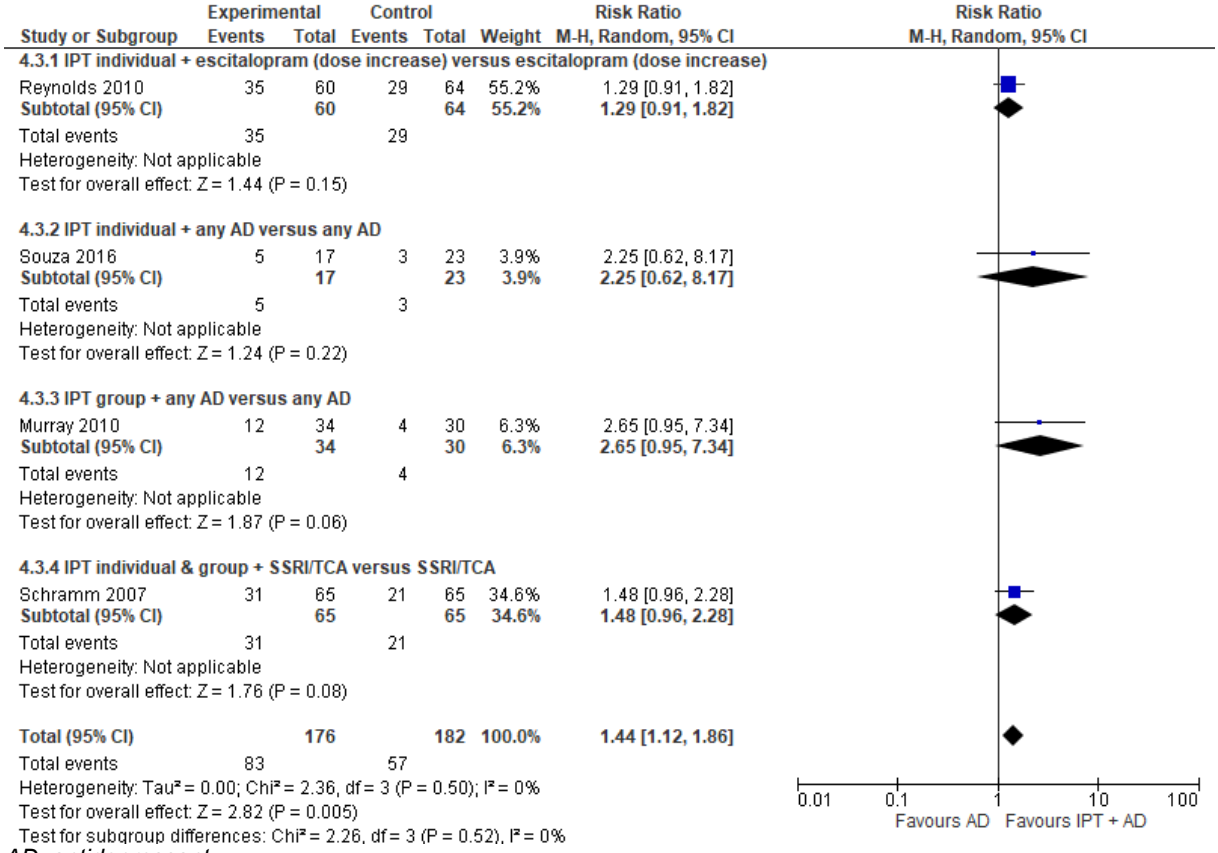
195 **Figure 46: Depression symptomatology at 12-month follow-up**



196 Test for subgroup differences: Not applicable
197 *AD: antidepressant*

198

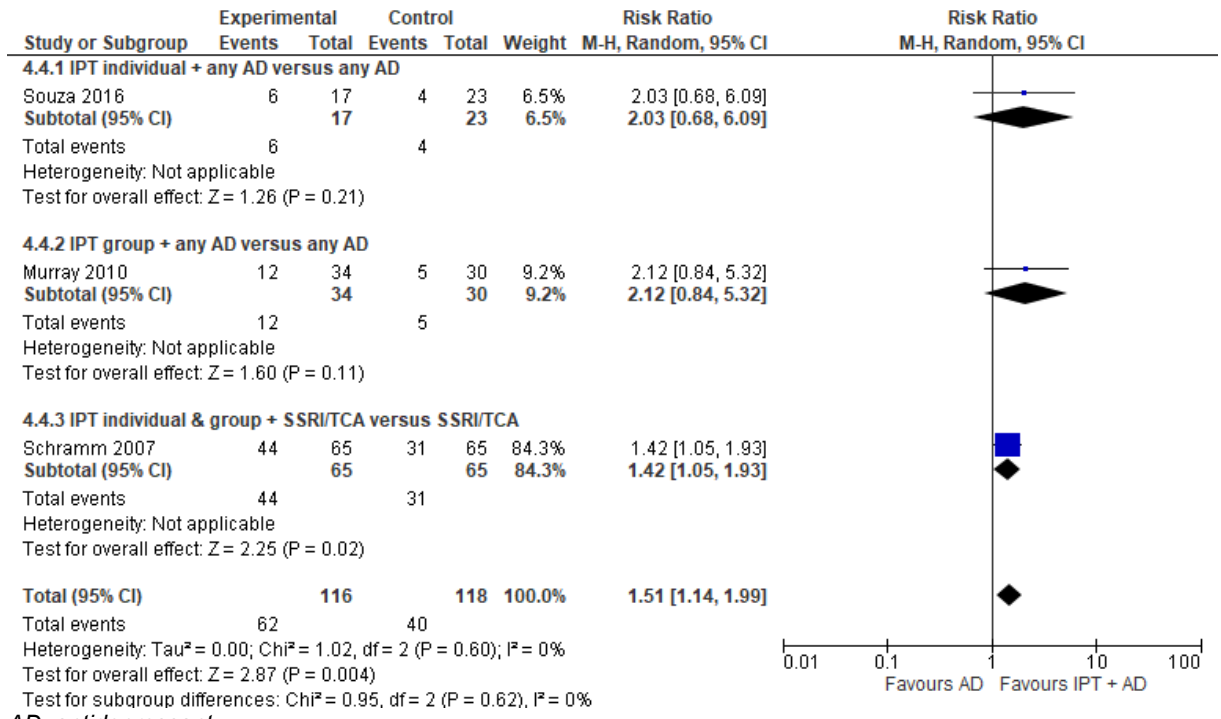
199 **Figure 47: Remission (ITT)**



200
201 *AD: antidepressant*

202

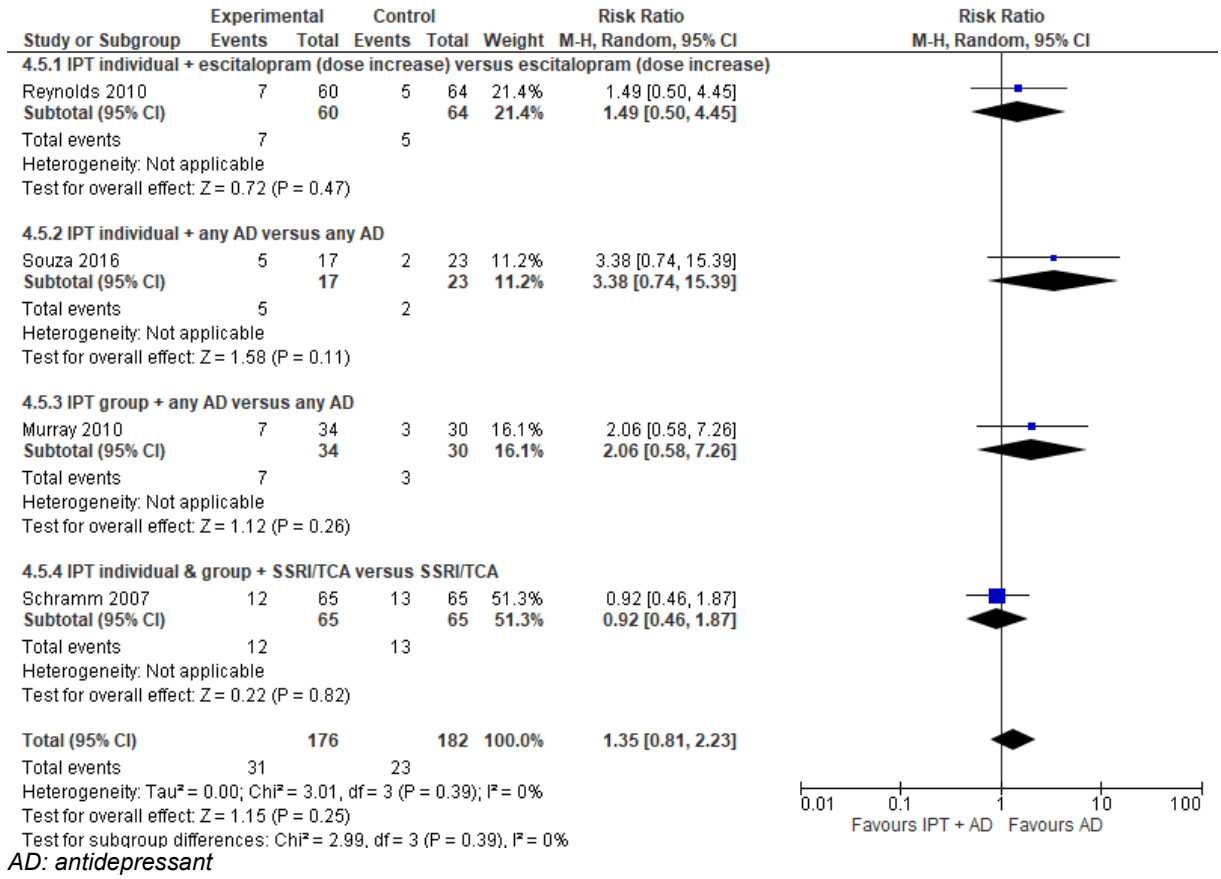
203 **Figure 48: Response (ITT)**



204
205 *AD: antidepressant*

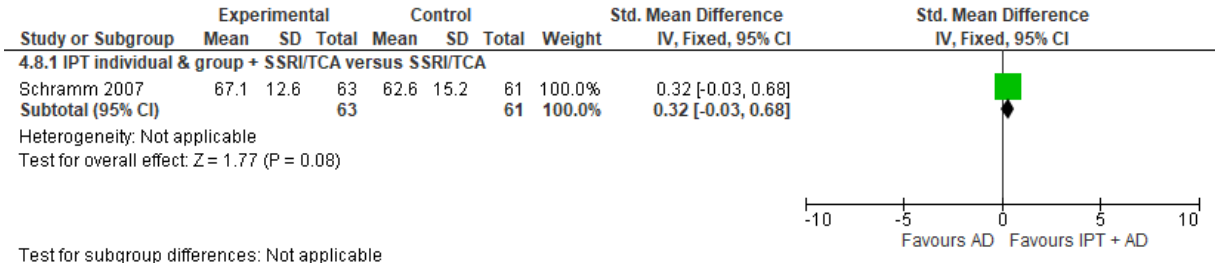
206

207 **Figure 49: Discontinuation due to any reason**



208
209 *AD: antidepressant*

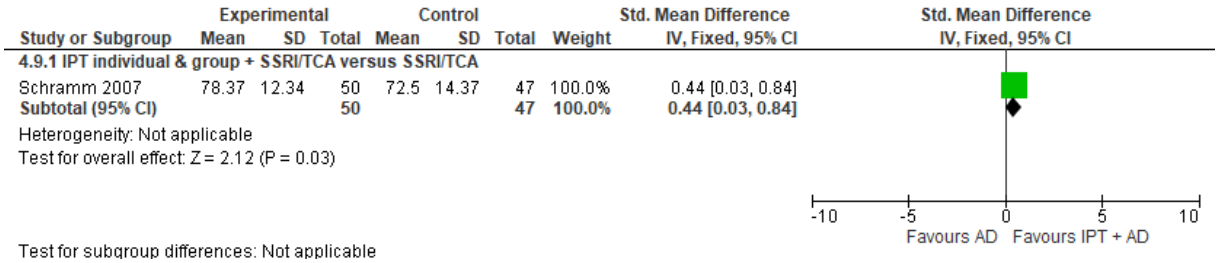
Figure 50: Global functioning endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

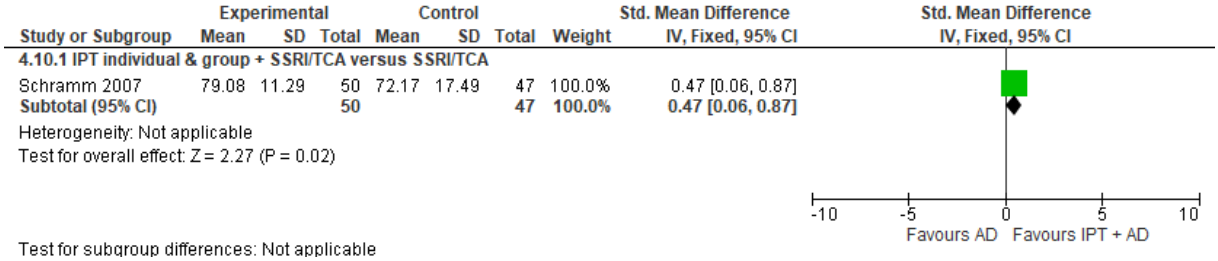
Figure 51: Global functioning at 3-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 52: Global functioning at 12-month follow-up

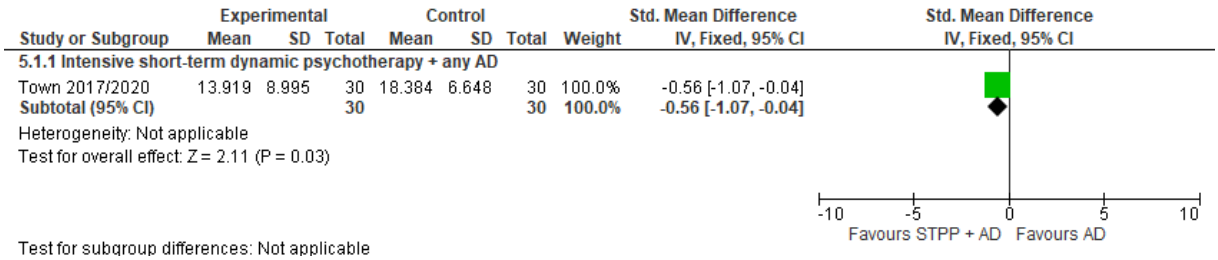


Test for subgroup differences: Not applicable

AD: antidepressant

Comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

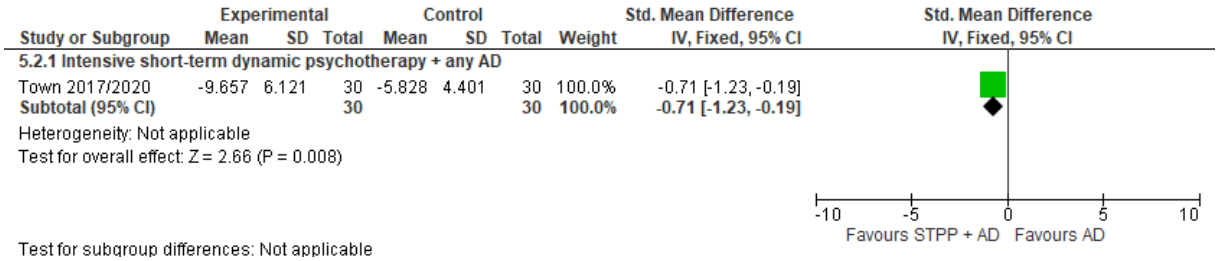
Figure 53: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

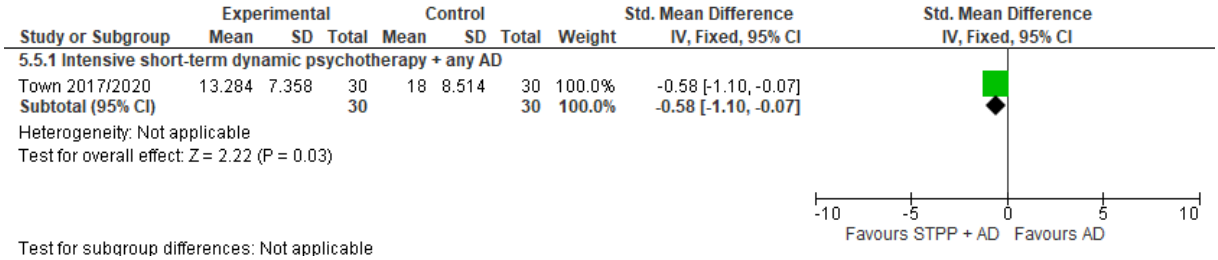
Figure 54: Depression symptomatology change score



Test for subgroup differences: Not applicable

AD: antidepressant

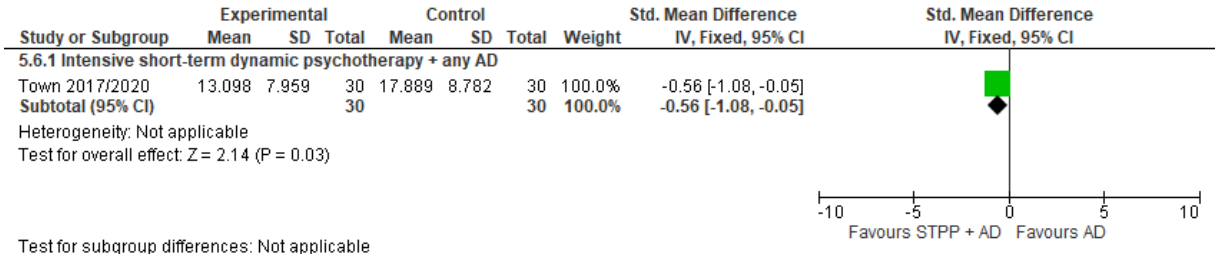
Figure 55: Depression symptomatology at 3-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

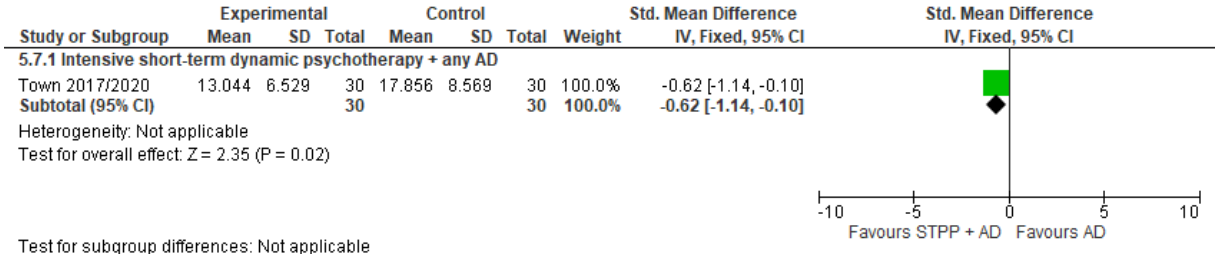
Figure 56: Depression symptomatology at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

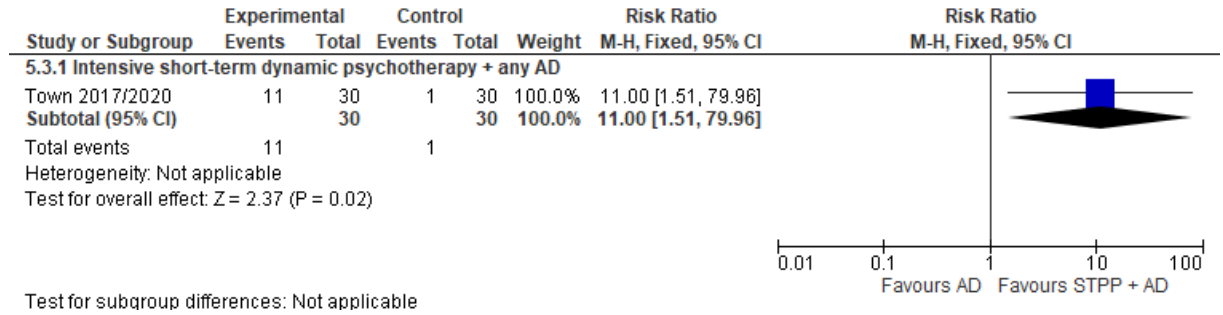
Figure 57: Depression symptomatology at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

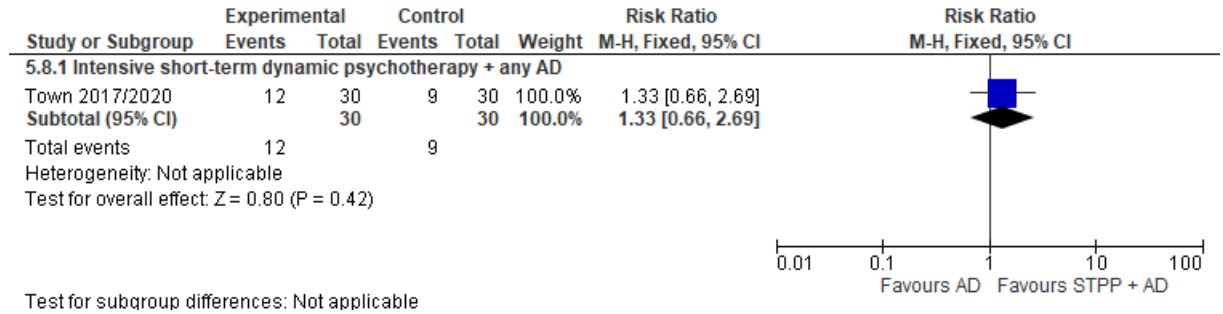
Figure 58: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

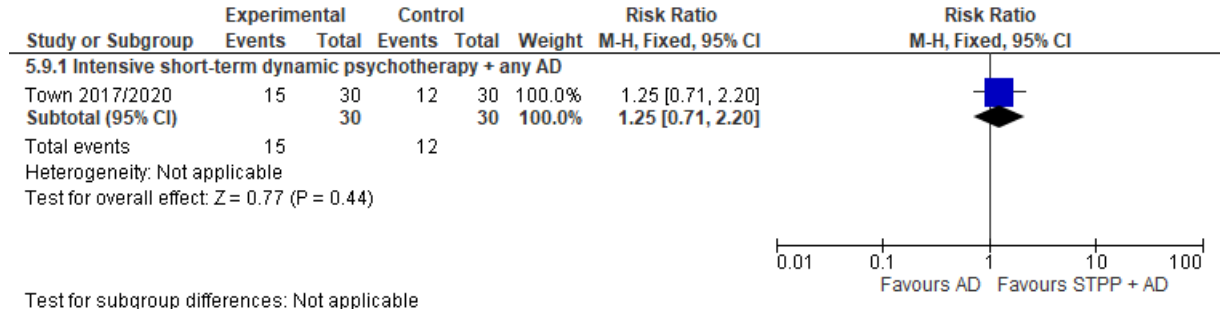
Figure 59: Remission (ITT) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

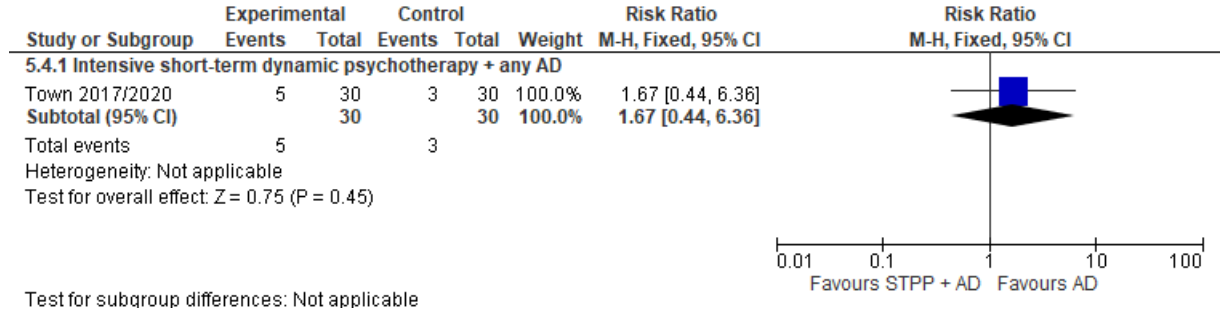
Figure 60: Response (ITT) at 12-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 61: Discontinuation due to any reason

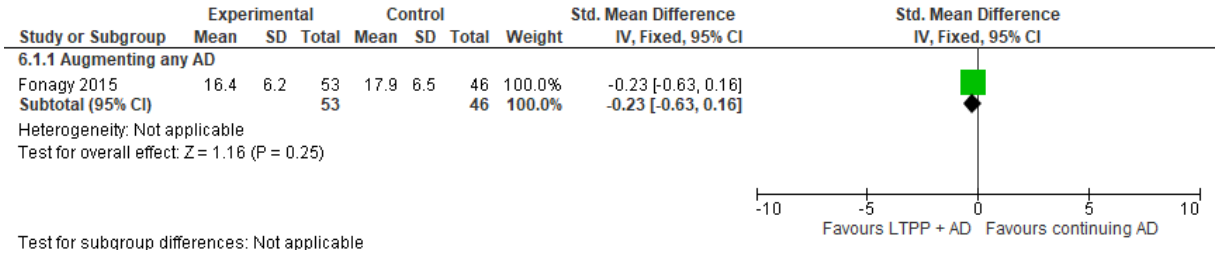


Test for subgroup differences: Not applicable

AD: antidepressant

Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

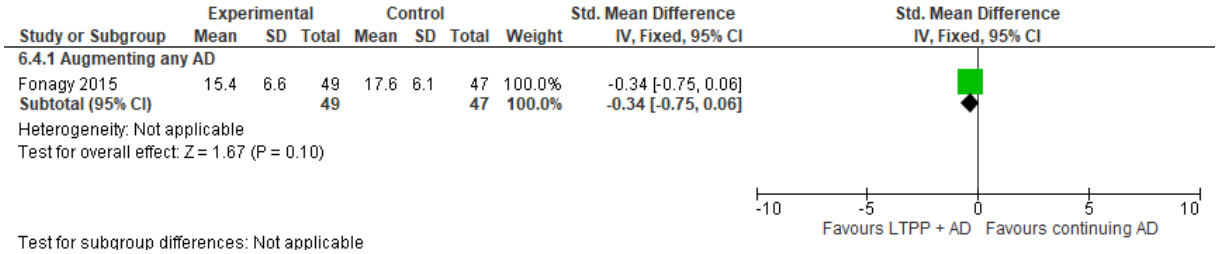
Figure 62: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

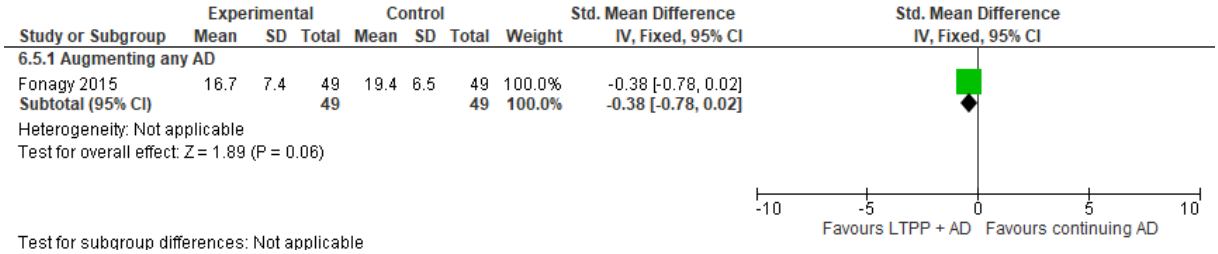
Figure 63: Depression symptomatology at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

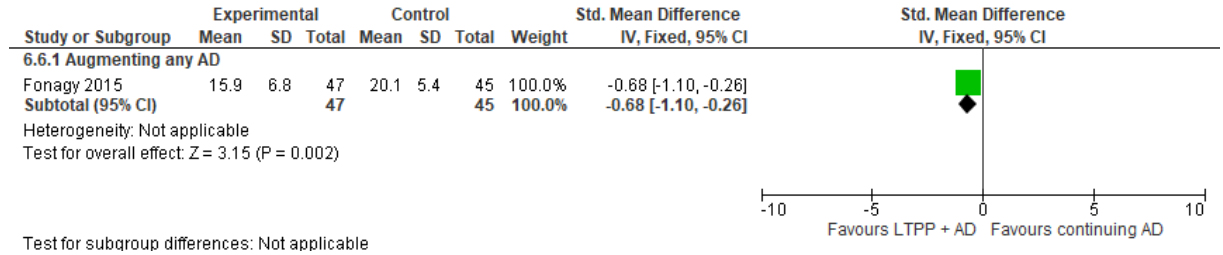
Figure 64: Depression symptomatology at 1-year follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

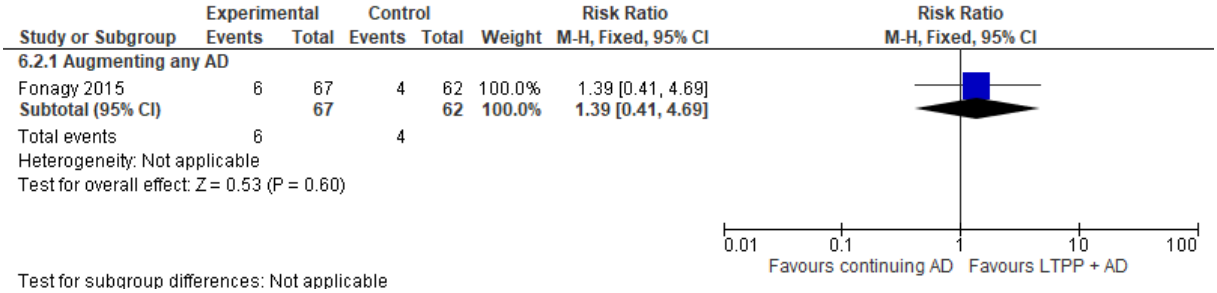
Figure 65: Depression symptomatology at 2-year follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

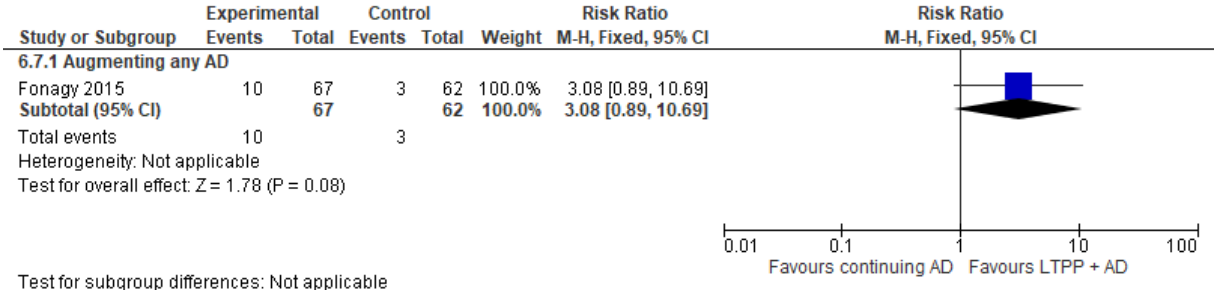
Figure 66: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

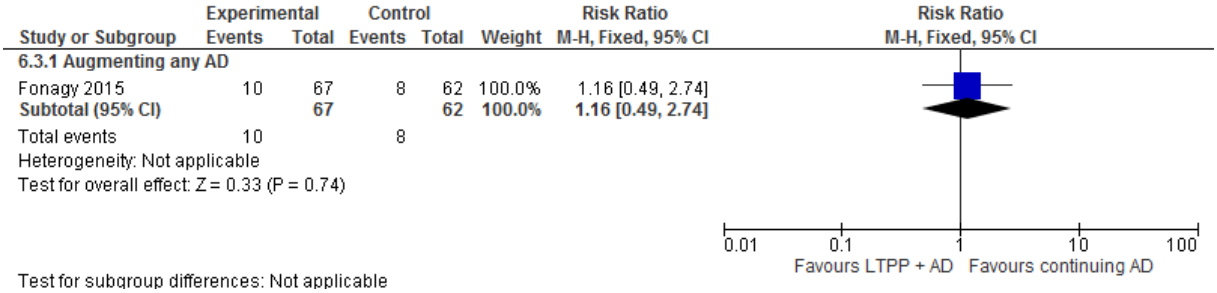
Figure 67: Remission (ITT) at 2-year follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 68: Discontinuation due to any reason

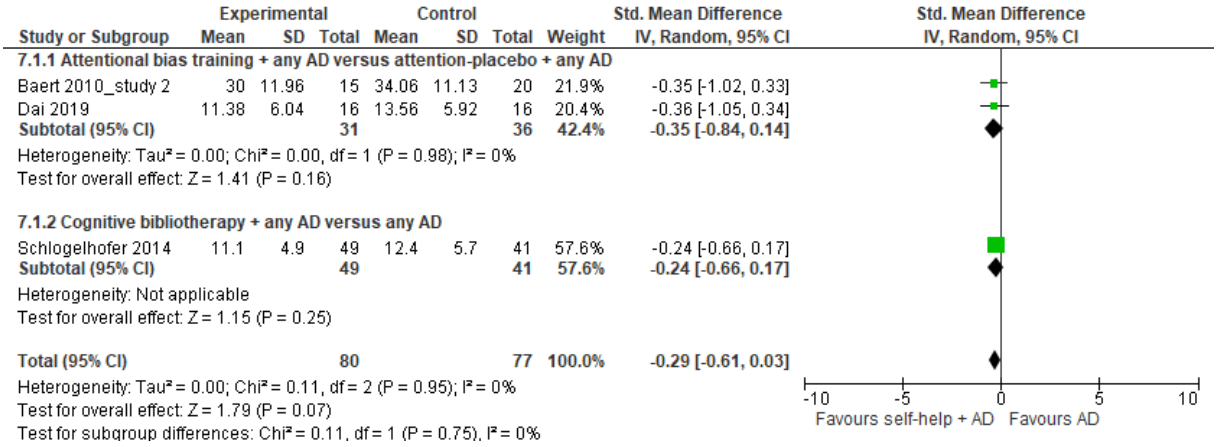


Test for subgroup differences: Not applicable

AD: antidepressant

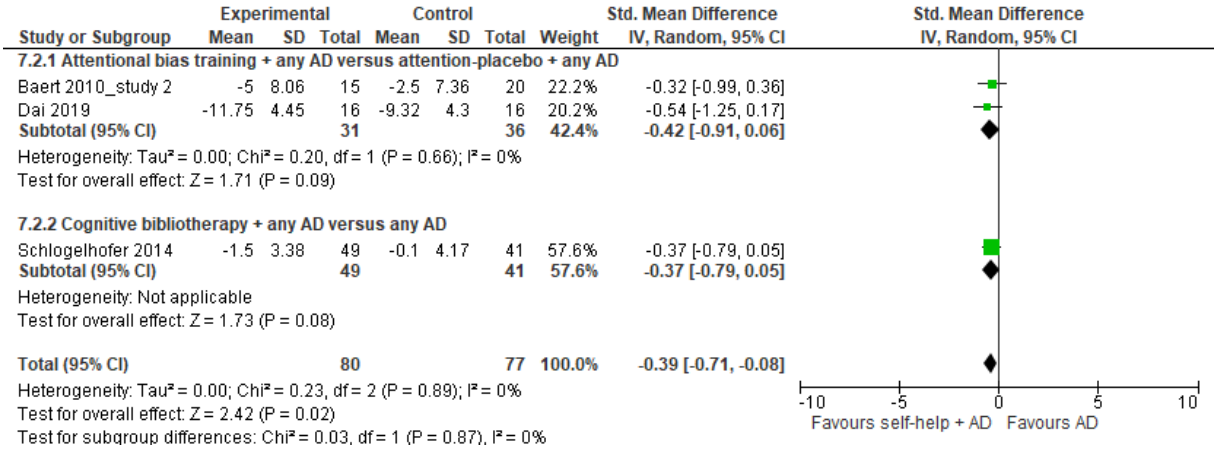
Comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/- attention-placebo)

Figure 69: Depression symptomatology endpoint



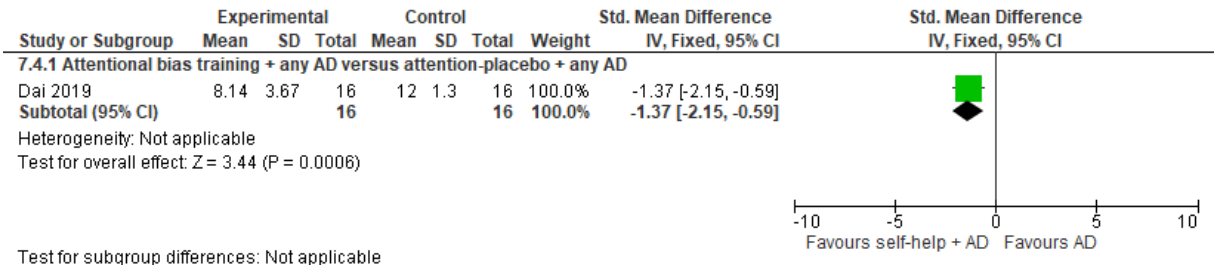
AD: antidepressant

Figure 70: Depression symptomatology change score



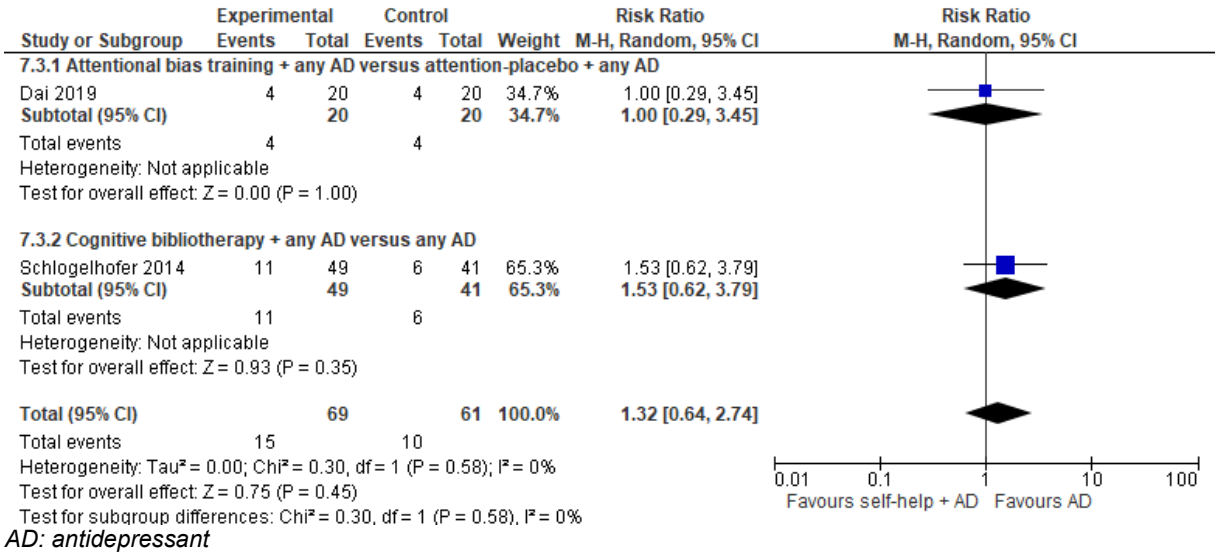
AD: antidepressant

Figure 71: Depression symptomatology at 1-month follow-up



AD: antidepressant

Figure 72: Discontinuation due to any reason



AD: antidepressant

Comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

Figure 73: Depression symptomatology endpoint

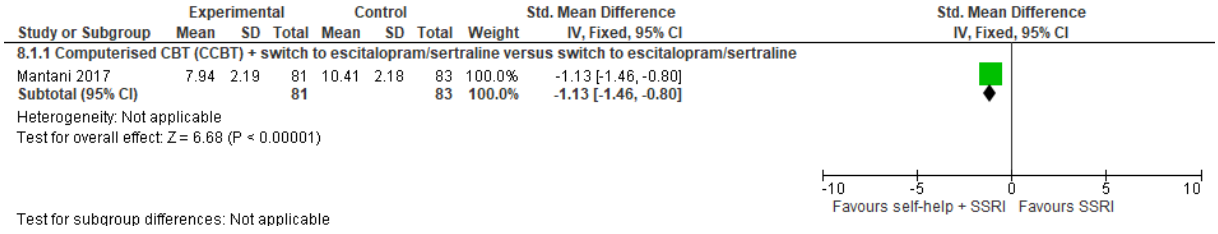


Figure 74: Depression symptomatology change score

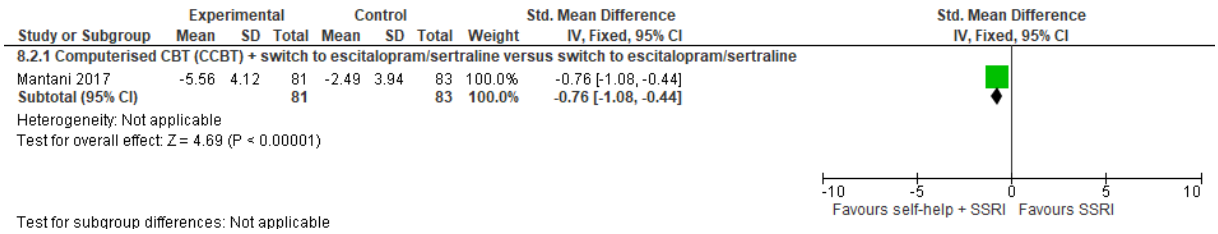


Figure 75: Remission (ITT)

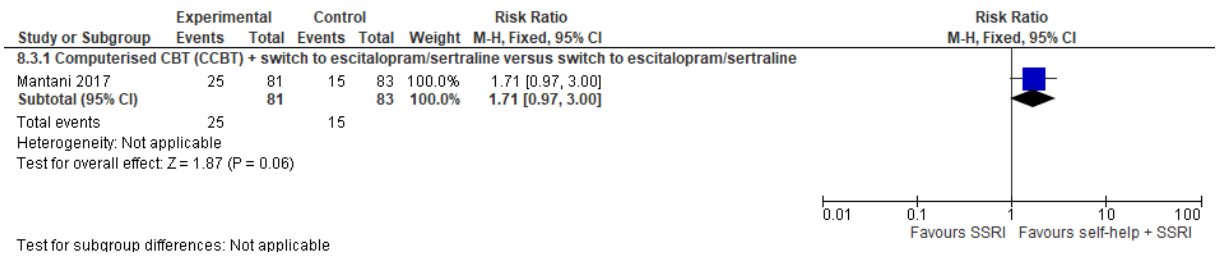
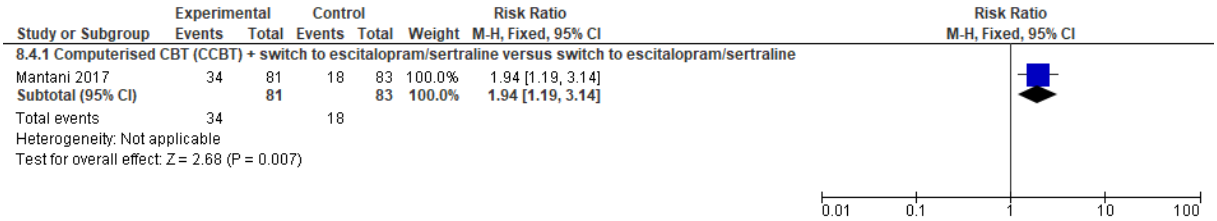
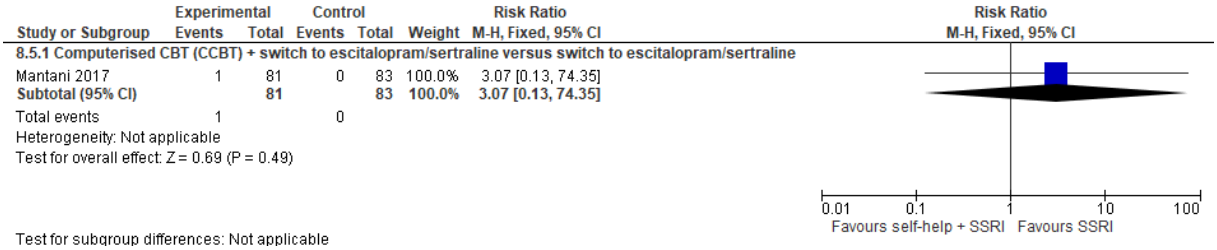


Figure 76: Response (ITT)



Test for subgroup differences: Not applicable

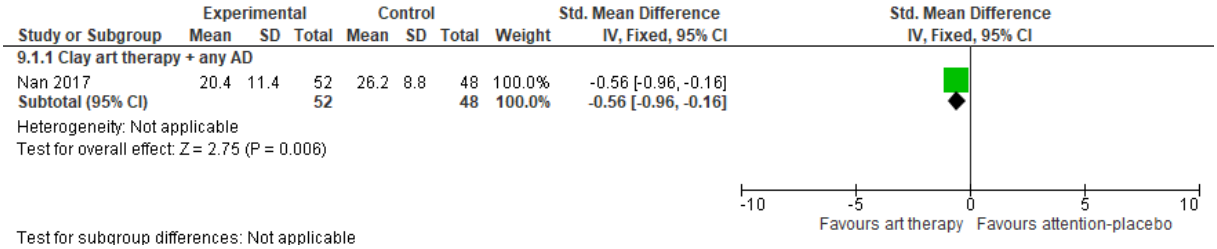
Figure 77: Discontinuation due to any reason



Test for subgroup differences: Not applicable

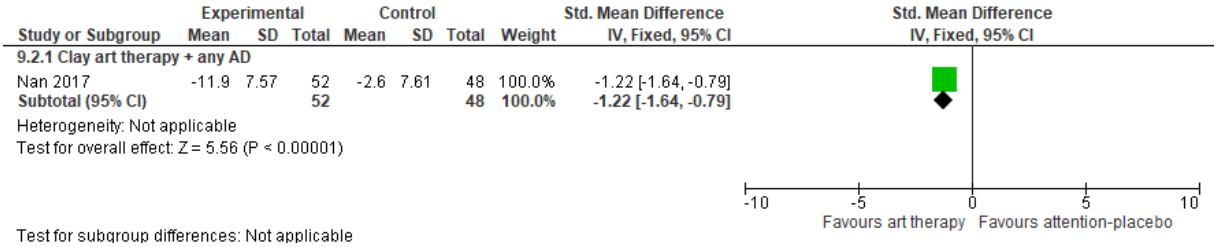
Comparison 9. Augmenting with art therapy versus attention-placebo

Figure 78: Depression symptomatology endpoint



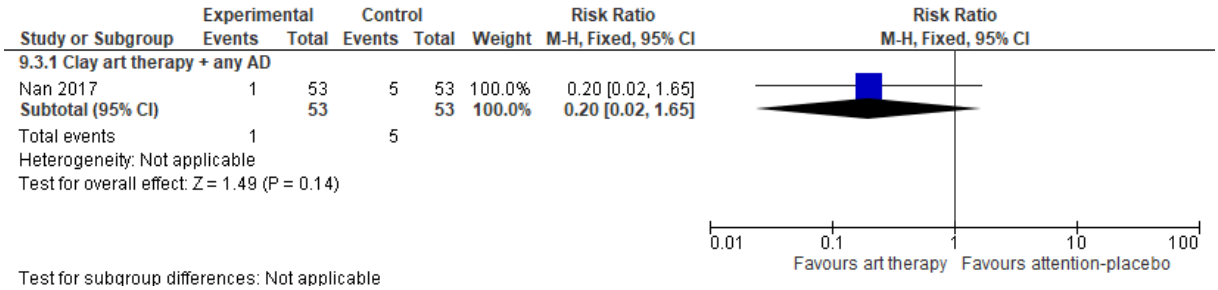
Test for subgroup differences: Not applicable

Figure 79: Depression symptomatology change score



Test for subgroup differences: Not applicable

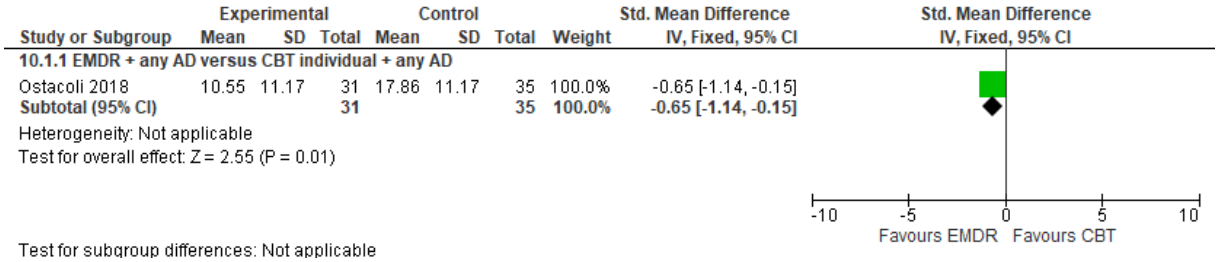
Figure 80: Discontinuation due to any reason



Test for subgroup differences: Not applicable

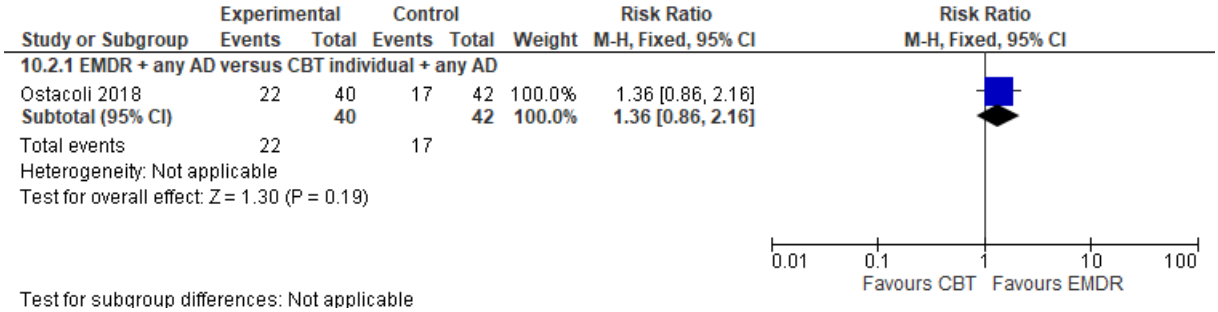
Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Figure 81: Depression symptomatology endpoint



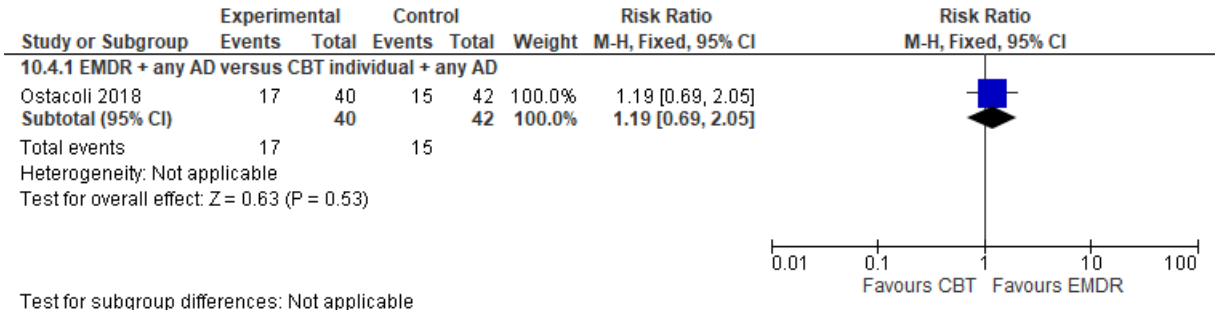
Test for subgroup differences: Not applicable

Figure 82: Remission (ITT)



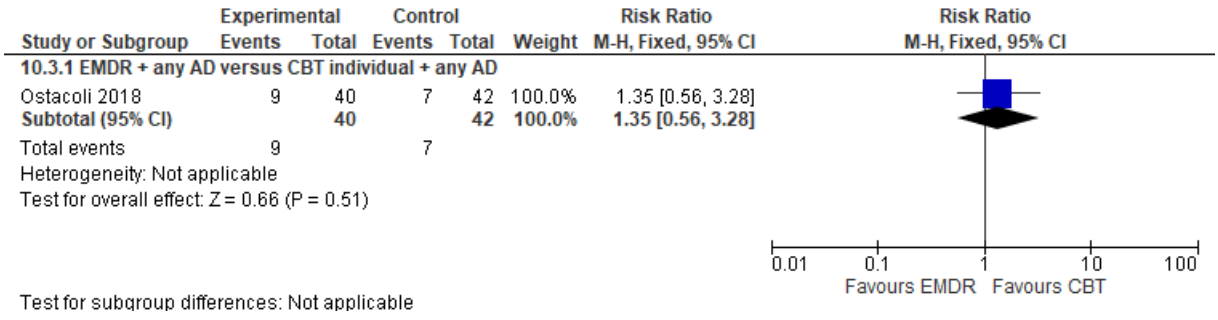
Test for subgroup differences: Not applicable

Figure 83: Remission (ITT) at 6-month follow-up



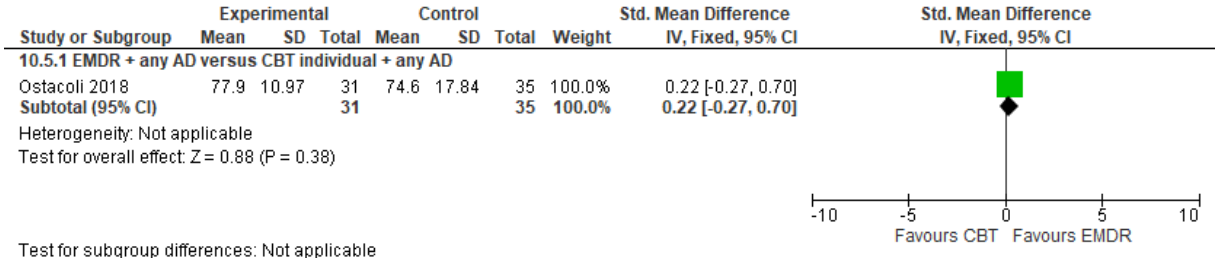
Test for subgroup differences: Not applicable

343 **Figure 84: Discontinuation due to any reason**



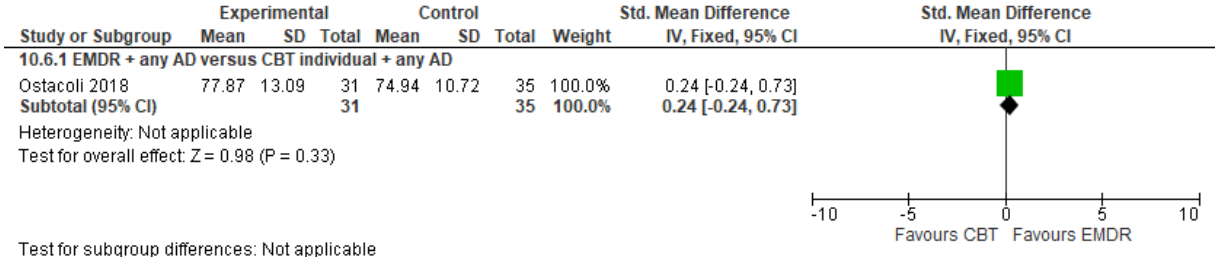
344 Test for subgroup differences: Not applicable

345 **Figure 85: Global functioning at endpoint**



346 Test for subgroup differences: Not applicable

347 **Figure 86: Global functioning at 6-month follow-up**

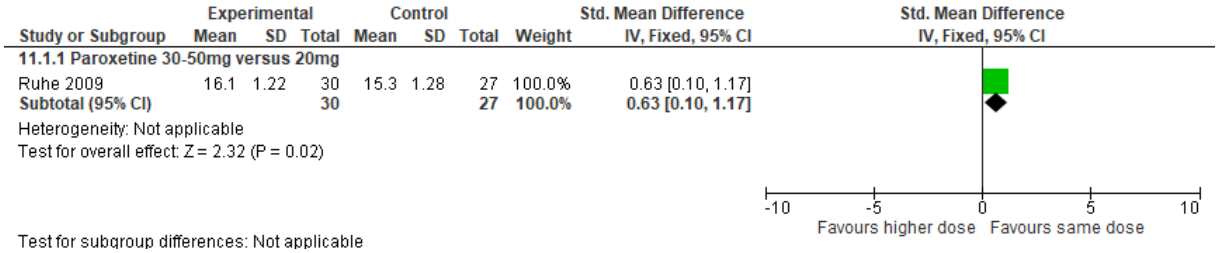


348 Test for subgroup differences: Not applicable

349

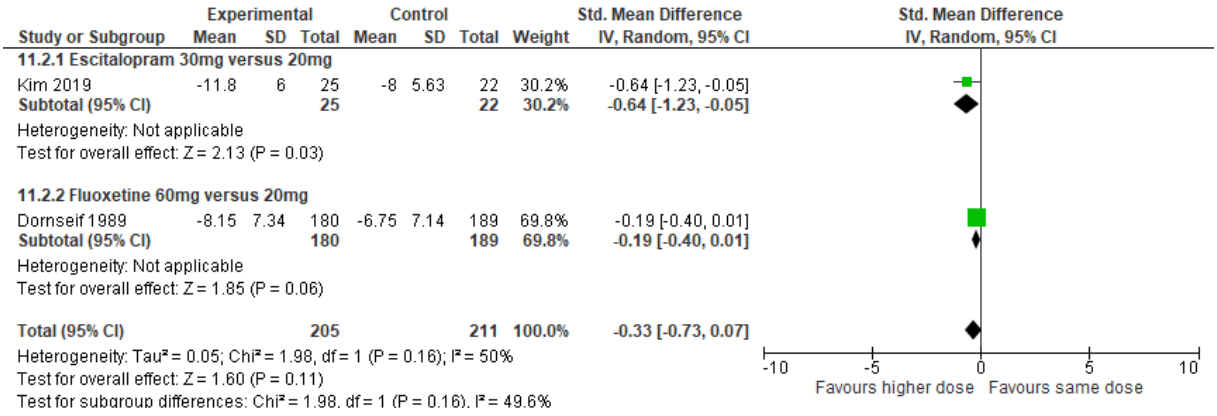
350 ***Comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose***

351 **Figure 87: Depression symptomatology endpoint**



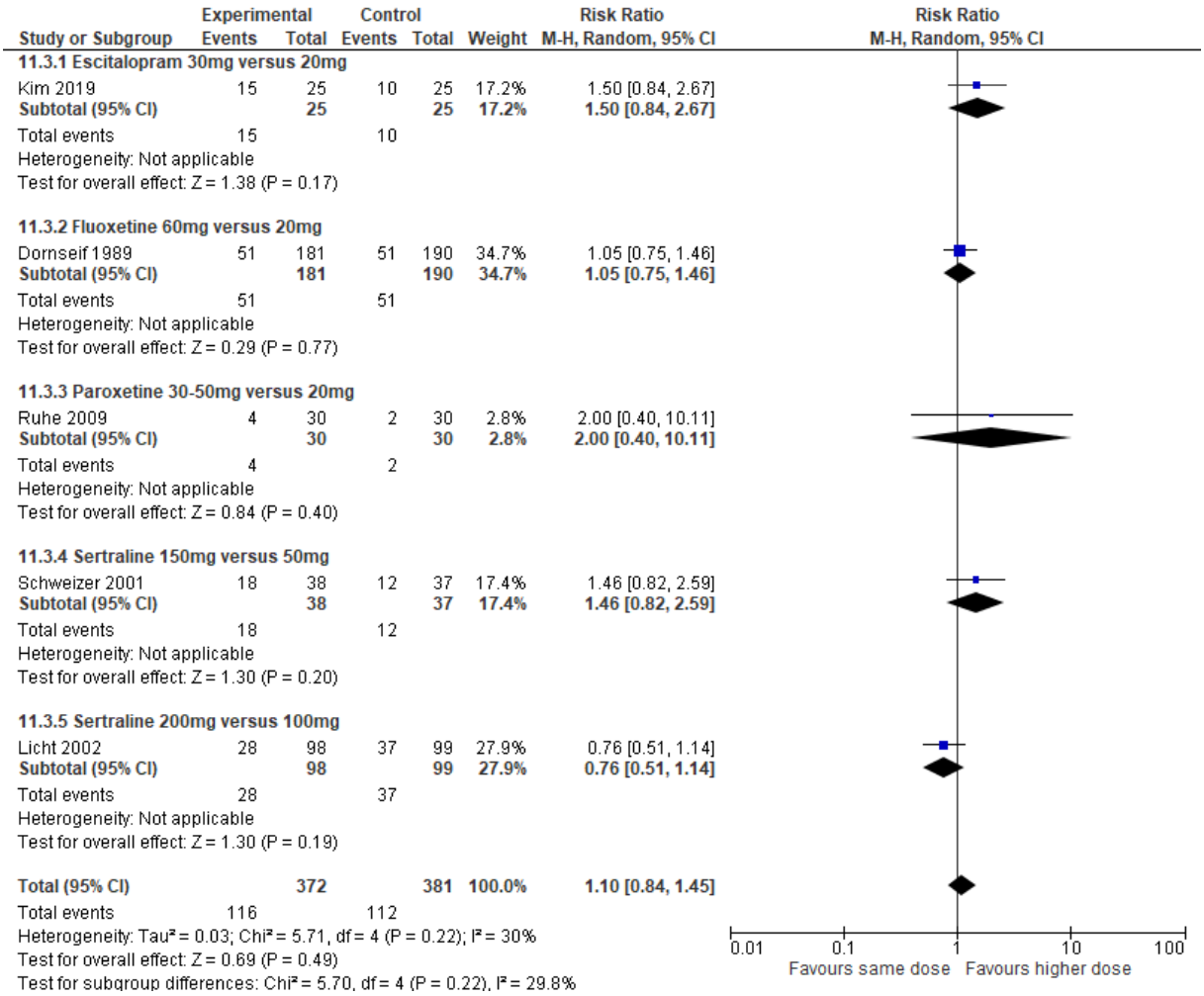
352 Test for subgroup differences: Not applicable

353 **Figure 88: Depression symptomatology change score**



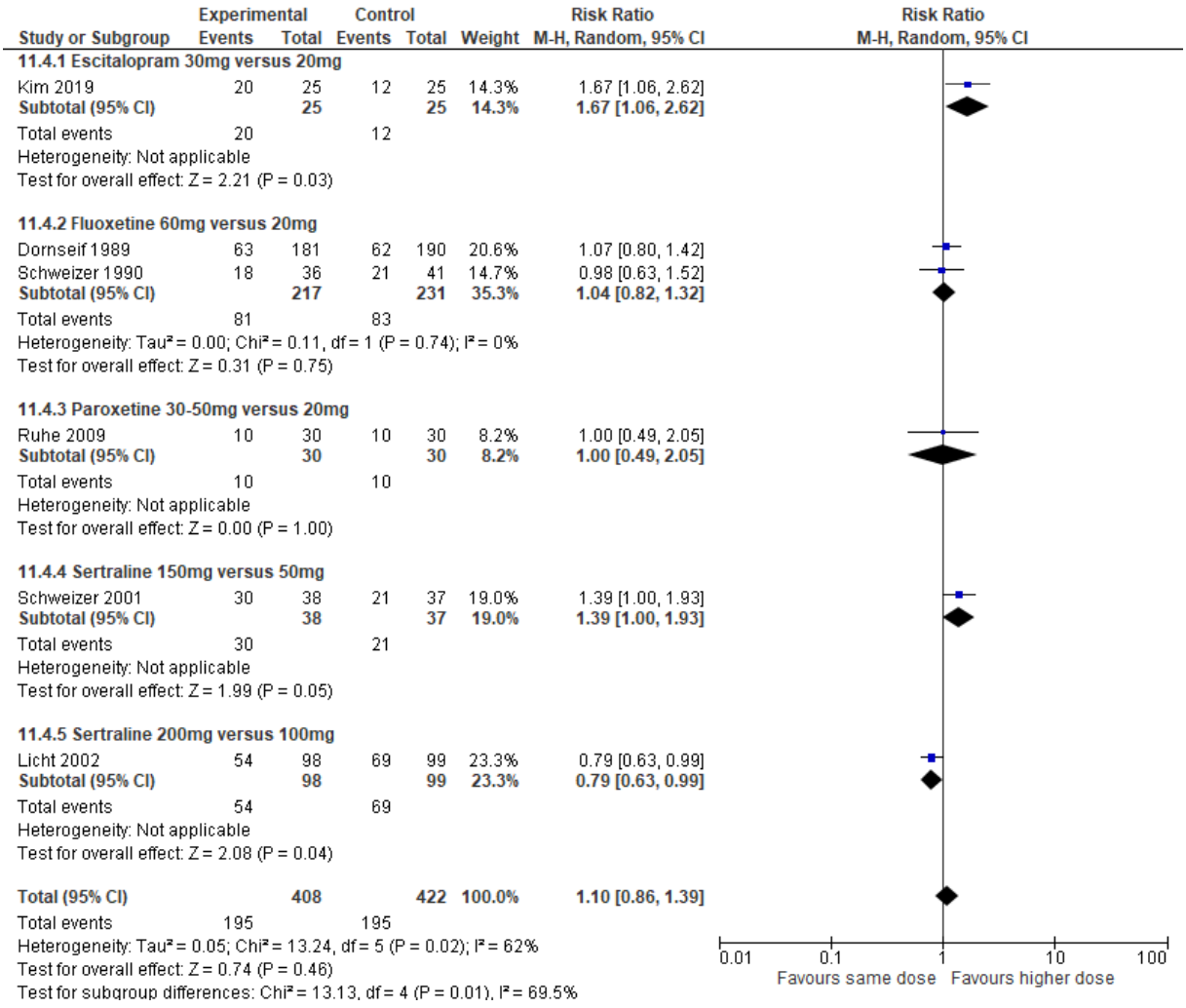
354

355 **Figure 89: Remission (ITT)**

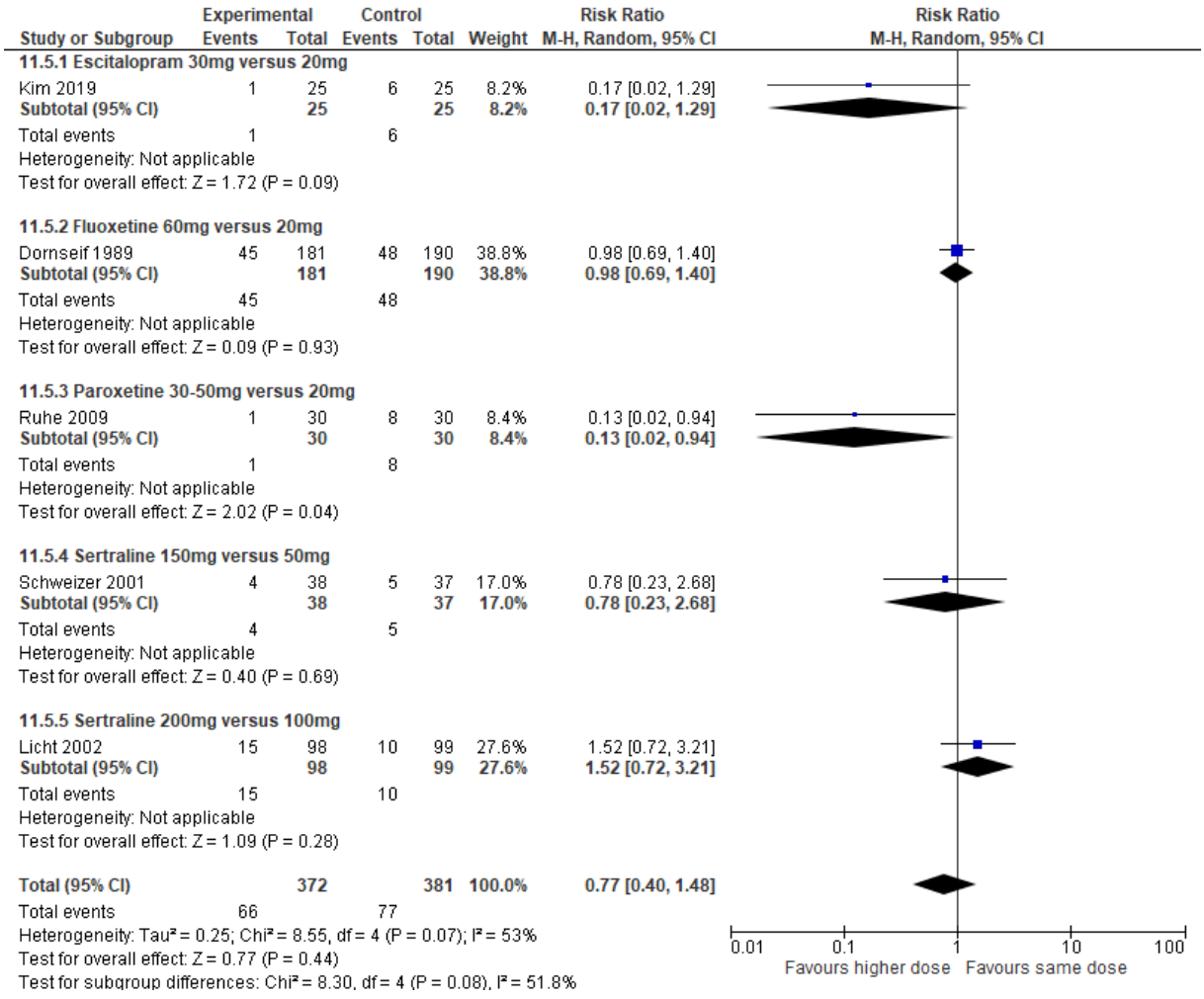


356

Figure 90: Response (ITT)

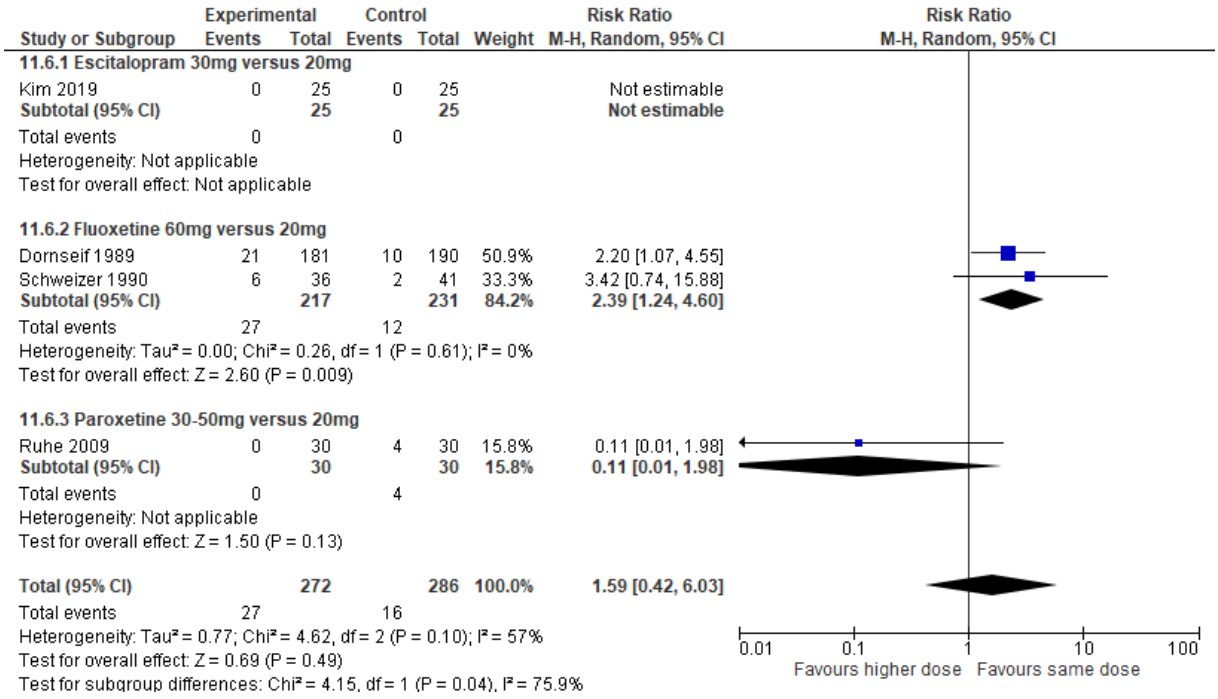


359 **Figure 91: Discontinuation due to any reason**



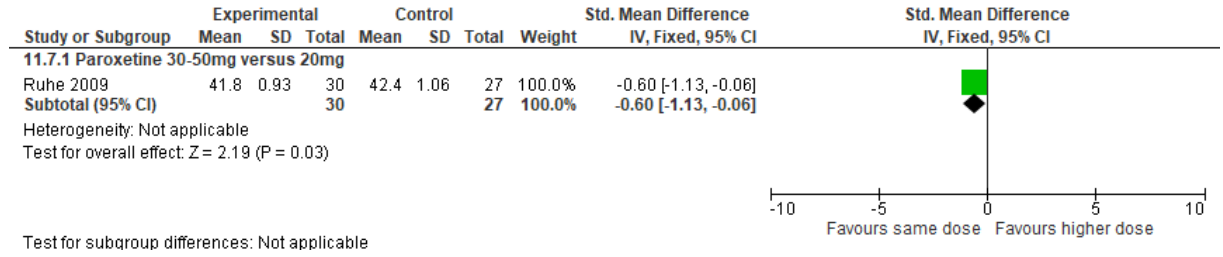
360

361 **Figure 92: Discontinuation due to side effects**



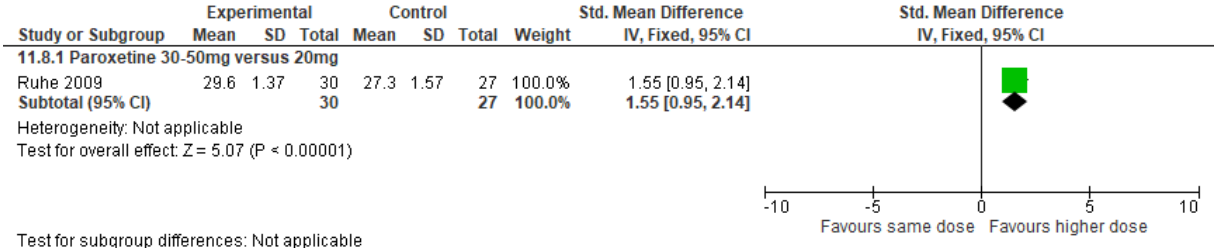
362

Figure 93: Quality of life physical component score (PCS) endpoint



Test for subgroup differences: Not applicable

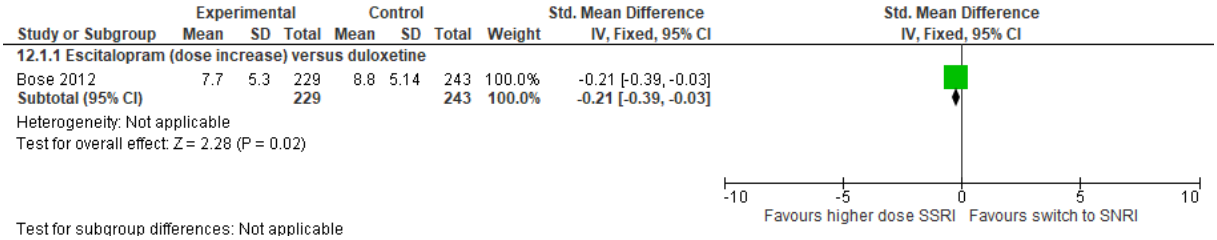
Figure 94: Quality of life mental component score (MCS) endpoint



Test for subgroup differences: Not applicable

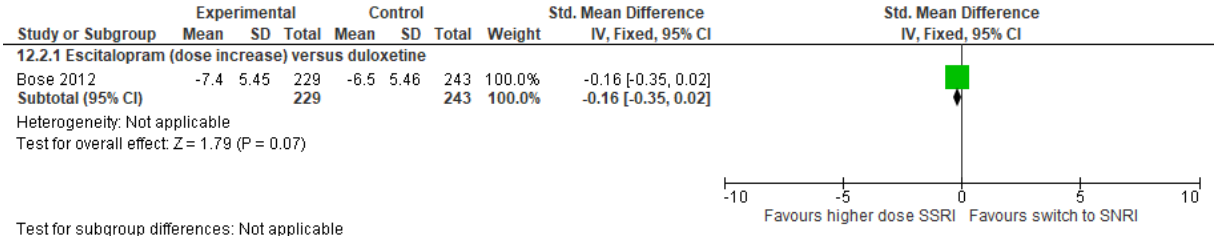
Comparison 12. Increasing the dose of SSRI versus switching to SNRI

Figure 95: Depression symptomatology endpoint



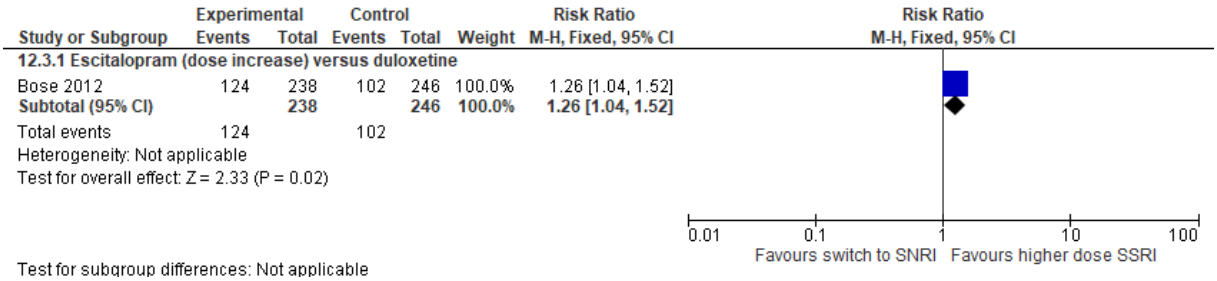
Test for subgroup differences: Not applicable

Figure 96: Depression symptomatology change score



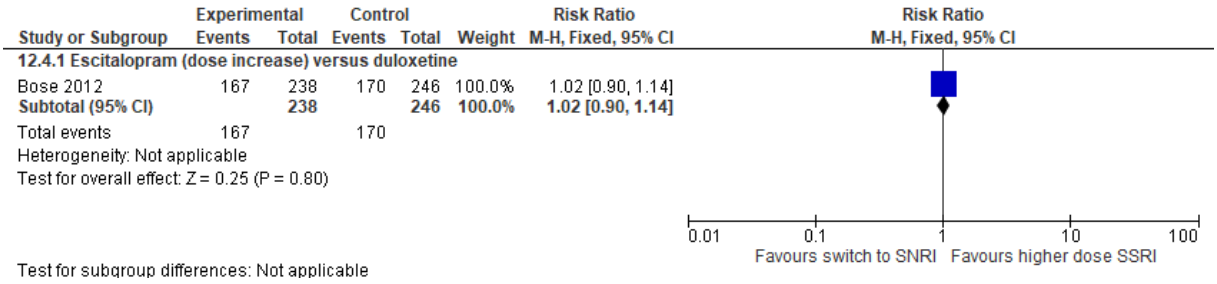
Test for subgroup differences: Not applicable

Figure 97: Remission (ITT)



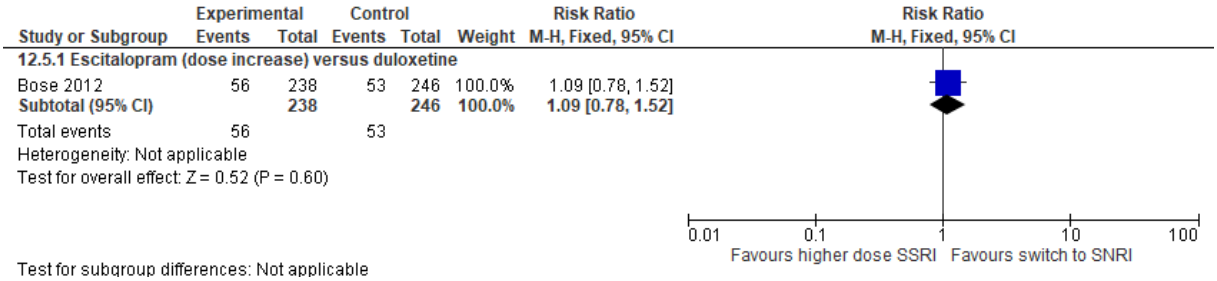
Test for subgroup differences: Not applicable

Figure 98: Response (ITT)



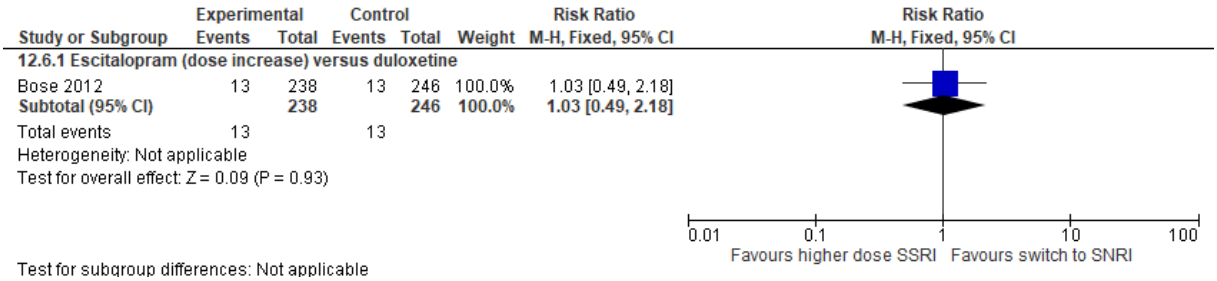
Test for subgroup differences: Not applicable

Figure 99: Discontinuation due to any reason



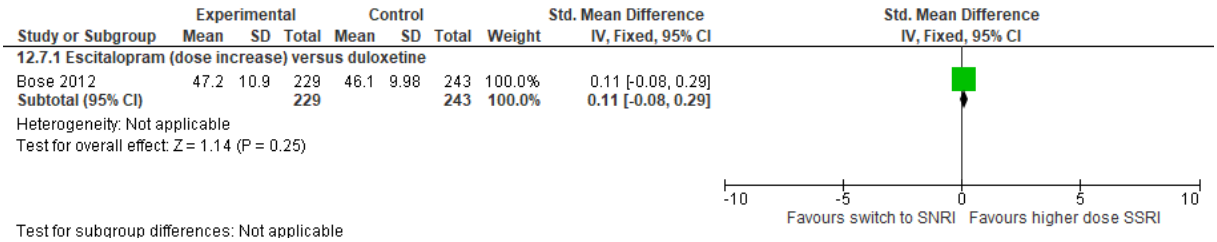
Test for subgroup differences: Not applicable

Figure 100: Discontinuation due to side effects



Test for subgroup differences: Not applicable

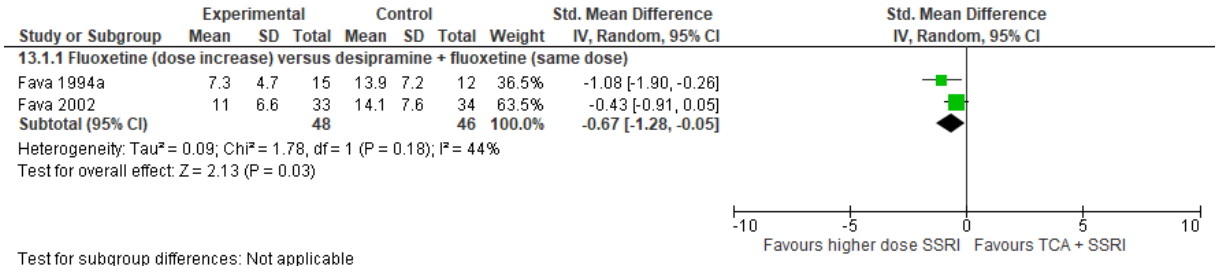
Figure 101: Quality of life endpoint



Test for subgroup differences: Not applicable

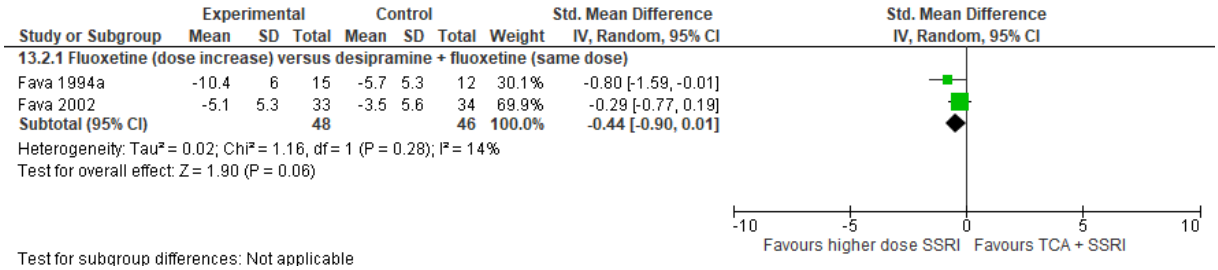
Comparison 13. Increasing the dose of SSRI versus augmenting with TCA

Figure 102: Depression symptomatology endpoint



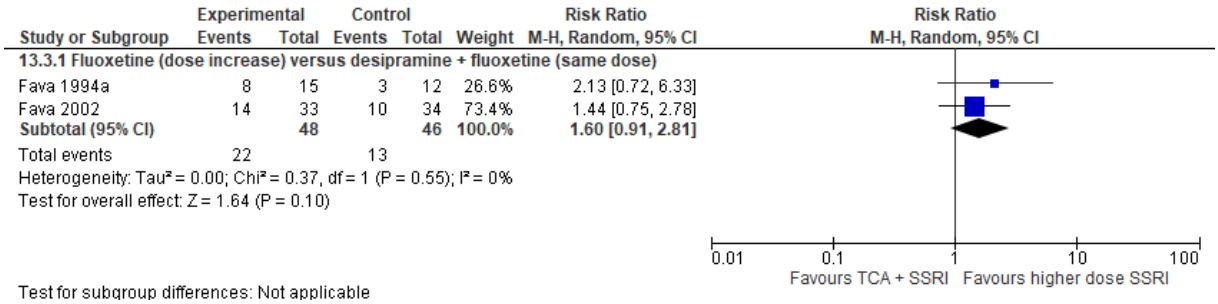
Test for subgroup differences: Not applicable

Figure 103: Depression symptomatology change score



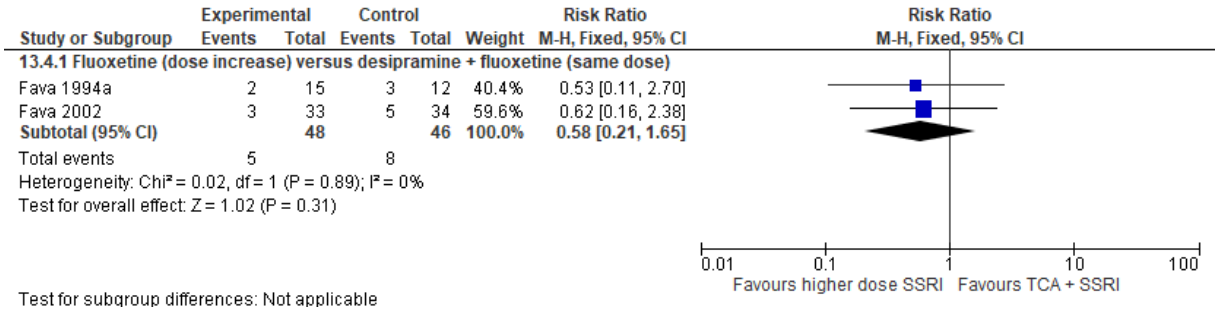
Test for subgroup differences: Not applicable

Figure 104: Remission (ITT)



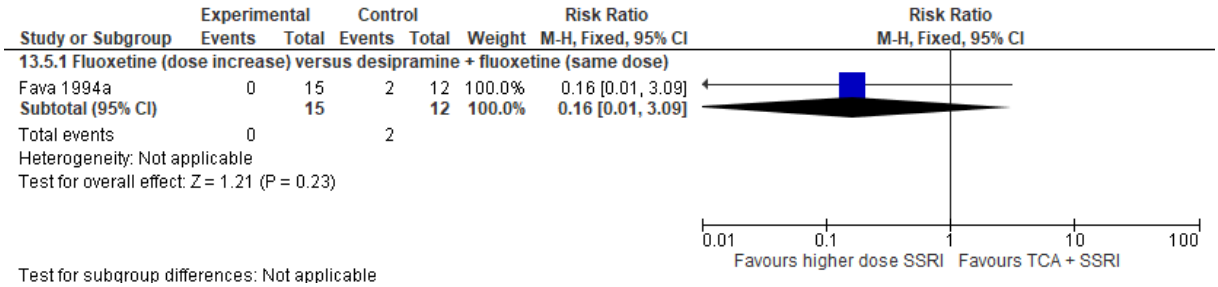
Test for subgroup differences: Not applicable

Figure 105: Discontinuation due to any reason



Test for subgroup differences: Not applicable

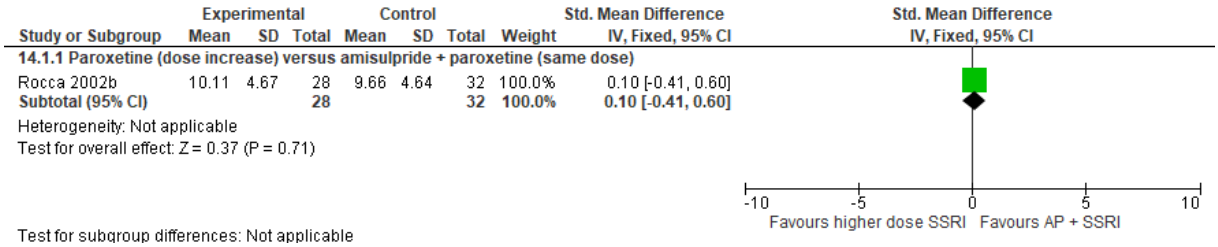
Figure 106: Discontinuation due to side effects



Test for subgroup differences: Not applicable

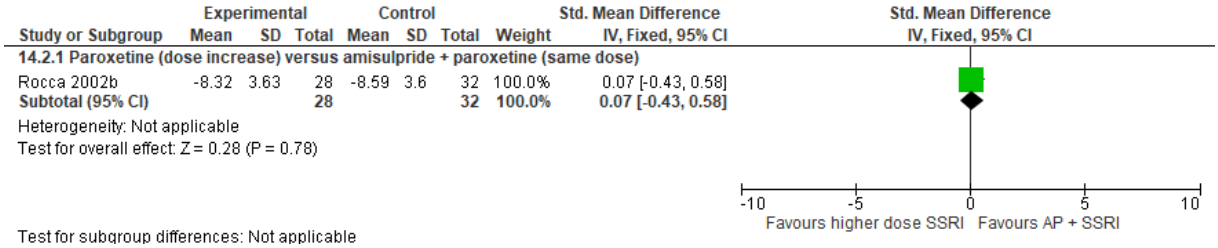
Comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Figure 107: Depression symptomatology endpoint



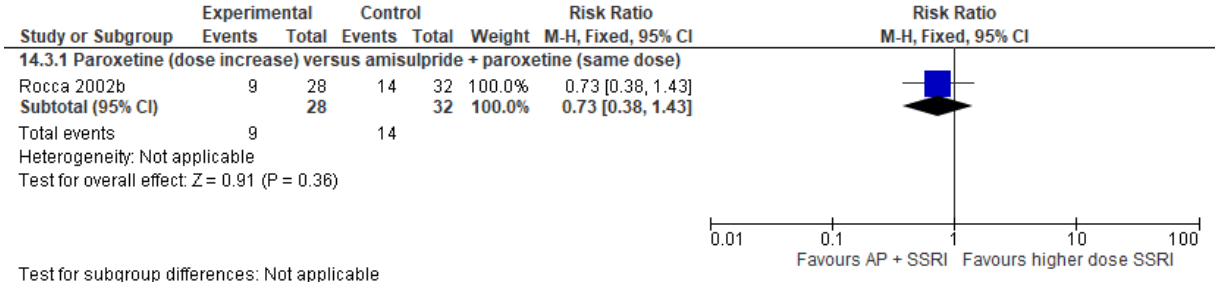
Test for subgroup differences: Not applicable

Figure 108: Depression symptomatology change score



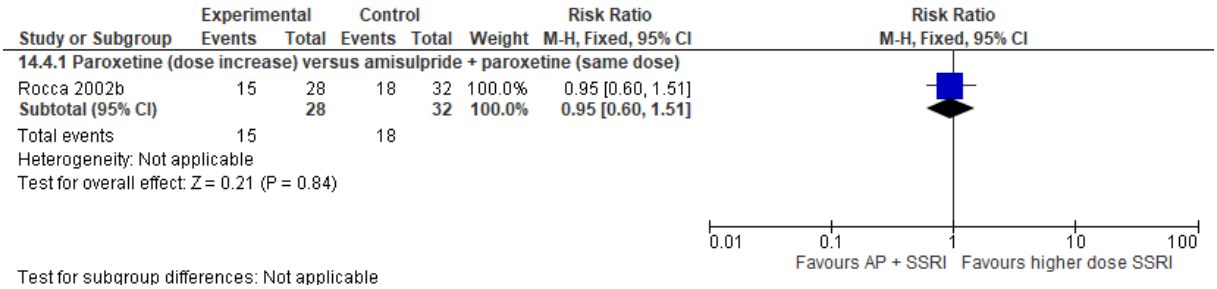
Test for subgroup differences: Not applicable

Figure 109: Remission (ITT)



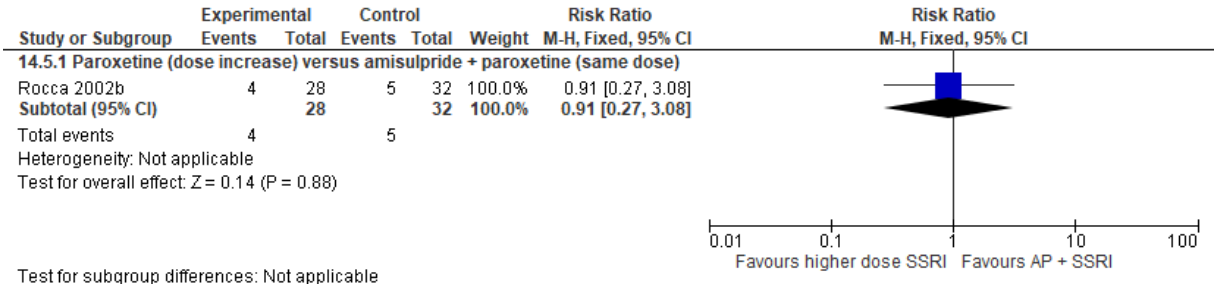
Test for subgroup differences: Not applicable

403 **Figure 110: Response (ITT)**



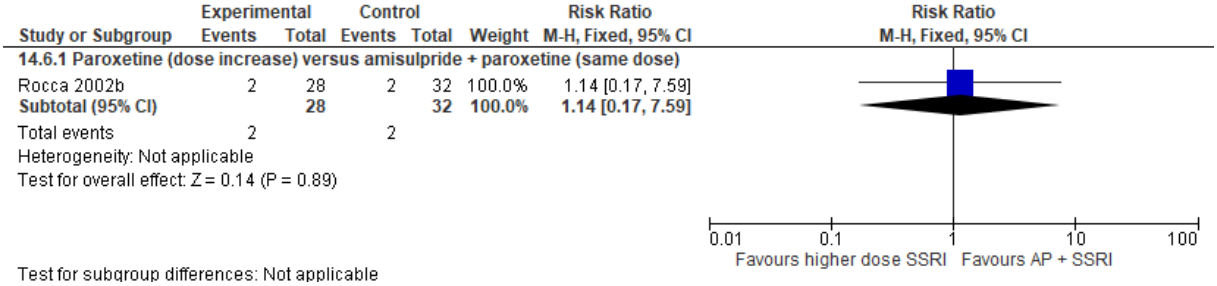
404 Test for subgroup differences: Not applicable

405 **Figure 111: Discontinuation due to any reason**



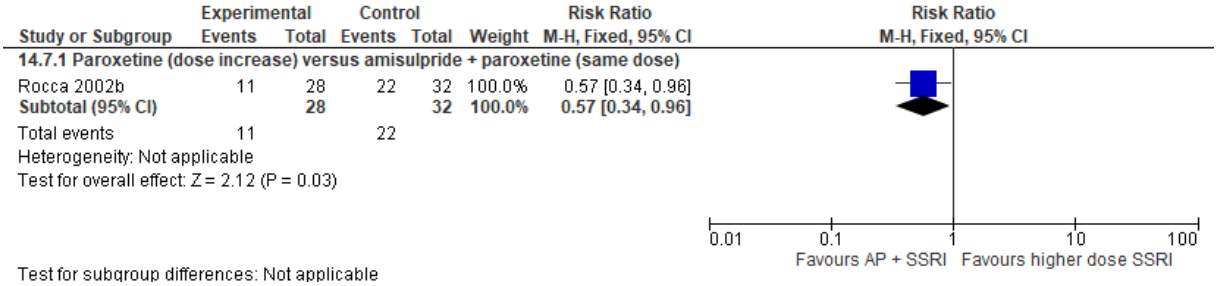
406 Test for subgroup differences: Not applicable

407 **Figure 112: Discontinuation due to side effects**



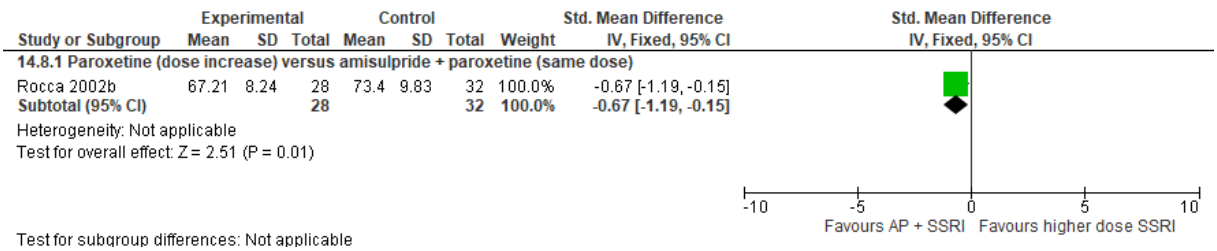
408 Test for subgroup differences: Not applicable

409 **Figure 113: Functional remission (GAF score ≥71)**



410 Test for subgroup differences: Not applicable

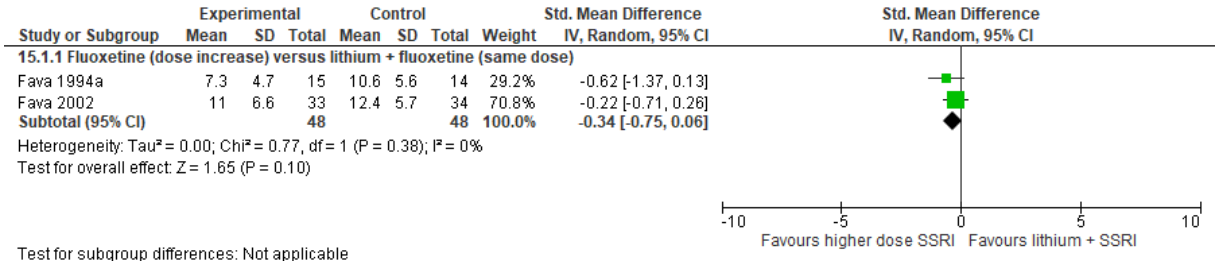
411 **Figure 114: Global functioning endpoint**



412 Test for subgroup differences: Not applicable

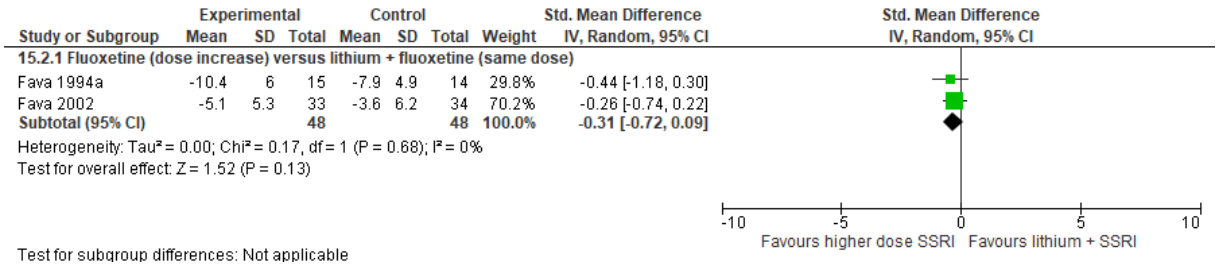
Comparison 15. Increasing the dose of SSRI versus augmenting with lithium

Figure 115: Depression symptomatology endpoint



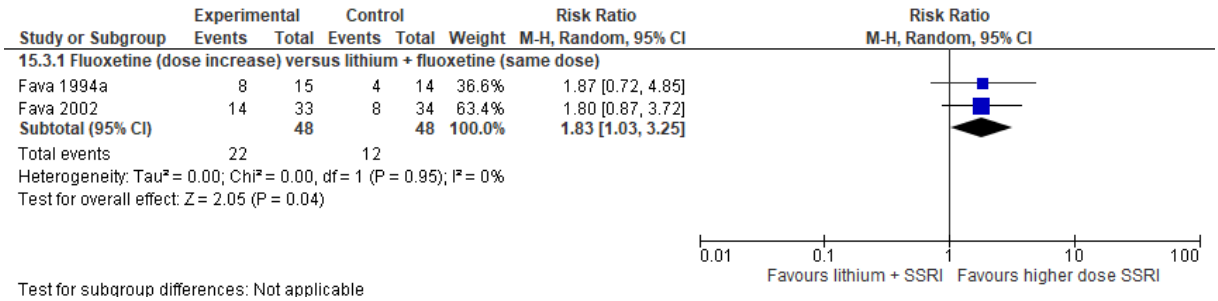
Test for subgroup differences: Not applicable

Figure 116: Depression symptomatology change score



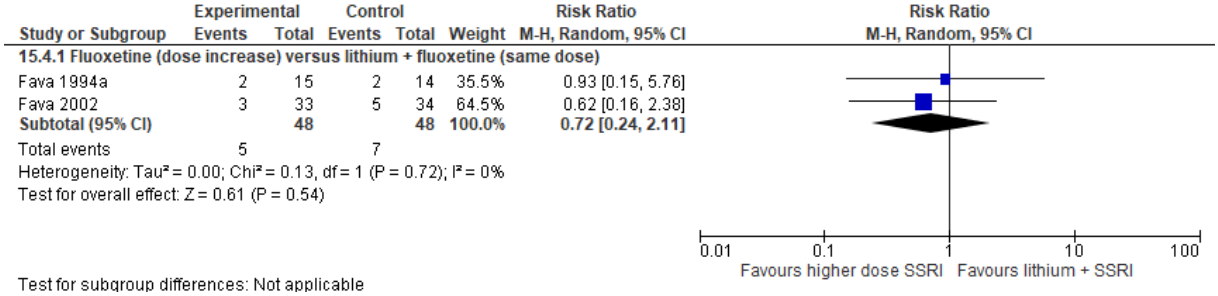
Test for subgroup differences: Not applicable

Figure 117: Remission (ITT)



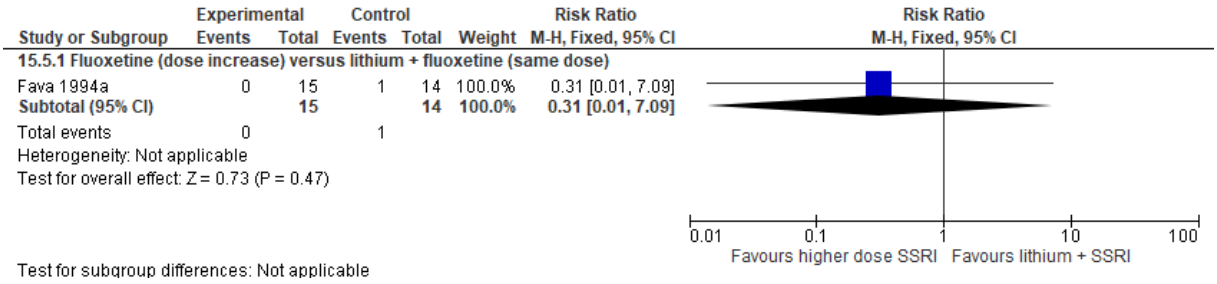
Test for subgroup differences: Not applicable

Figure 118: Discontinuation due to any reason



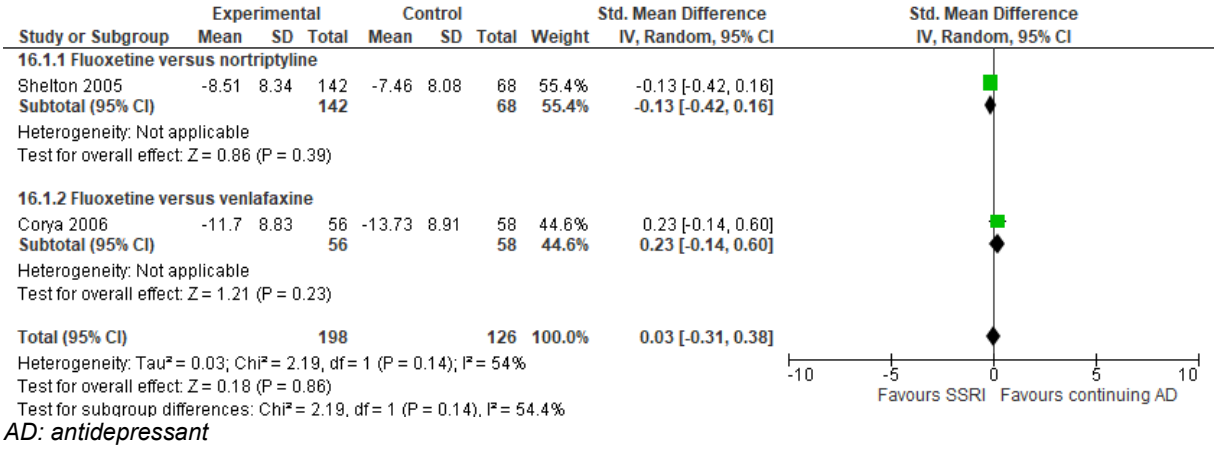
Test for subgroup differences: Not applicable

Figure 119: Discontinuation due to side effects



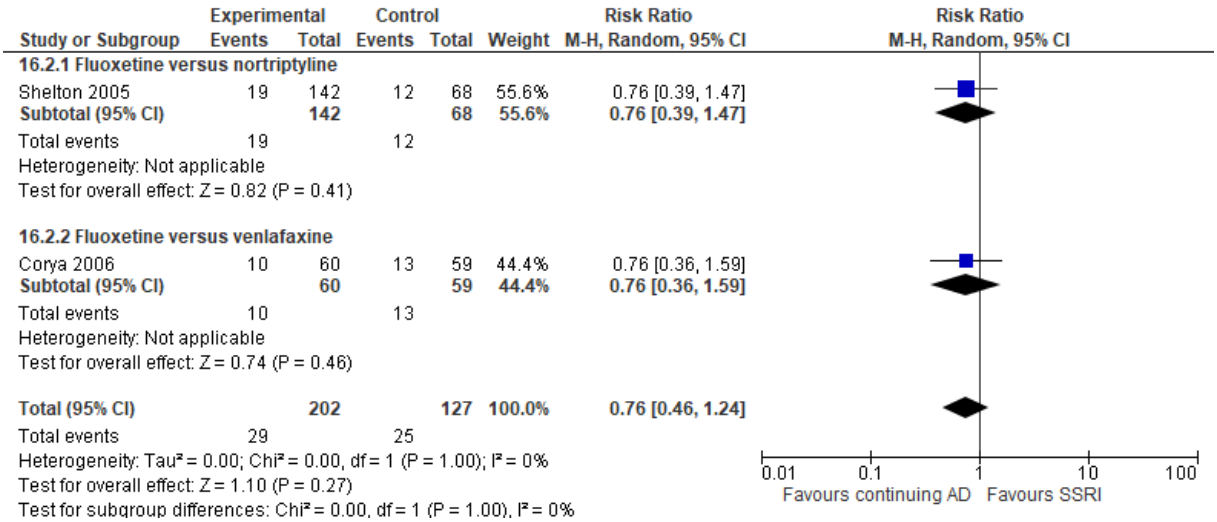
Comparison 16. Switching to SSRI versus continuing with antidepressant

Figure 120: Depression symptomatology change score



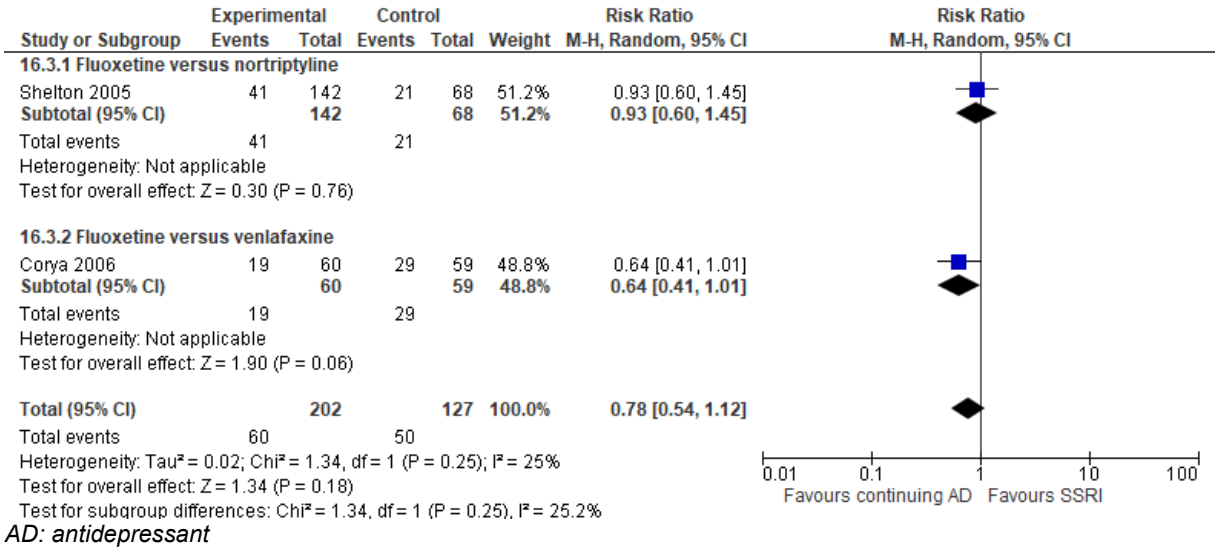
AD: antidepressant

Figure 121: Remission (ITT)



AD: antidepressant

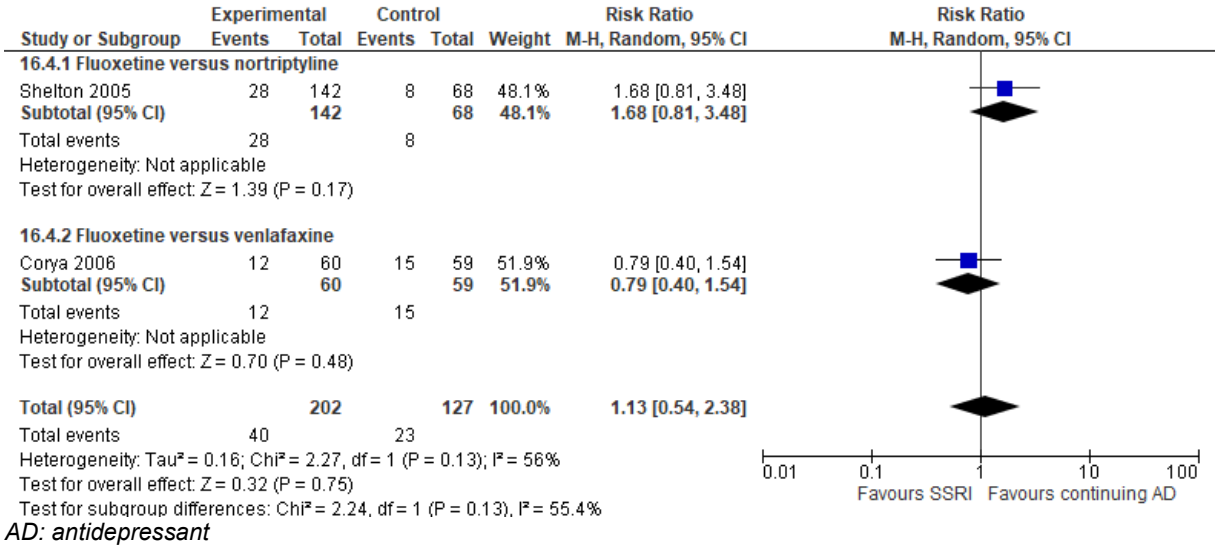
435 **Figure 122: Response (ITT)**



436
437 *AD: antidepressant*

438

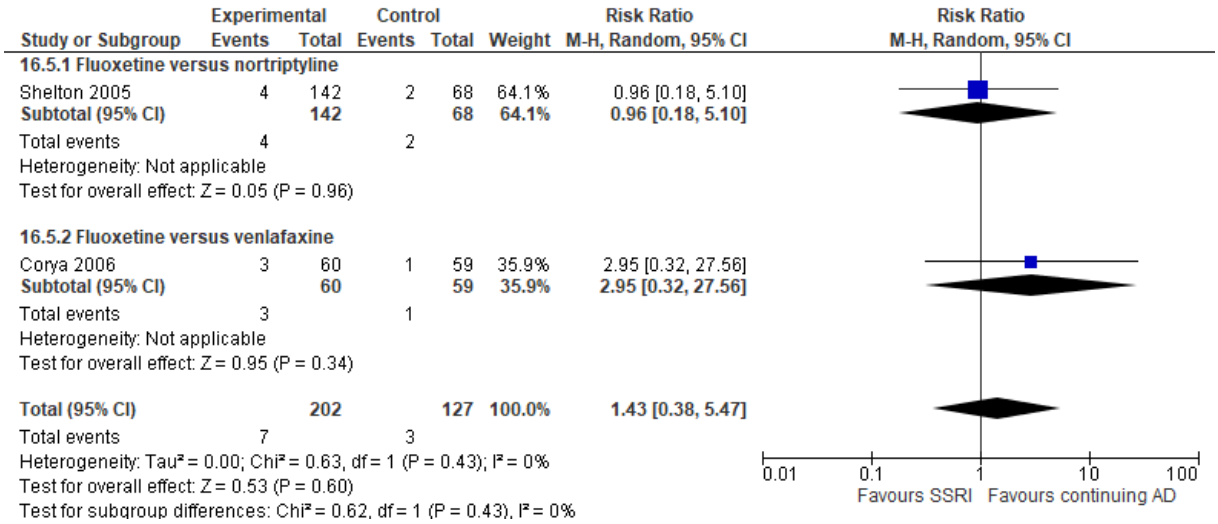
439 **Figure 123: Discontinuation due to any reason**



440
441 *AD: antidepressant*

442

Figure 124: Discontinuation due to side effects



AD: antidepressant

Comparison 17. Switching to a different SSRI versus continuing same SSRI

Figure 125: Remission (ITT)

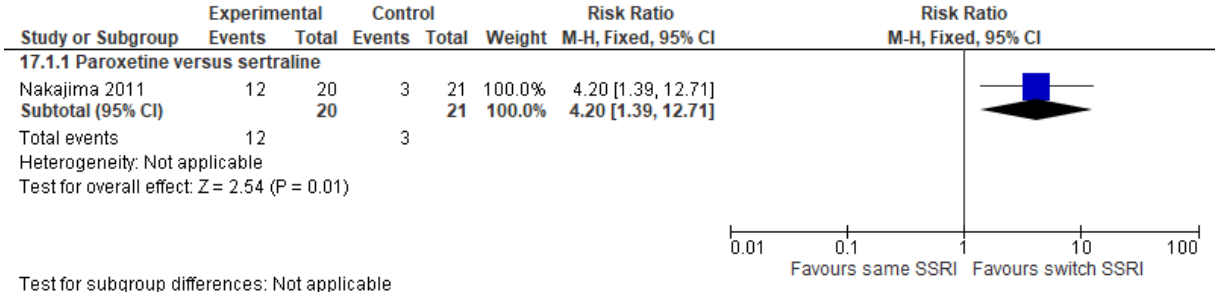


Figure 126: Response (ITT)

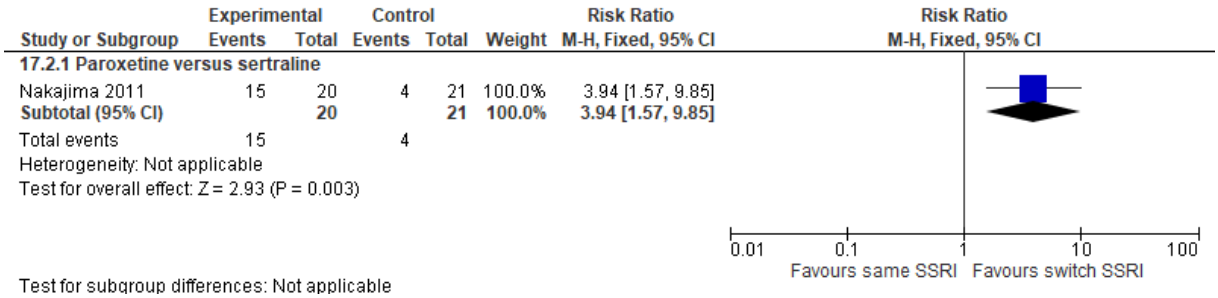


Figure 127: Discontinuation due to any reason

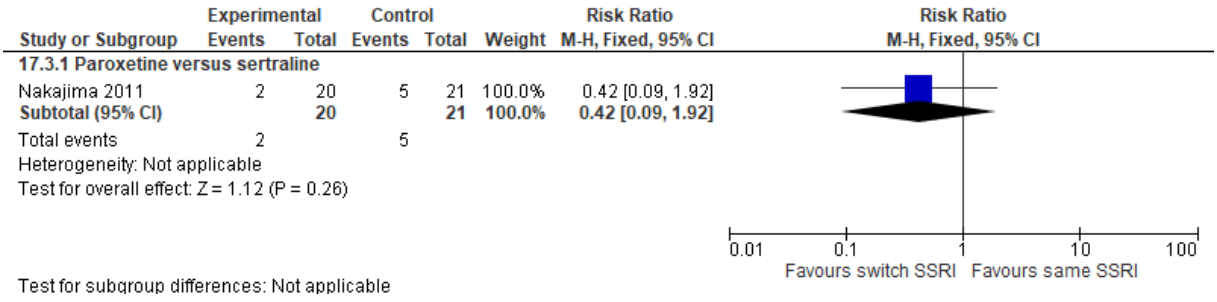
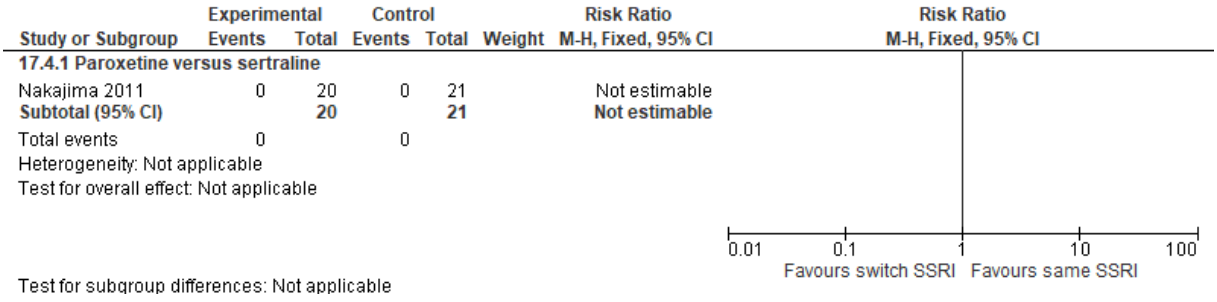


Figure 128: Discontinuation due to side effects



Comparison 18. Switching to SSRI versus antipsychotic

Figure 129: Depression symptomatology change score

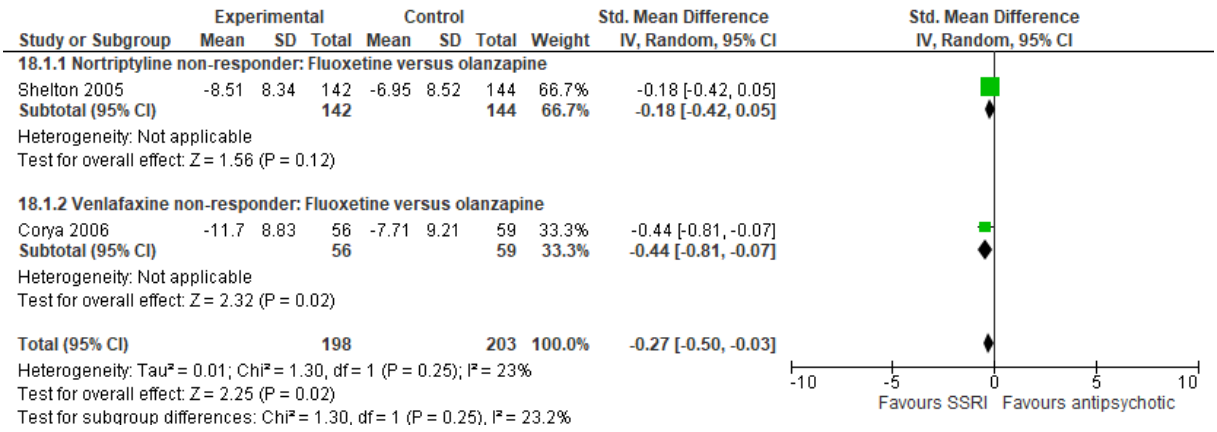


Figure 130: Remission (ITT)

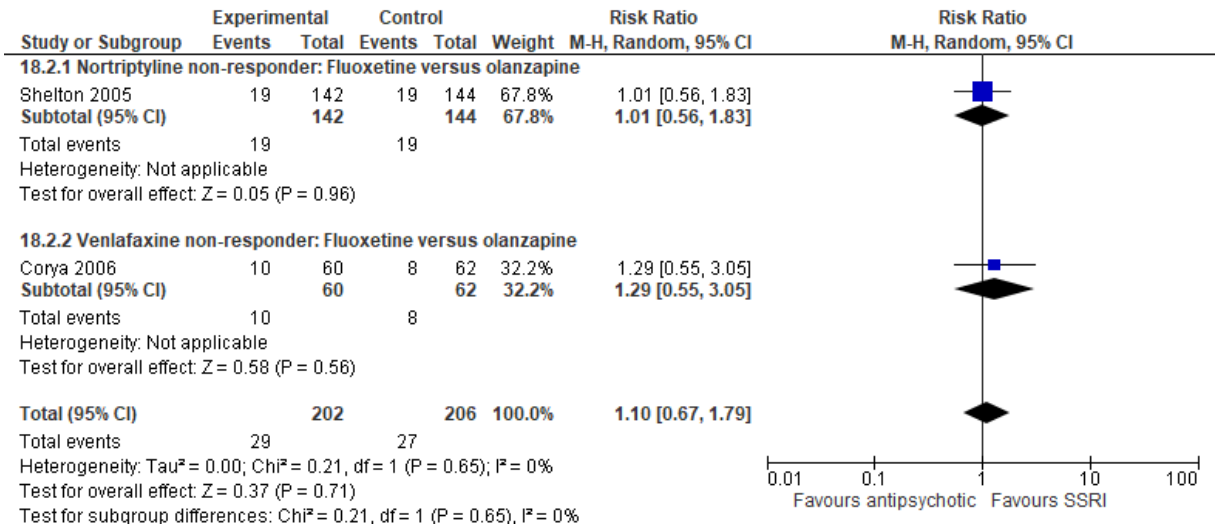


Figure 131: Response (ITT)

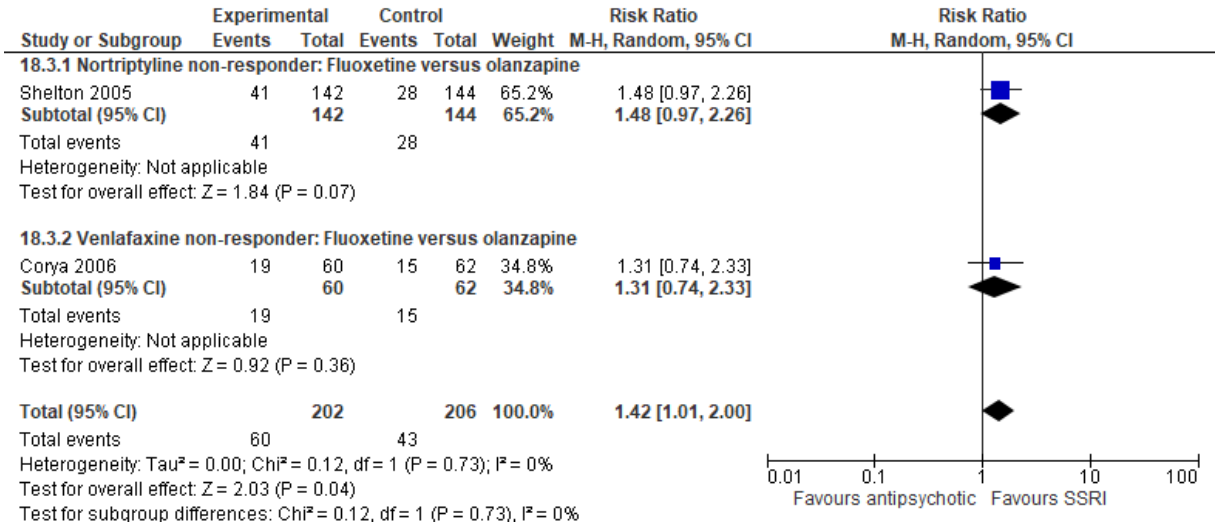


Figure 132: Discontinuation due to any reason

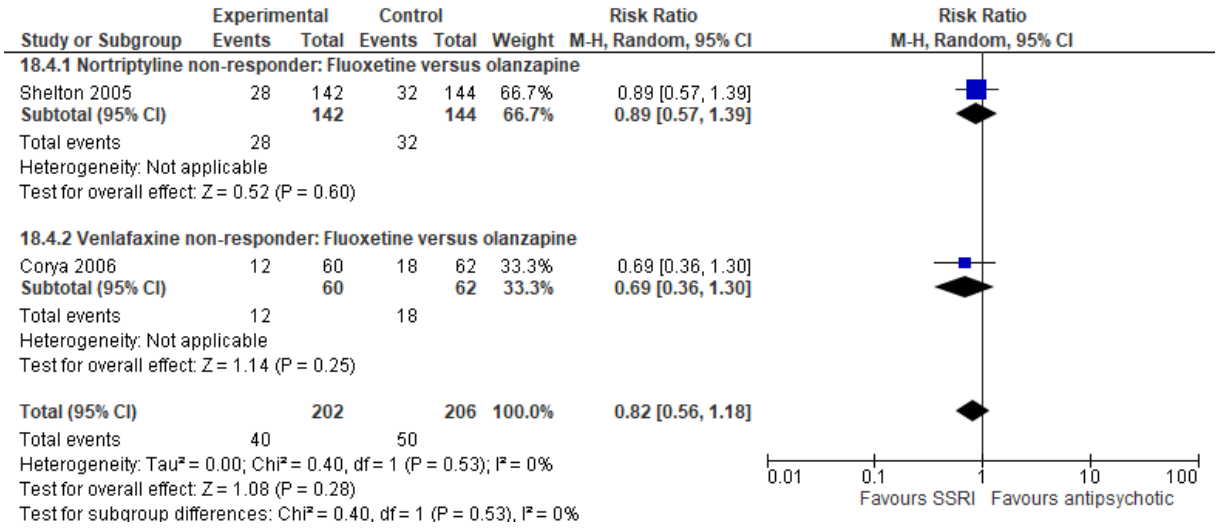
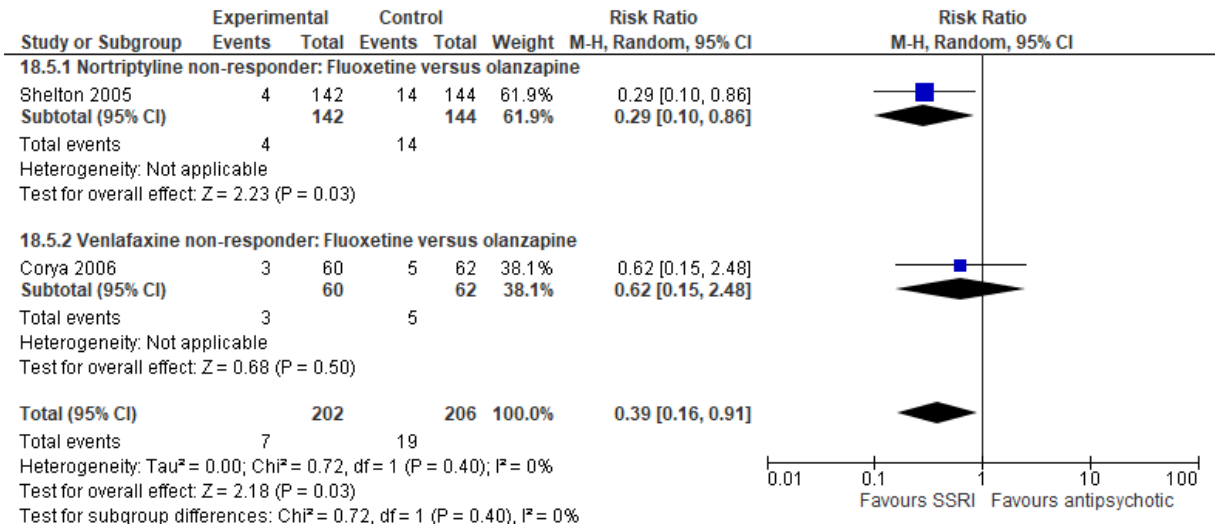
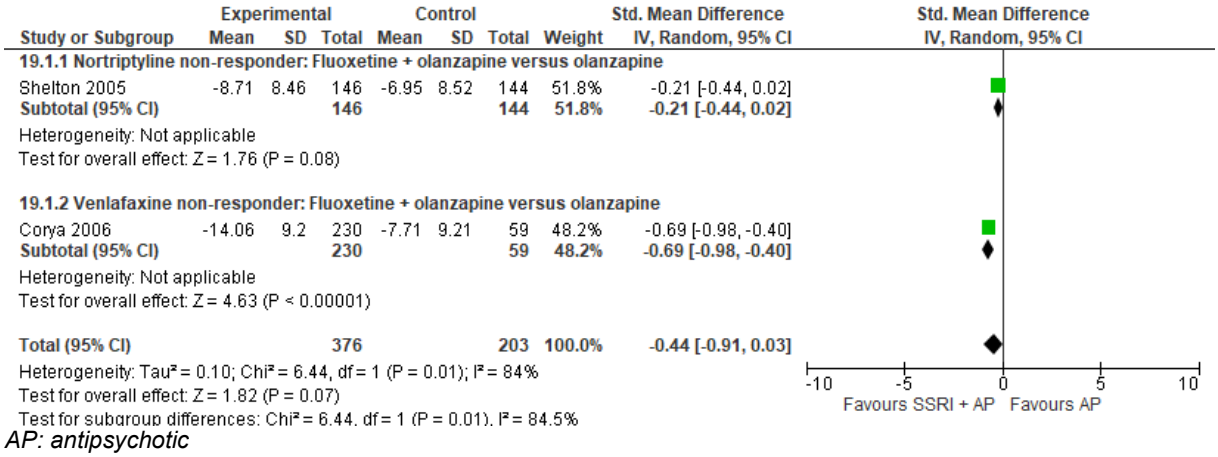


Figure 133: Discontinuation due to side effects



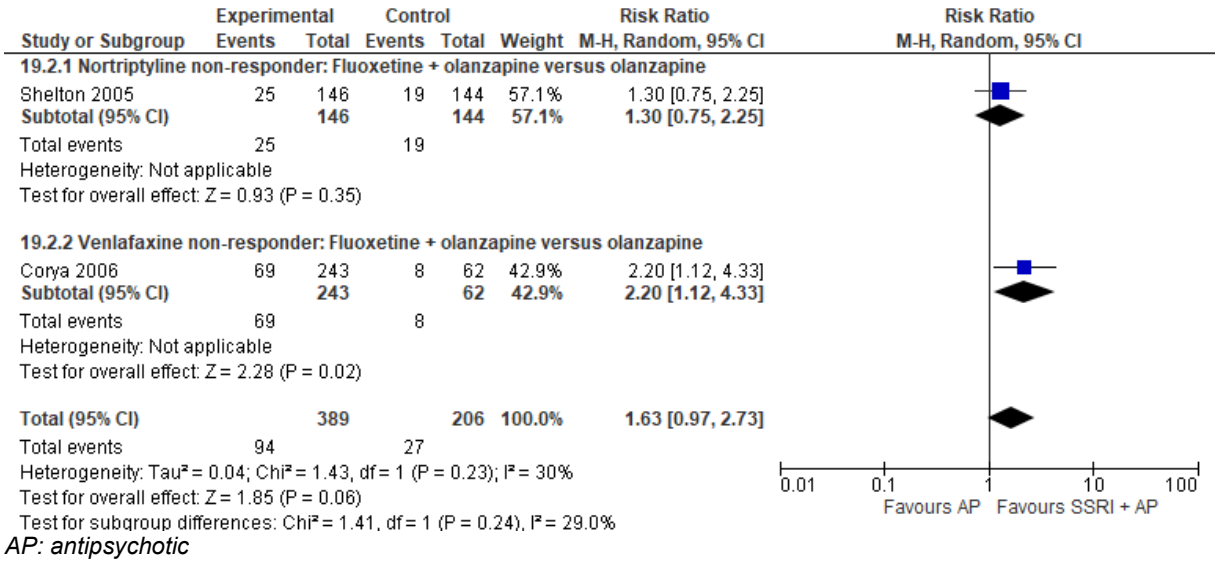
Comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

Figure 134: Depression symptomatology change score



AP: antipsychotic

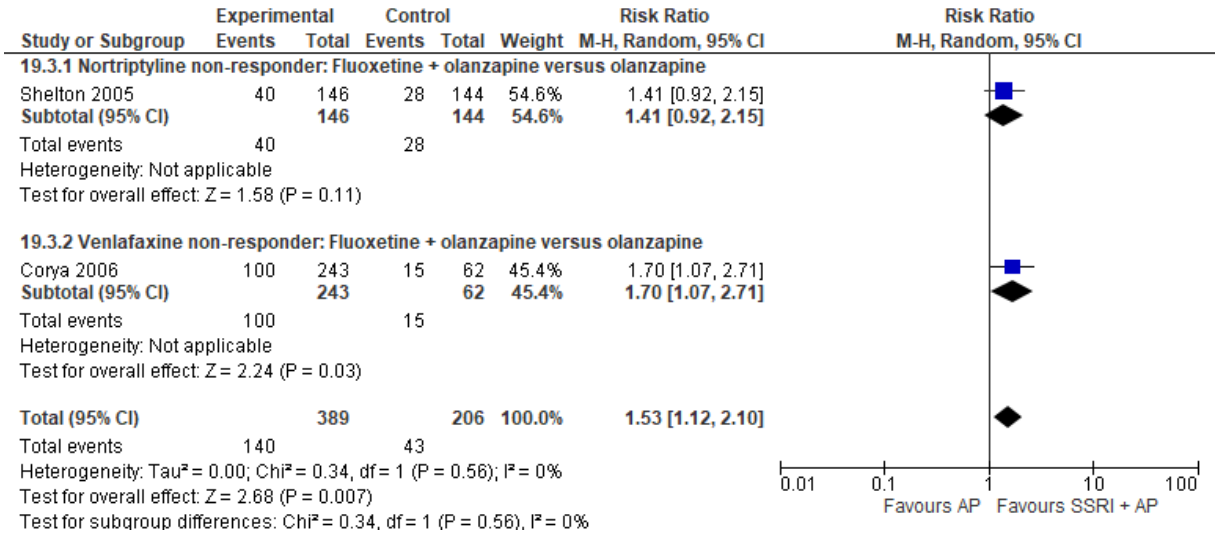
476 **Figure 135: Remission (ITT)**



477
478 *AP: antipsychotic*

479

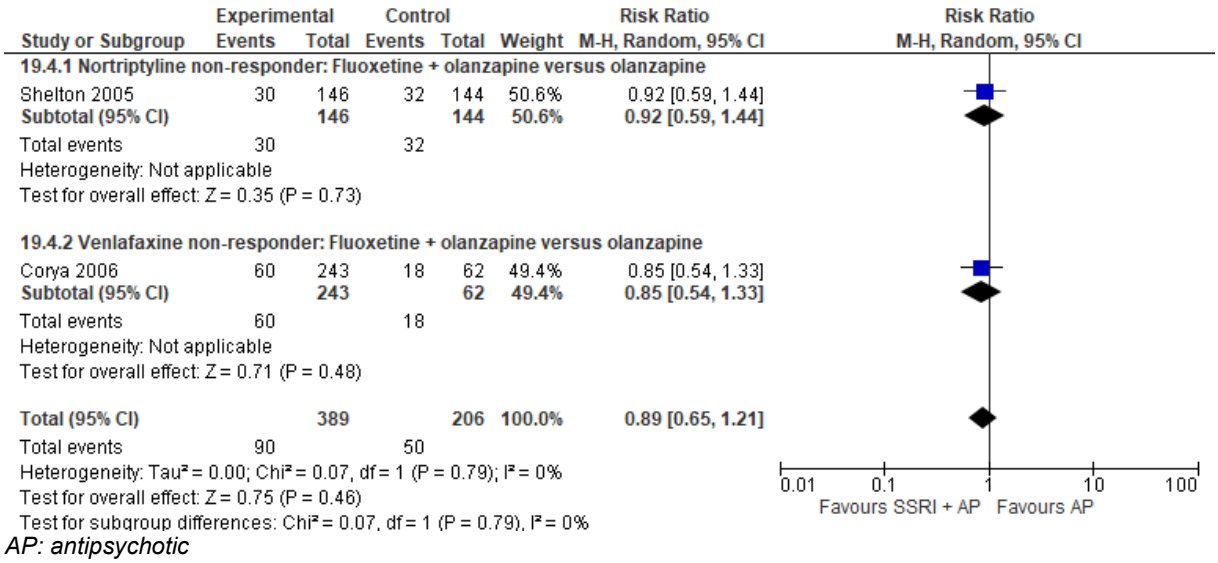
480 **Figure 136: Response (ITT)**



481
482 *AP: antipsychotic*

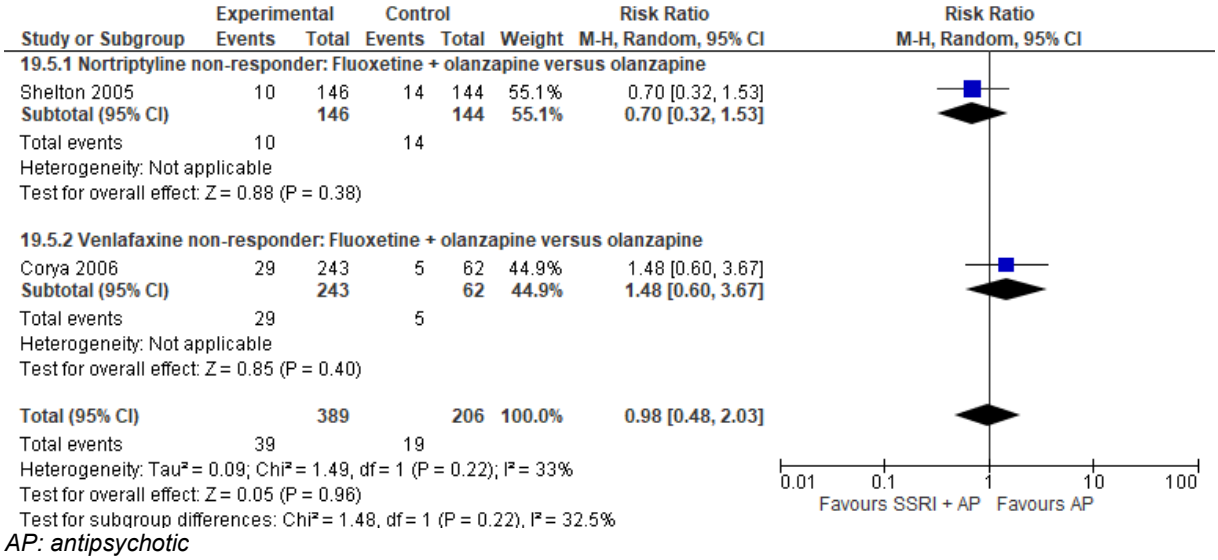
483

Figure 137: Discontinuation due to any reason



AP: antipsychotic

Figure 138: Discontinuation due to side effects



AP: antipsychotic

Comparison 20. Augmenting with SSRI versus augmenting with lithium

Figure 139: Depression symptomatology change score

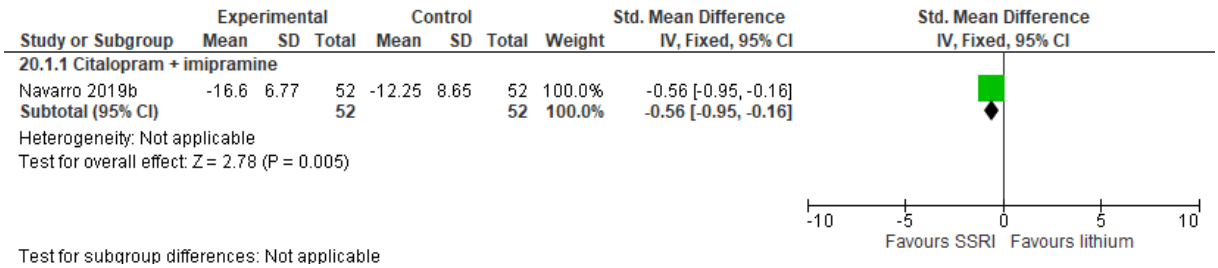
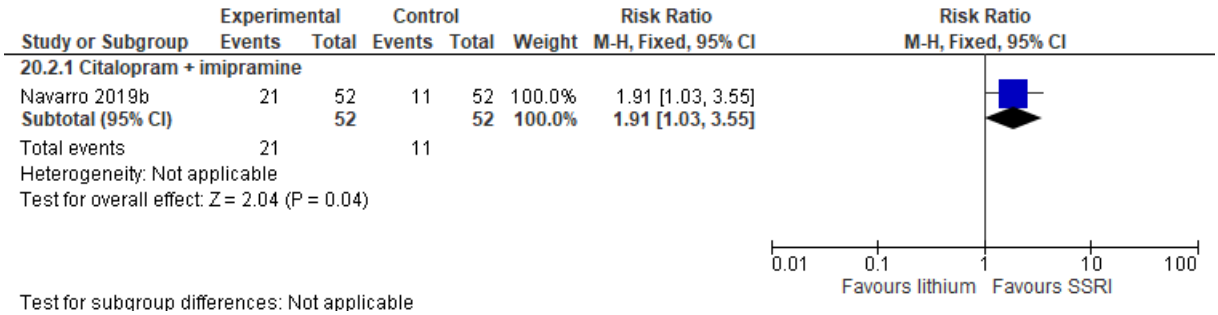


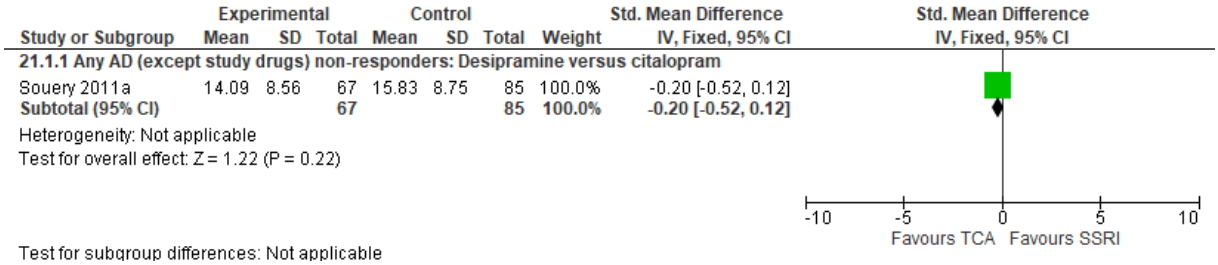
Figure 140: Remission (ITT)



Test for subgroup differences: Not applicable

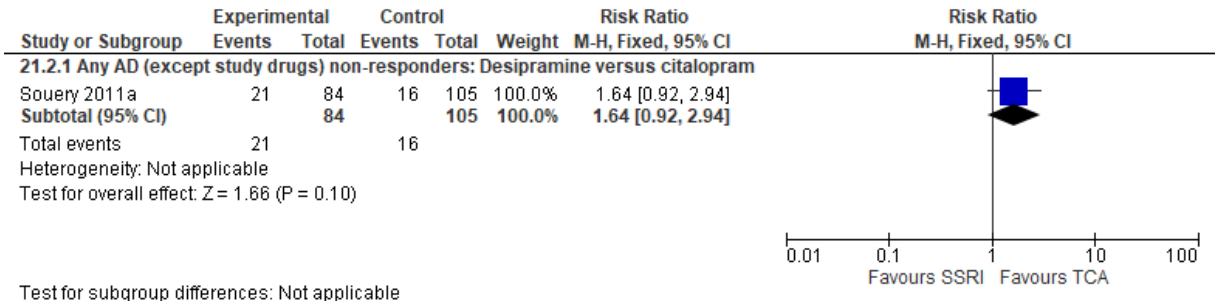
Comparison 21. Switching to TCA versus SSRI

Figure 141: Depression symptomatology endpoint



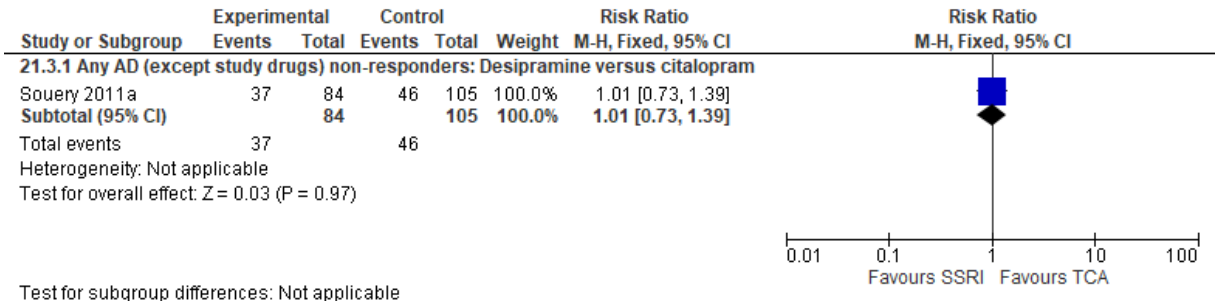
Test for subgroup differences: Not applicable

Figure 142: Remission (ITT)



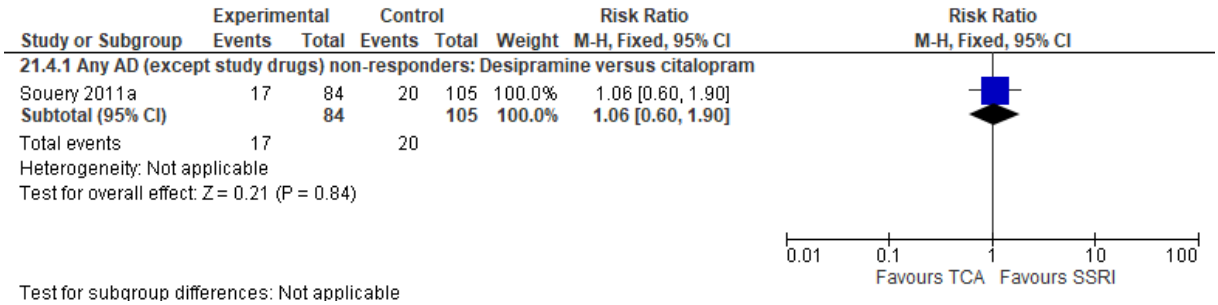
Test for subgroup differences: Not applicable

Figure 143: Response (ITT)



Test for subgroup differences: Not applicable

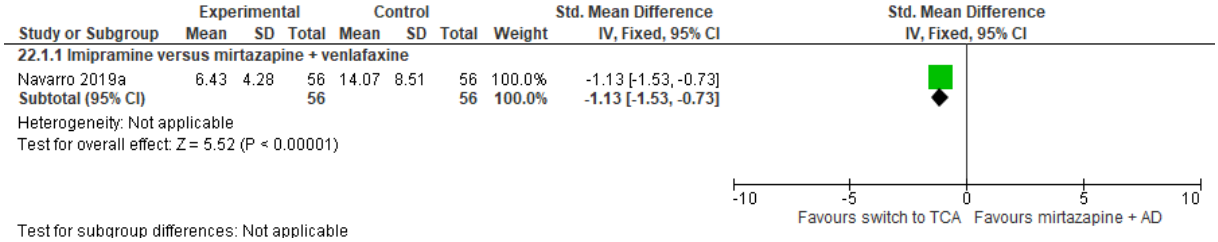
Figure 144: Discontinuation due to any reason



Test for subgroup differences: Not applicable

Comparison 22. Switching to TCA versus augmenting with mirtazapine

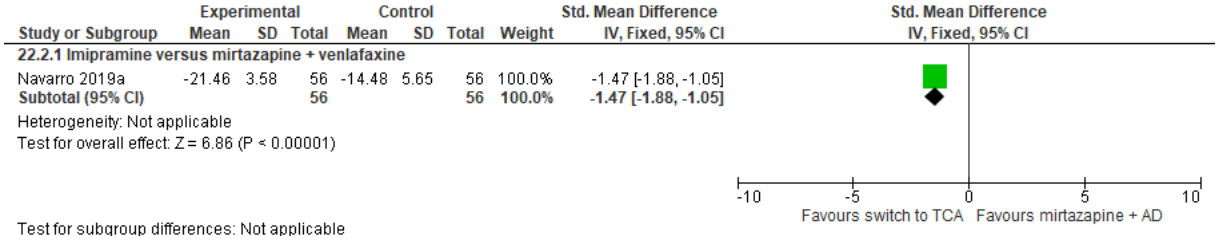
Figure 145: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

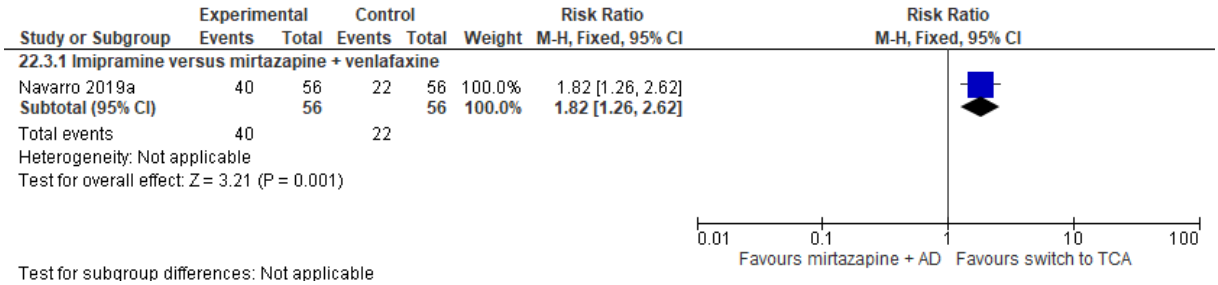
Figure 146: Depression symptomatology change score



Test for subgroup differences: Not applicable

AD: antidepressant

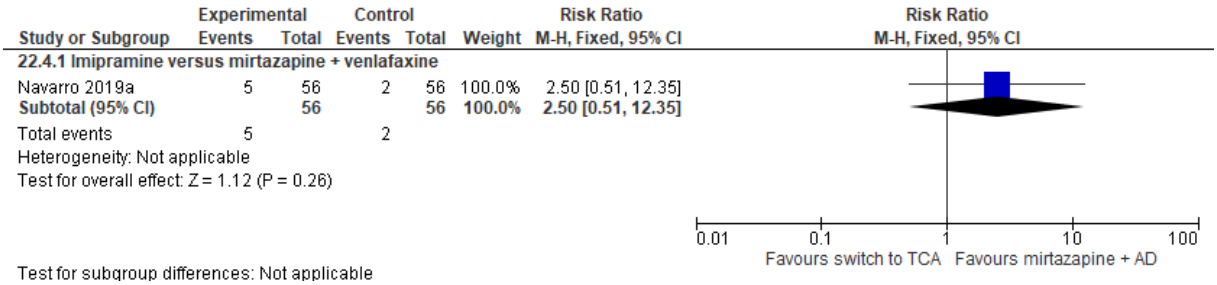
Figure 147: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 148: Discontinuation due to any reason

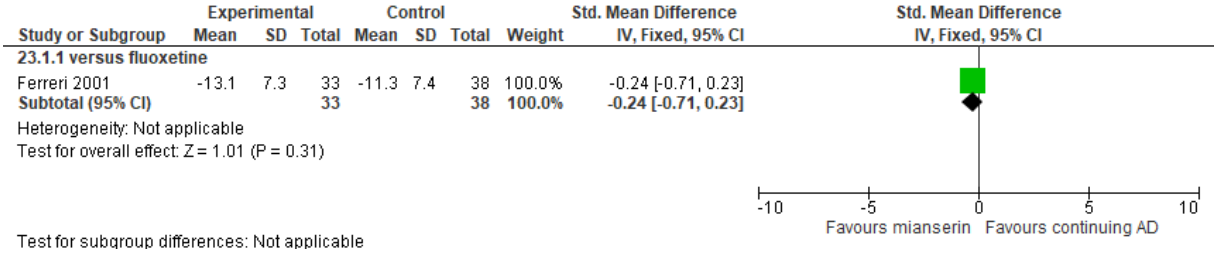


Test for subgroup differences: Not applicable

AD: antidepressant

Comparison 23. Switching to mianserin versus continuing with antidepressant

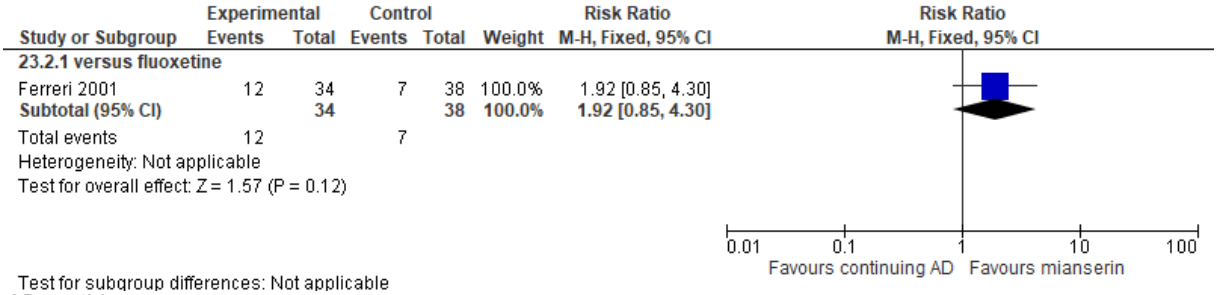
Figure 149: Depression symptomatology change score



Test for subgroup differences: Not applicable

AD: antidepressant

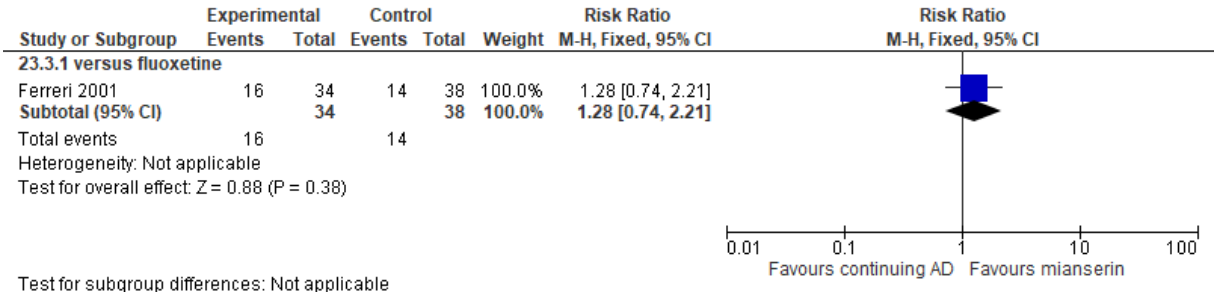
Figure 150: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

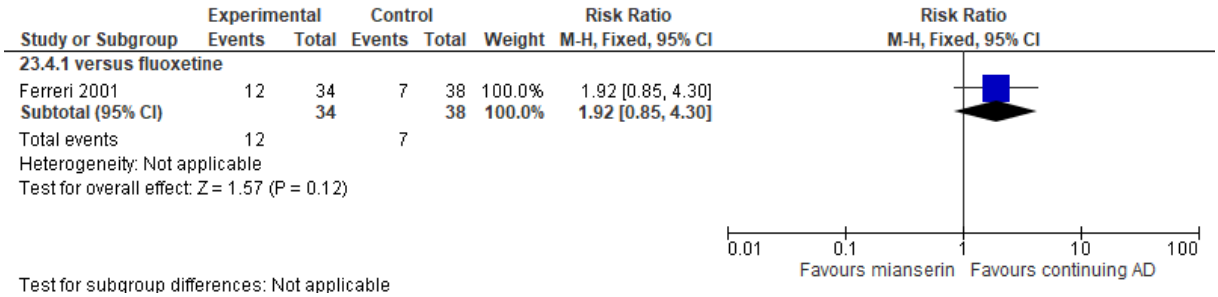
Figure 151: Response (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

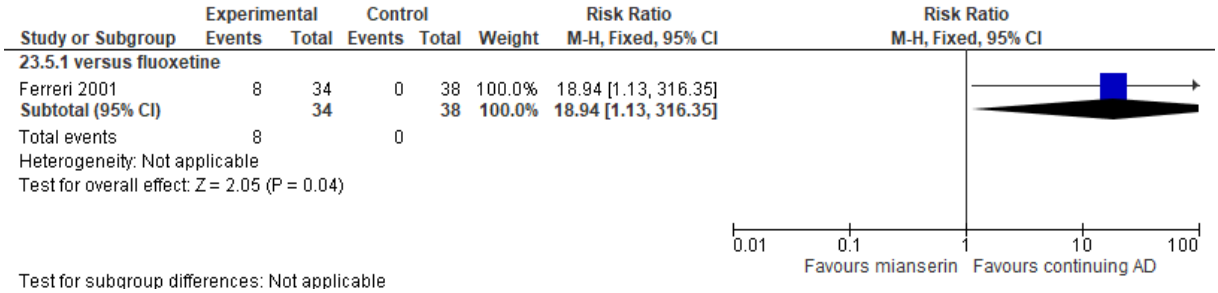
Figure 152: Discontinuation due to any reason



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 153: Discontinuation due to side effects

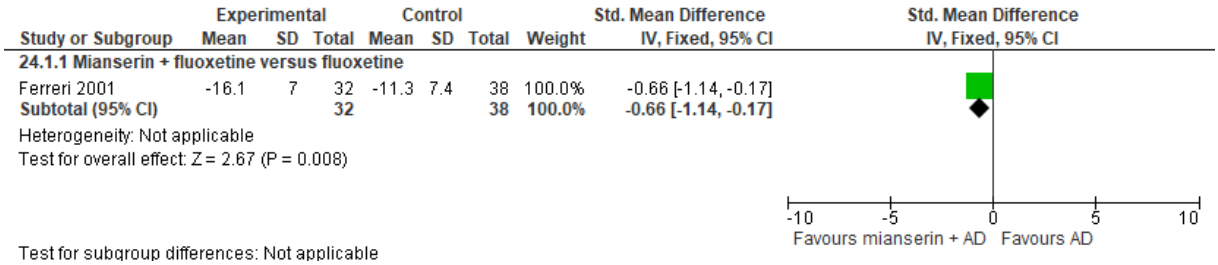


Test for subgroup differences: Not applicable

AD: antidepressant

Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

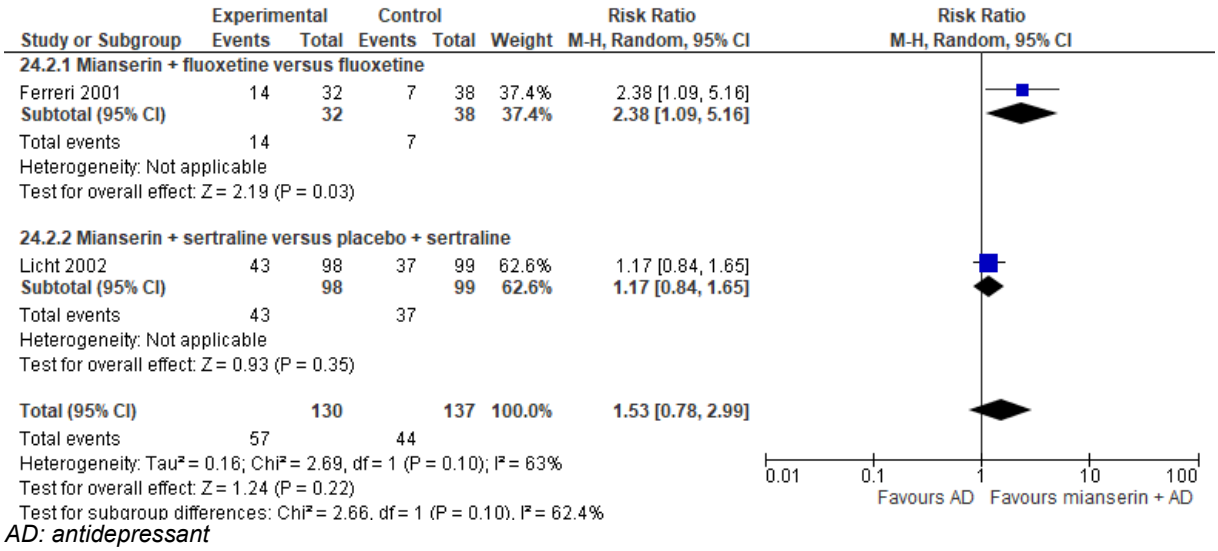
Figure 154: Depression symptomatology change score



Test for subgroup differences: Not applicable

AD: antidepressant

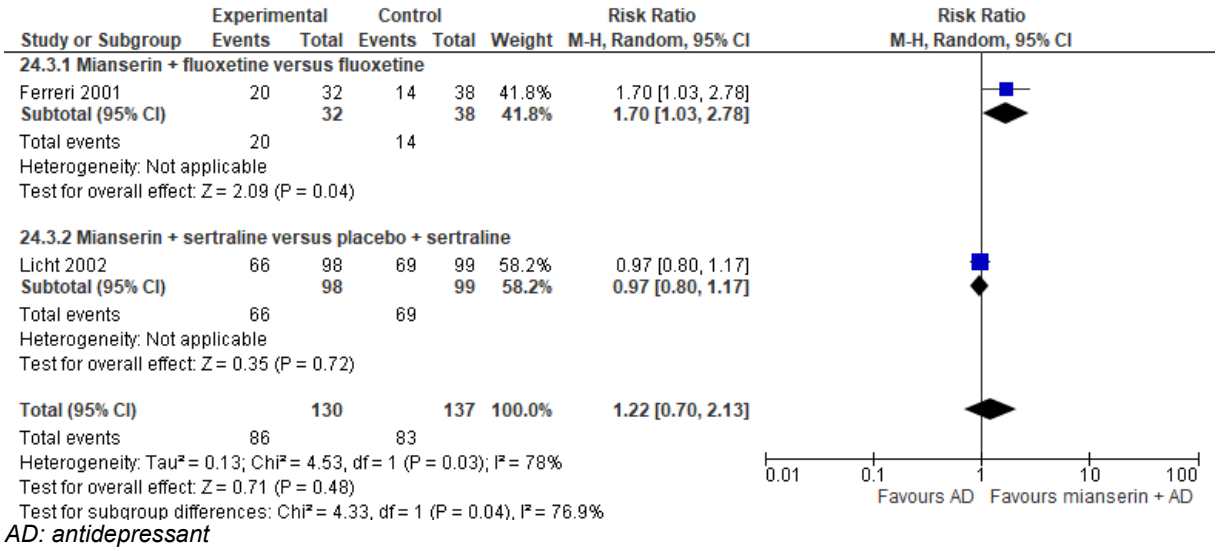
554 **Figure 155: Remission (ITT)**



555
556 *AD: antidepressant*

557

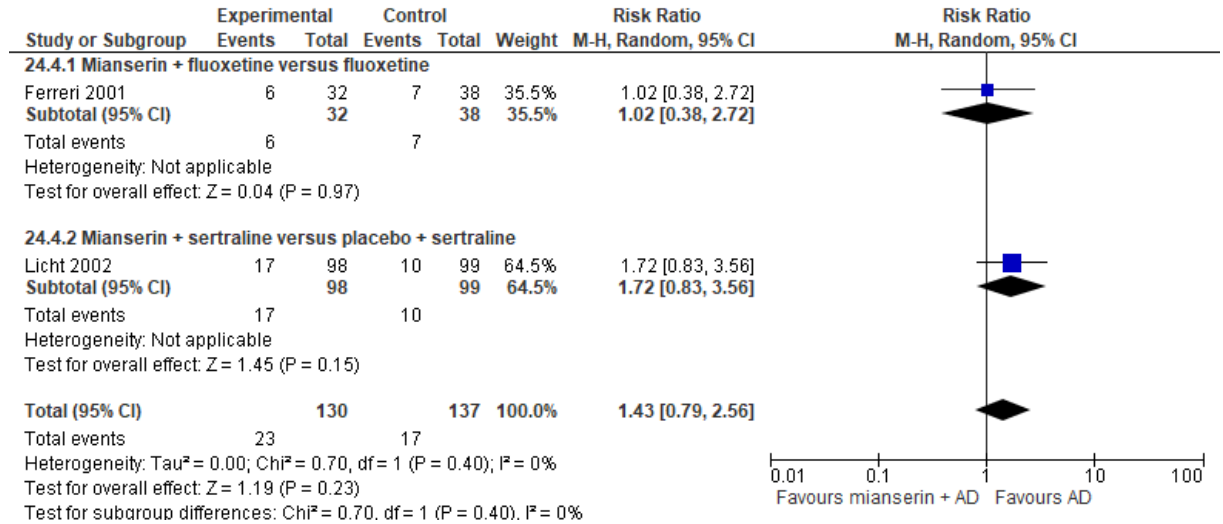
558 **Figure 156: Response (ITT)**



559
560 *AD: antidepressant*

561

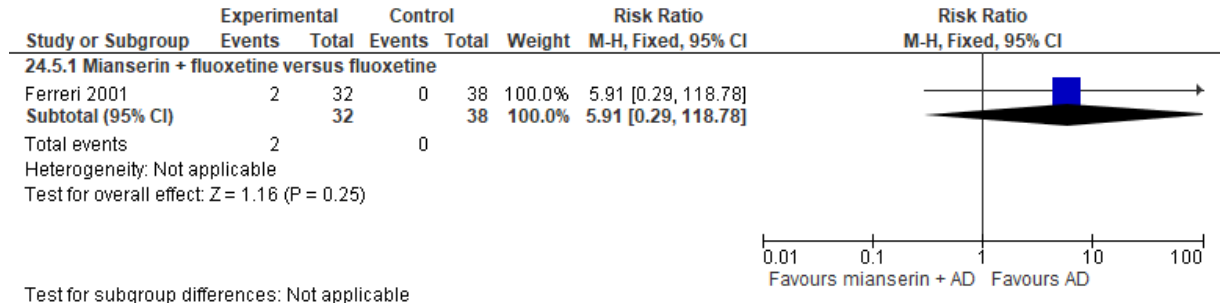
562 **Figure 157: Discontinuation due to any reason**



563
564 *AD: antidepressant*

565

566 **Figure 158: Discontinuation due to side effects**



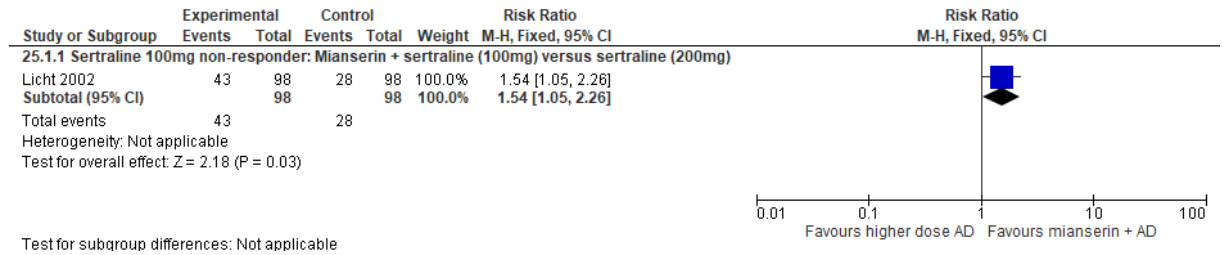
567
568 *AD: antidepressant*

569

570

571 ***Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant***

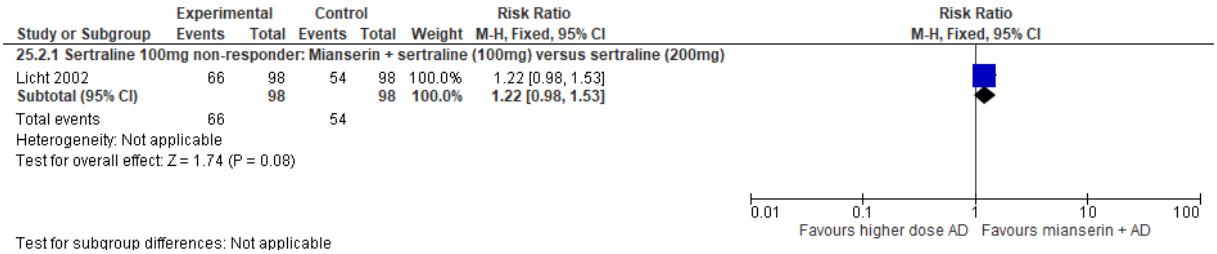
572 **Figure 159: Remission (ITT)**



573
574 *AD: antidepressant*

575

576 **Figure 160: Response (ITT)**

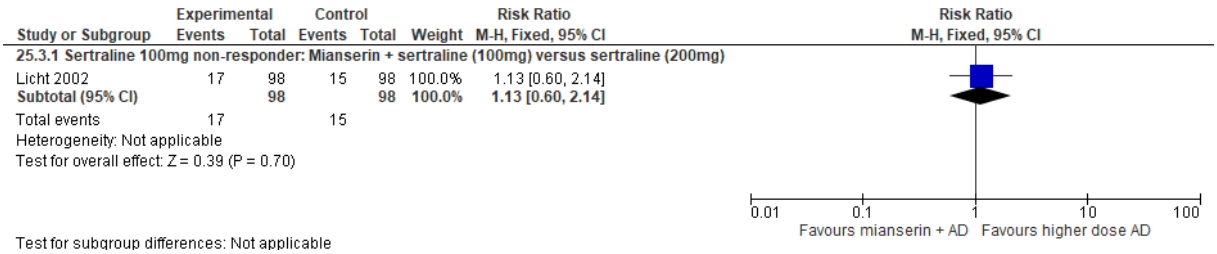


577 Test for subgroup differences: Not applicable

578 *AD: antidepressant*

579

580 **Figure 161: Discontinuation due to any reason**



581 Test for subgroup differences: Not applicable

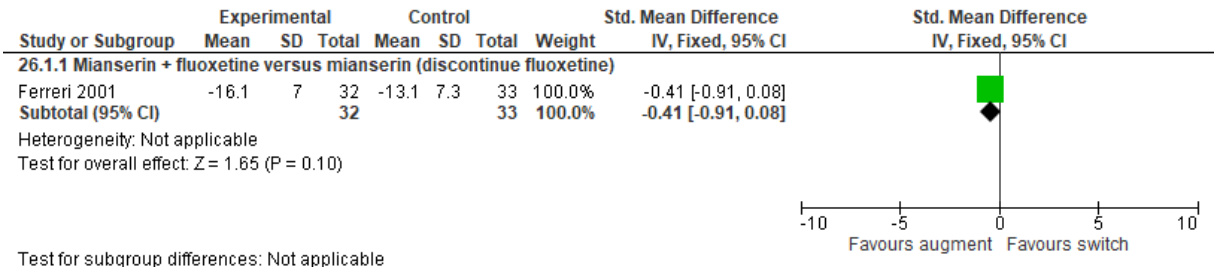
582 *AD: antidepressant*

583

584

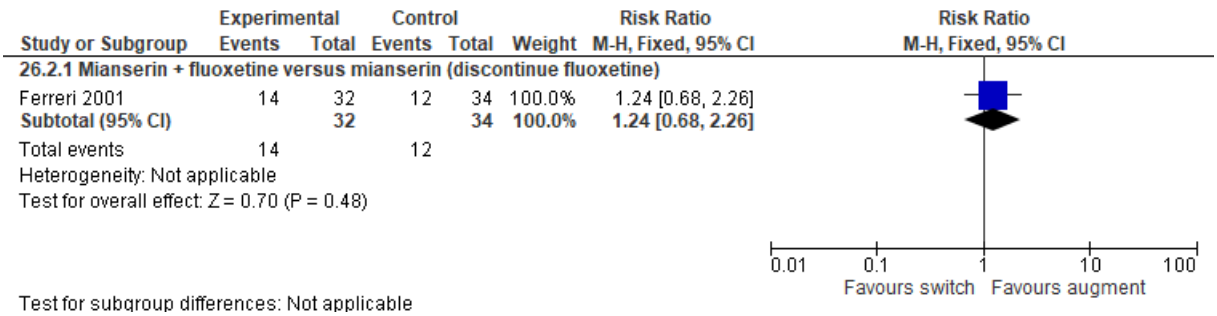
585 ***Comparison 26. Augmenting with mianserin versus switch to mianserin***

586 **Figure 162: Depression symptomatology change score**



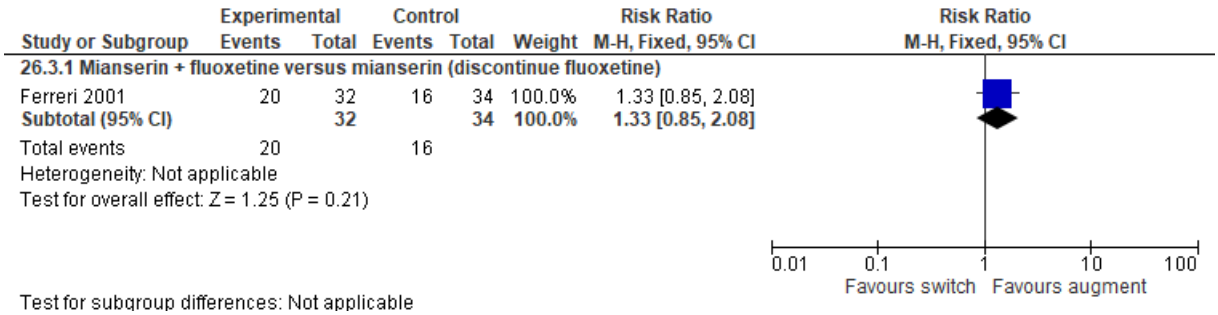
587 Test for subgroup differences: Not applicable

588 **Figure 163: Remission (ITT)**



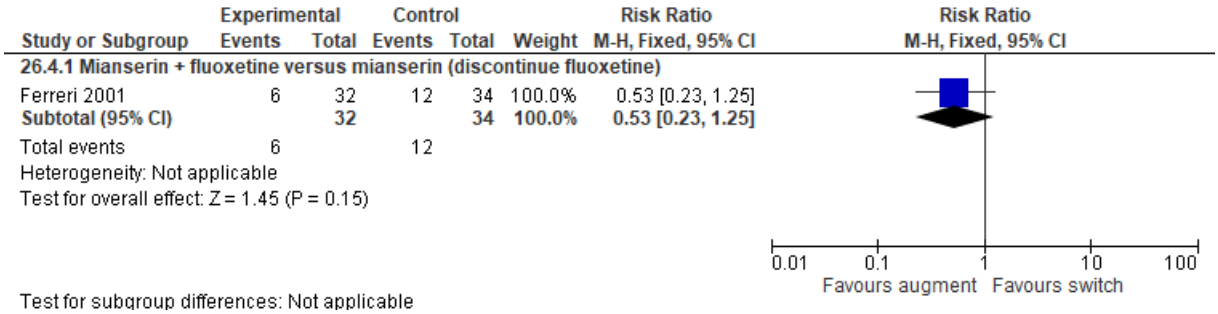
589 Test for subgroup differences: Not applicable

590 **Figure 164: Response (ITT)**



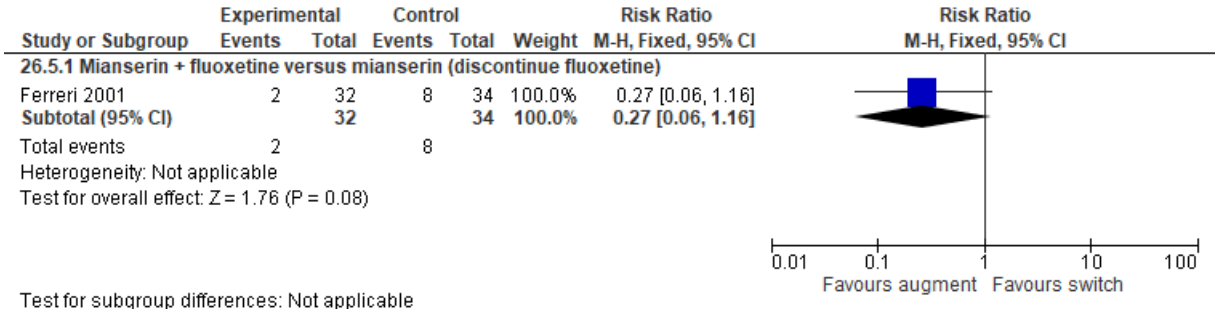
591 Test for subgroup differences: Not applicable

592 **Figure 165: Discontinuation due to any reason**



593 Test for subgroup differences: Not applicable

594 **Figure 166: Discontinuation due to side effects**

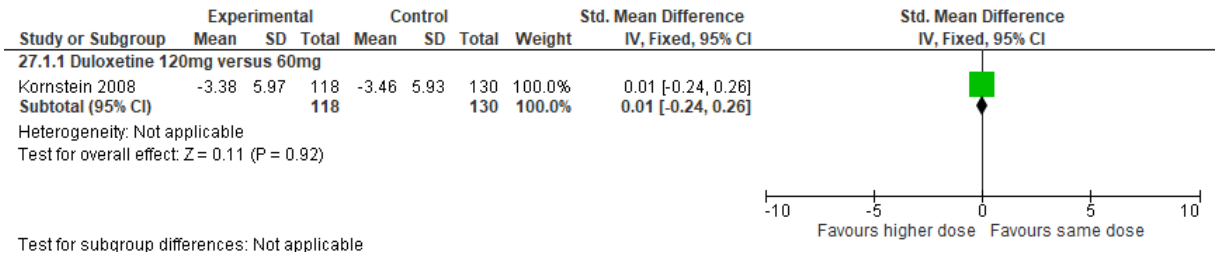


595 Test for subgroup differences: Not applicable

596

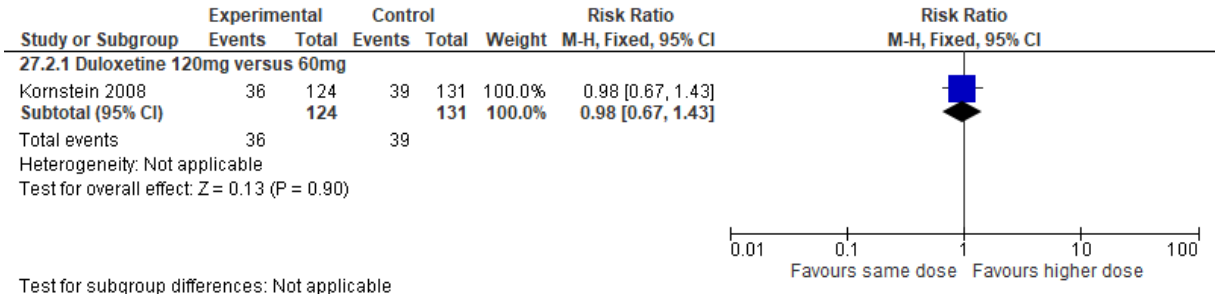
597 ***Comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose***

598 **Figure 167: Depression symptomatology change score**



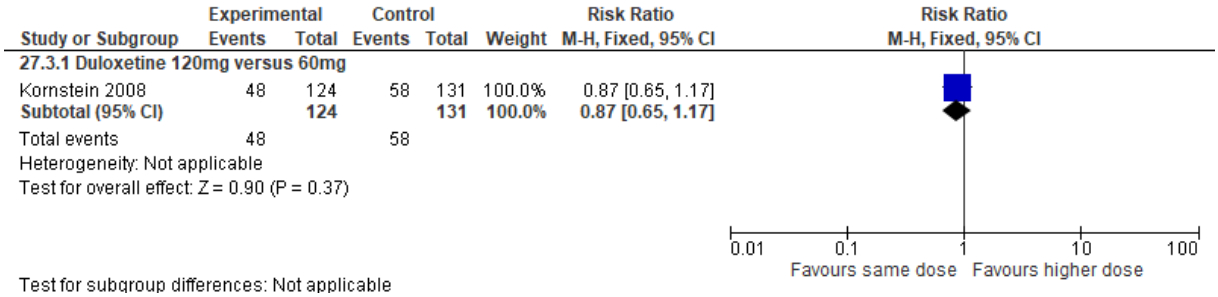
599 Test for subgroup differences: Not applicable

Figure 168: Remission (ITT)



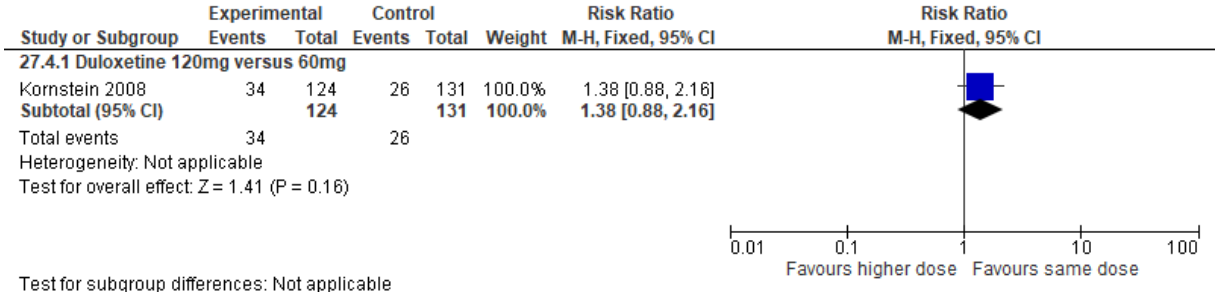
Test for subgroup differences: Not applicable

Figure 169: Response (ITT)



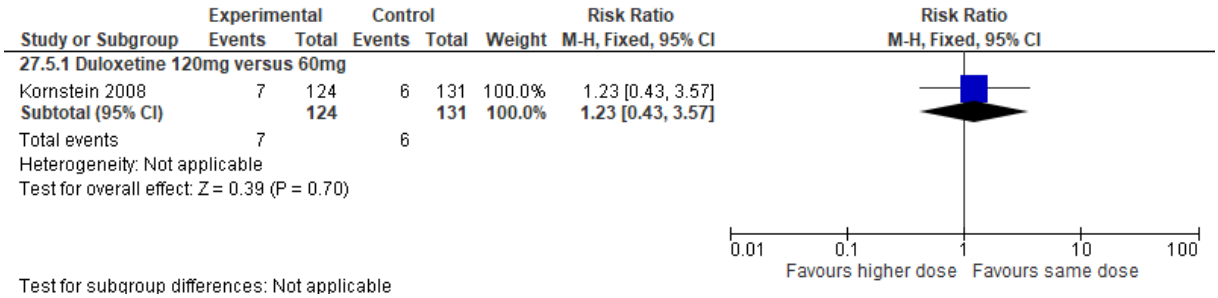
Test for subgroup differences: Not applicable

Figure 170: Discontinuation due to any reason



Test for subgroup differences: Not applicable

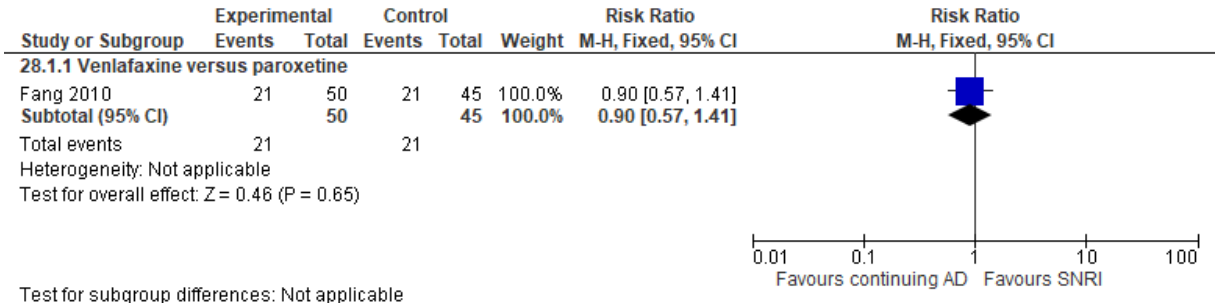
Figure 171: Discontinuation due to side effects



Test for subgroup differences: Not applicable

Comparison 28. Switching to SNRI versus continuing with antidepressant

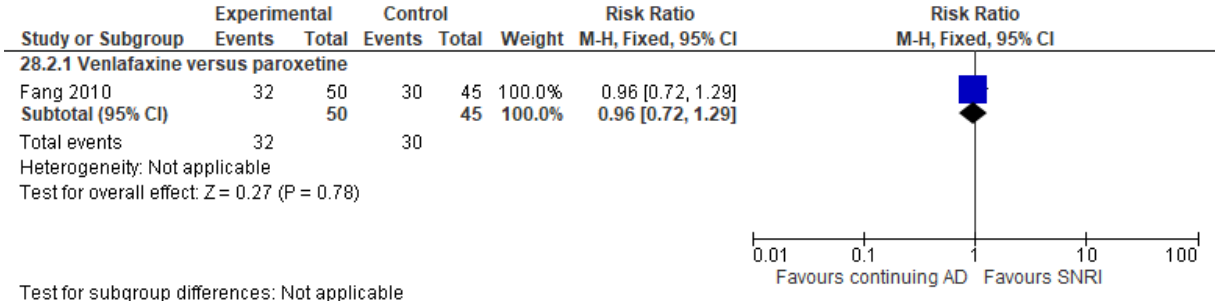
Figure 172: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

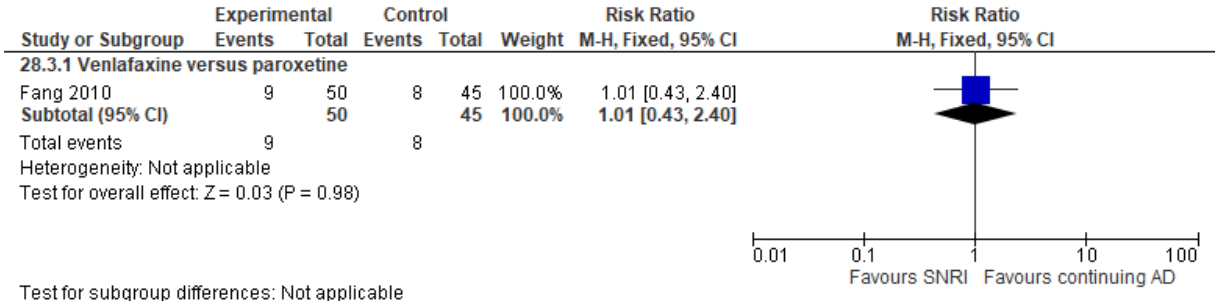
Figure 173: Response (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

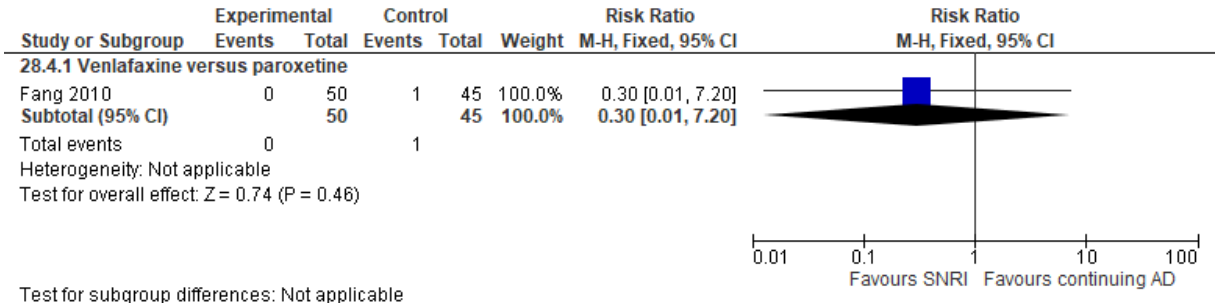
Figure 174: Discontinuation due to any reason



Test for subgroup differences: Not applicable

AD: antidepressant

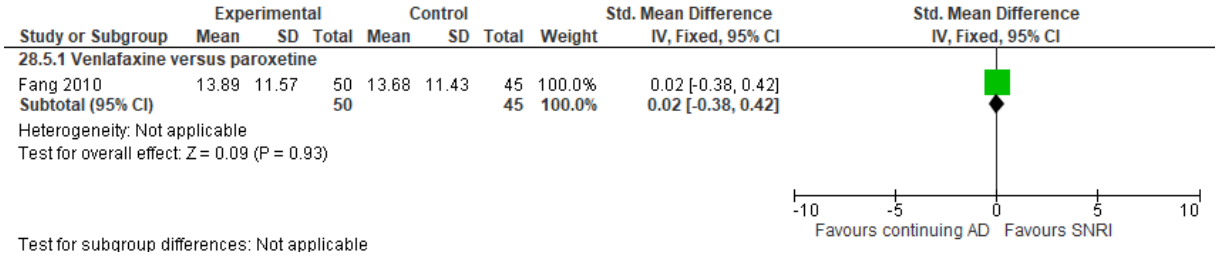
622 **Figure 175: Discontinuation due to side effects**



623 Test for subgroup differences: Not applicable
624 *AD: antidepressant*

625

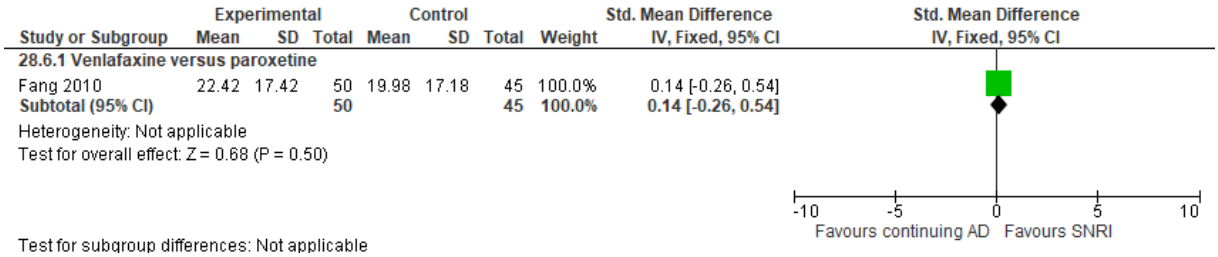
626 **Figure 176: Quality of life physical component score (PCS) change score**



627 Test for subgroup differences: Not applicable
628 *AD: antidepressant*

629

630 **Figure 177: Quality of life mental component score (MCS) change score**



631 Test for subgroup differences: Not applicable
632 *AD: antidepressant*

633

634

Comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Figure 178: Depression symptomatology change score

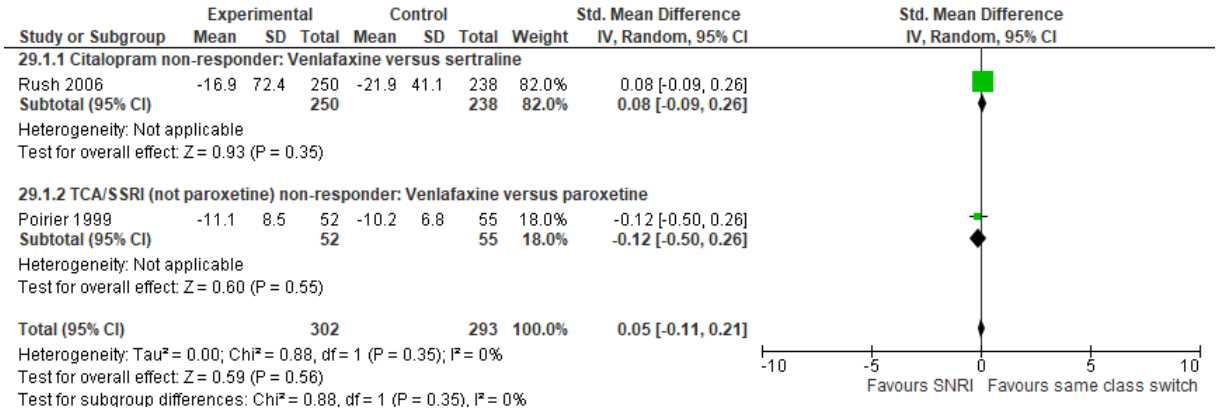
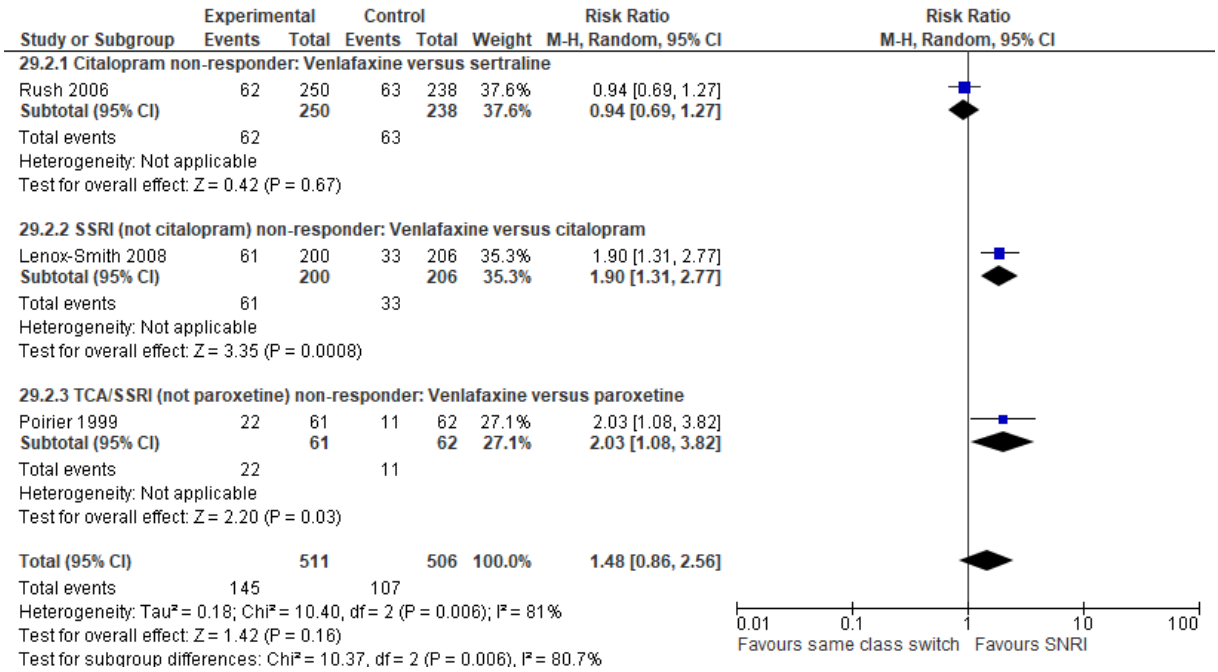
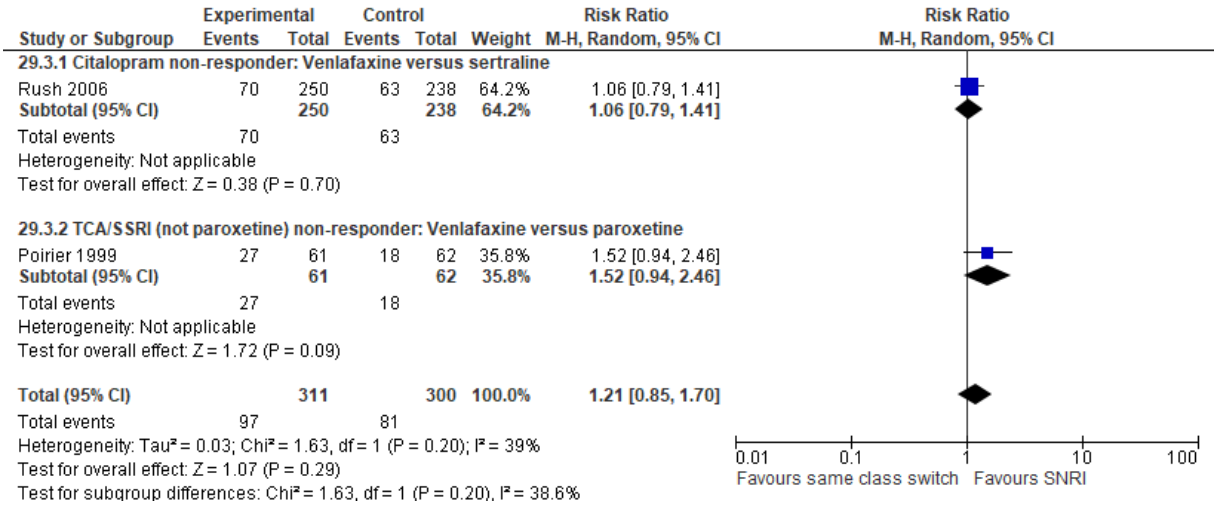


Figure 179: Remission (ITT)

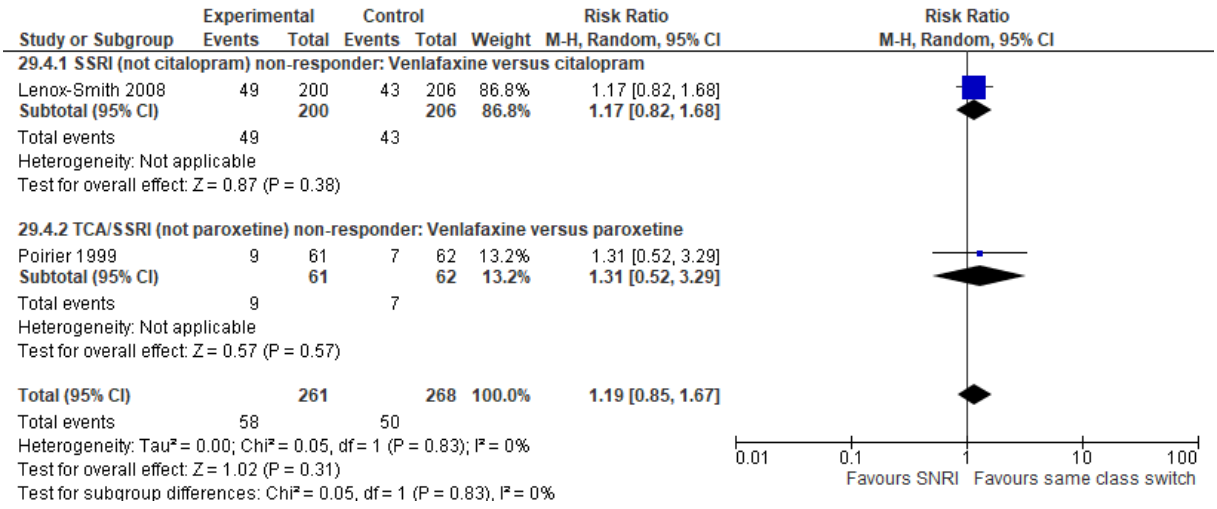


641 **Figure 180: Response (ITT)**



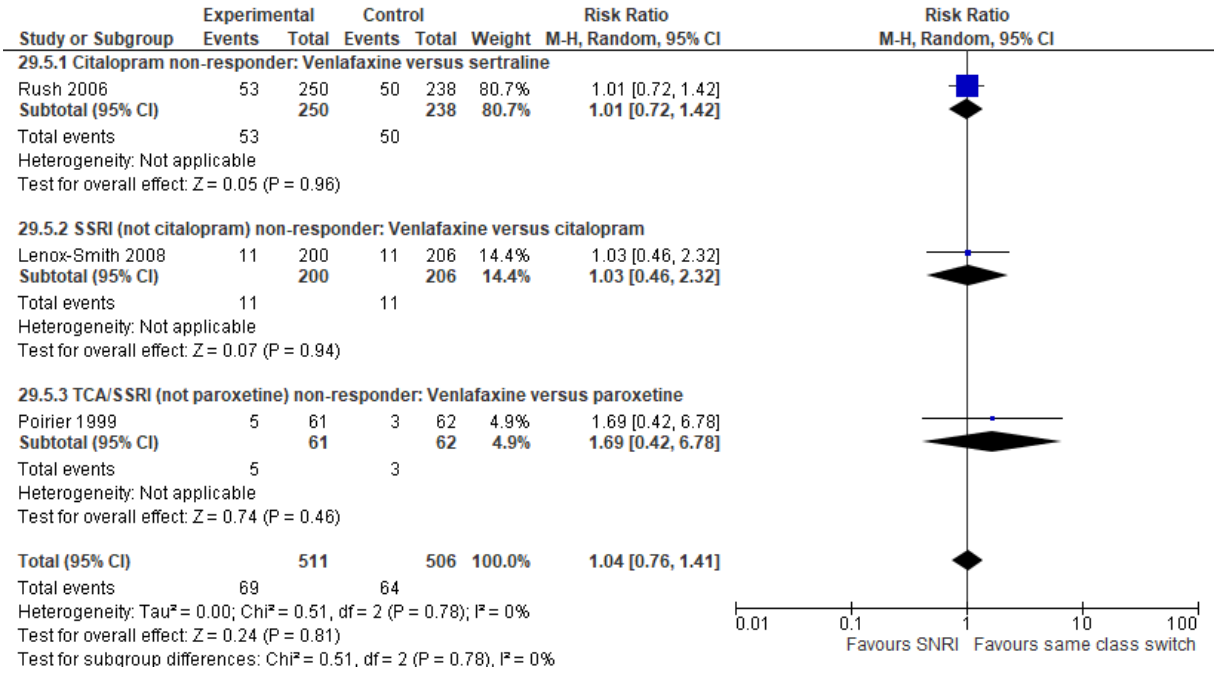
642

643 **Figure 181: Discontinuation due to any reason**



644

Figure 182: Discontinuation due to side effects



Comparison 30. Switching to SNRI versus switching to bupropion

Figure 183: Depression symptomatology change score

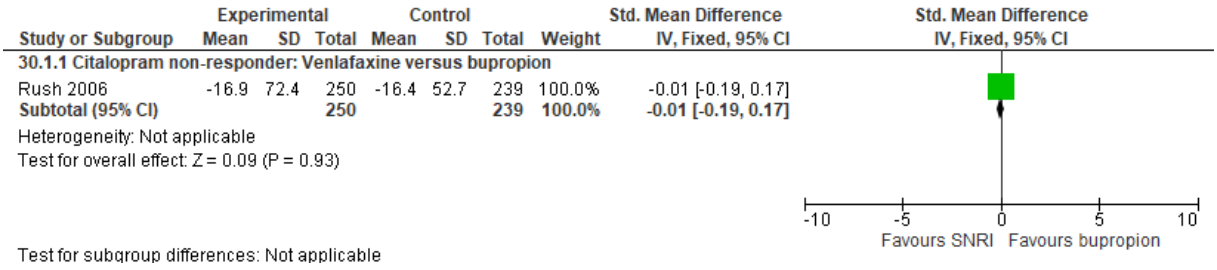
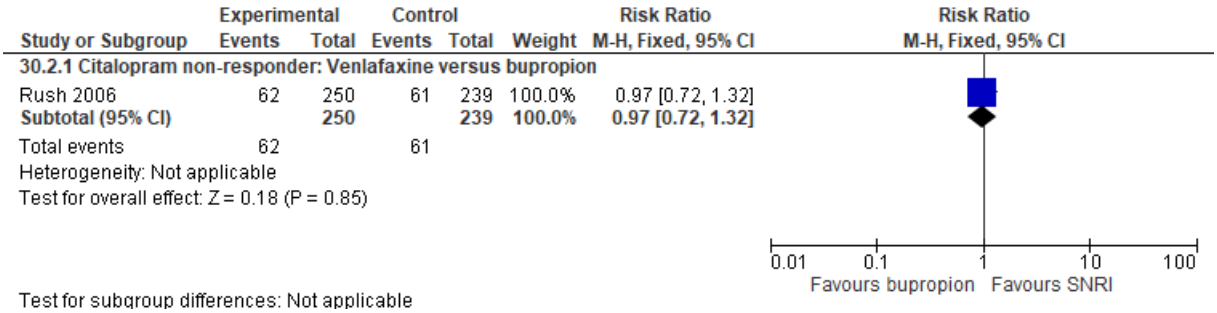
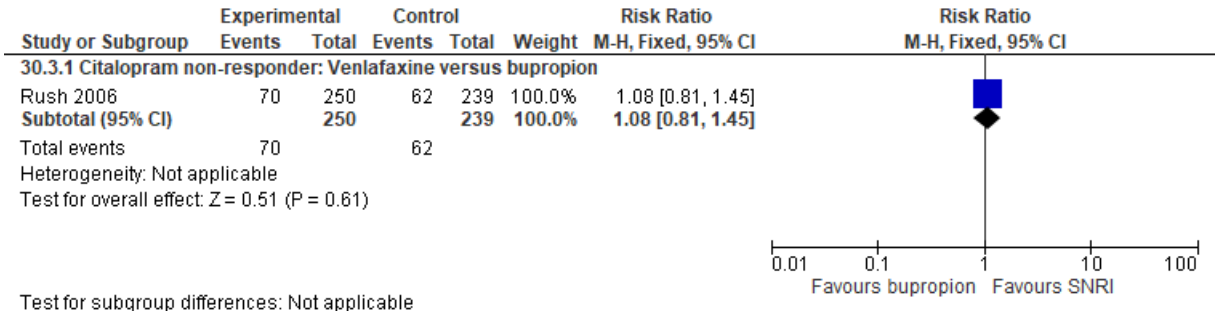


Figure 184: Remission (ITT)

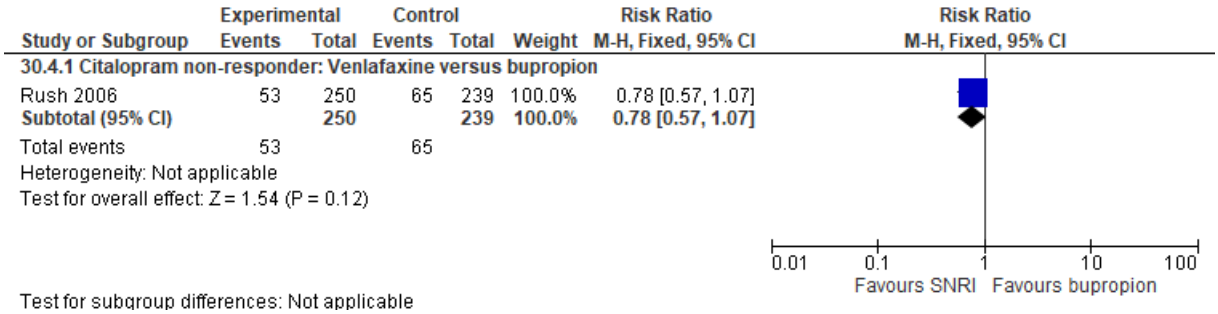


653 **Figure 185: Response (ITT)**



654 Test for subgroup differences: Not applicable

655 **Figure 186: Discontinuation due to side effects**

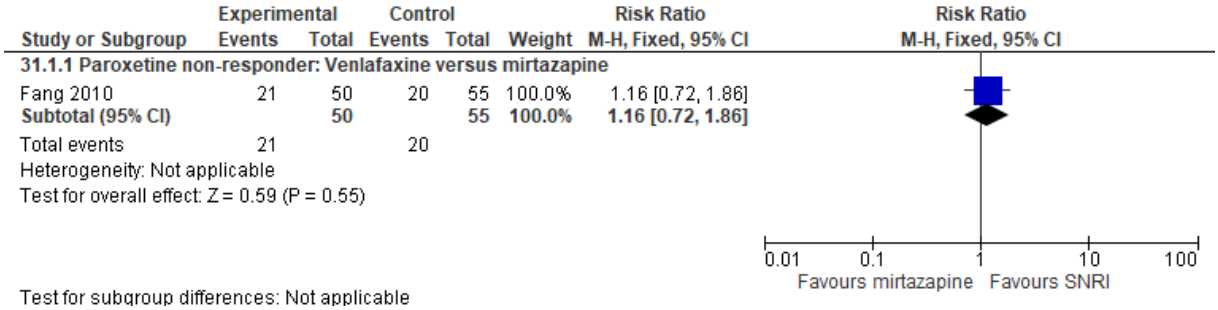


656 Test for subgroup differences: Not applicable

657

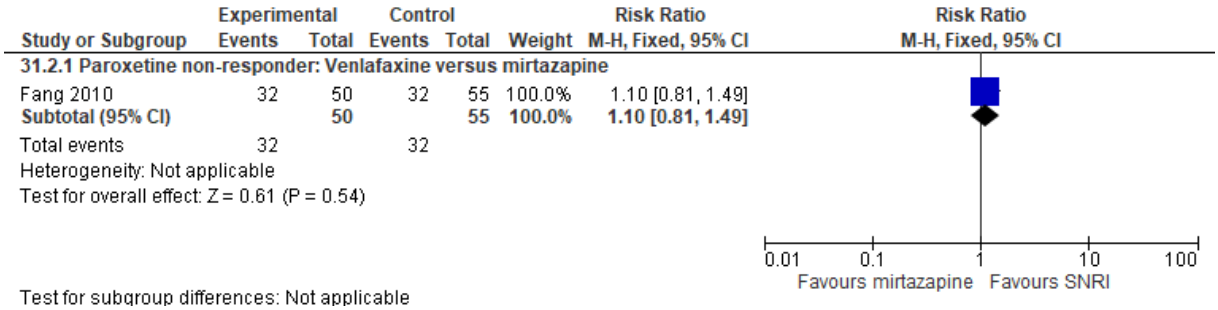
658 ***Comparison 31. Switching to SNRI versus switching to mirtazapine***

659 **Figure 187: Remission (ITT)**



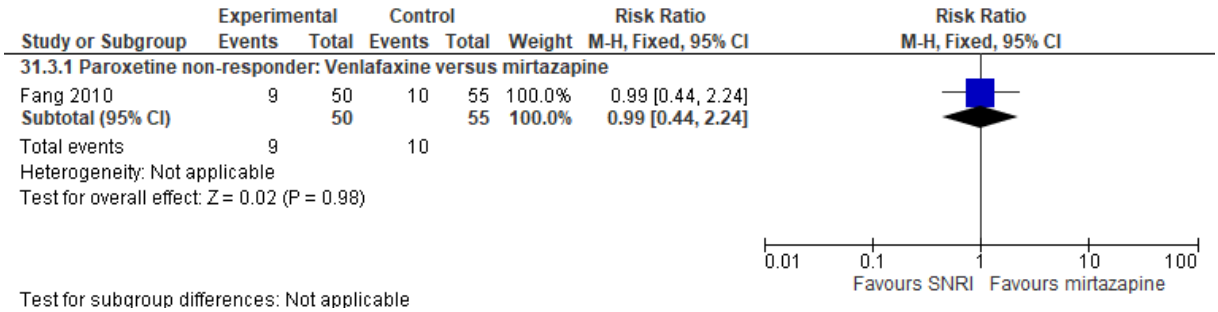
660 Test for subgroup differences: Not applicable

661 **Figure 188: Response (ITT)**



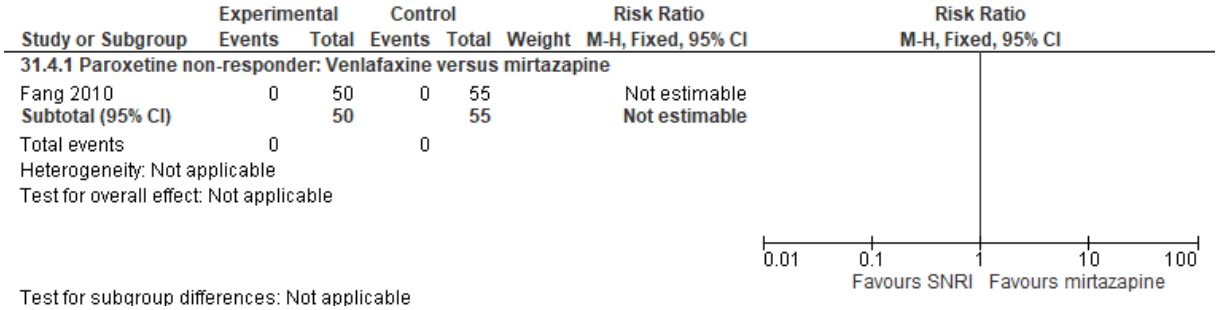
662 Test for subgroup differences: Not applicable

663 **Figure 189: Discontinuation due to any reason**



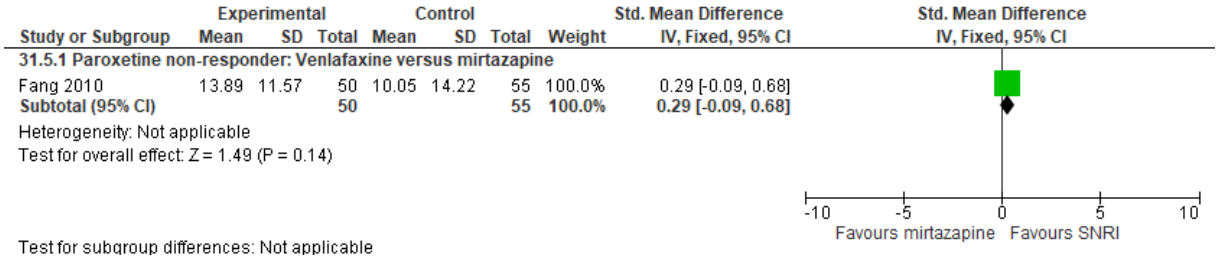
664 Test for subgroup differences: Not applicable

665 **Figure 190: Discontinuation due to side effects**



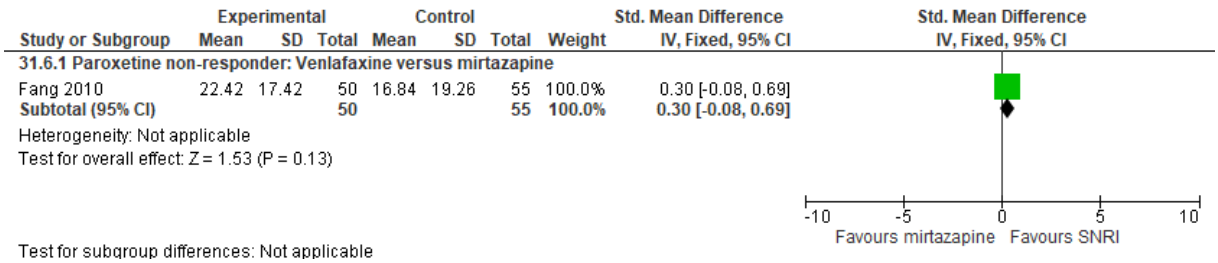
666 Test for subgroup differences: Not applicable

667 **Figure 191: Quality of life physical component score (PCS) change score**



668 Test for subgroup differences: Not applicable

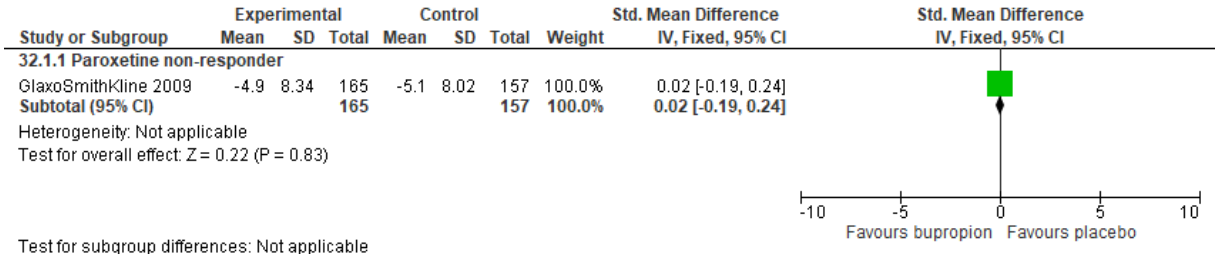
669 **Figure 192: Quality of life mental component score (MCS) change score**



670 Test for subgroup differences: Not applicable

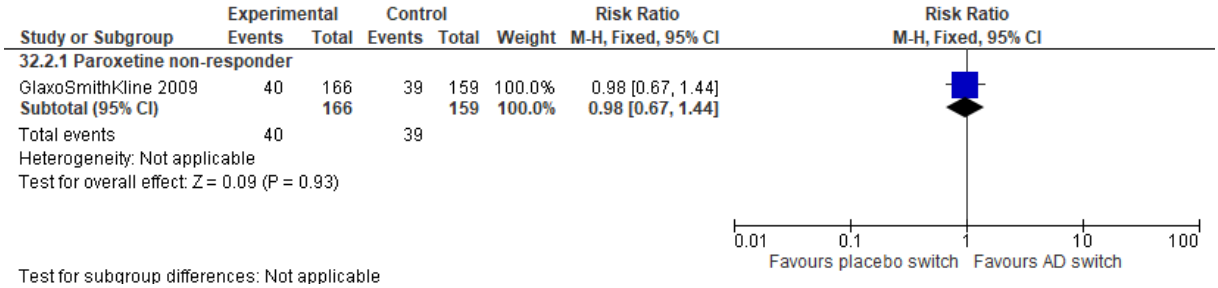
Comparison 32. Switching to bupropion versus placebo

Figure 193: Depression symptomatology change score



Test for subgroup differences: Not applicable

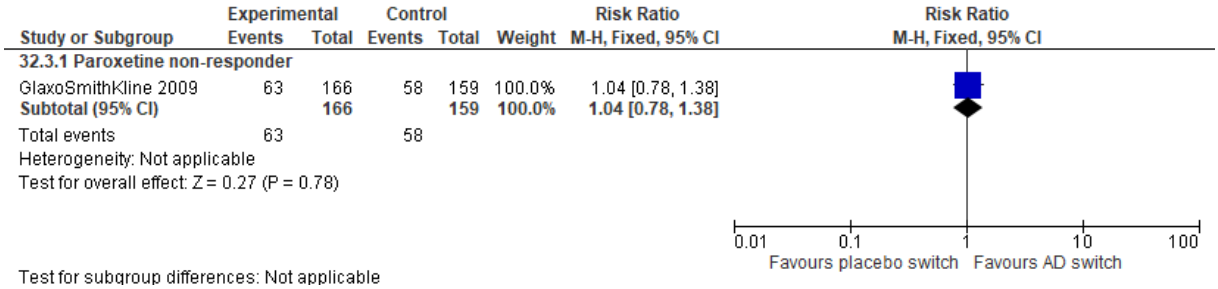
Figure 194: Remission (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

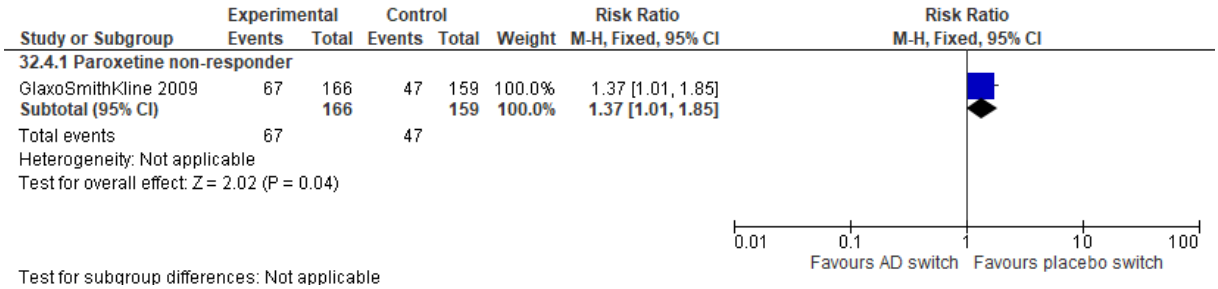
Figure 195: Response (ITT)



Test for subgroup differences: Not applicable

AD: antidepressant

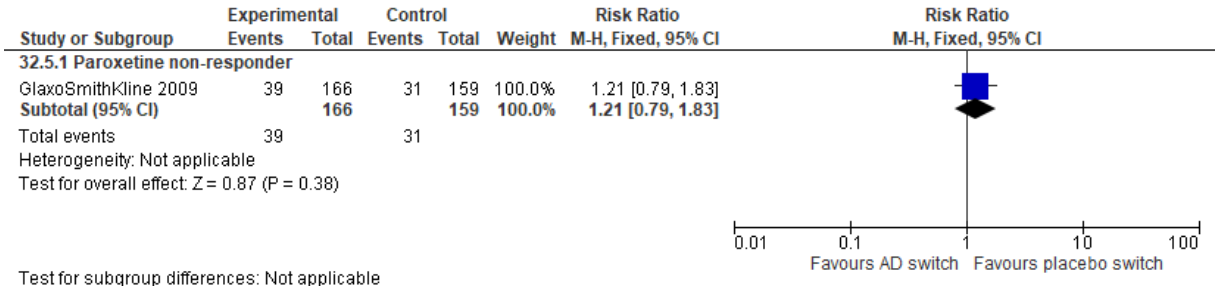
Figure 196: Discontinuation due to any reason



Test for subgroup differences: Not applicable

AD: antidepressant

686 **Figure 197: Discontinuation due to side effects**



687 Test for subgroup differences: Not applicable

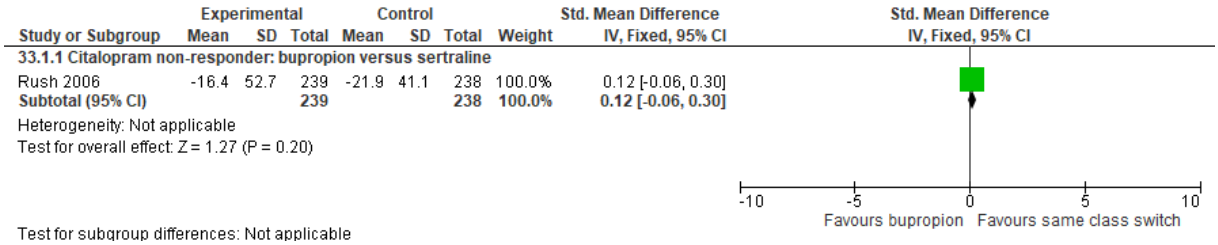
688 *AD: antidepressant*

689

690

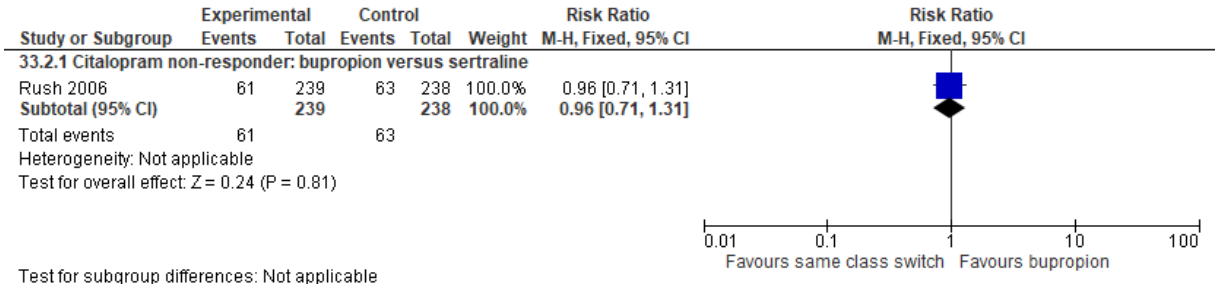
691 ***Comparison 33. Switching to bupropion versus switching to another antidepressant from***
692 ***same class***

693 **Figure 198: Depression symptomatology change score**



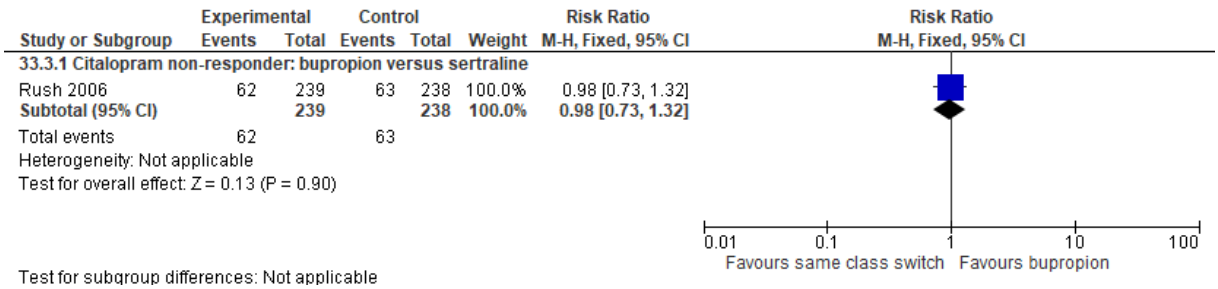
694 Test for subgroup differences: Not applicable

695 **Figure 199: Remission (ITT)**



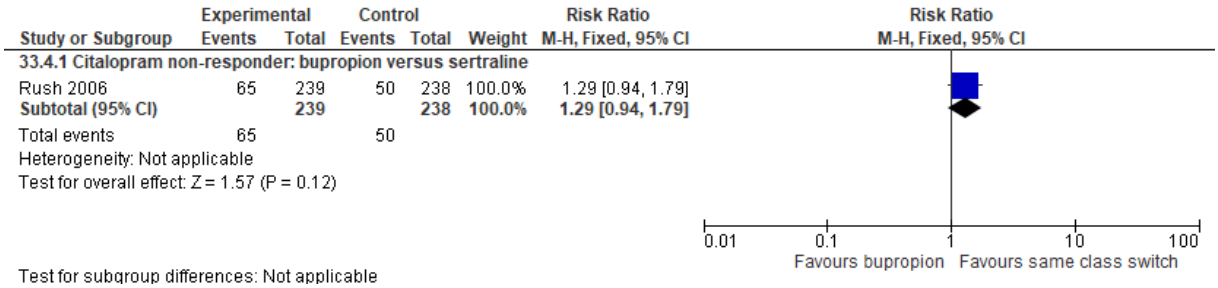
696 Test for subgroup differences: Not applicable

697 **Figure 200: Response (ITT)**



698 Test for subgroup differences: Not applicable

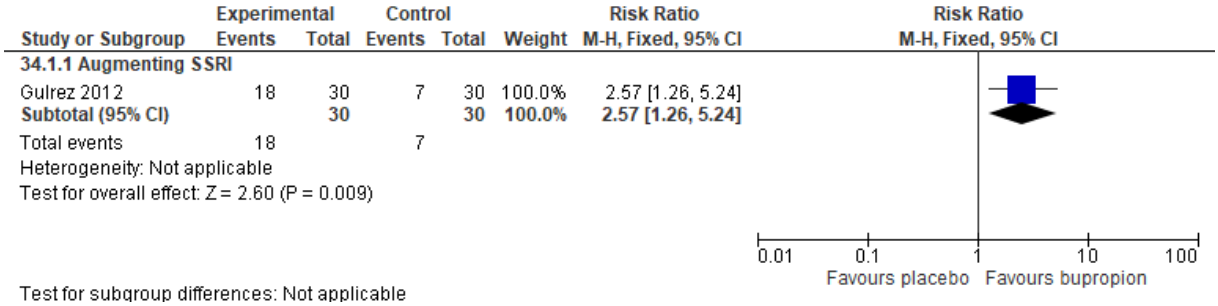
Figure 201: Discontinuation due to side effects



Test for subgroup differences: Not applicable

Comparison 34. Augmenting with bupropion versus placebo

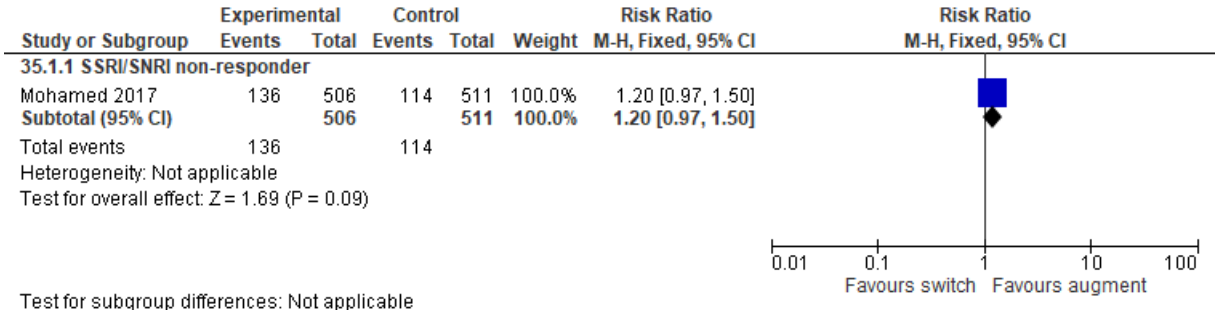
Figure 202: Remission (ITT)



Test for subgroup differences: Not applicable

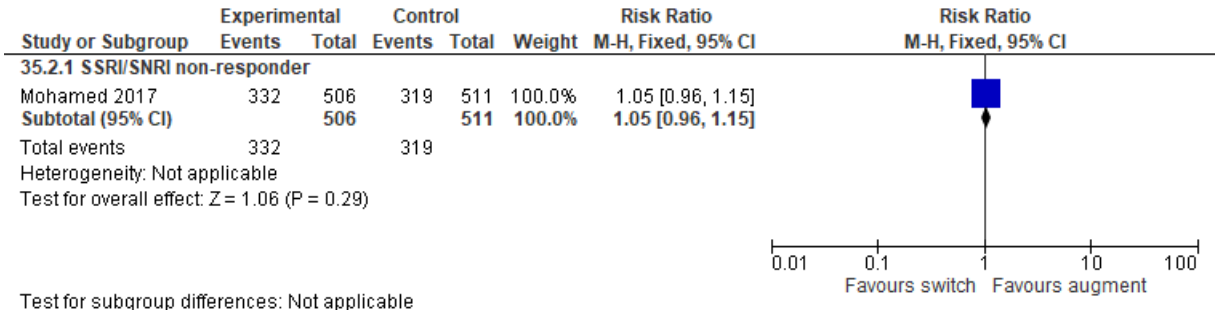
Comparison 35. Augmenting with bupropion versus switching to bupropion

Figure 203: Remission (ITT)



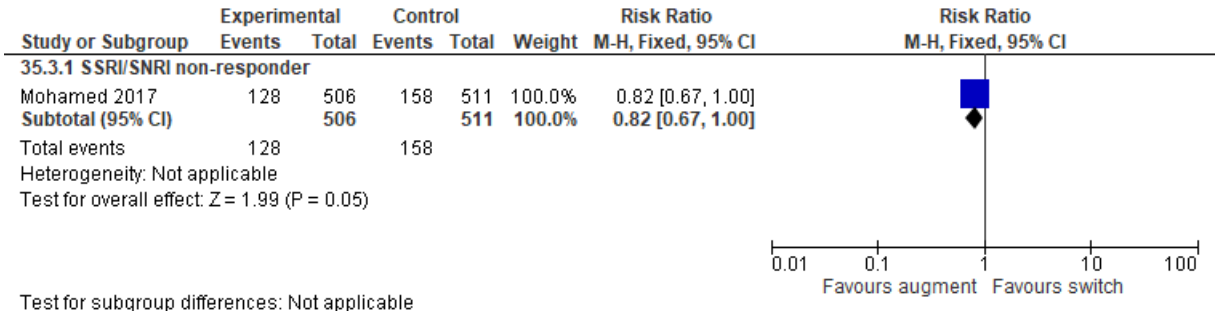
Test for subgroup differences: Not applicable

Figure 204: Response (ITT)



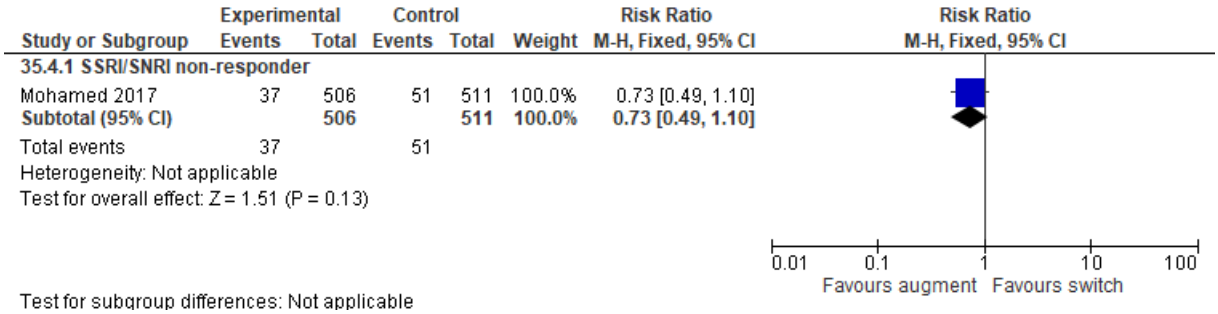
Test for subgroup differences: Not applicable

Figure 205: Discontinuation due to any reason



Test for subgroup differences: Not applicable

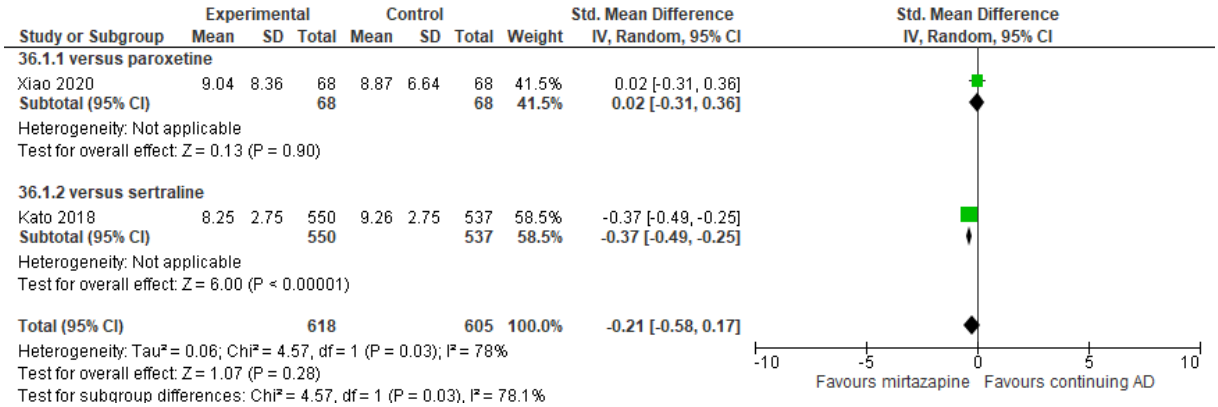
Figure 206: Discontinuation due to side effects



Test for subgroup differences: Not applicable

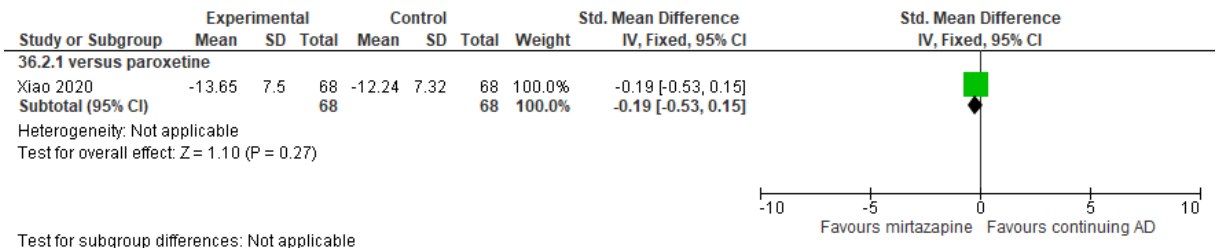
Comparison 36. Switching to mirtazapine versus continuing with antidepressant

Figure 207: Depression symptomatology endpoint



AD: antidepressant

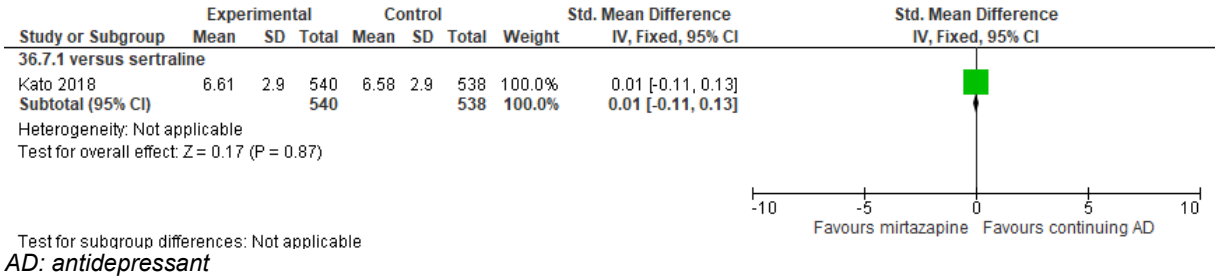
Figure 208: Depression symptomatology change score



Test for subgroup differences: Not applicable

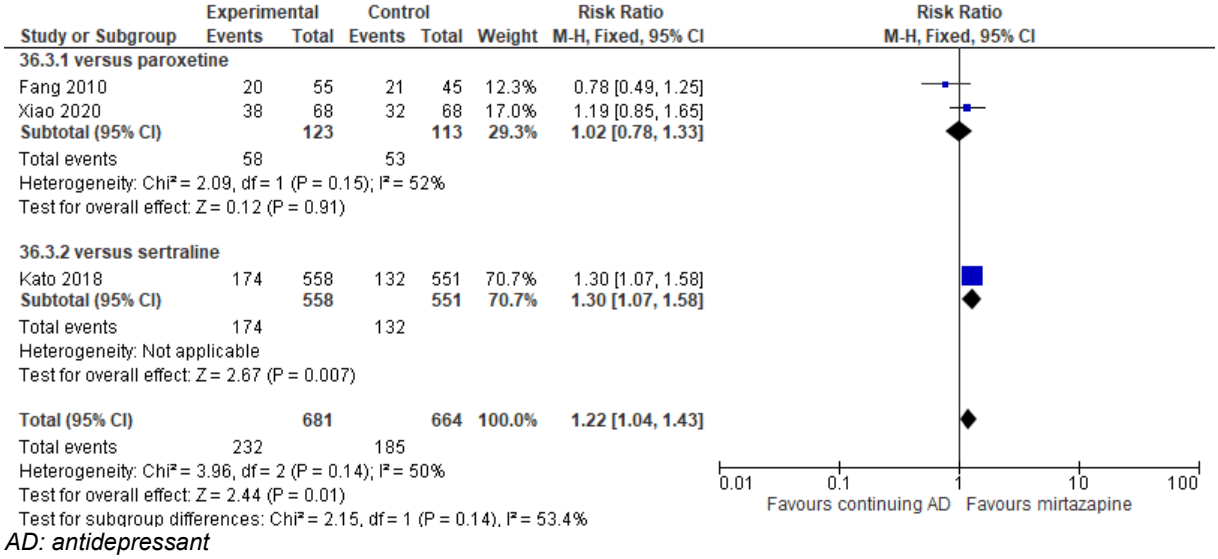
AD: antidepressant

Figure 209: Depression symptomatology at 4-month follow-up



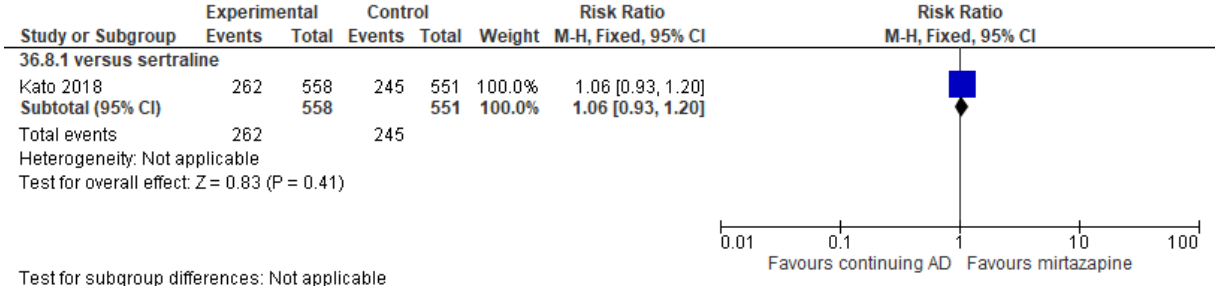
AD: antidepressant

Figure 210: Remission (ITT)



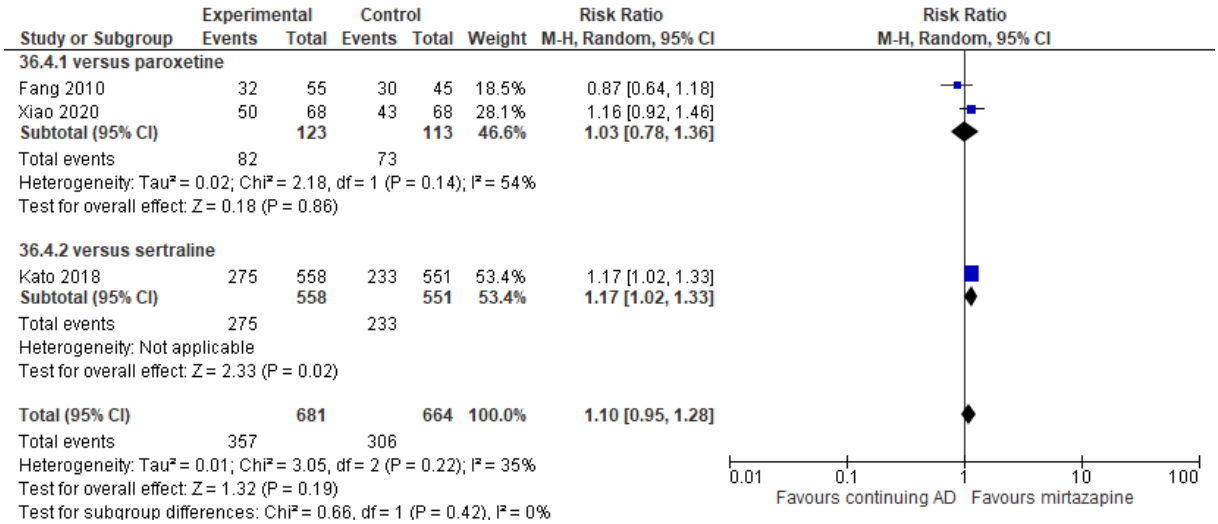
AD: antidepressant

Figure 211: Remission (ITT) at 4-month follow-up



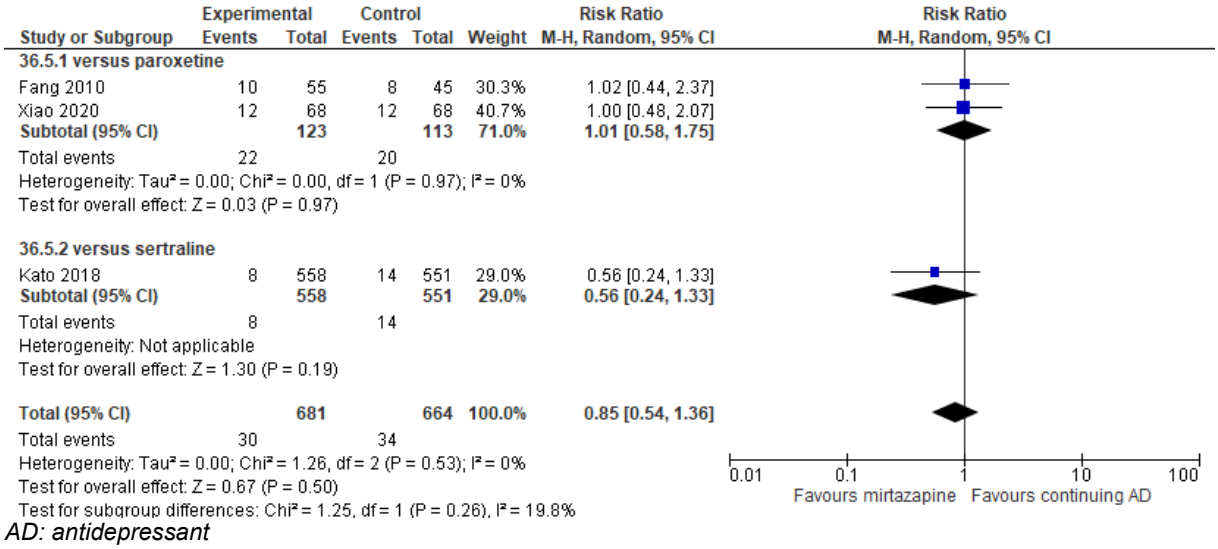
AD: antidepressant

Figure 212: Response (ITT)



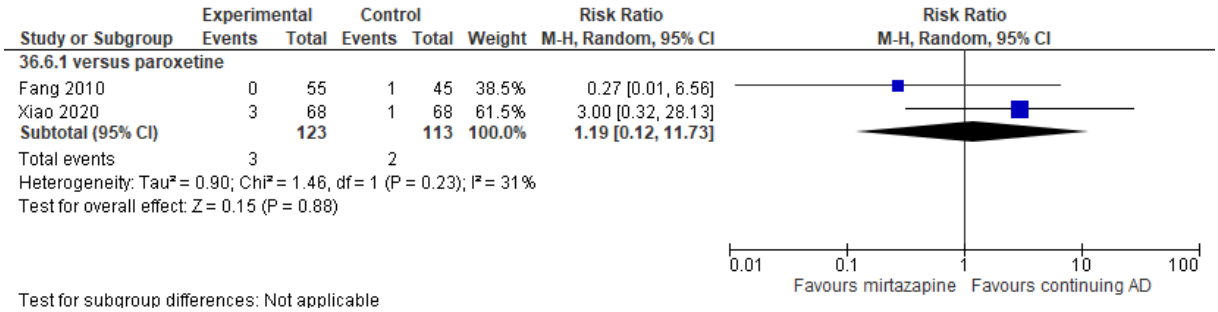
AD: antidepressant

Figure 213: Discontinuation due to any reason



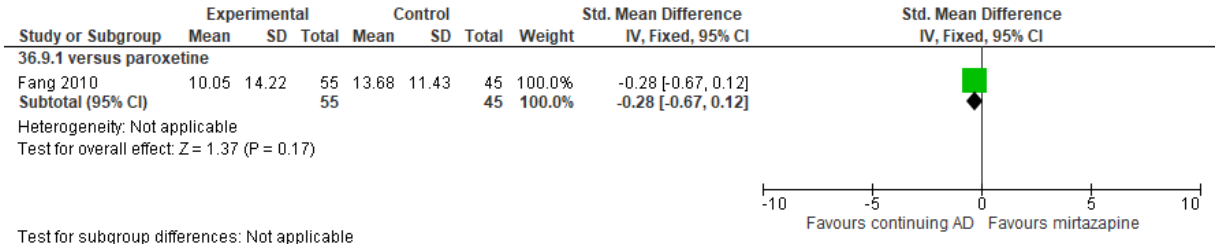
AD: antidepressant

Figure 214: Discontinuation due to side effects



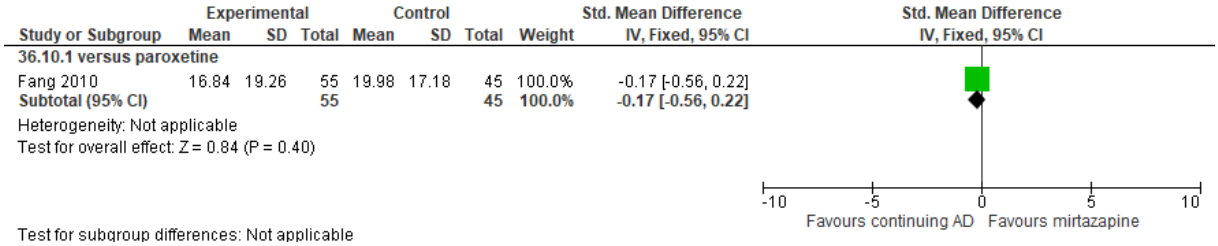
AD: antidepressant

Figure 215: Quality of life physical component score (PCS) change score



AD: antidepressant

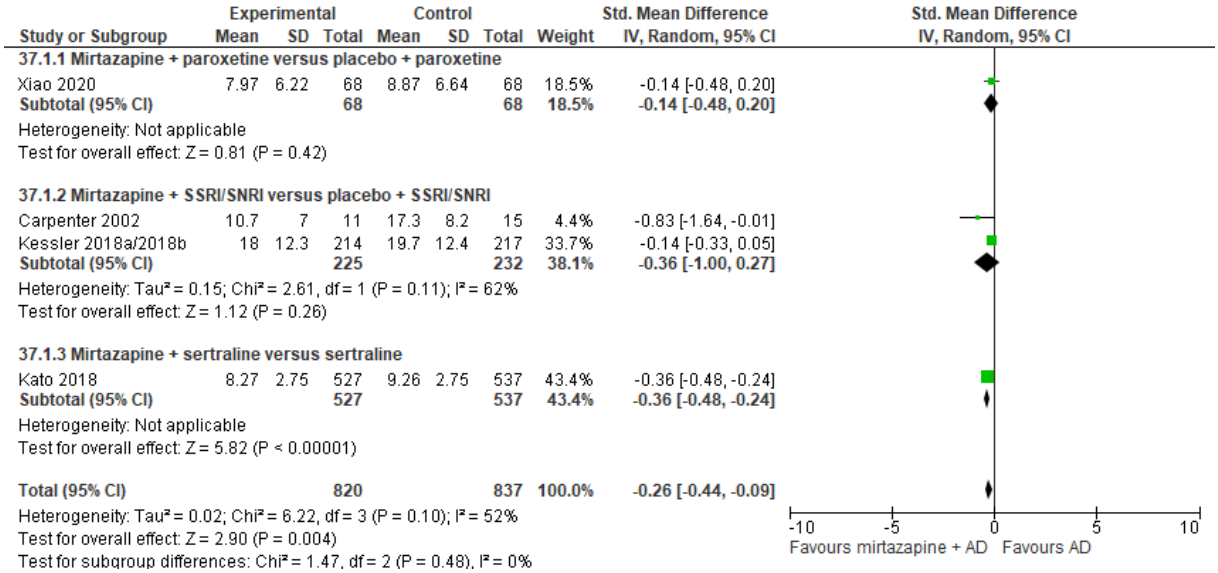
Figure 216: Quality of life mental component score (MCS) change score



AD: antidepressant

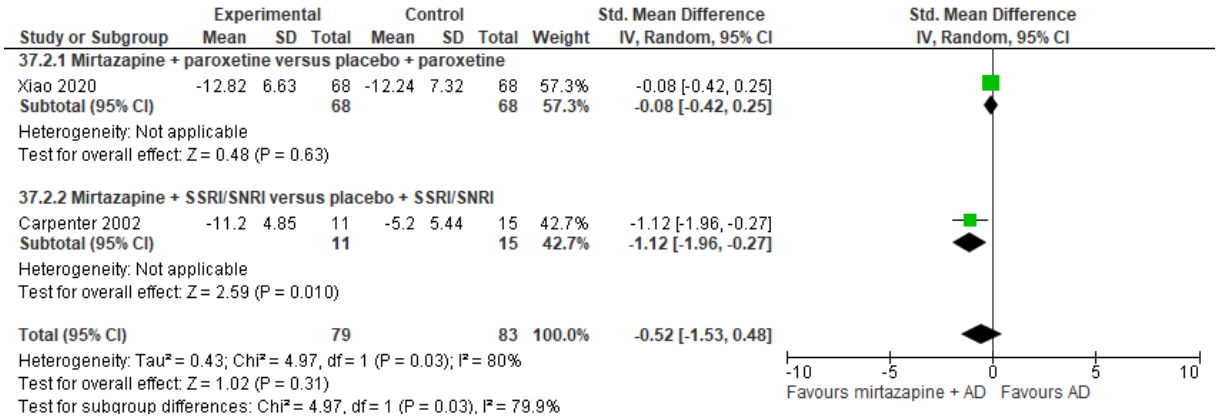
Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/- placebo)

Figure 217: Depression symptomatology endpoint



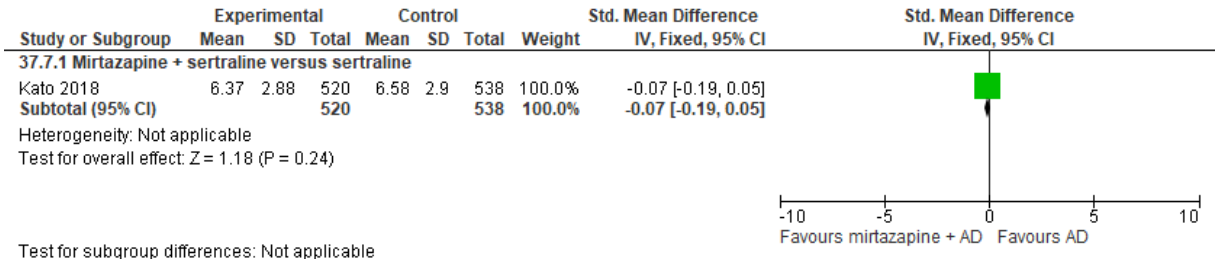
AD: antidepressant

Figure 218: Depression symptomatology change score



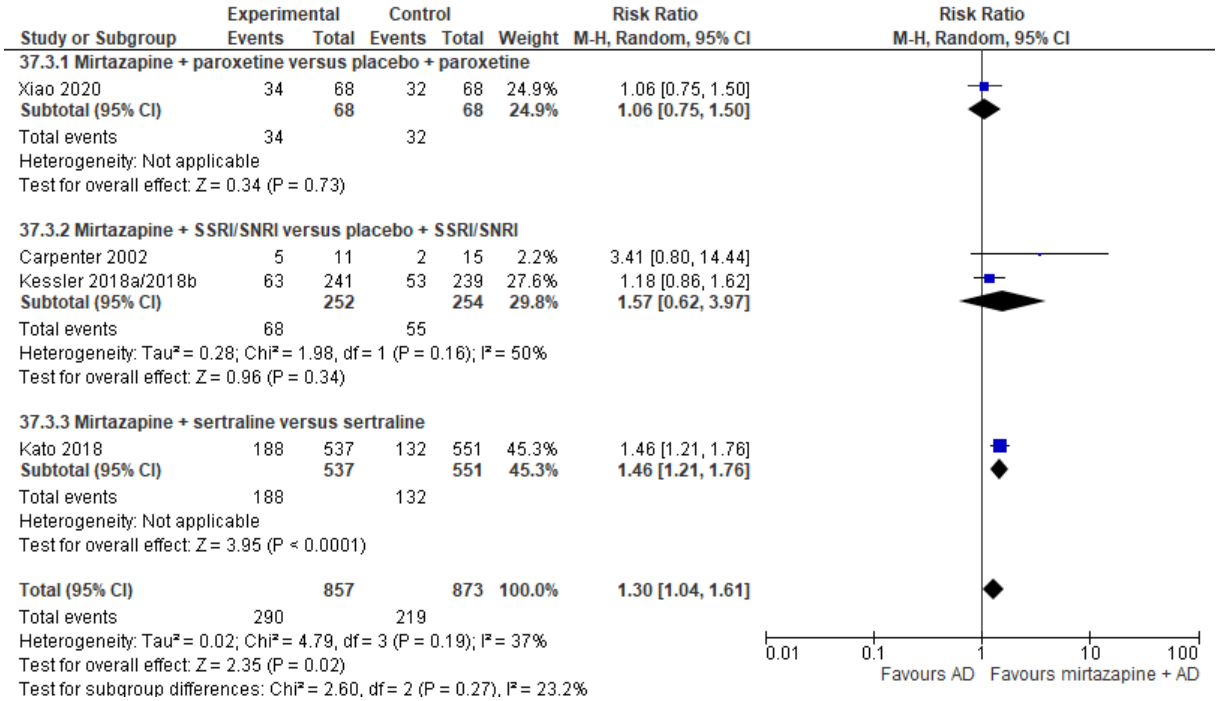
AD: antidepressant

Figure 219: Depression symptomatology at 4-month follow-up



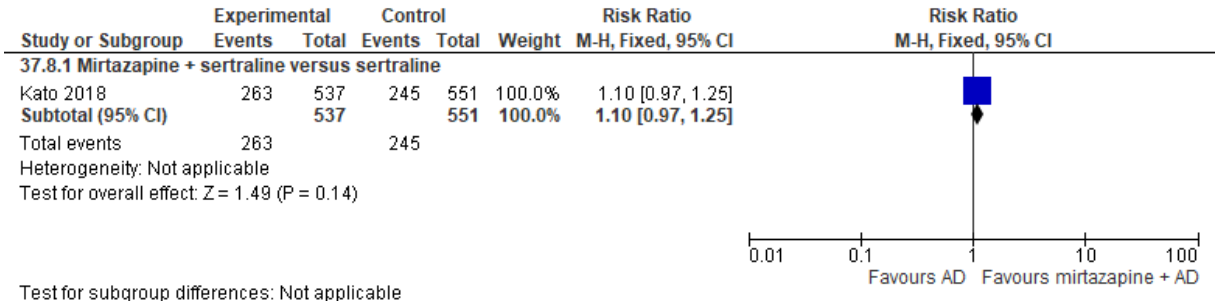
AD: antidepressant

Figure 220: Remission (ITT)



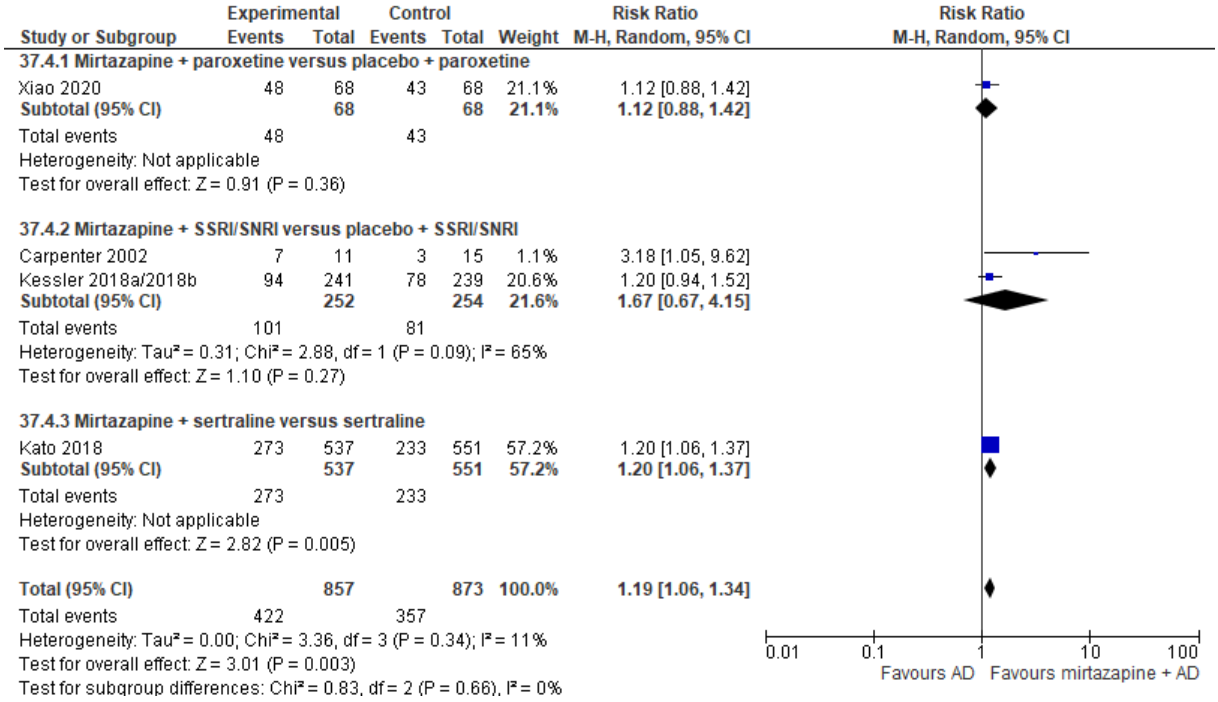
AD: antidepressant

Figure 221: Remission (ITT) at 4-month follow-up



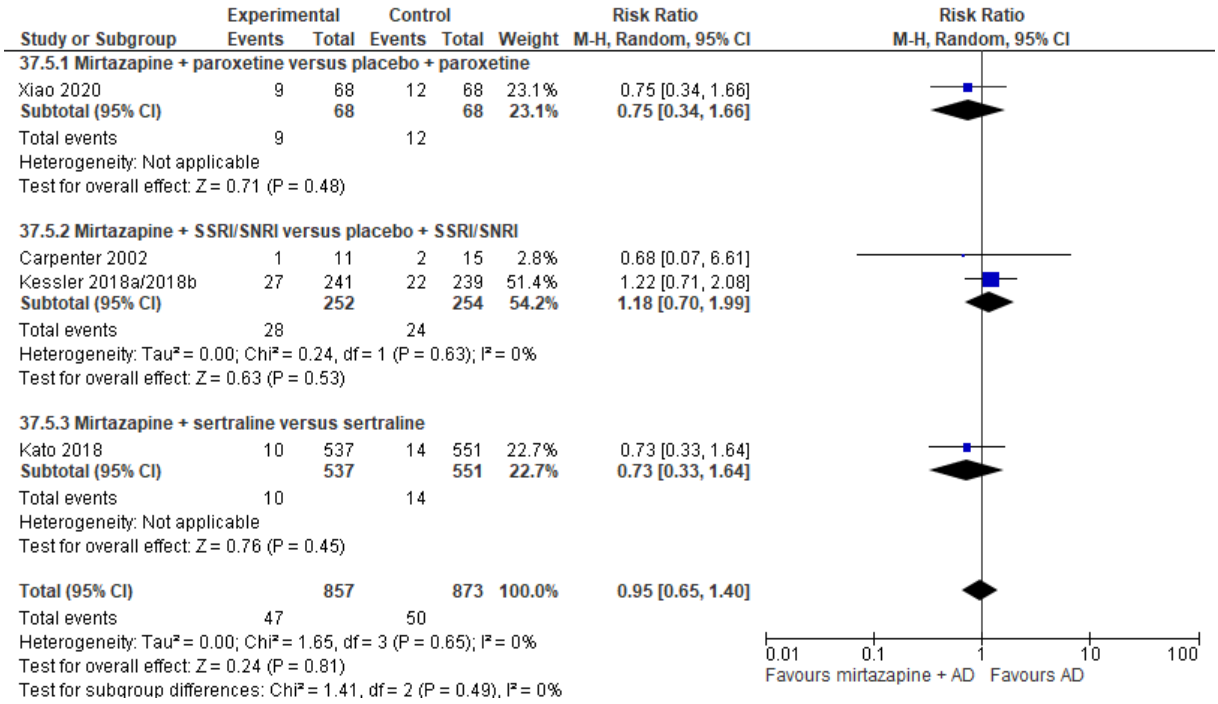
AD: antidepressant

Figure 222: Response (ITT)



AD: antidepressant

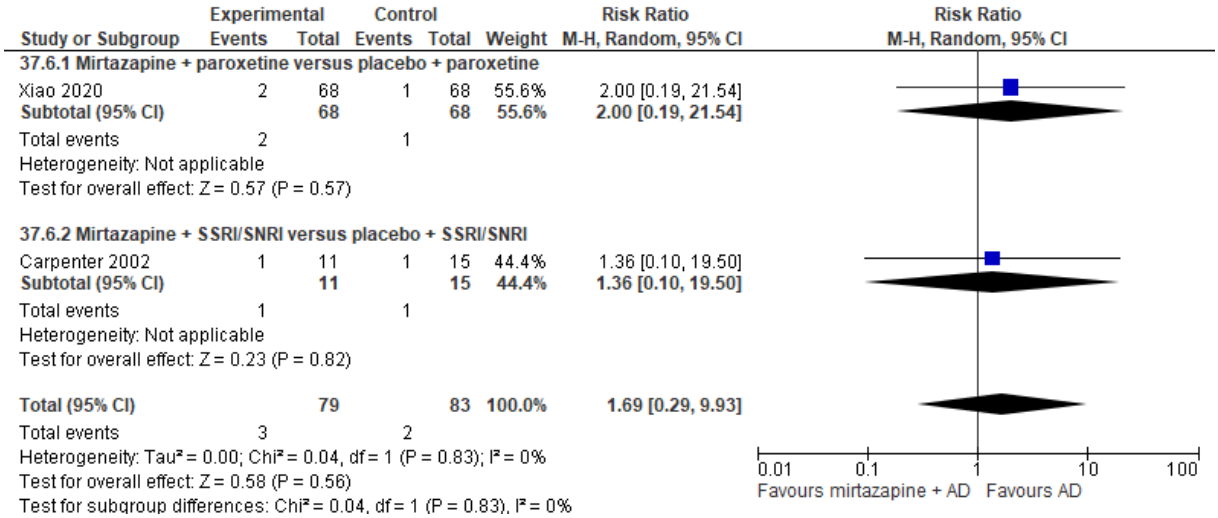
784 **Figure 223: Discontinuation due to any reason**



785
786 *AD: antidepressant*

787

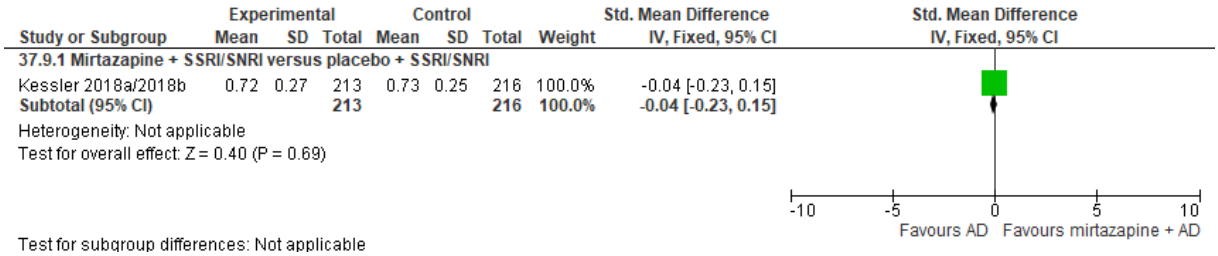
788 **Figure 224: Discontinuation due to side effects**



789
790 *AD: antidepressant*

791

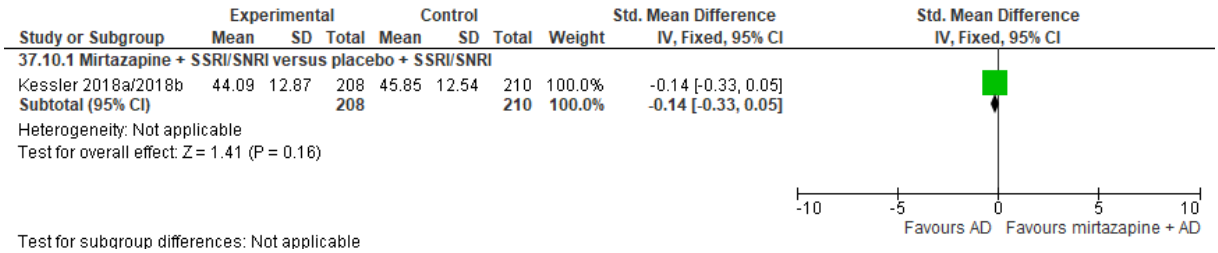
Figure 225: Quality of life endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

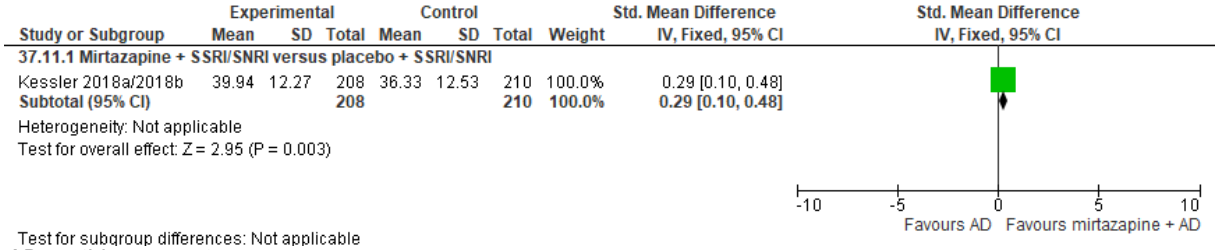
Figure 226: Quality of life physical component score (PCS) endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

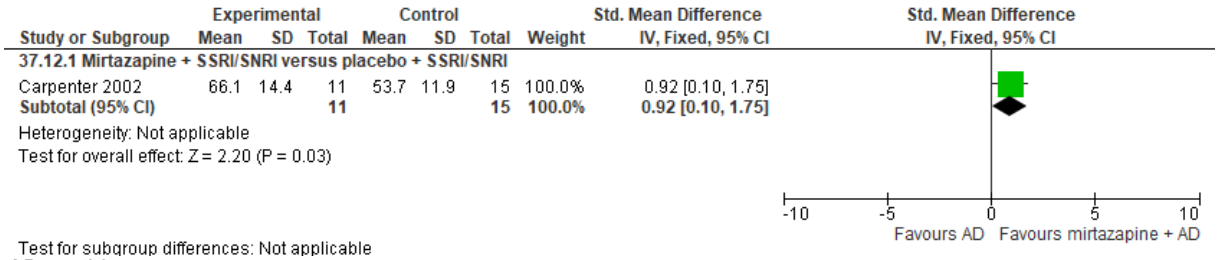
Figure 227: Quality of life mental component score (MCS) endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 228: Global functioning endpoint

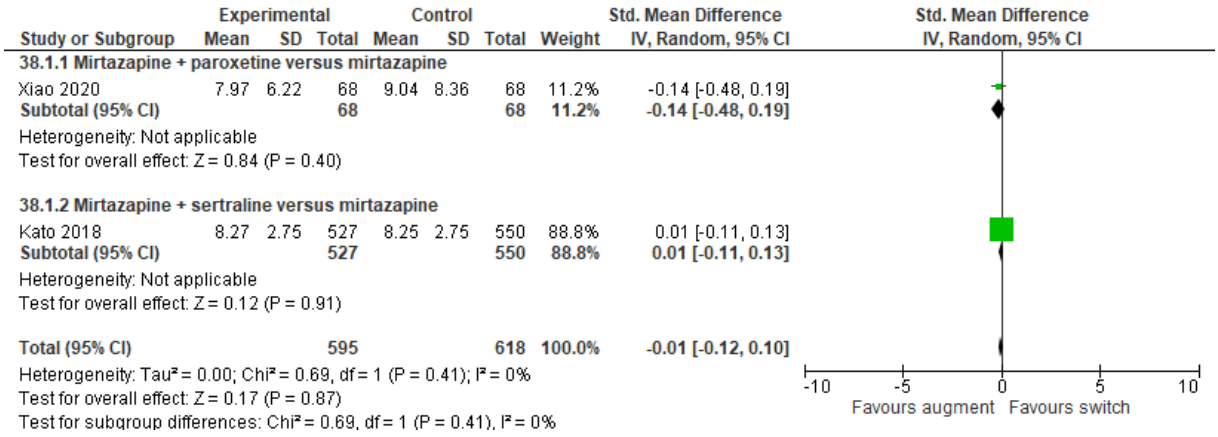


Test for subgroup differences: Not applicable

AD: antidepressant

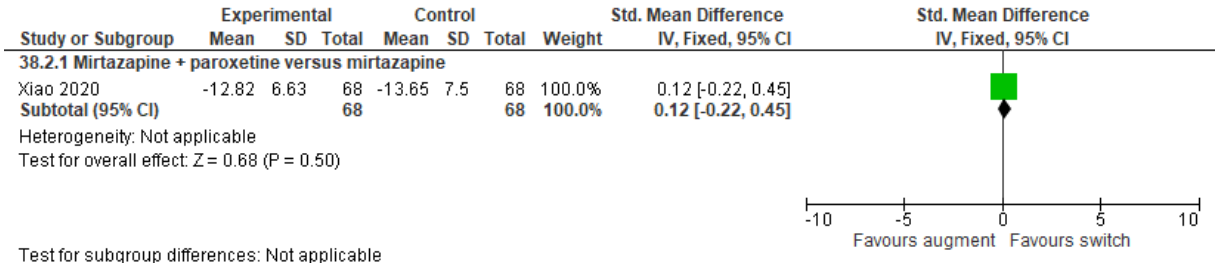
809 ***Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine***

810 **Figure 229: Depression symptomatology endpoint**



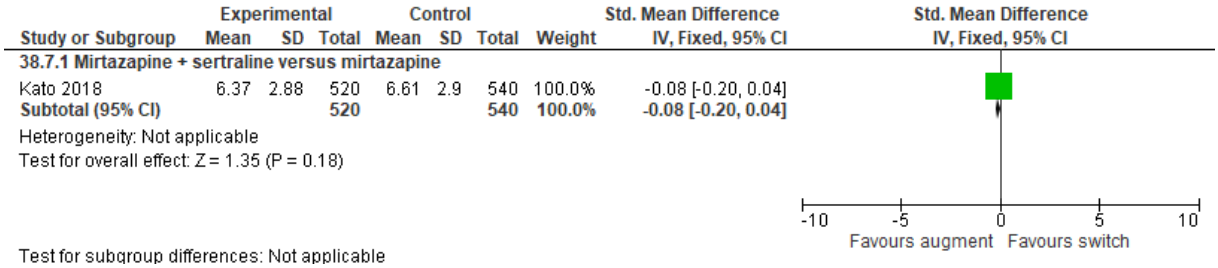
811

812 **Figure 230: Depression symptomatology change score**



813

814 **Figure 231: Depression symptomatology at 4-month follow-up**



815

Figure 232: Remission (ITT)

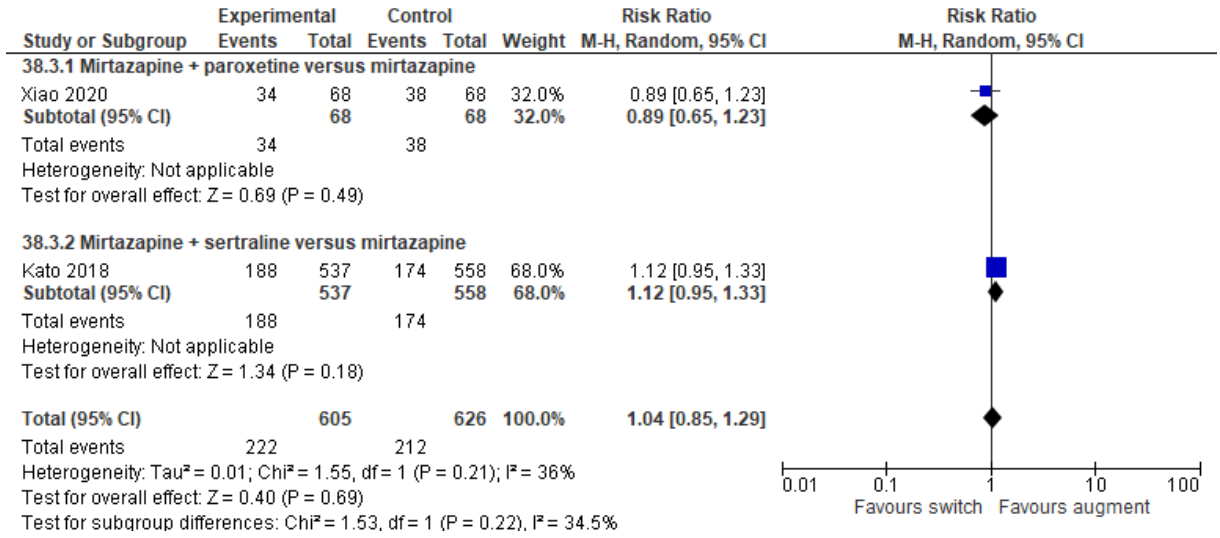


Figure 233: Remission (ITT) at 4-month follow-up

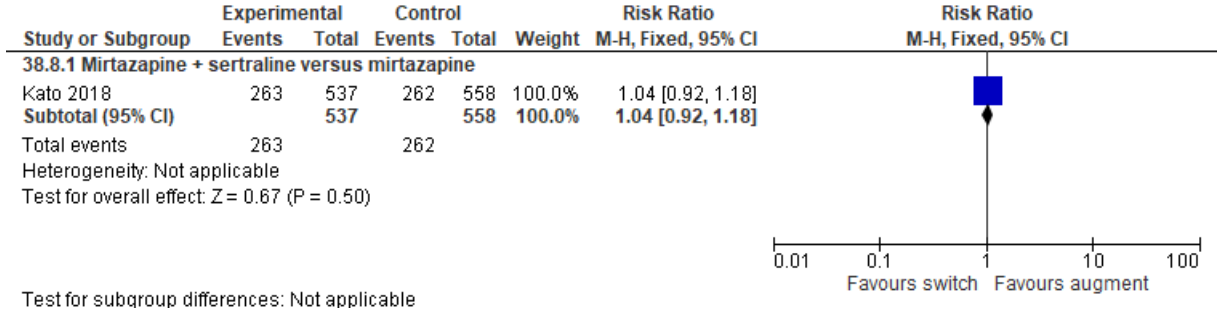


Figure 234: Response (ITT)

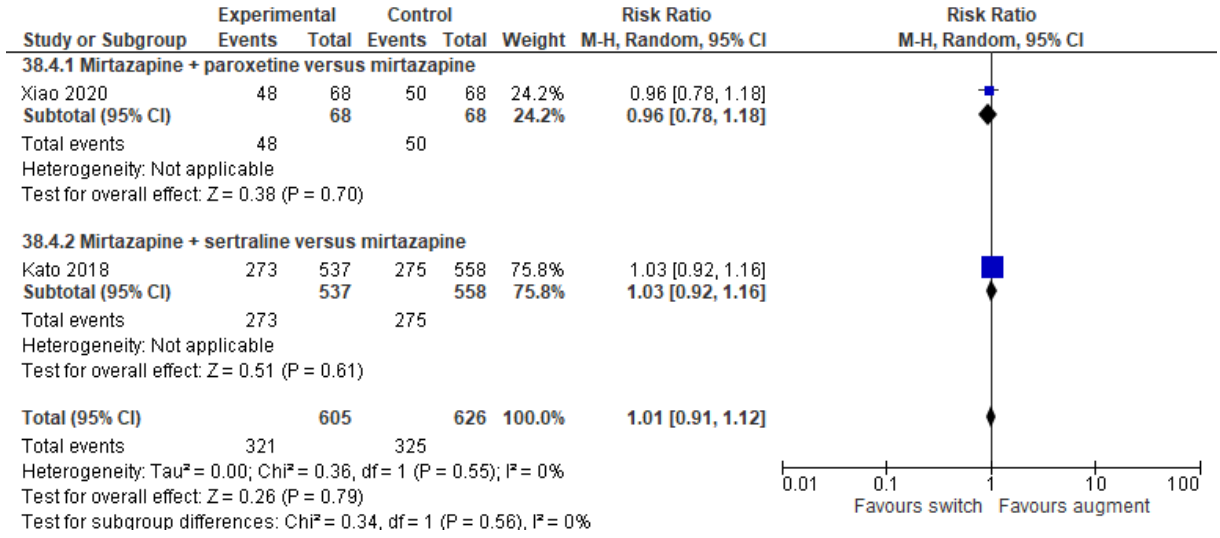


Figure 235: Discontinuation due to any reason

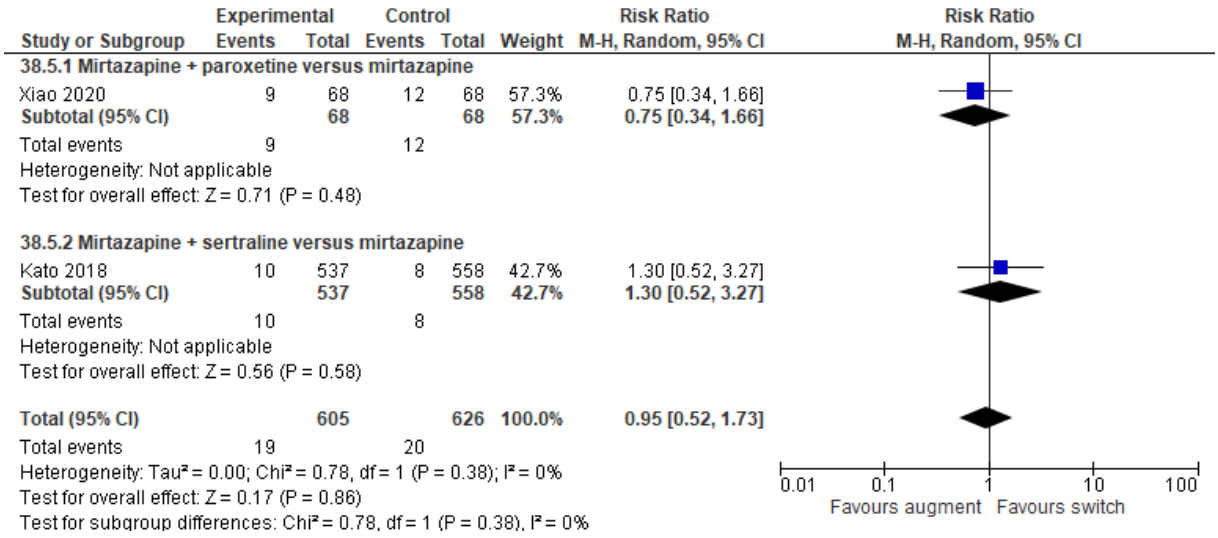
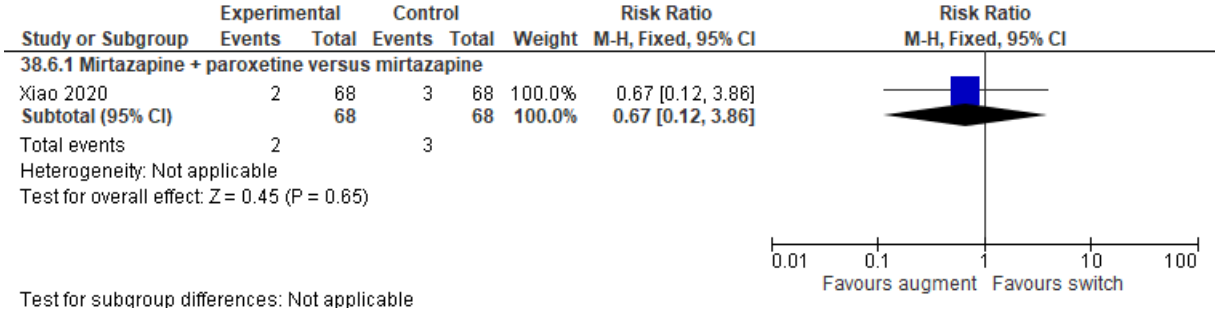
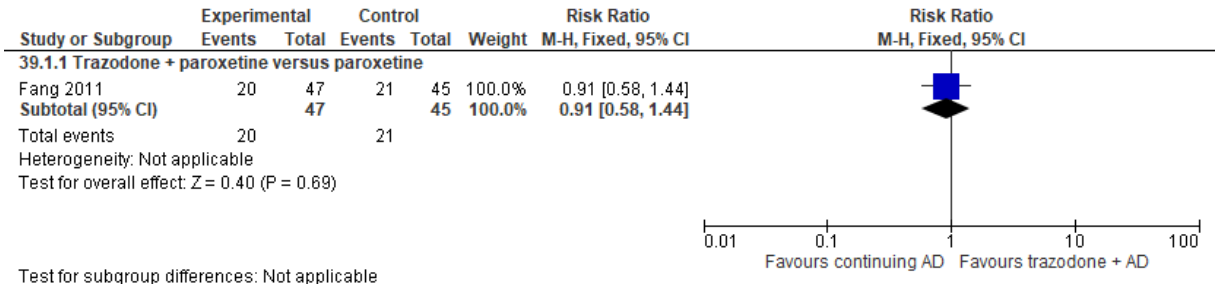


Figure 236: Discontinuation due to side effects



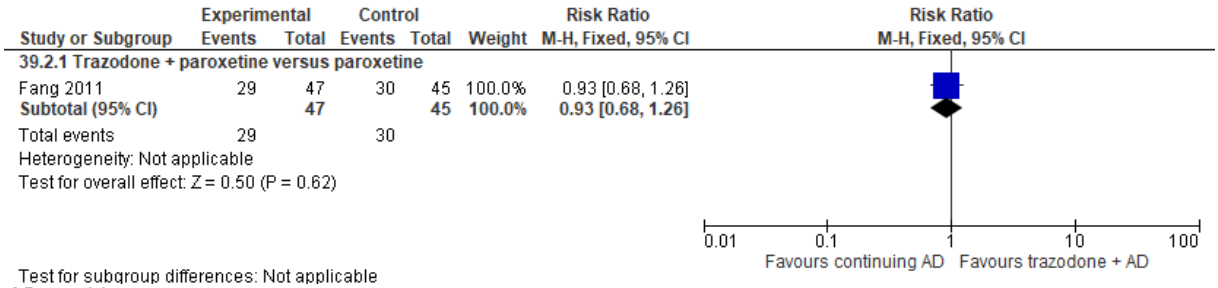
Comparison 39. Augmenting with trazodone versus continuing with antidepressant

Figure 237: Remission (ITT)



AD: antidepressant

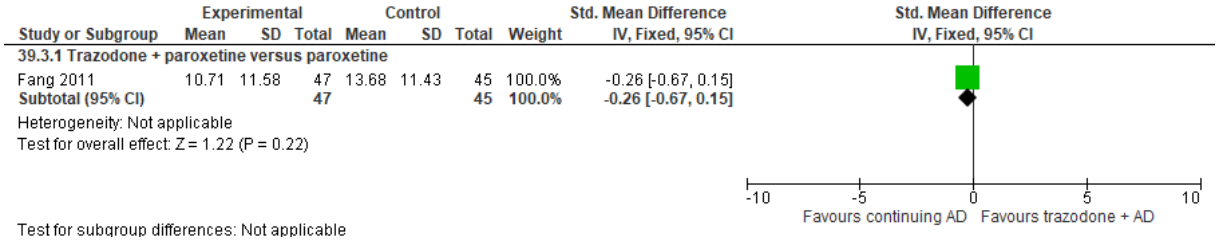
832 **Figure 238: Response (ITT)**



833 Test for subgroup differences: Not applicable
834 *AD: antidepressant*

835

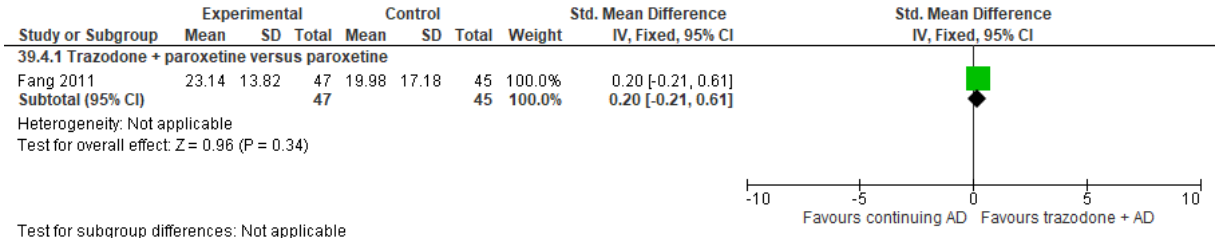
836 **Figure 239: Quality of life physical component score (PCS) change score**



837 Test for subgroup differences: Not applicable
838 *AD: antidepressant*

839

840 **Figure 240: Quality of life mental component score (MCS) change score**



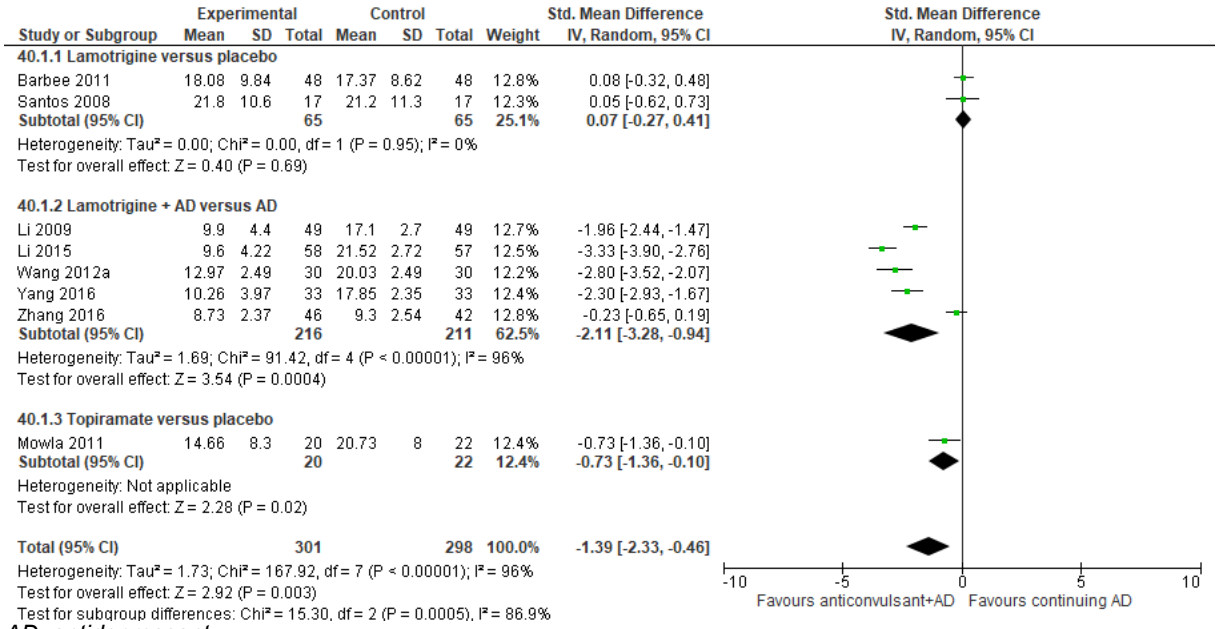
841 Test for subgroup differences: Not applicable
842 *AD: antidepressant*

843

844

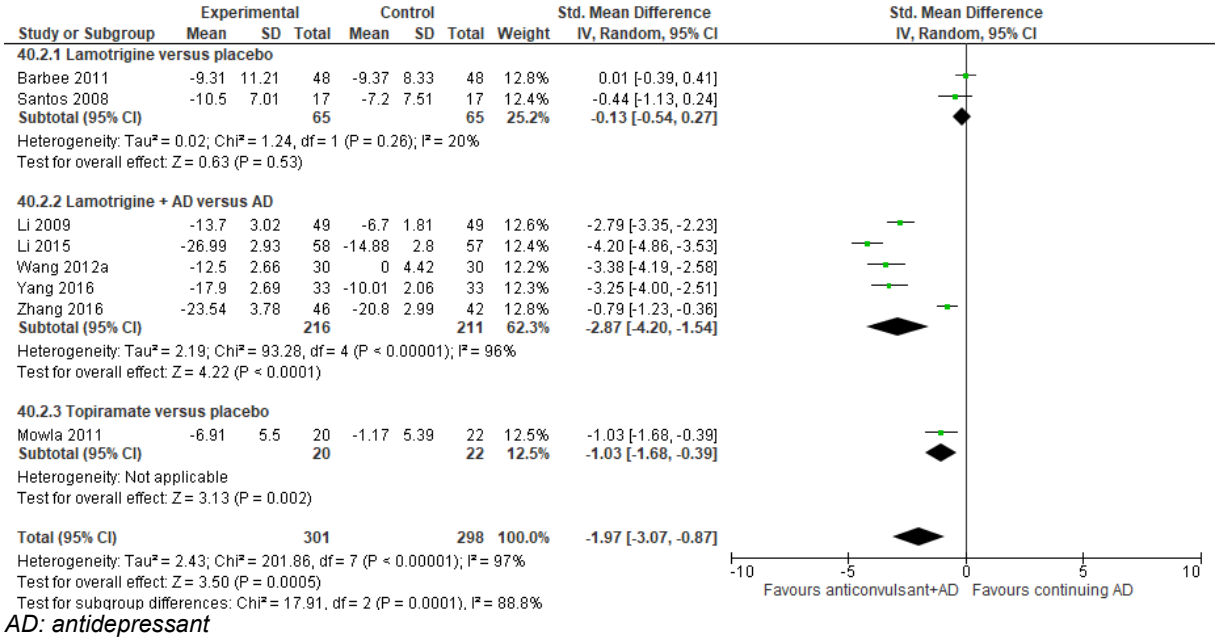
Comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)

Figure 241: Depression symptomatology endpoint



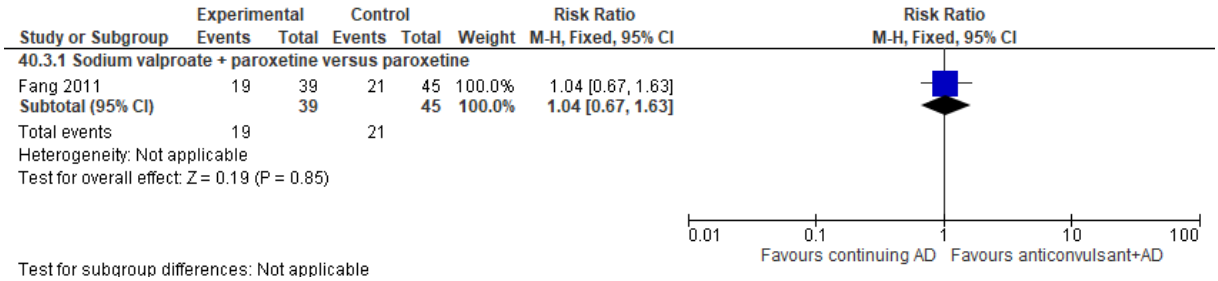
AD: antidepressant

Figure 242: Depression symptomatology change score



AD: antidepressant

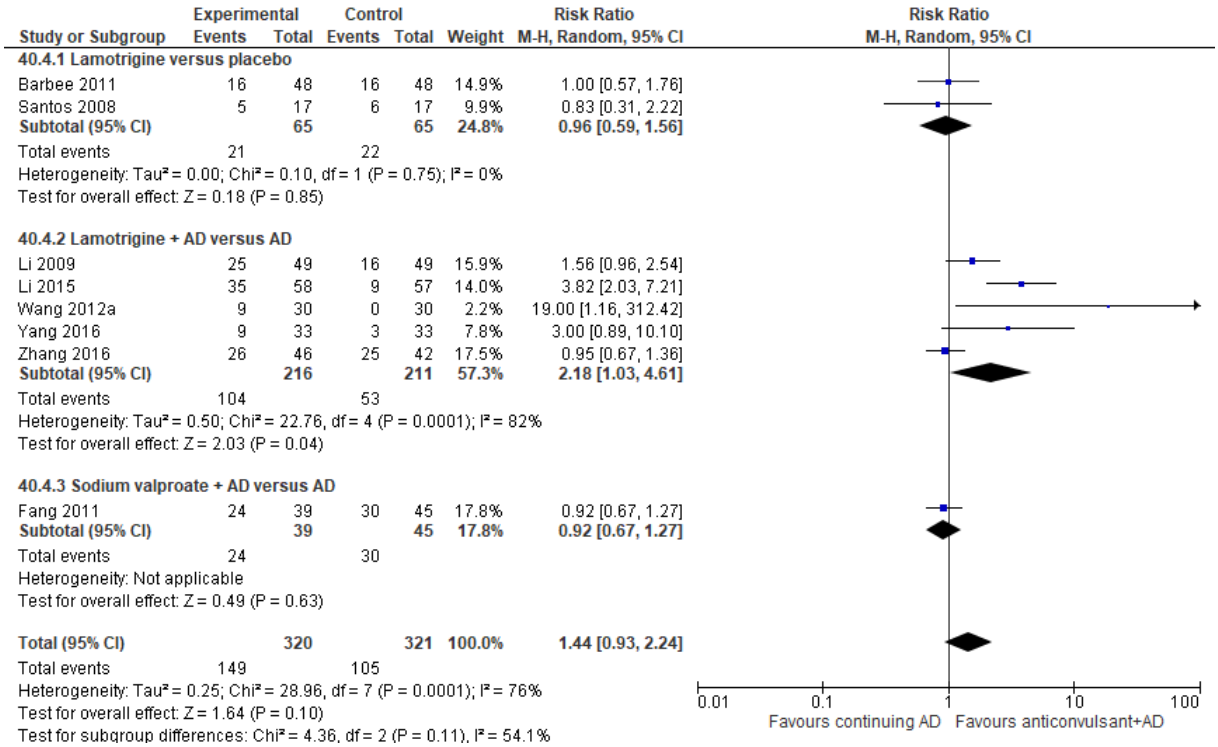
855 **Figure 243: Remission (ITT)**



856 Test for subgroup differences: Not applicable
857 *AD: antidepressant*

858

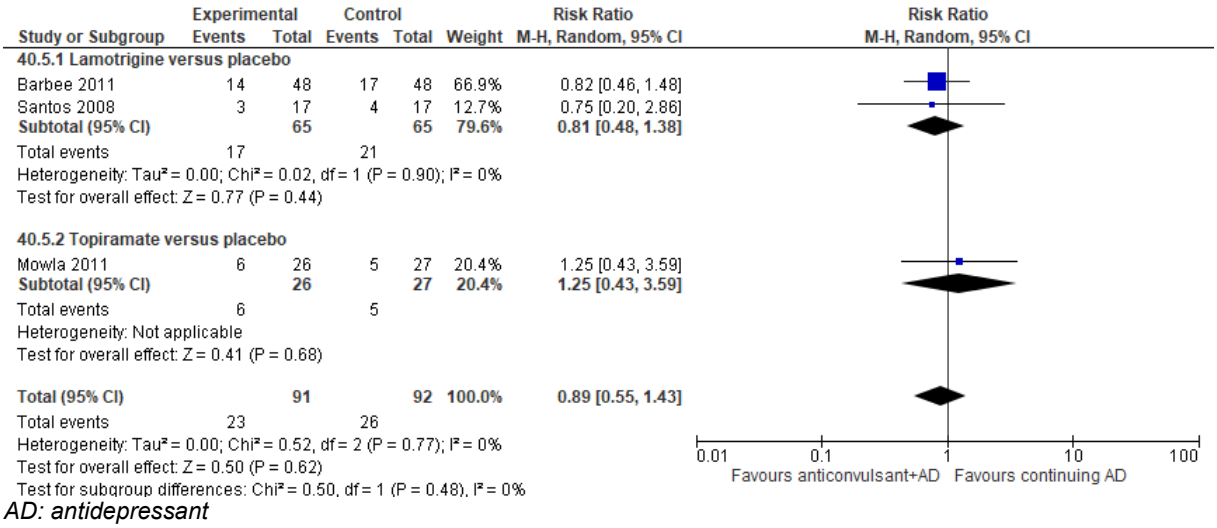
859 **Figure 244: Response (ITT)**



860 Test for subgroup differences: Chi² = 4.36, df = 2 (P = 0.11), I² = 54.1%
861 *AD: antidepressant*

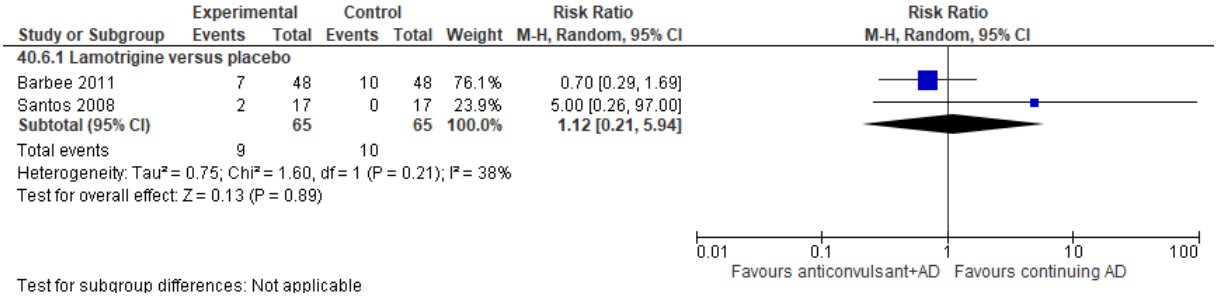
862

Figure 245: Discontinuation due to any reason



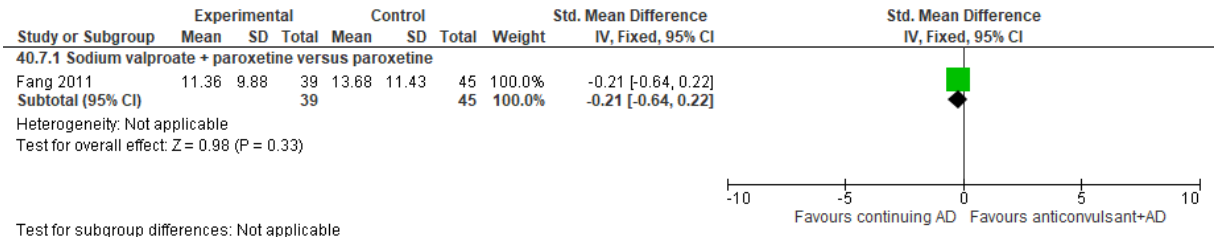
AD: antidepressant

Figure 246: Discontinuation due to side effects



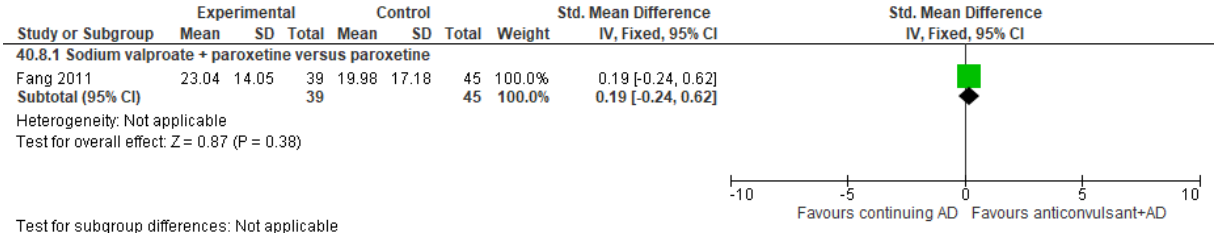
AD: antidepressant

Figure 247: Quality of life physical component score (PCS) change score



AD: antidepressant

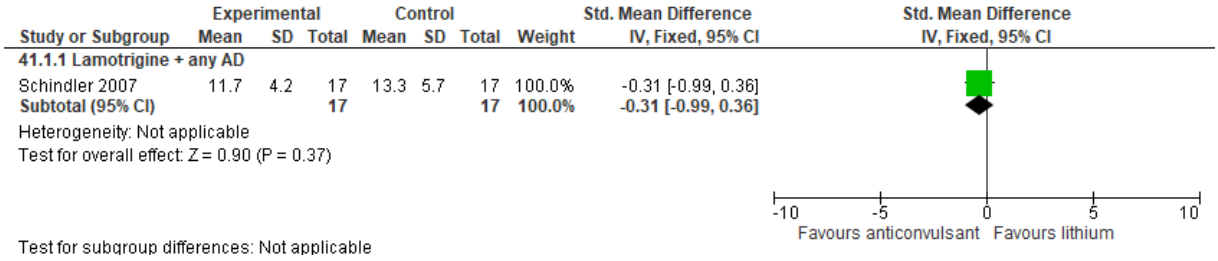
Figure 248: Quality of life mental component score (MCS) change score



AD: antidepressant

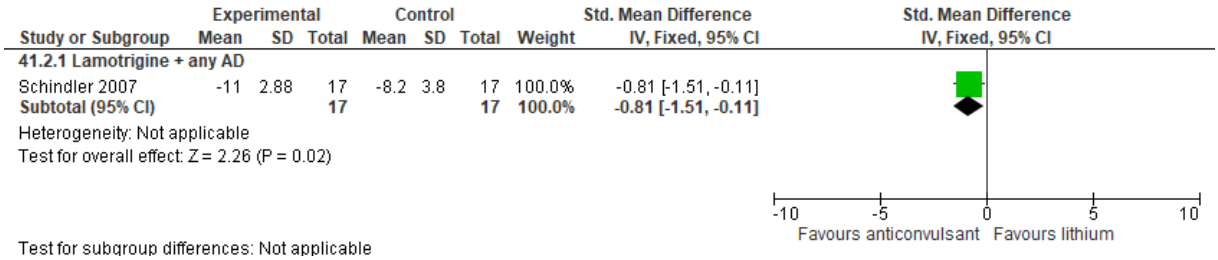
Comparison 41. Augmenting with anticonvulsant versus lithium

Figure 249: Depression symptomatology endpoint



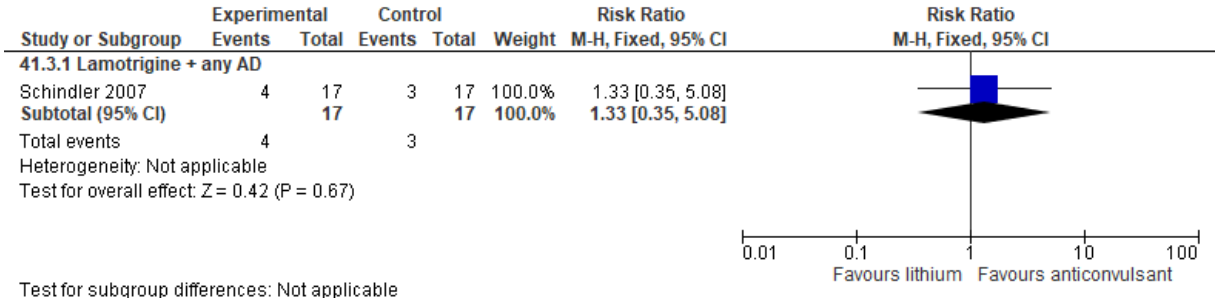
Test for subgroup differences: Not applicable

Figure 250: Depression symptomatology change score



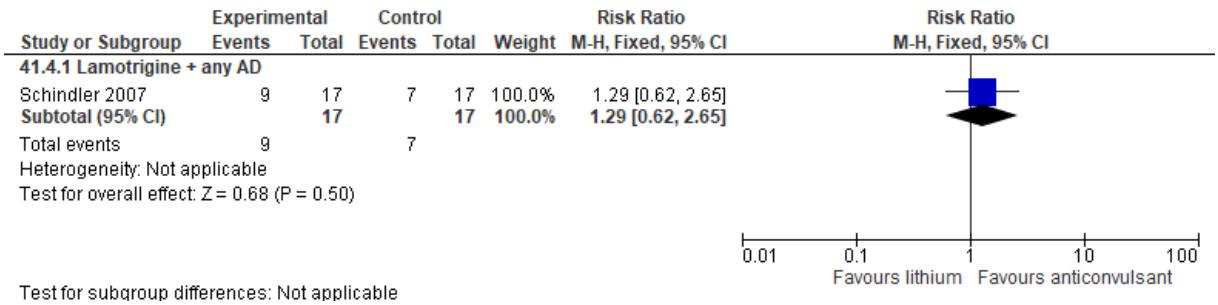
Test for subgroup differences: Not applicable

Figure 251: Remission (ITT)



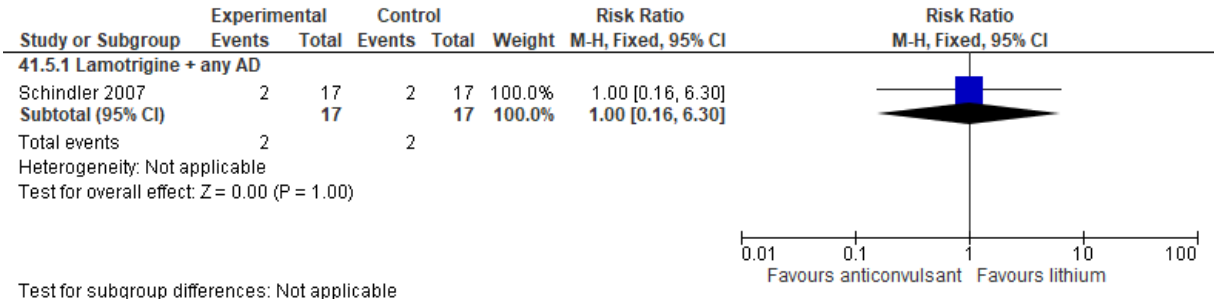
Test for subgroup differences: Not applicable

Figure 252: Response (ITT)



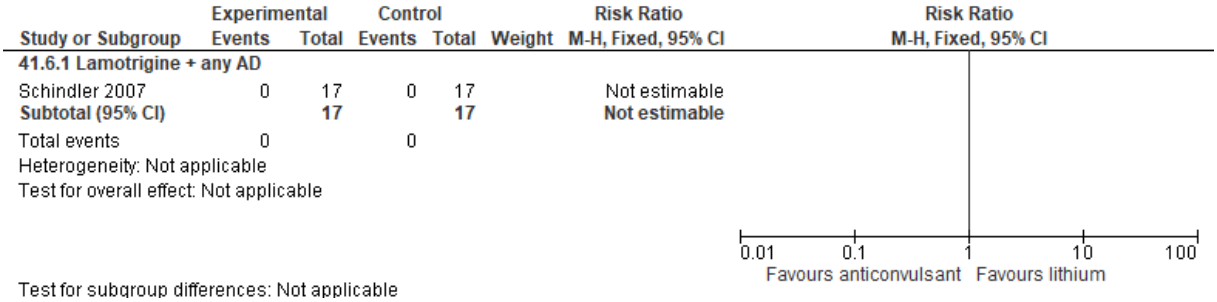
Test for subgroup differences: Not applicable

Figure 253: Discontinuation due to any reason



Test for subgroup differences: Not applicable

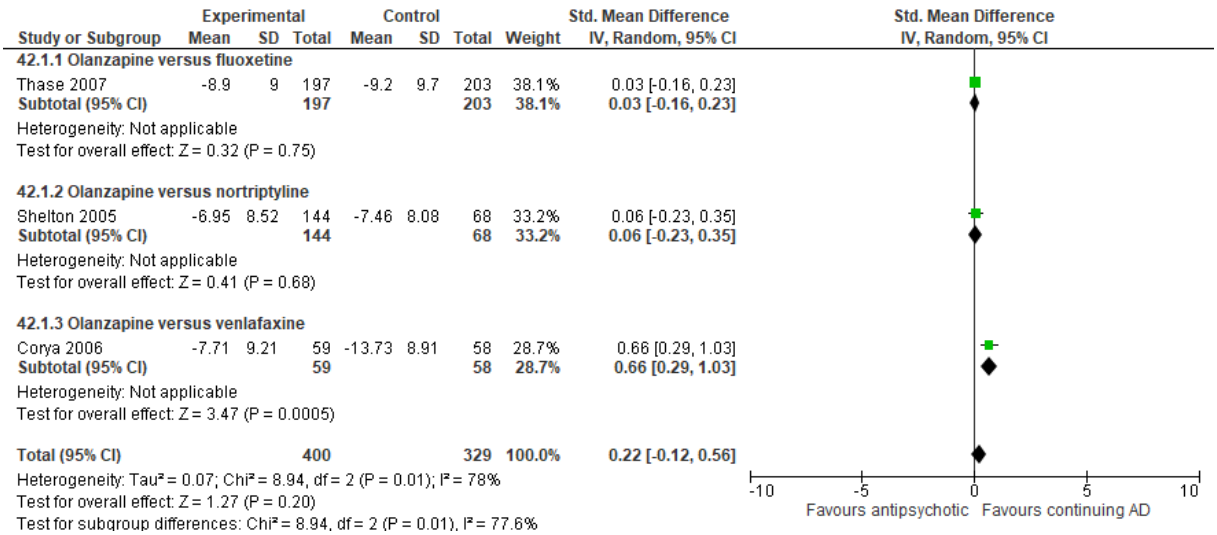
Figure 254: Discontinuation due to side effects



Test for subgroup differences: Not applicable

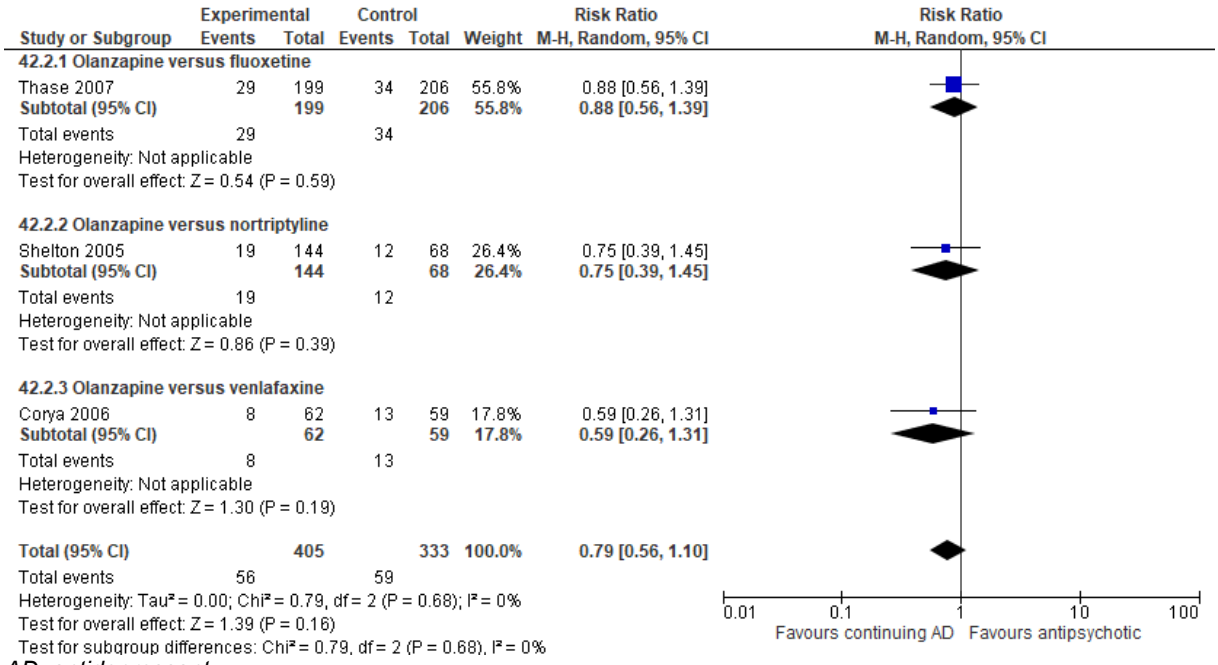
Comparison 42. Switching to antipsychotic versus continuing with antidepressant

Figure 255: Depression symptomatology change score



AD: antidepressant

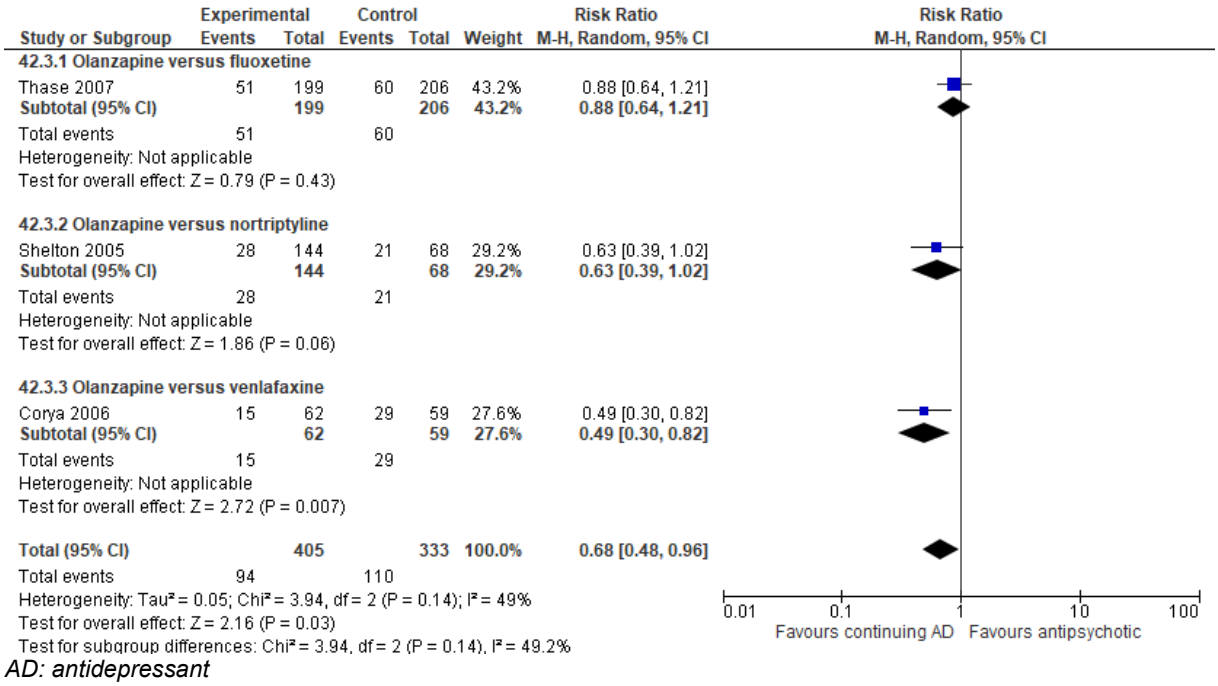
899 **Figure 256: Remission (ITT)**



900
901 *AD: antidepressant*

902

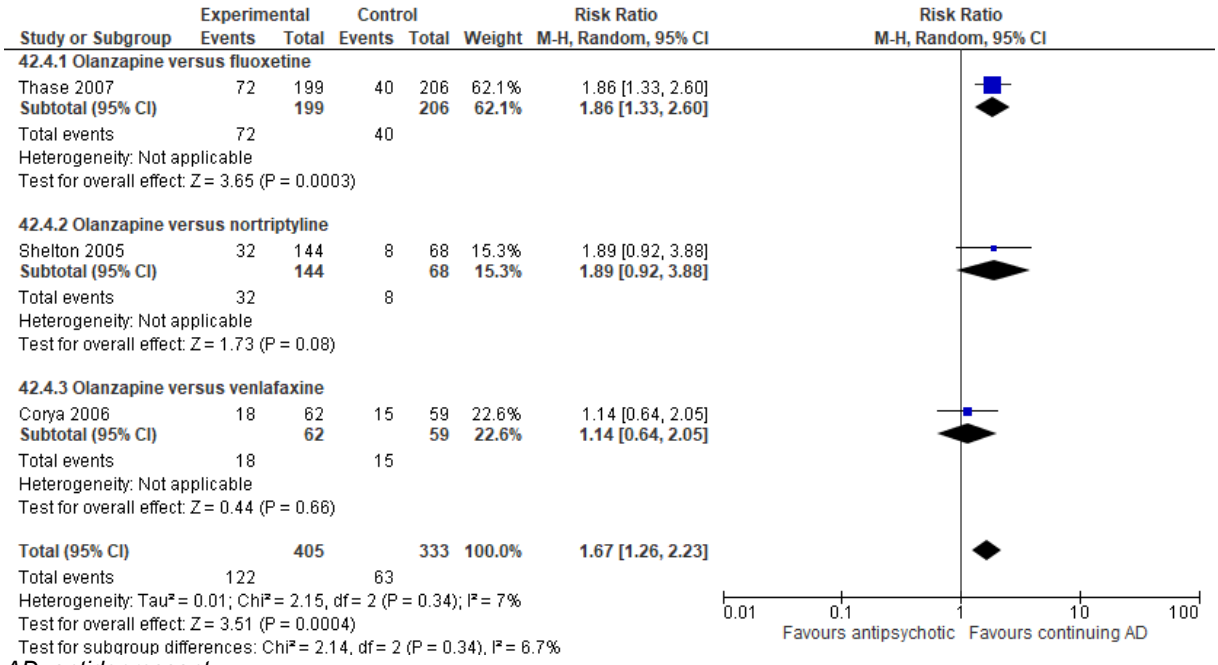
903 **Figure 257: Response (ITT)**



904
905 *AD: antidepressant*

906

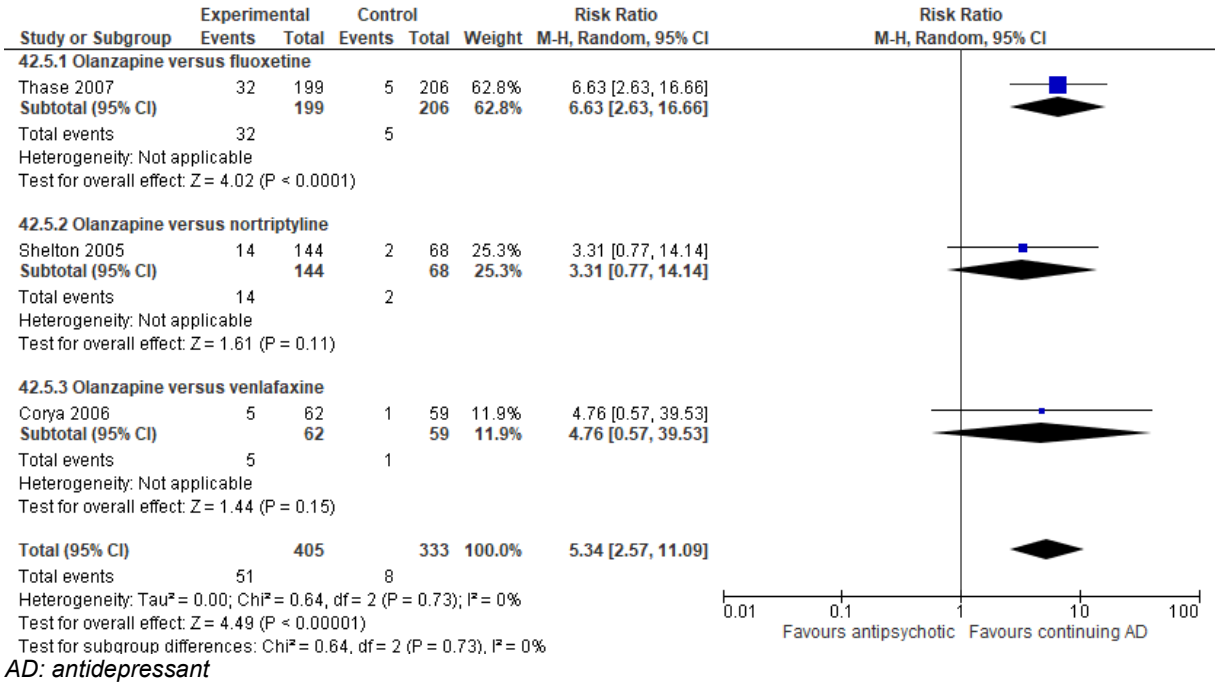
907 **Figure 258: Discontinuation due to any reason**



908
909 *AD: antidepressant*

910

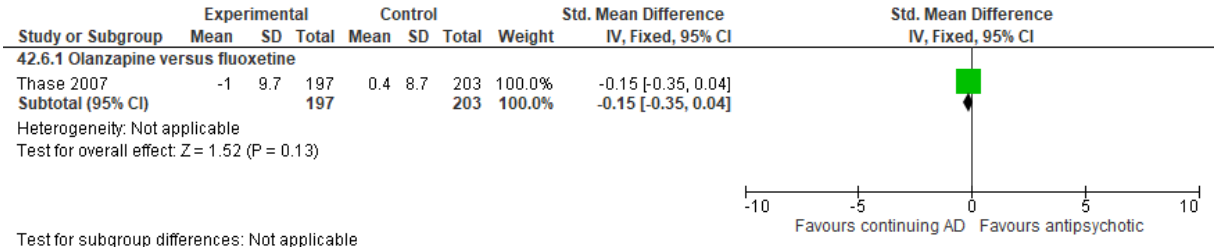
911 **Figure 259: Discontinuation due to side effects**



912
913 *AD: antidepressant*

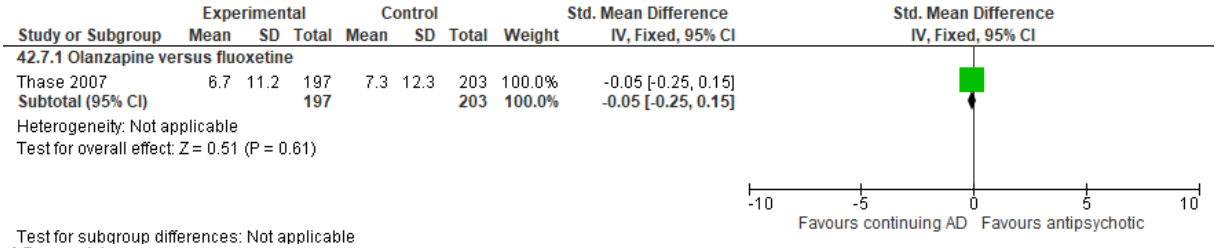
914

Figure 260: Quality of life physical component score (PCS) change score



AD: antidepressant

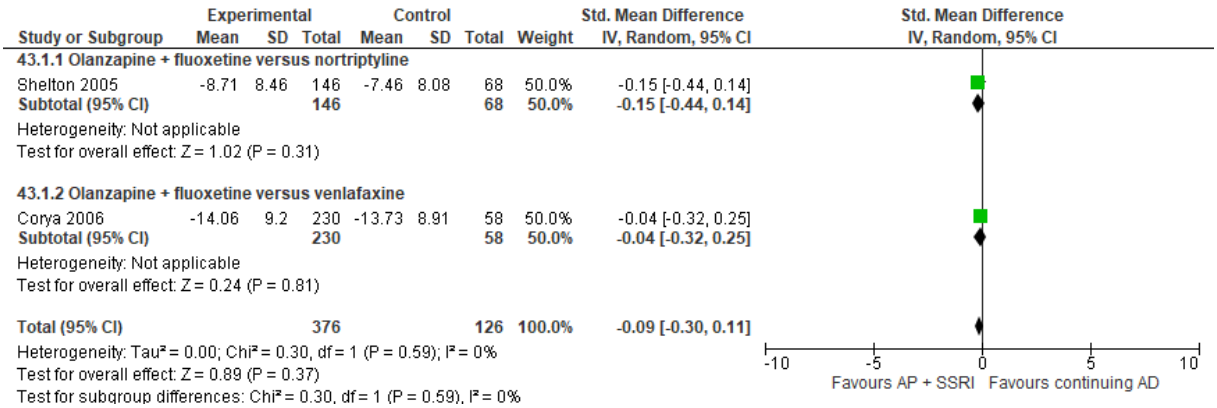
Figure 261: Quality of life mental component score (MCS) change score



AD: antidepressant

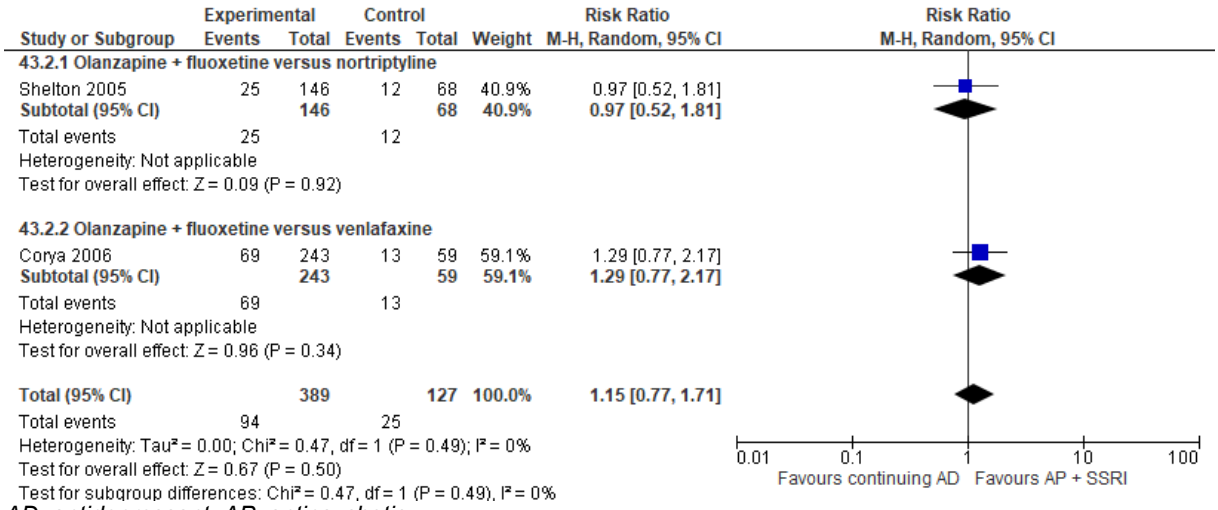
Comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

Figure 262: Depression symptomatology change score



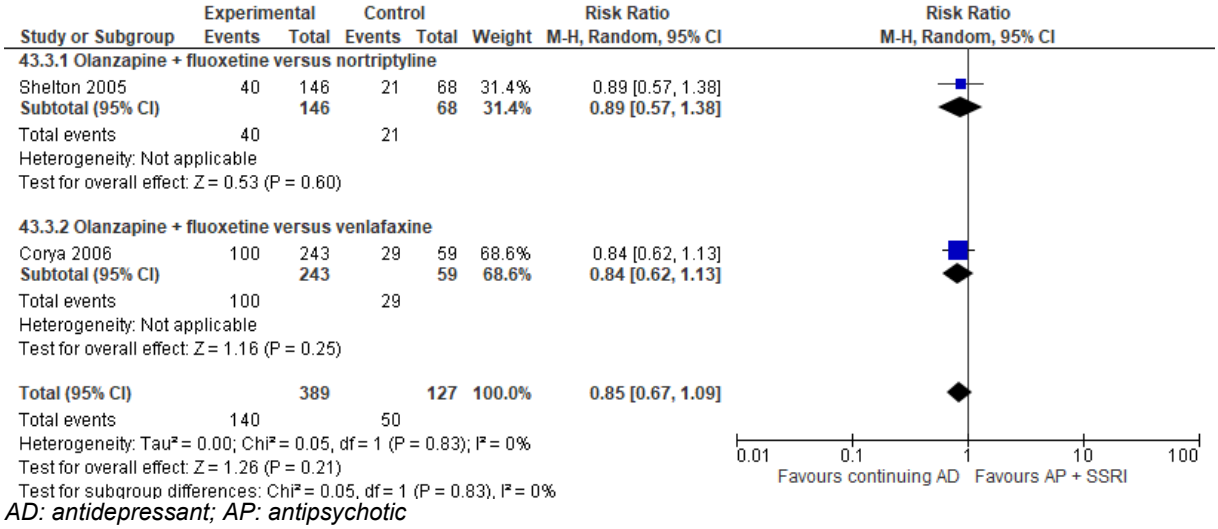
AD: antidepressant; AD: antipsychotic

Figure 263: Remission (ITT)



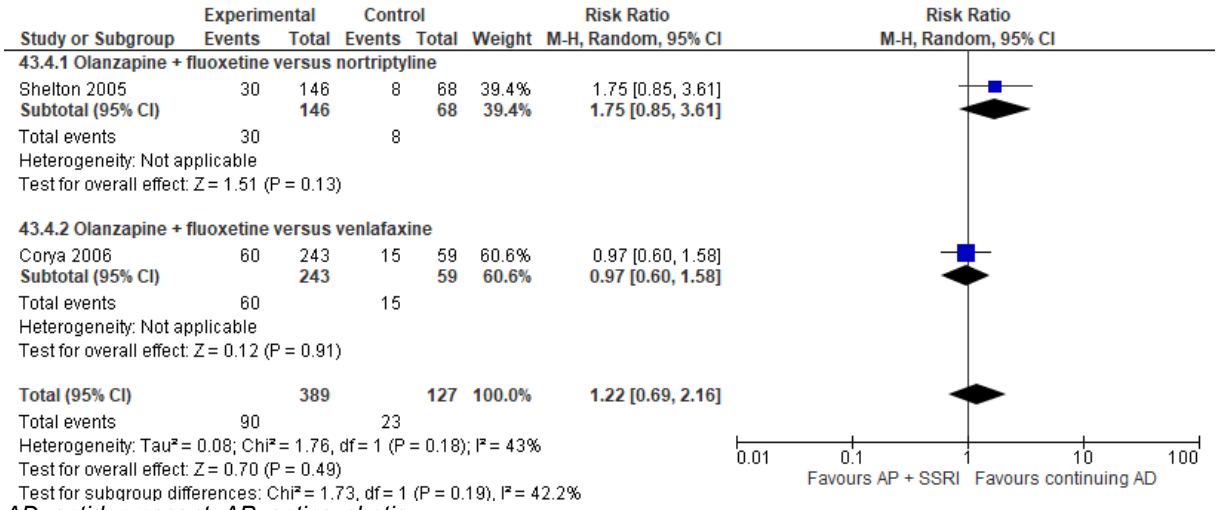
AD: antidepressant; AP: antipsychotic

Figure 264: Response (ITT)



AD: antidepressant; AP: antipsychotic

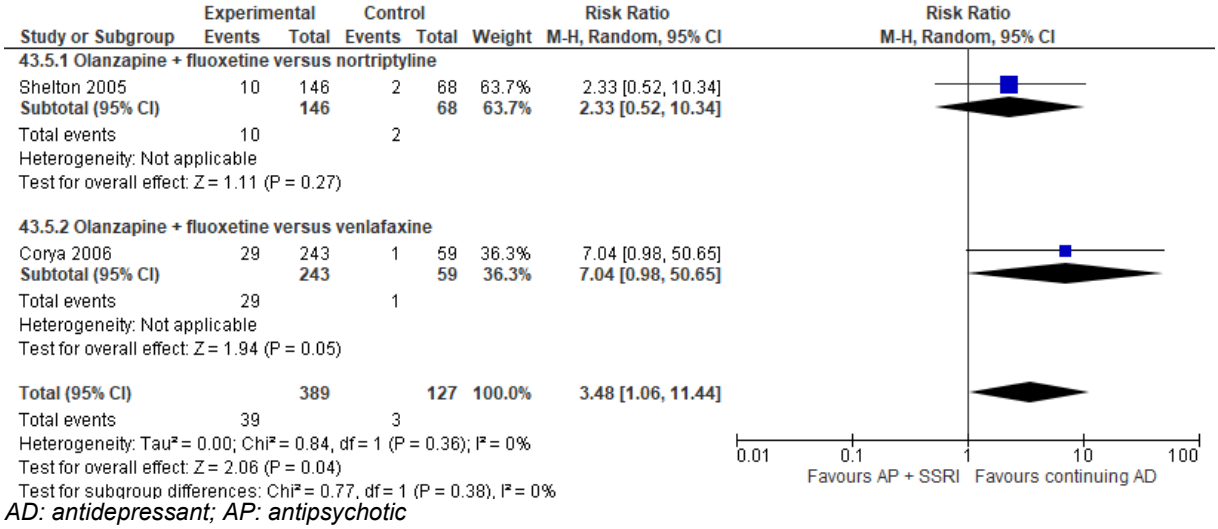
938 **Figure 265: Discontinuation due to any reason**



939
940 *AD: antidepressant; AP: antipsychotic*

941

942 **Figure 266: Discontinuation due to side effects**



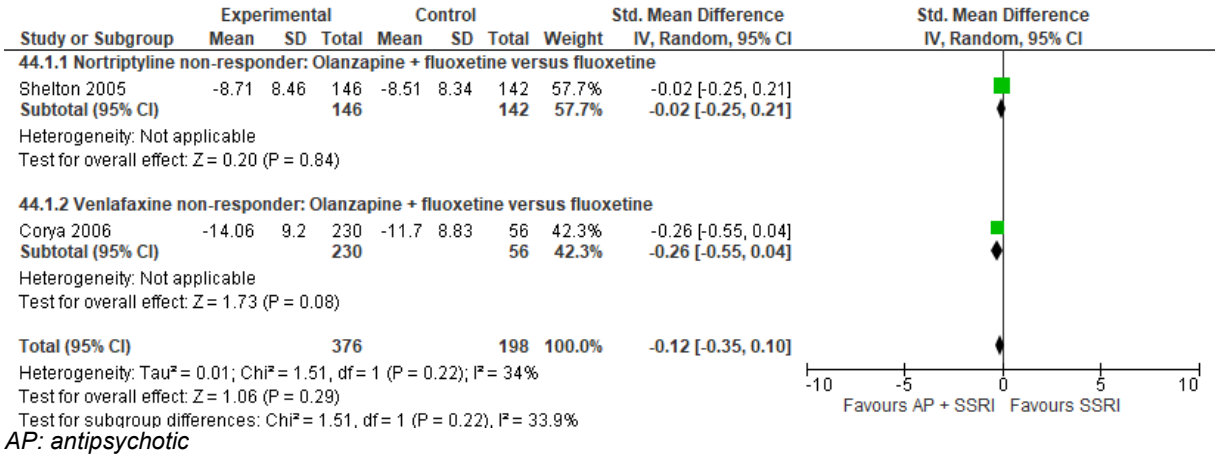
943
944 *AD: antidepressant; AP: antipsychotic*

945

946

947 ***Comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only***

948 **Figure 267: Depression symptomatology change score**

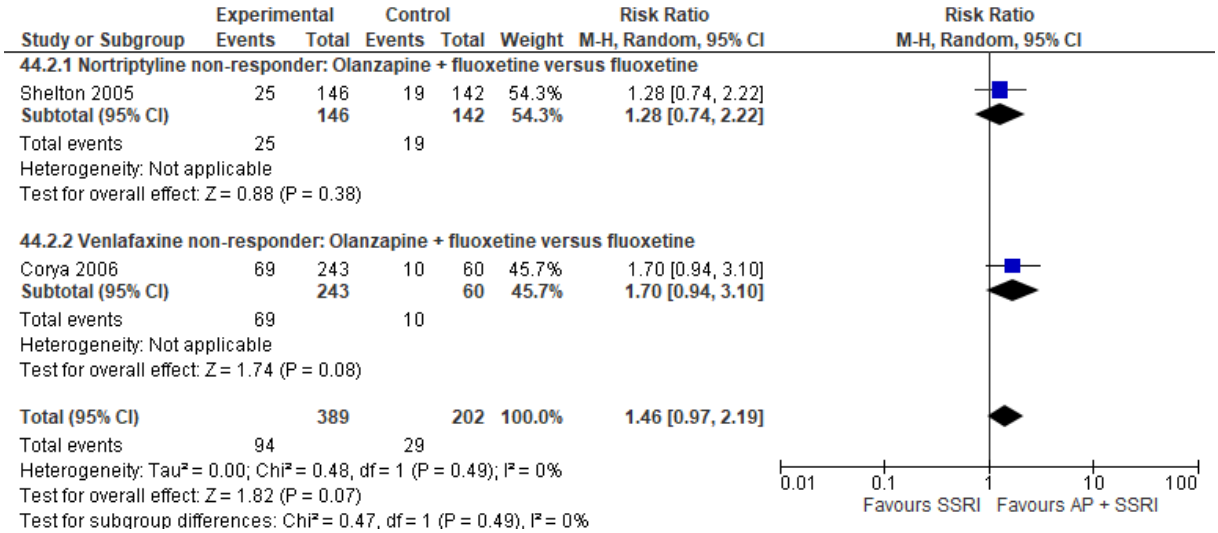


949 *AP: antipsychotic*

950

951

952 **Figure 268: Remission (ITT)**

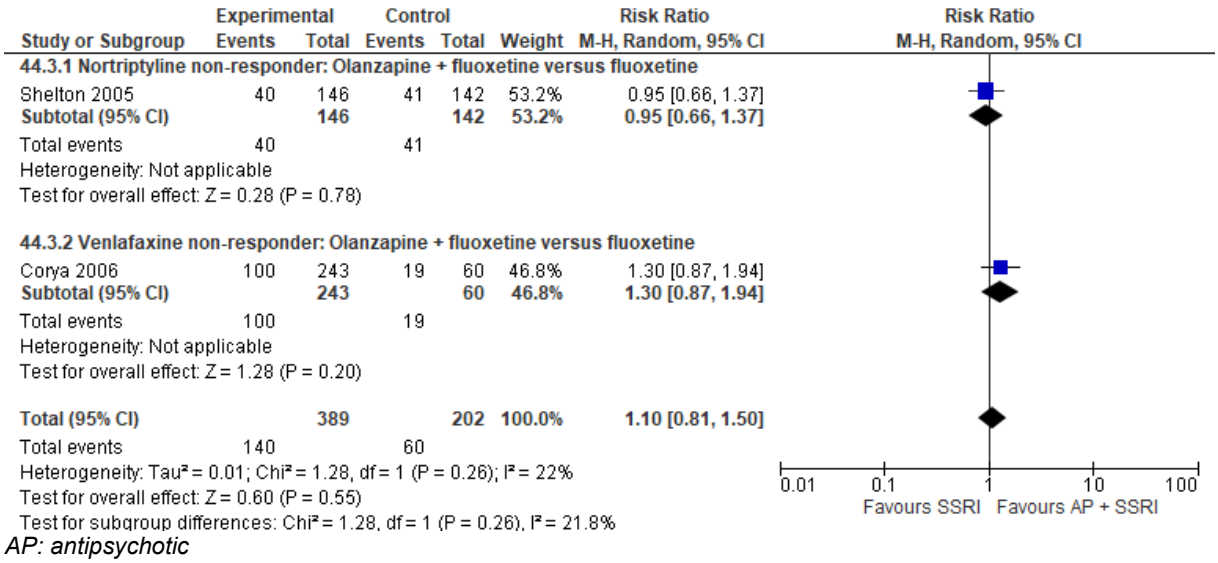


953 *AP: antipsychotic*

954

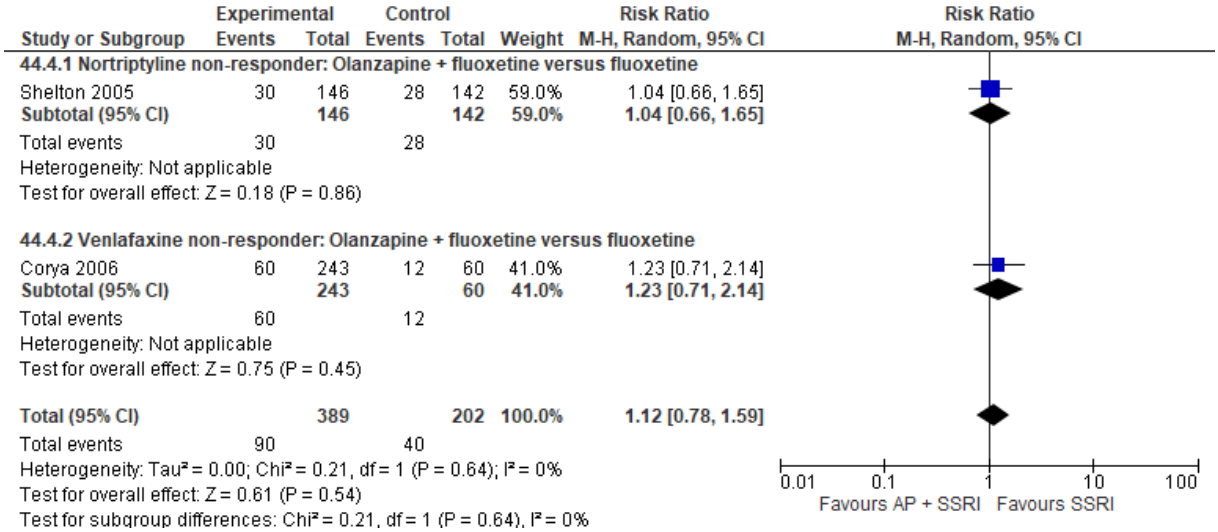
955

Figure 269: Response (ITT)



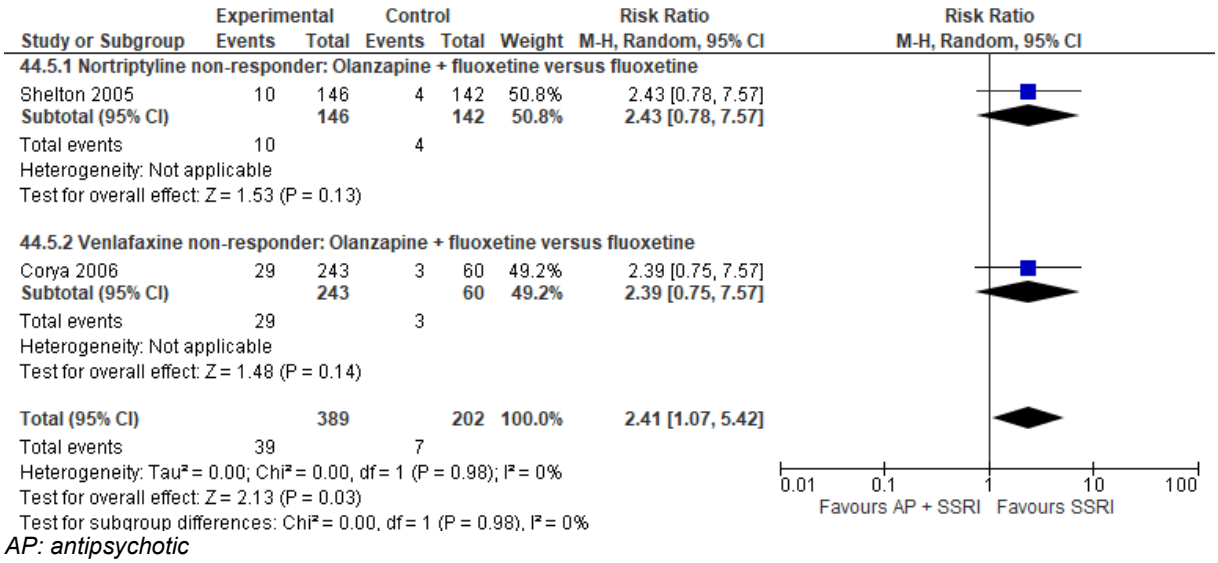
AP: antipsychotic

Figure 270: Discontinuation due to any reason



AP: antipsychotic

964 **Figure 271: Discontinuation due to side effects**



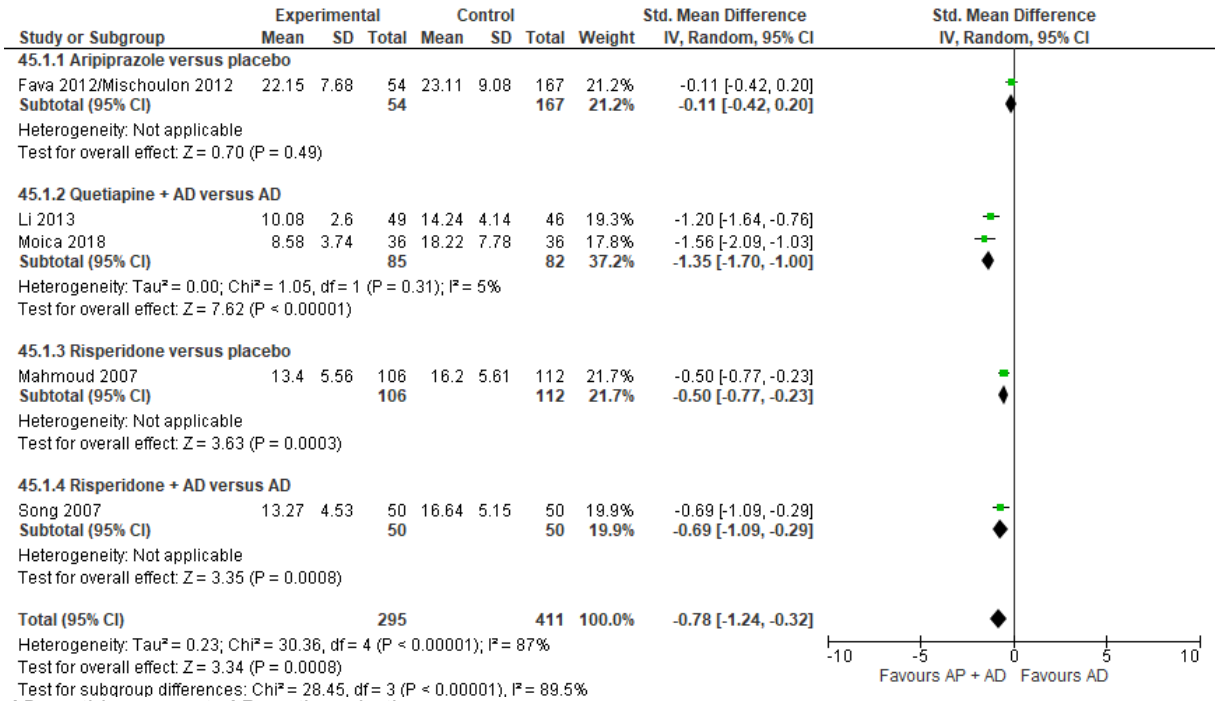
965
966 *AP: antipsychotic*

967

968

969 ***Comparison 45. Augmenting with antipsychotic versus antidepressant-only or***
970 ***antidepressant + placebo***

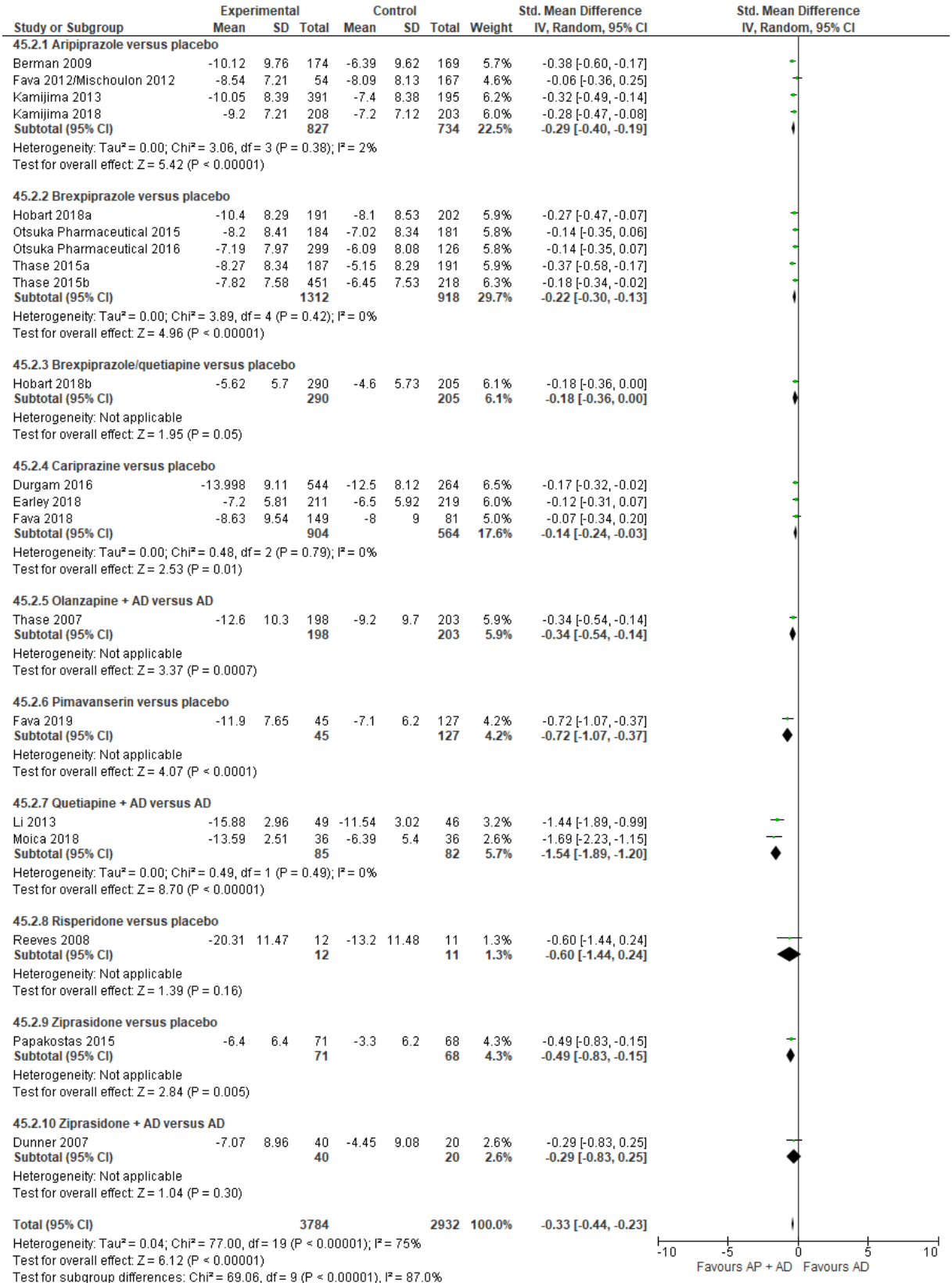
971 **Figure 272: Depression symptomatology endpoint**



972
973 *AD: antidepressant; AP: antipsychotic*

974

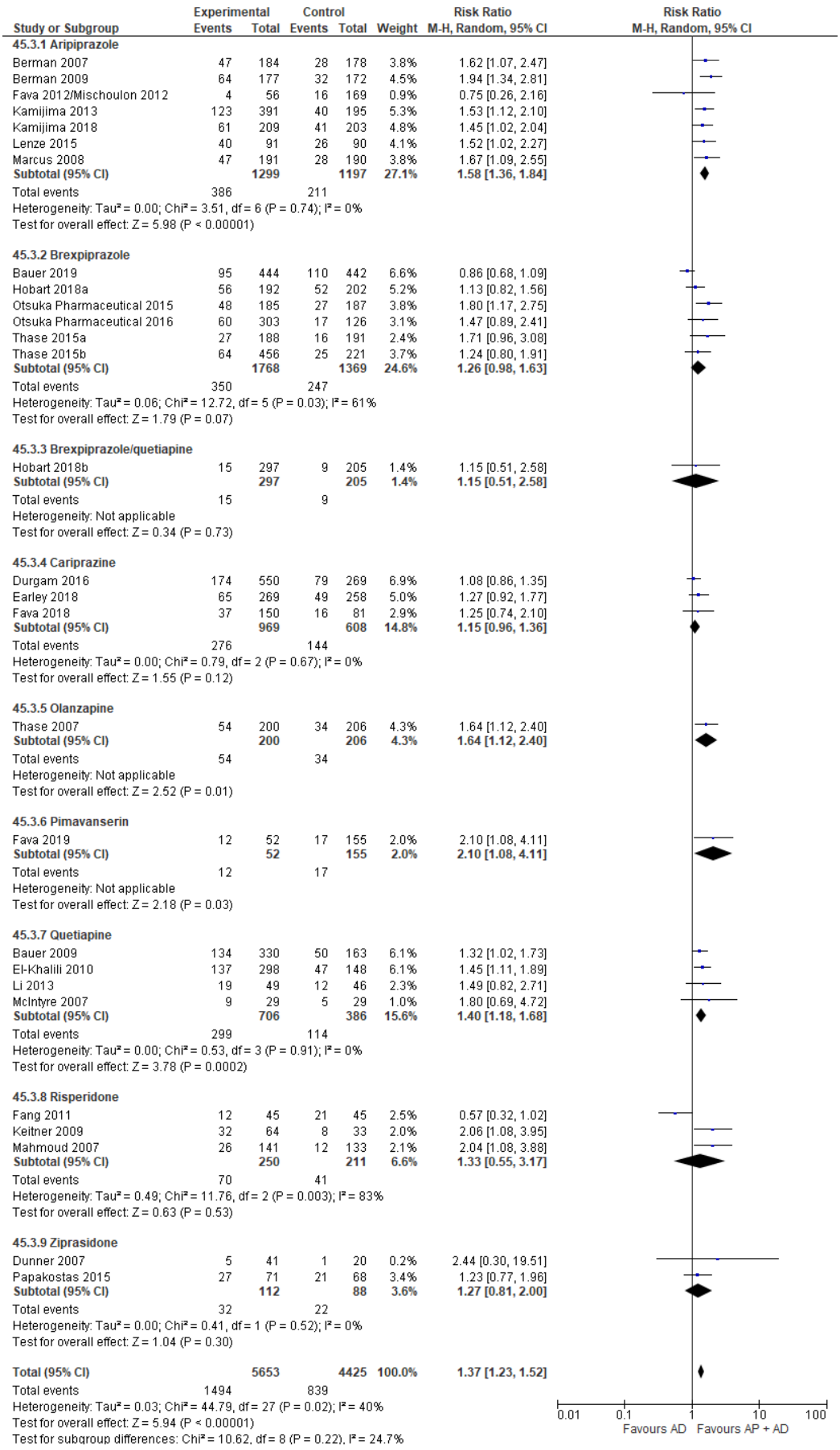
975 **Figure 273: Depression symptomatology change score**



976
977 *AD: antidepressant; AP: antipsychotic*

978

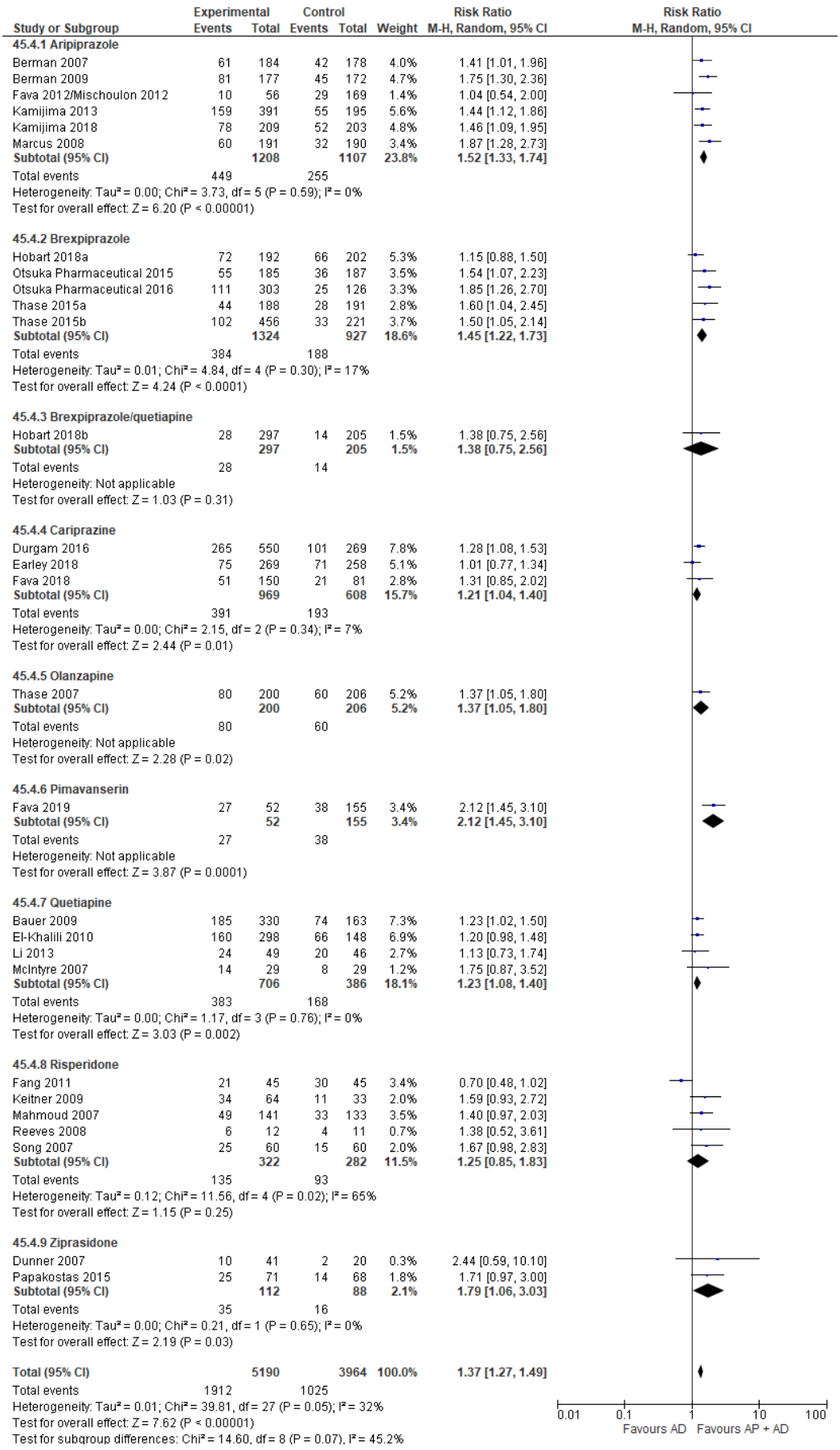
979 **Figure 274: Remission (ITT)**



980

AD: antidepressant; AP: antipsychotic

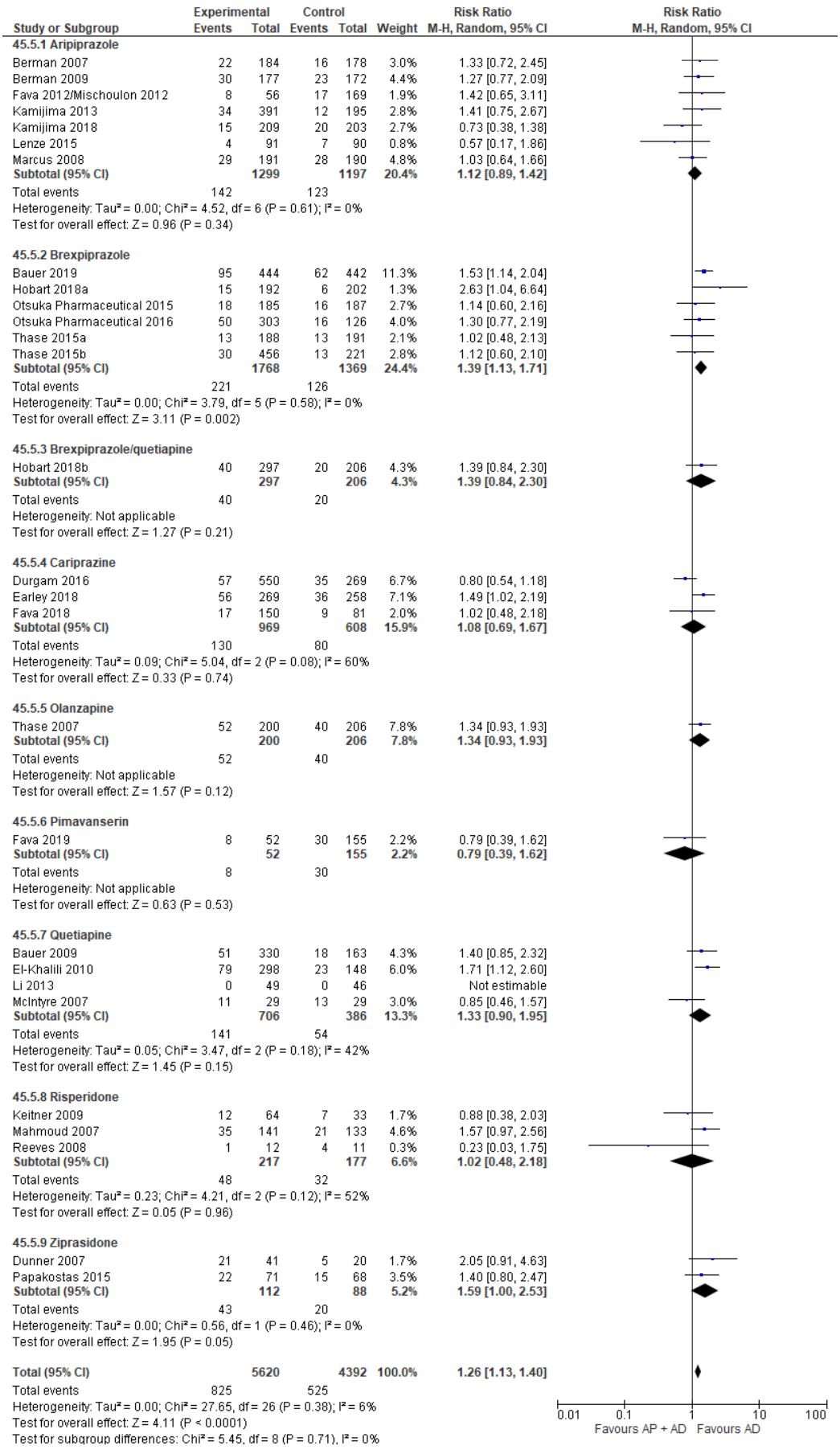
982 **Figure 275: Response (ITT)**



983

984 *AD: antidepressant; AP: antipsychotic*

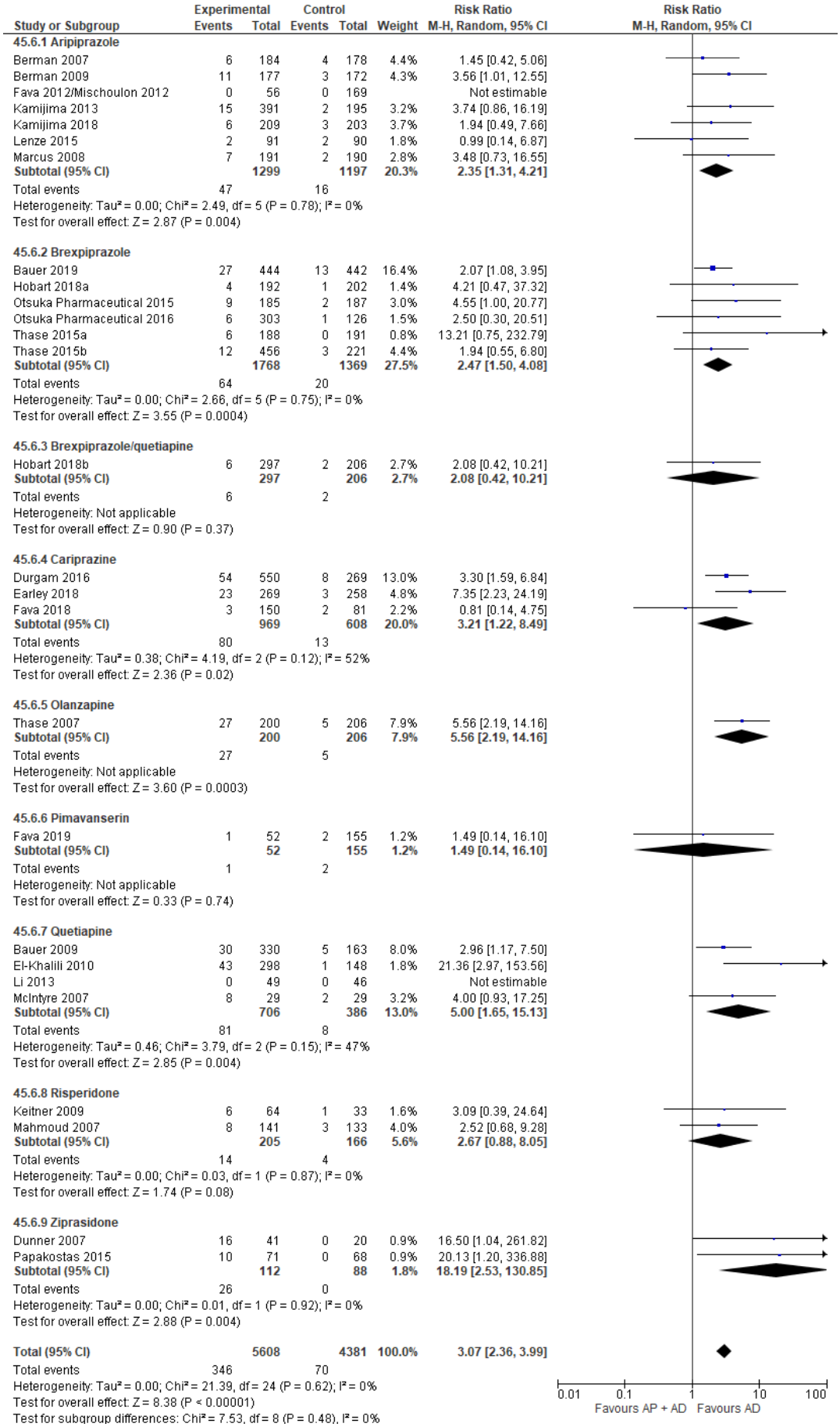
985 **Figure 276: Discontinuation due to any reason**



986

987 *<Insert Note here>*
988 *AD: antidepressant; AP: antipsychotic*

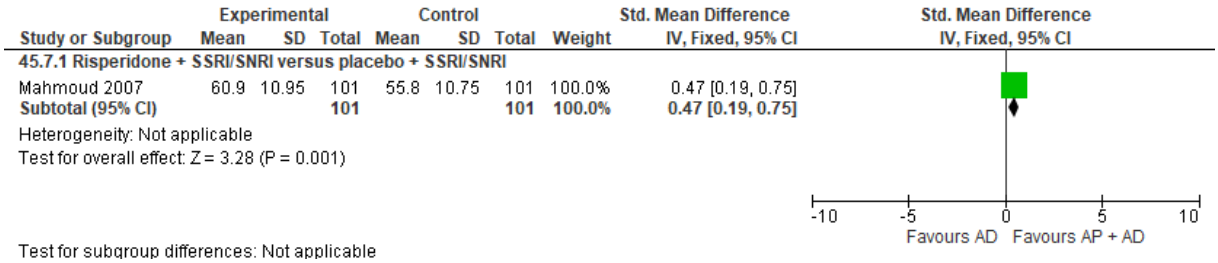
989 **Figure 277: Discontinuation due to side effects**



AD: antidepressant; AP: antipsychotic

992

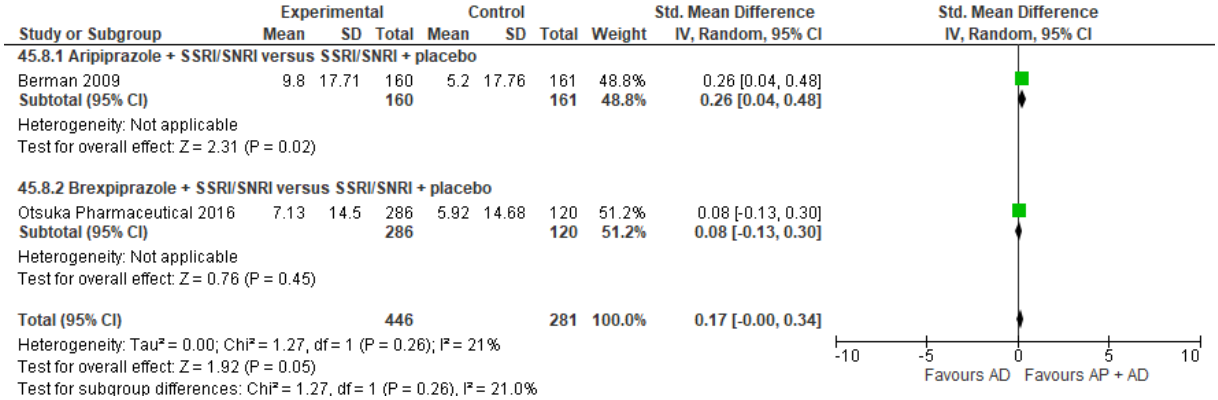
993 **Figure 278: Quality of life endpoint**



994
995 *AD: antidepressant; AP: antipsychotic*

996

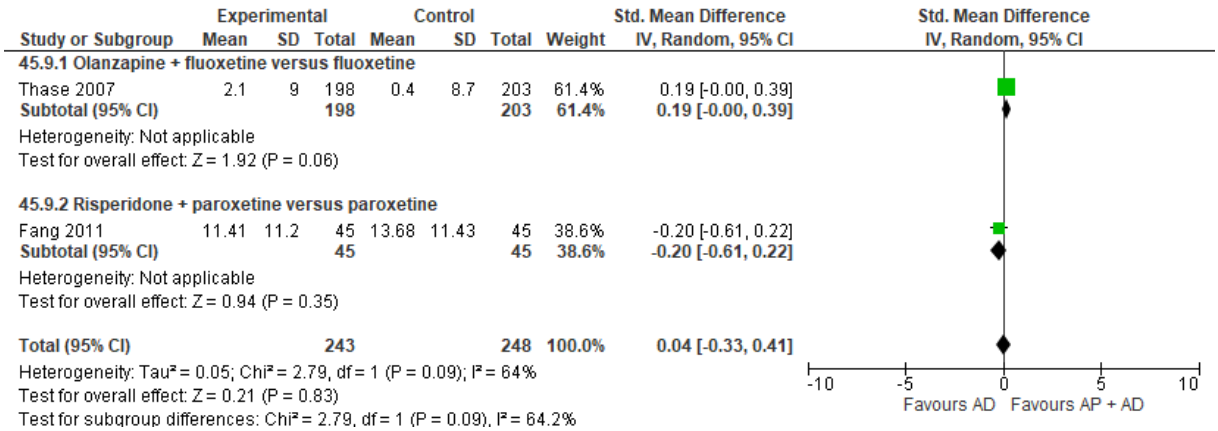
997 **Figure 279: Quality of life change score**



998
999 *AD: antidepressant; AP: antipsychotic*

1000

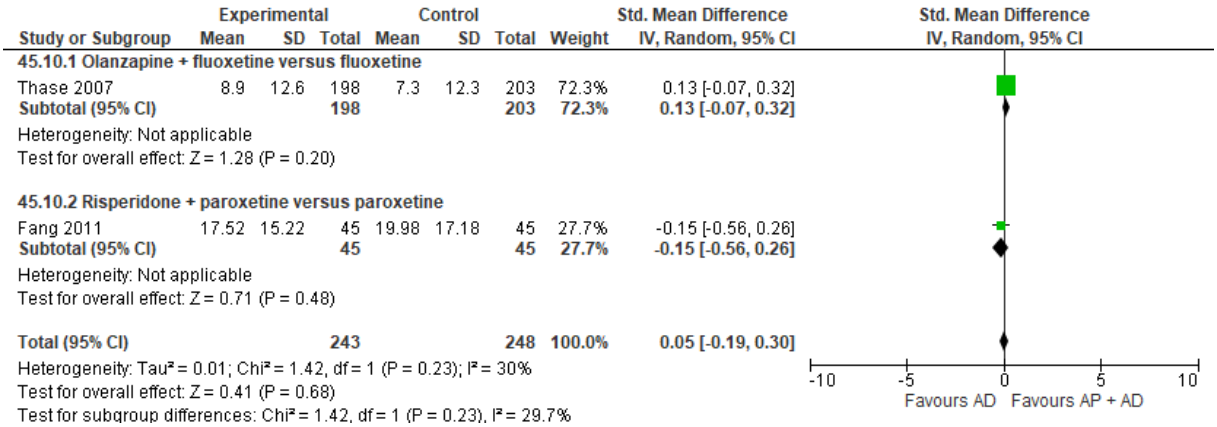
1001 **Figure 280: Quality of life physical component score (PCS) change score**



1002
1003 *AD: antidepressant; AP: antipsychotic*

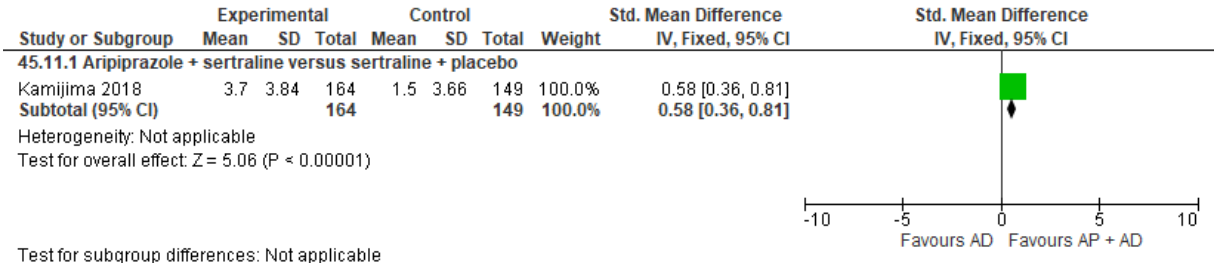
1004

Figure 281: Quality of life mental component score (MCS) change score



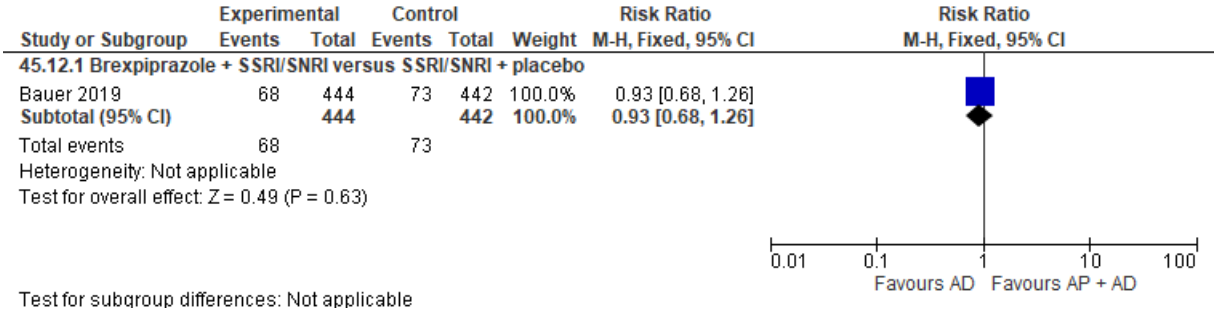
AD: antidepressant; AP: antipsychotic

Figure 282: Global functioning change score



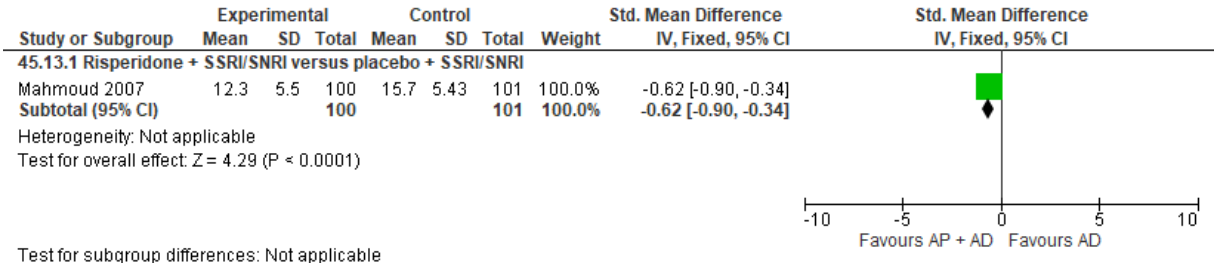
AD: antidepressant; AP: antipsychotic

Figure 283: Functional remission (≤6 total score on SDS and all SDS domain scores ≤2)



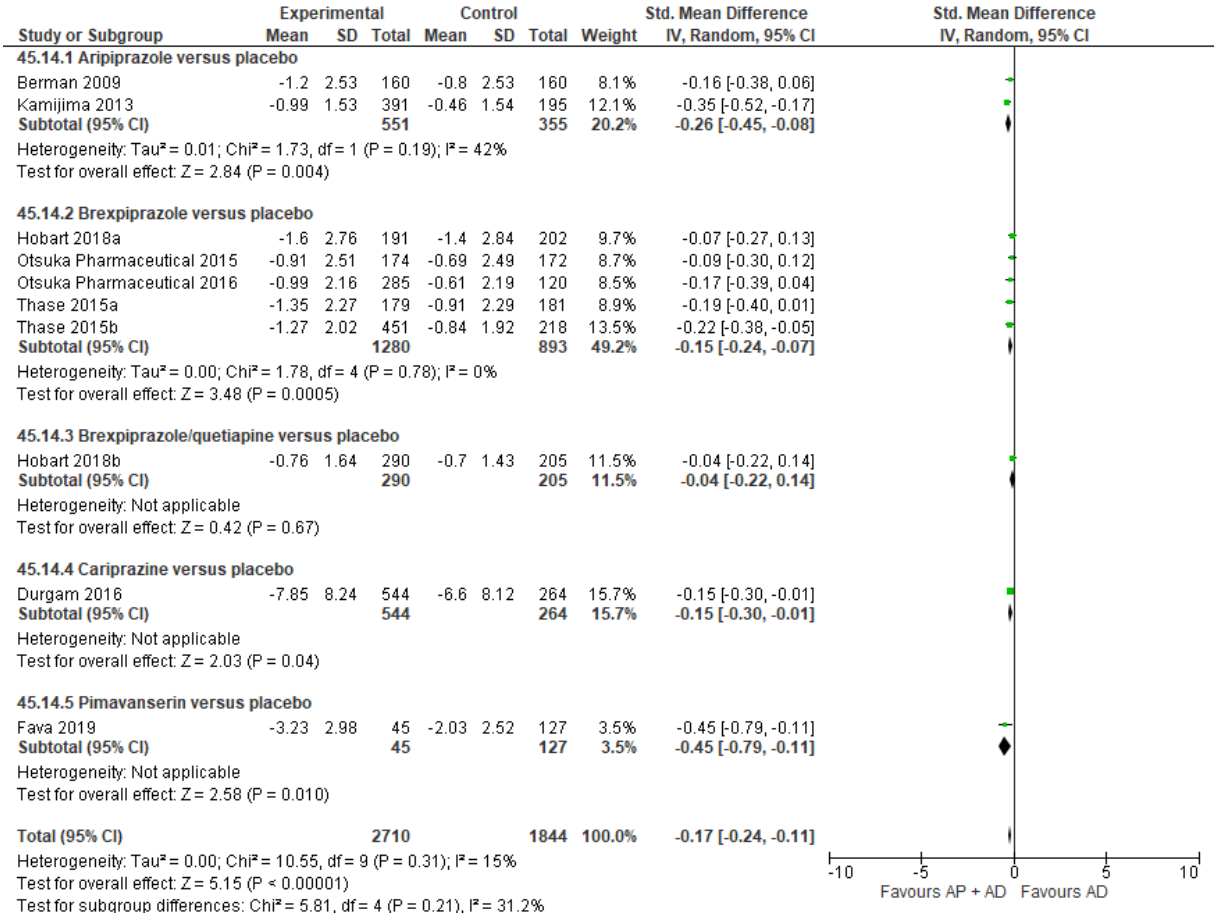
AD: antidepressant; AP: antipsychotic

Figure 284: Functional impairment endpoint



AD: antidepressant; AP: antipsychotic

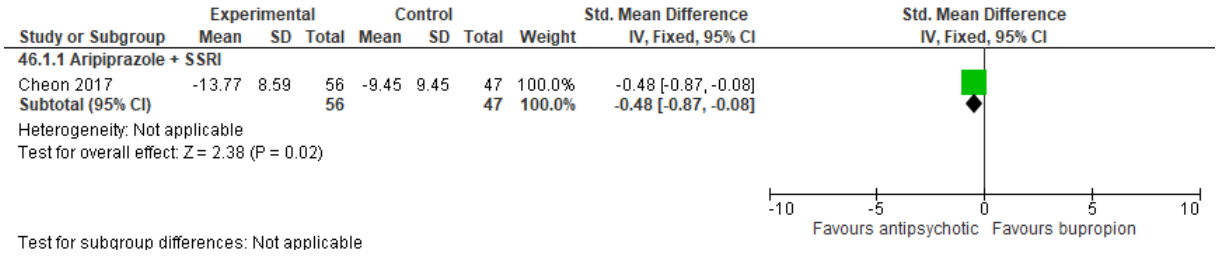
Figure 285: Functional impairment change score



AD: antidepressant; AP: antipsychotic

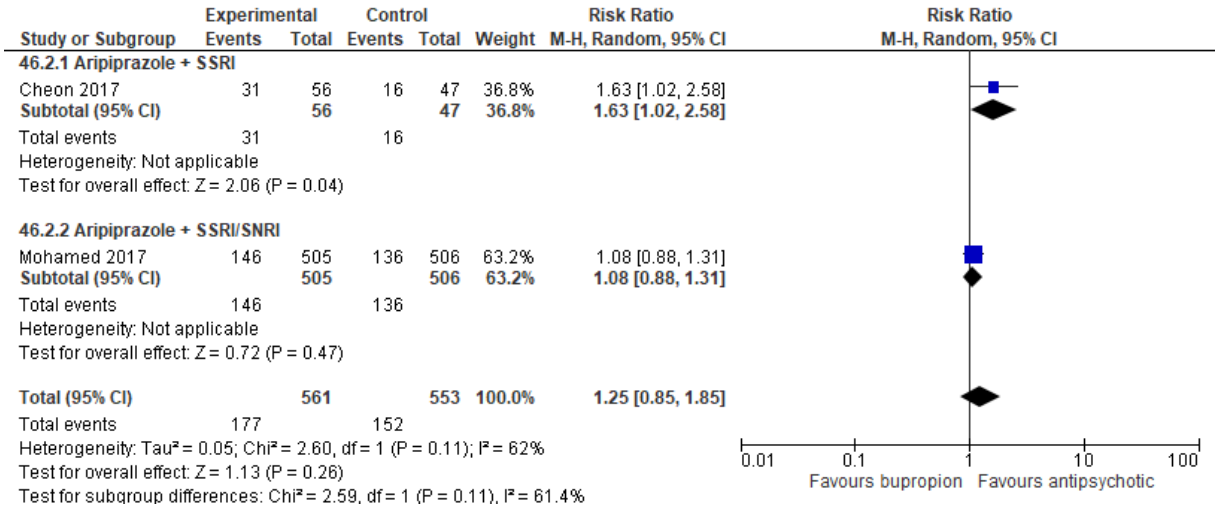
Comparison 46. Augmenting with antipsychotic versus bupropion

Figure 286: Depression symptomatology change score



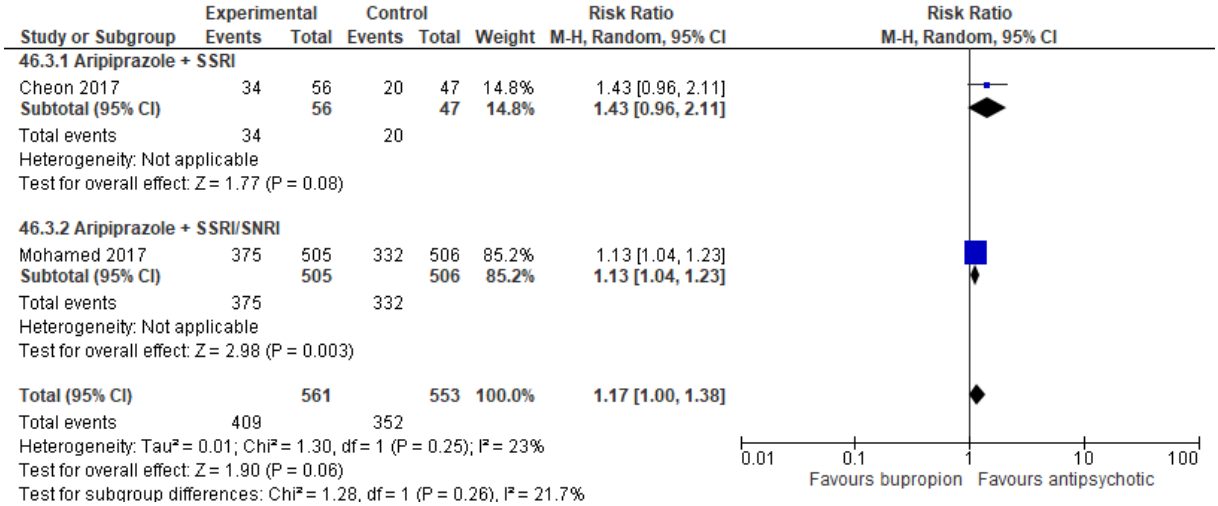
Test for subgroup differences: Not applicable

Figure 287: Remission (ITT)



Test for subgroup differences: Chi² = 2.59, df = 1 (P = 0.11), I² = 61.4%

Figure 288: Response (ITT)



Test for subgroup differences: Chi² = 1.28, df = 1 (P = 0.26), I² = 21.7%

Figure 289: Discontinuation due to any reason

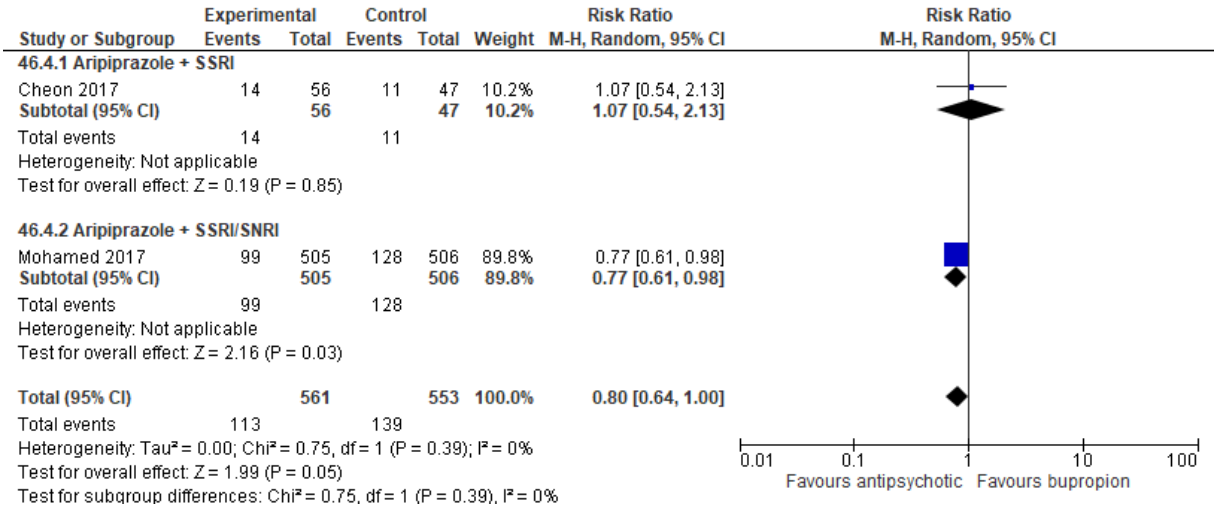
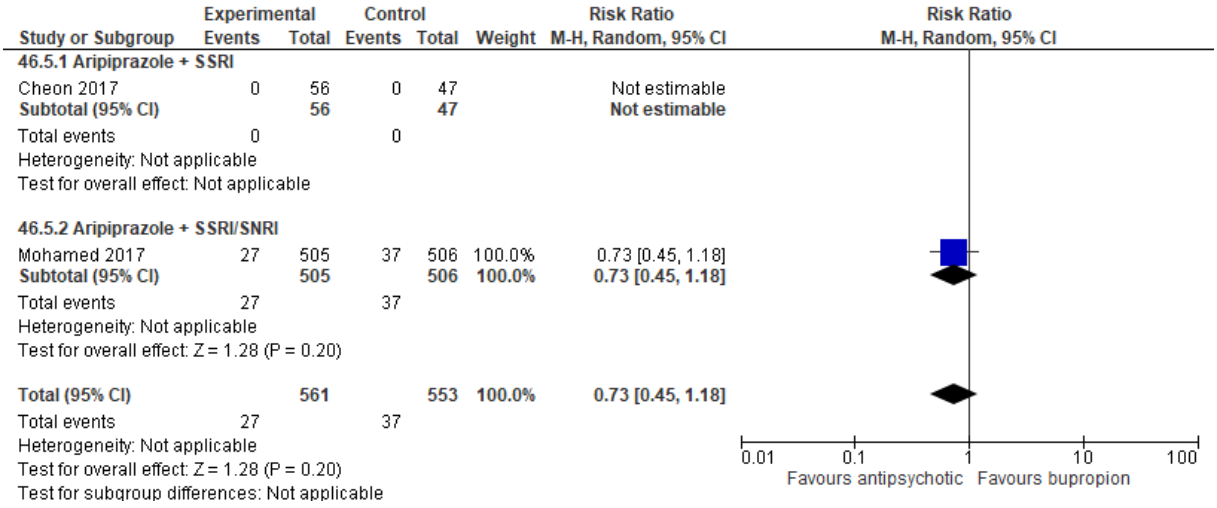
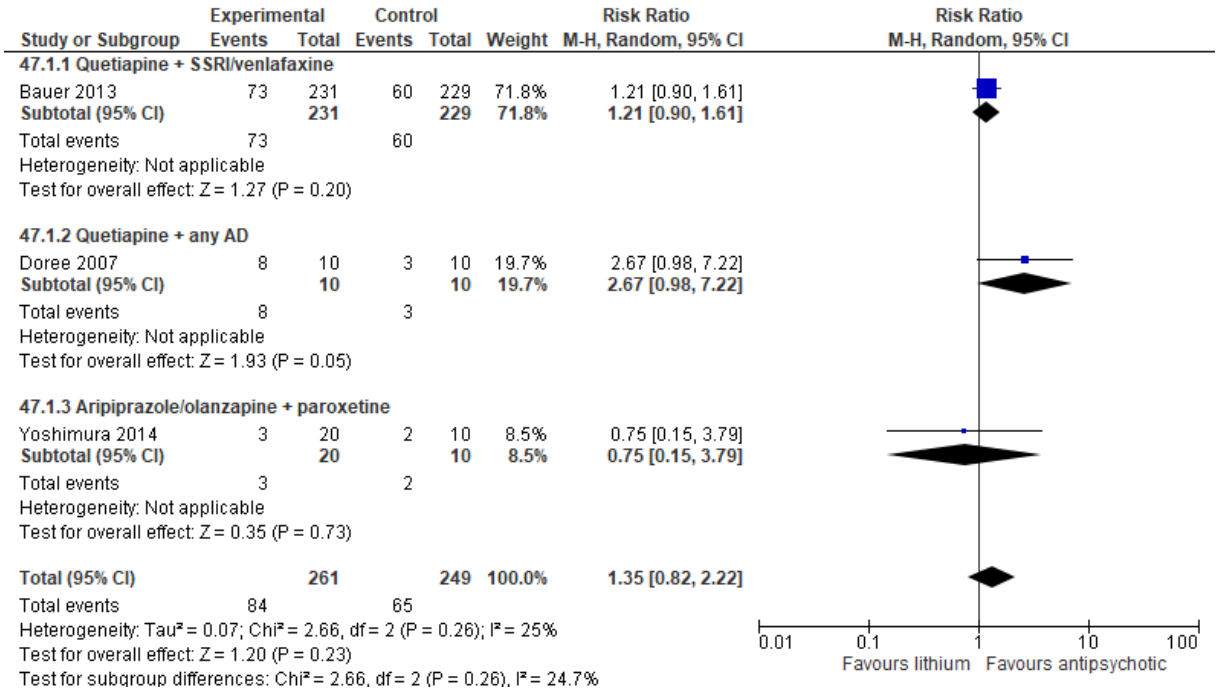


Figure 290: Discontinuation due to side effects



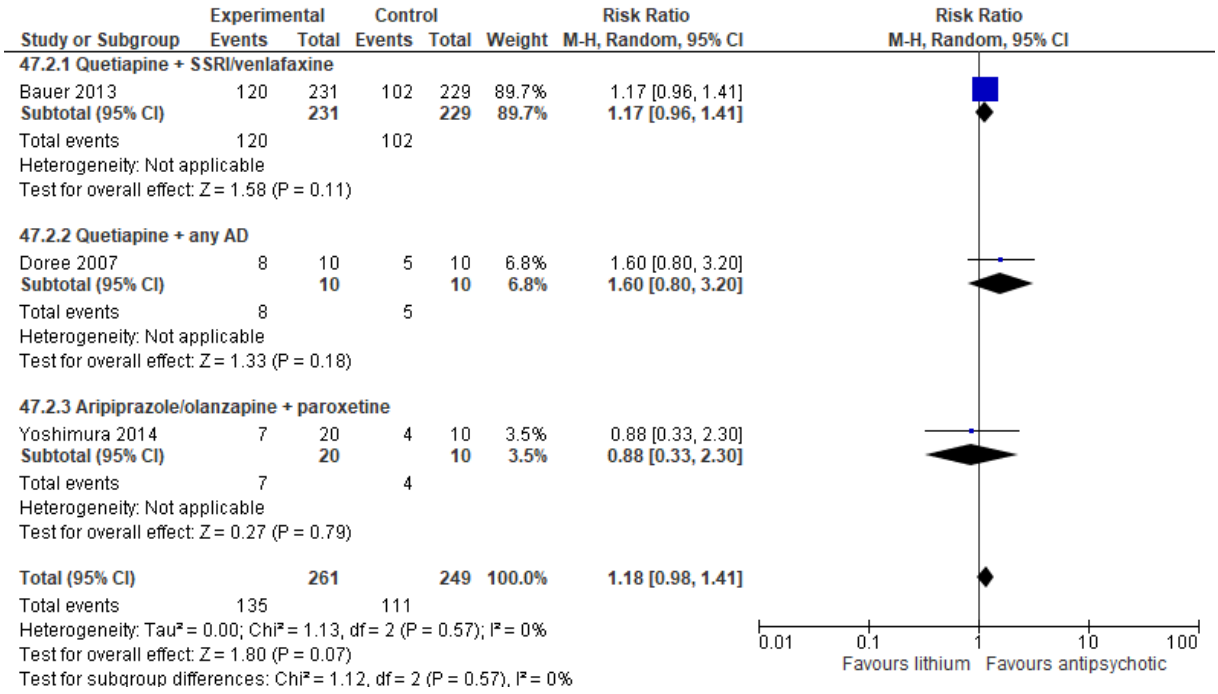
1039 ***Comparison 47. Augmenting with antipsychotic versus lithium***

1040 **Figure 291: Remission (ITT)**



1041

1042 **Figure 292: Response (ITT)**



1043

Figure 293: Discontinuation due to any reason

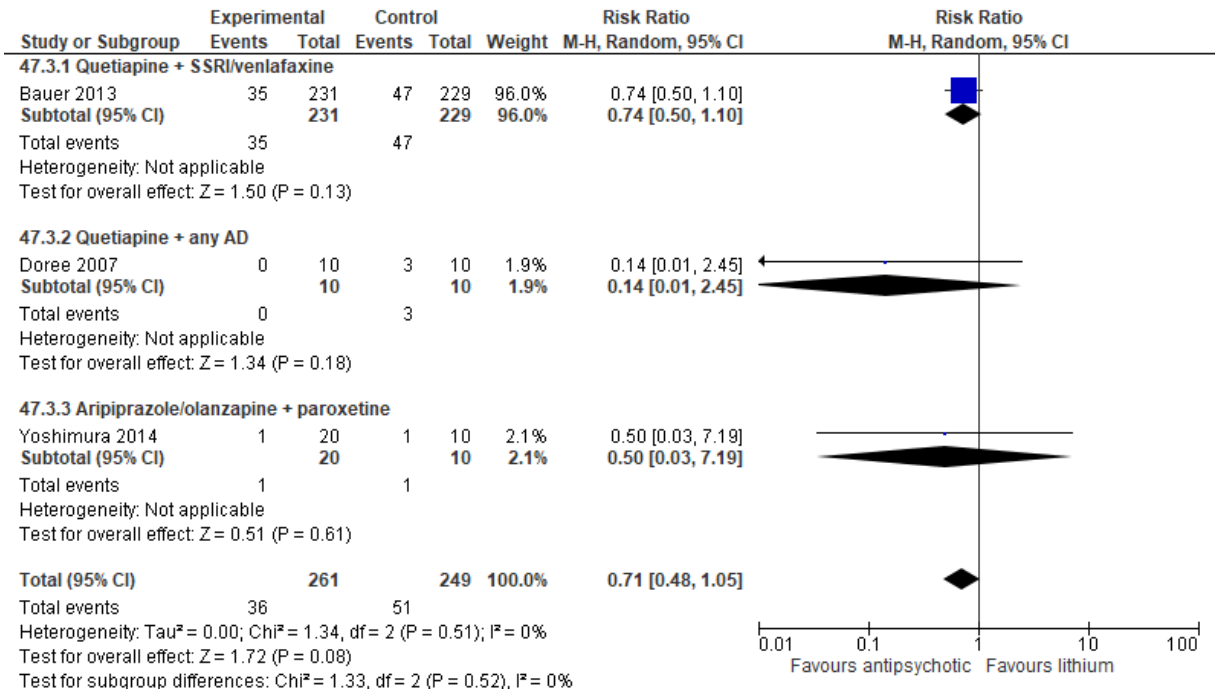
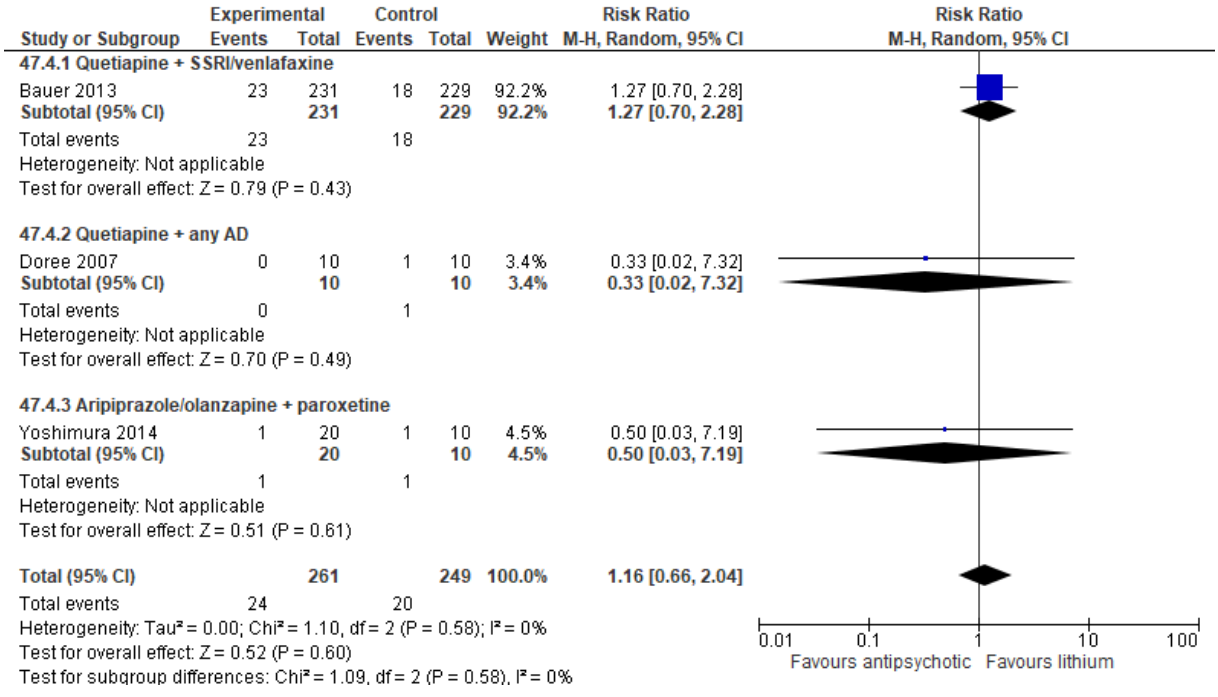
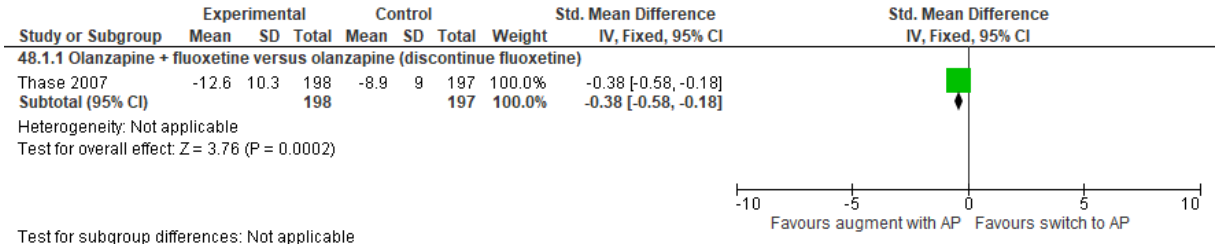


Figure 294: Discontinuation due to side effects



1049 ***Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic***

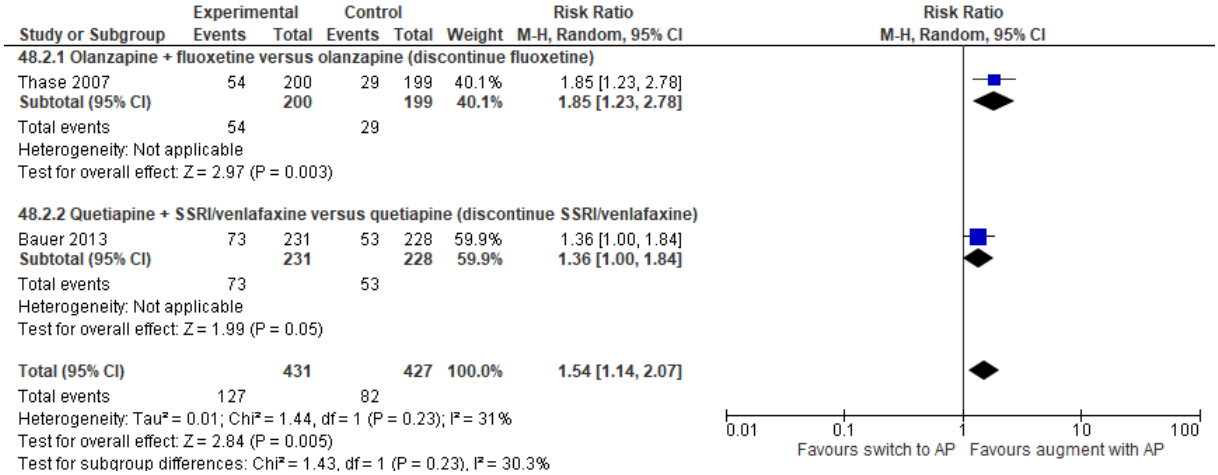
1050 **Figure 295: Depression symptomatology change score**



1051
1052 *AP: antipsychotic*

1053

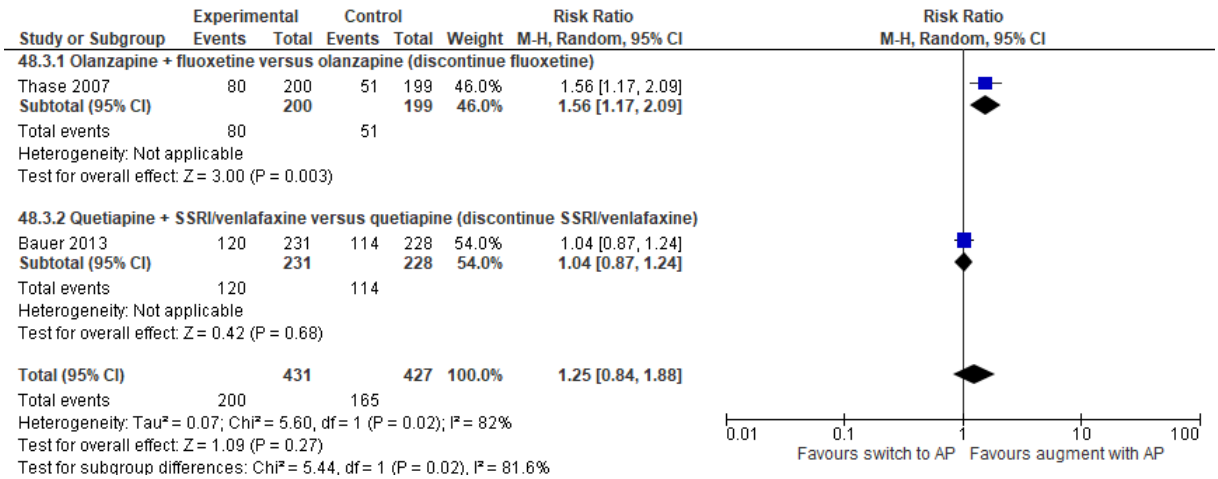
1054 **Figure 296: Remission (ITT)**



1055
1056 *AP: antipsychotic*

1057

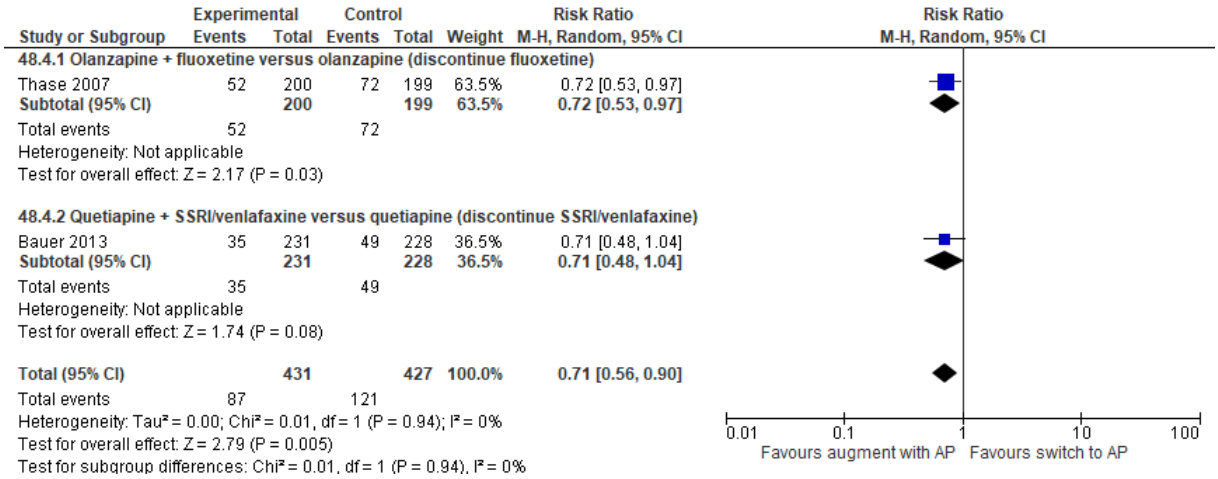
1058 **Figure 297: Response (ITT)**



1059
1060 *AP: antipsychotic*

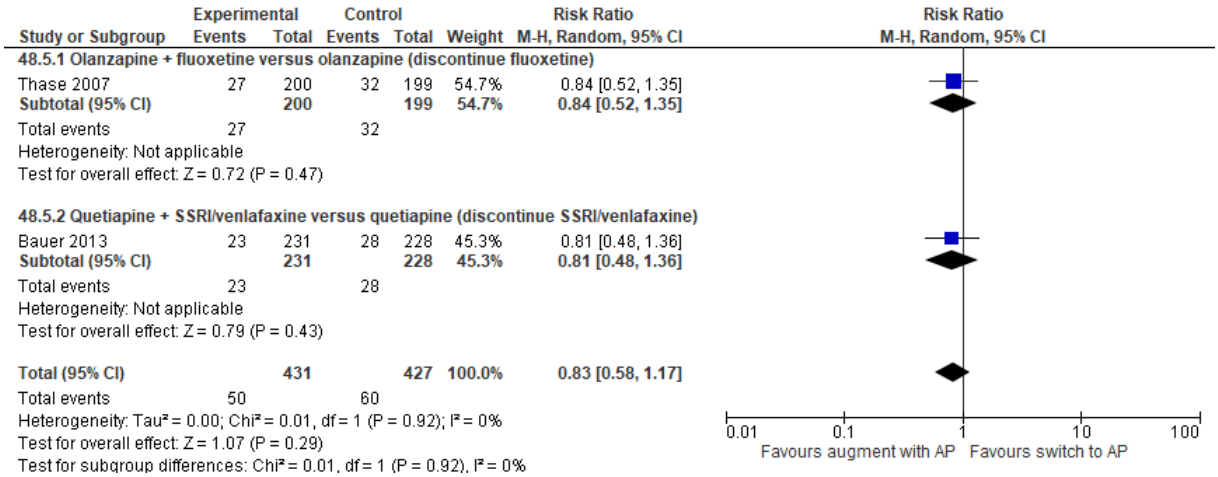
1061

Figure 298: Discontinuation due to any reason



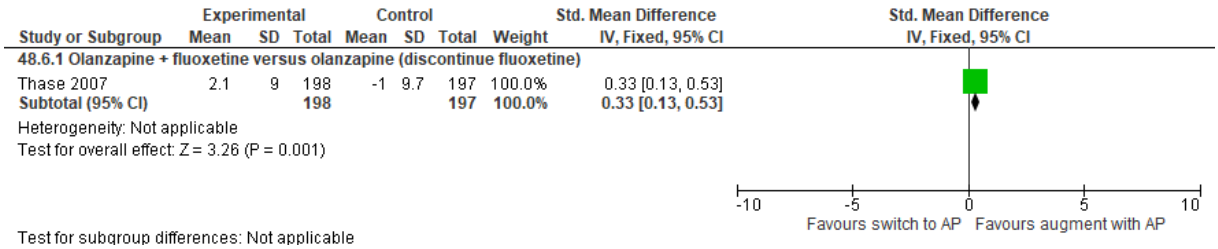
AP: antipsychotic

Figure 299: Discontinuation due to side effects



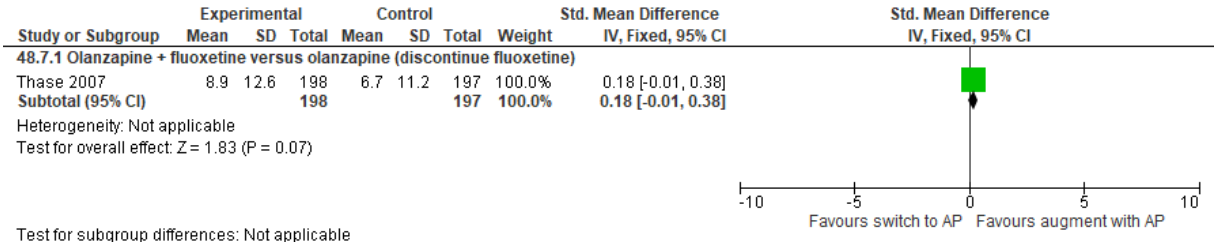
AP: antipsychotic

Figure 300: Quality of life physical component score (PCS) change score



AP: antipsychotic

Figure 301: Quality of life mental component score (MCS) change score

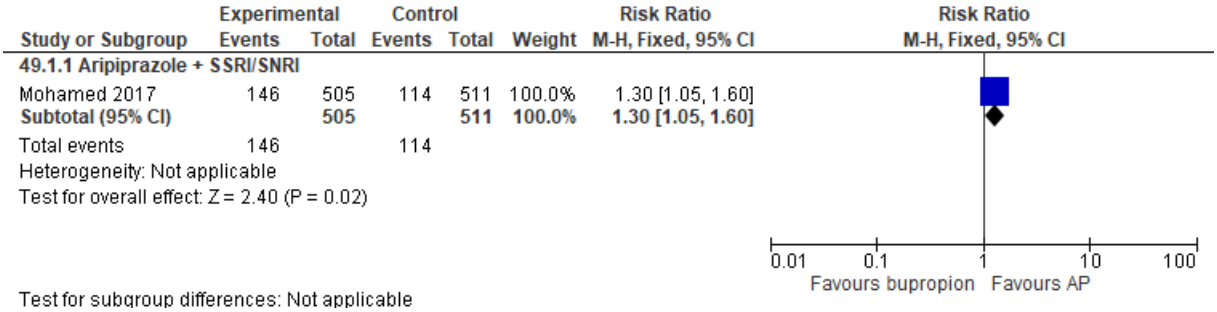


Test for subgroup differences: Not applicable

AP: antipsychotic

Comparison 49. Augmenting with antipsychotic versus switch to bupropion

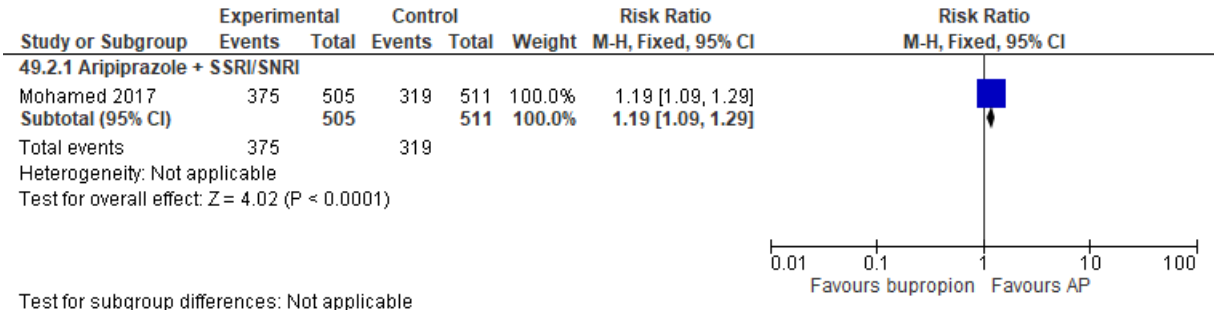
Figure 302: Remission (ITT)



Test for subgroup differences: Not applicable

AP: antipsychotic

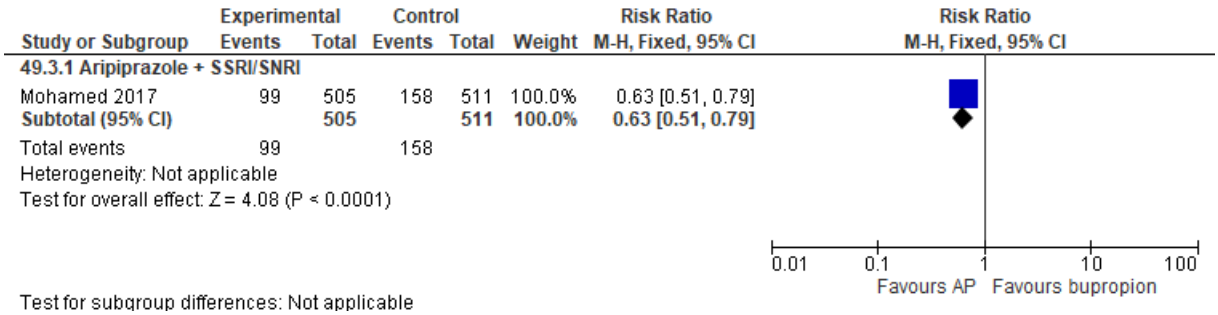
Figure 303: Response (ITT)



Test for subgroup differences: Not applicable

AP: antipsychotic

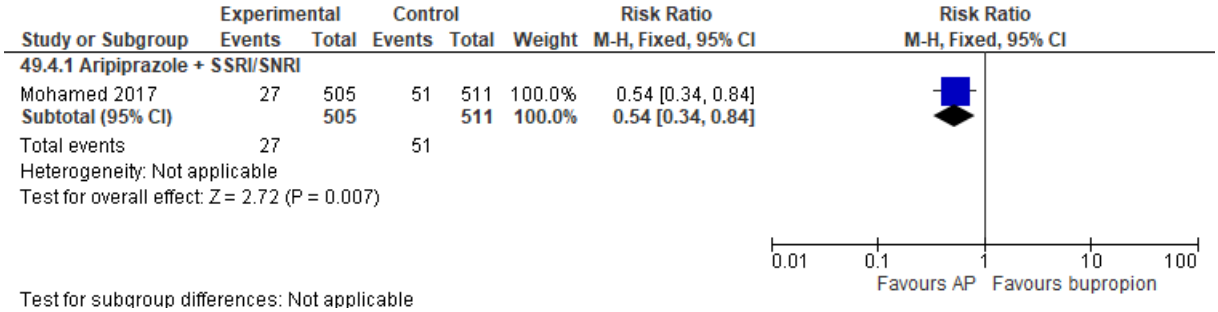
Figure 304: Discontinuation due to any reason



Test for subgroup differences: Not applicable

AP: antipsychotic

Figure 305: Discontinuation due to side effects

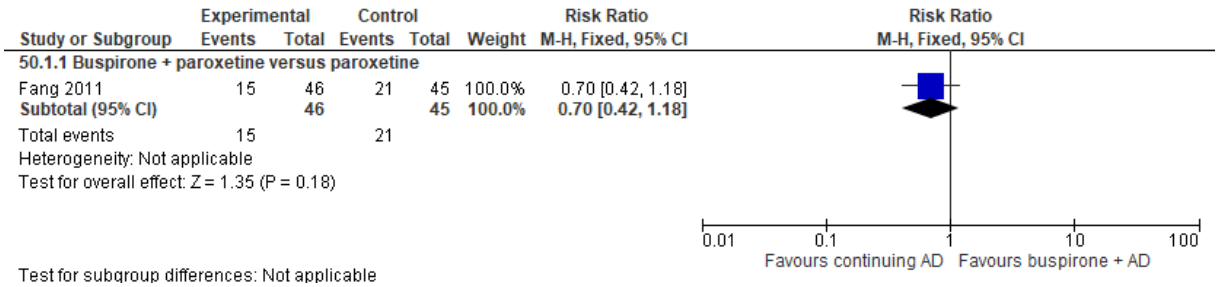


Test for subgroup differences: Not applicable

AP: antipsychotic

Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/- placebo)

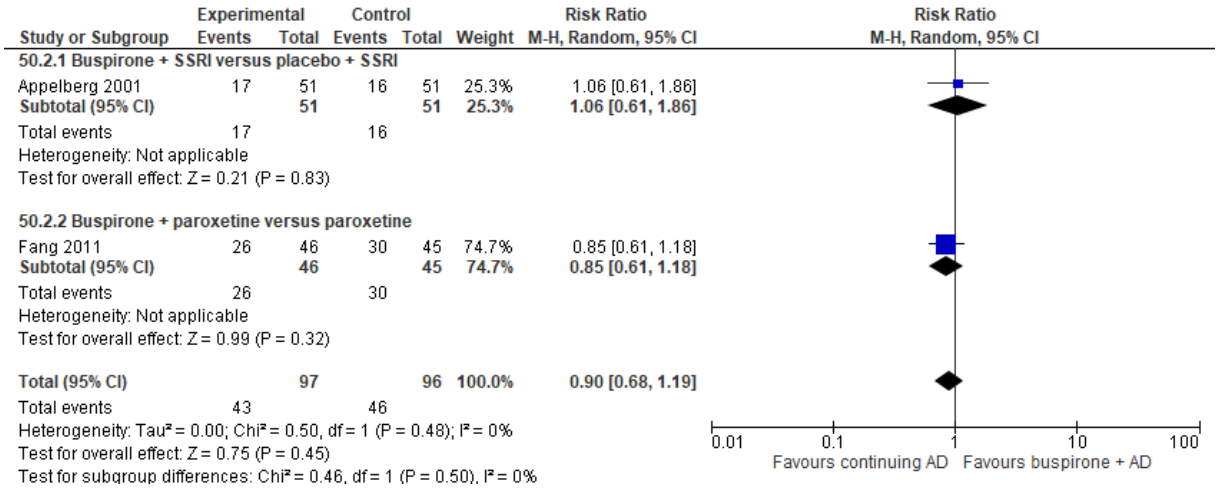
Figure 306: Remission (ITT)



Test for subgroup differences: Not applicable

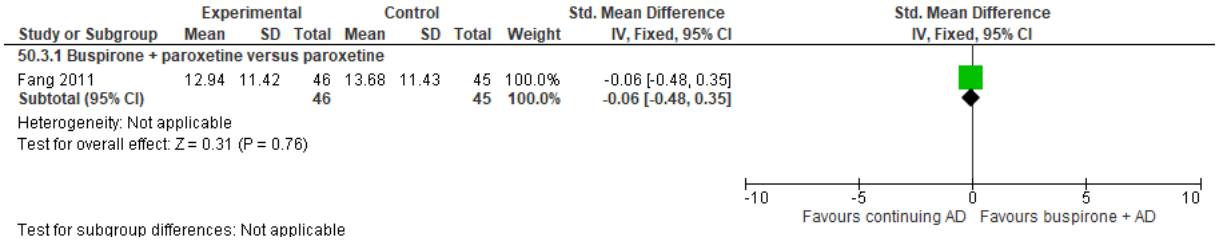
AD: antidepressant

Figure 307: Response (ITT)



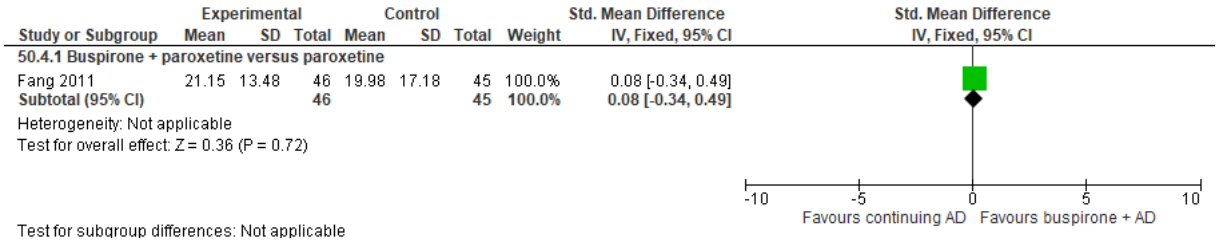
AD: antidepressant

Figure 308: Quality of life physical component score (PCS) change score



AD: antidepressant

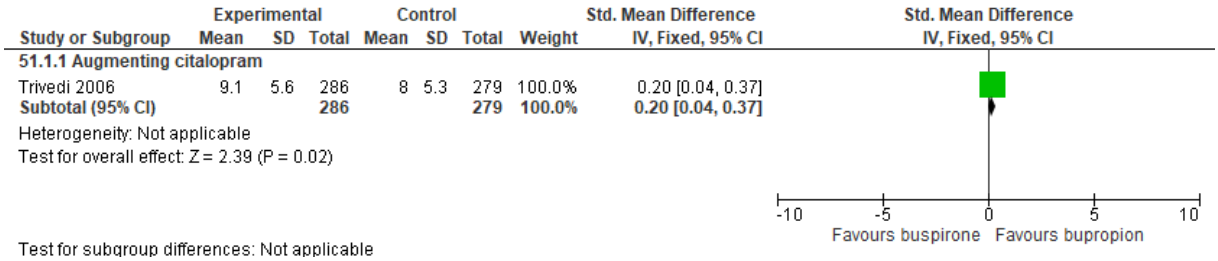
Figure 309: Quality of life mental component score (MCS) change score



AD: antidepressant

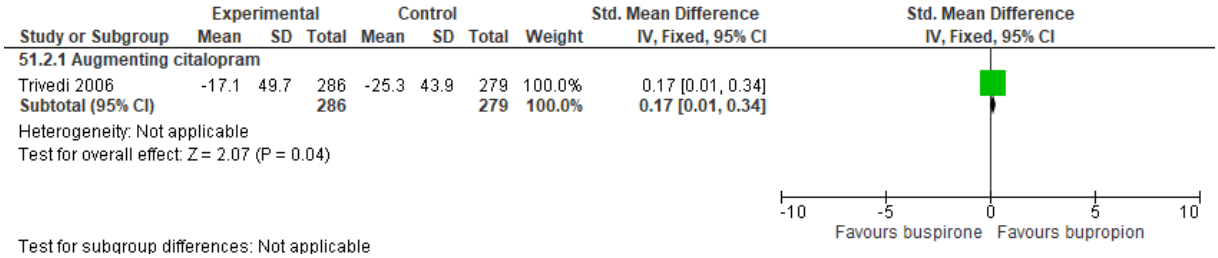
1116 ***Comparison 51. Augmenting with buspirone versus bupropion***

1117 **Figure 310: Depression symptomatology endpoint**



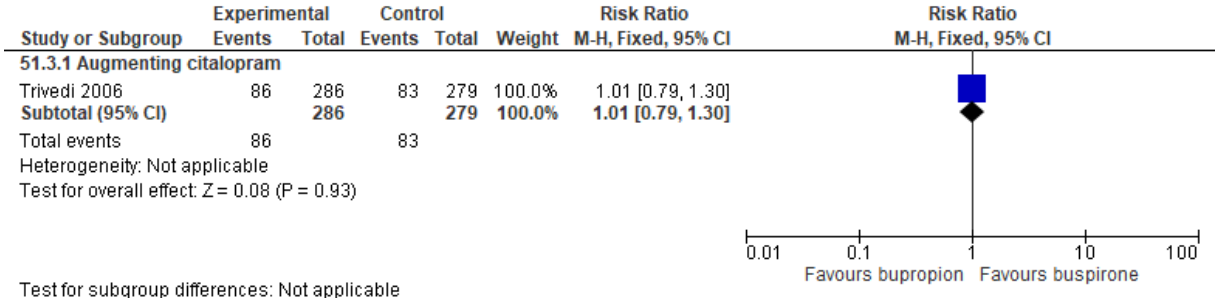
1118 Test for subgroup differences: Not applicable

1119 **Figure 311: Depression symptomatology change score**



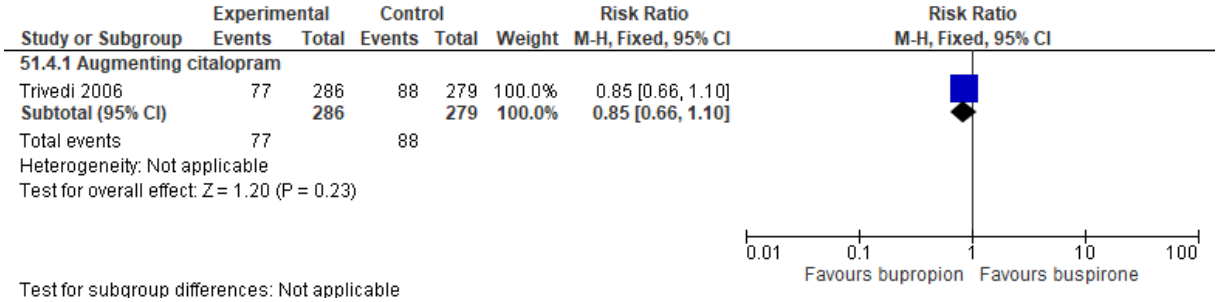
1120 Test for subgroup differences: Not applicable

1121 **Figure 312: Remission (ITT)**



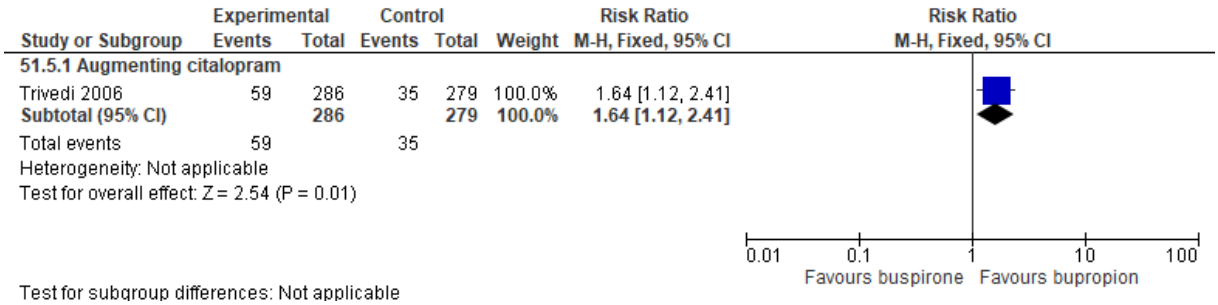
1122 Test for subgroup differences: Not applicable

1123 **Figure 313: Response (ITT)**



1124 Test for subgroup differences: Not applicable

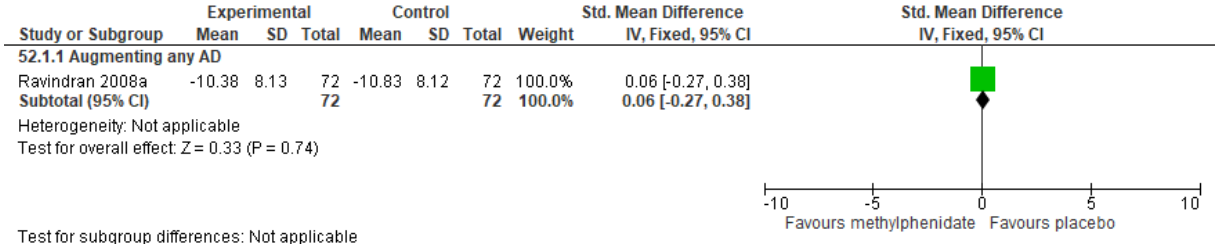
Figure 314: Discontinuation due to side effects



Test for subgroup differences: Not applicable

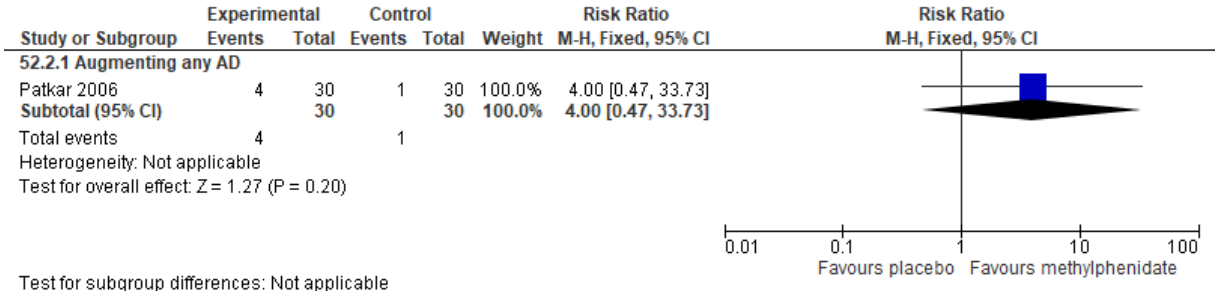
Comparison 52. Augmenting with methylphenidate versus placebo

Figure 315: Depression symptomatology change score



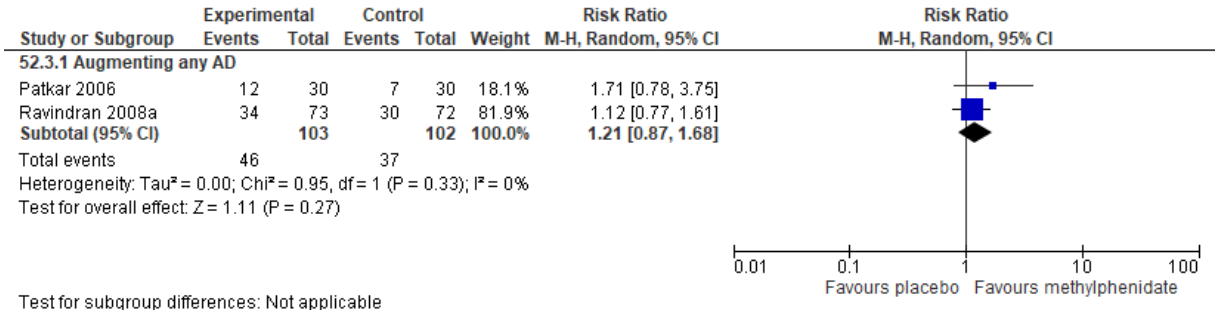
Test for subgroup differences: Not applicable

Figure 316: Remission (ITT)



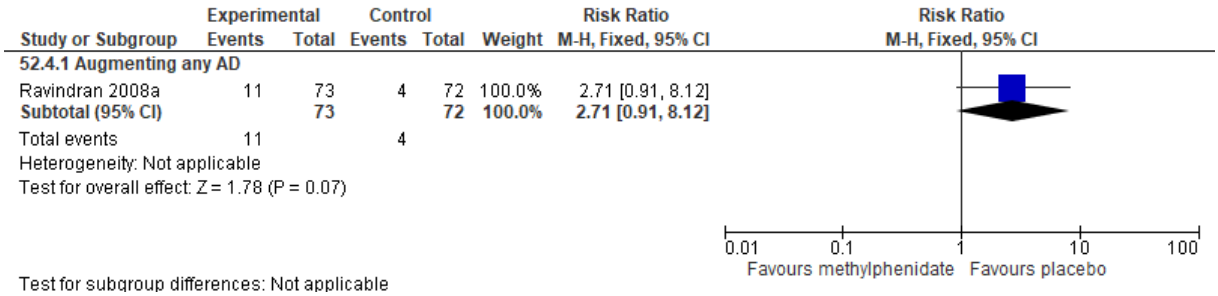
Test for subgroup differences: Not applicable

Figure 317: Response (ITT)



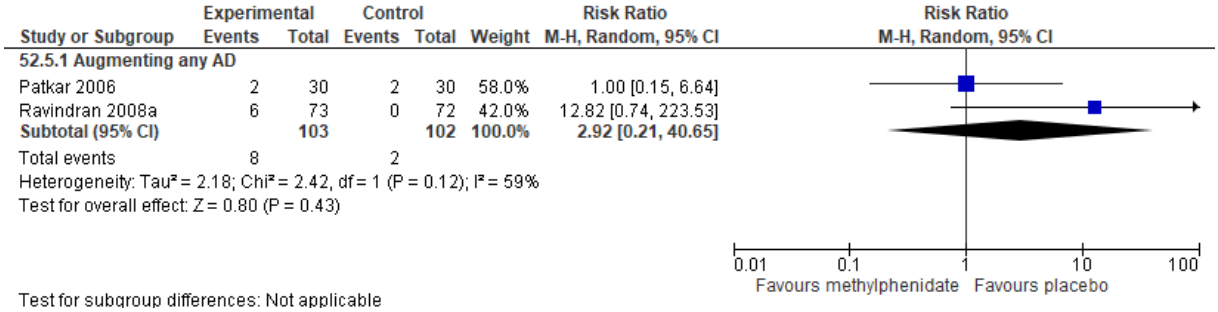
Test for subgroup differences: Not applicable

Figure 318: Discontinuation due to any reason



Test for subgroup differences: Not applicable

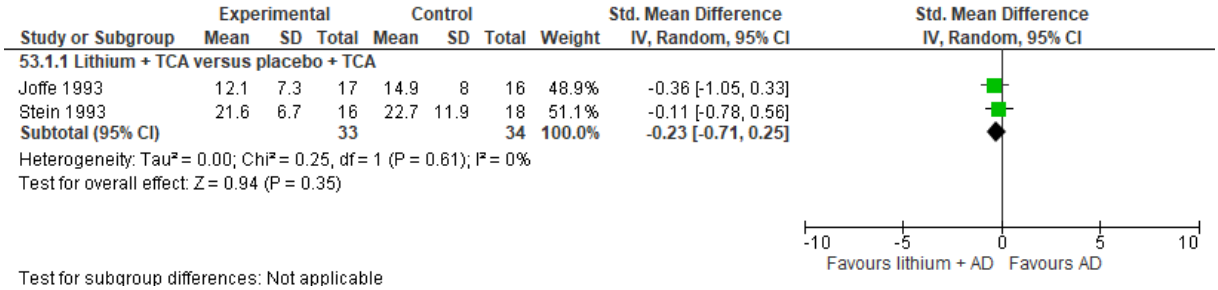
Figure 319: Discontinuation due to side effects



Test for subgroup differences: Not applicable

Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/- placebo)

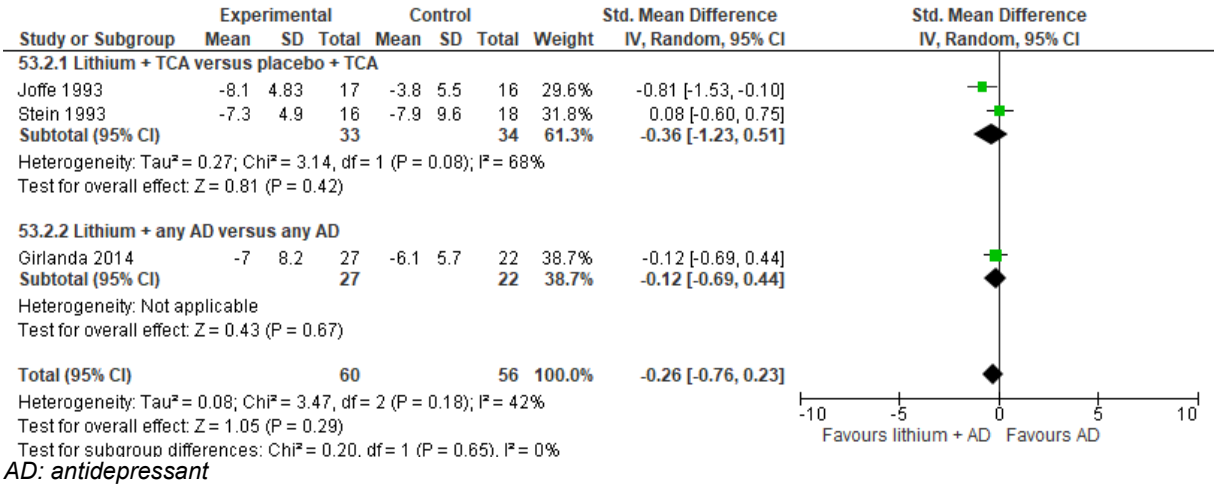
Figure 320: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

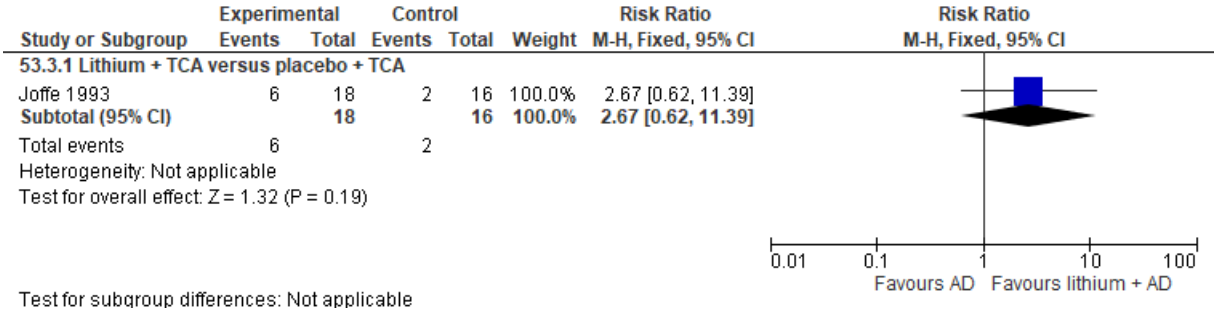
AD: antidepressant

Figure 321: Depression symptomatology change score



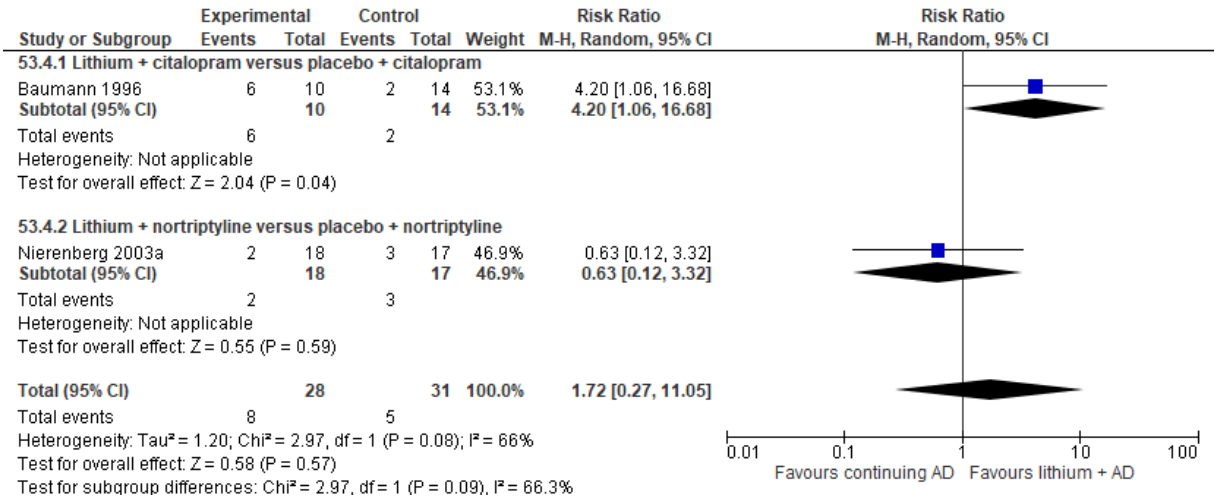
AD: antidepressant

Figure 322: Remission (ITT)



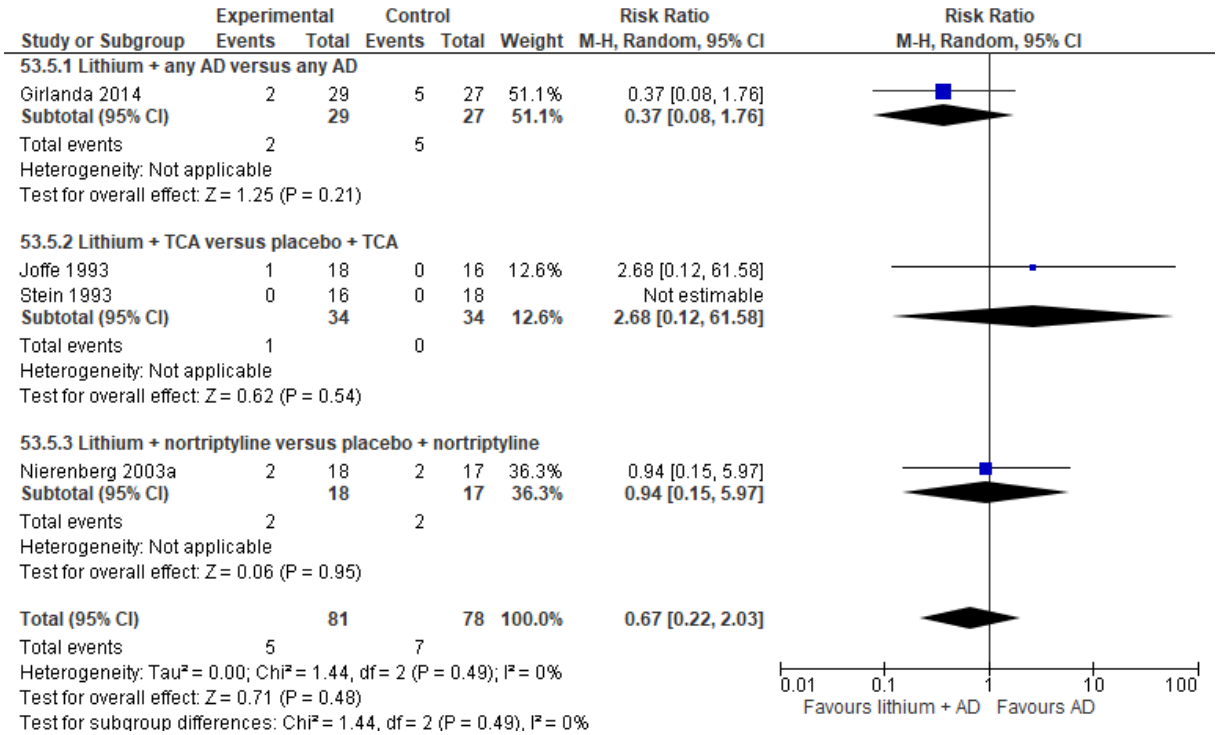
AD: antidepressant

Figure 323: Response (ITT)



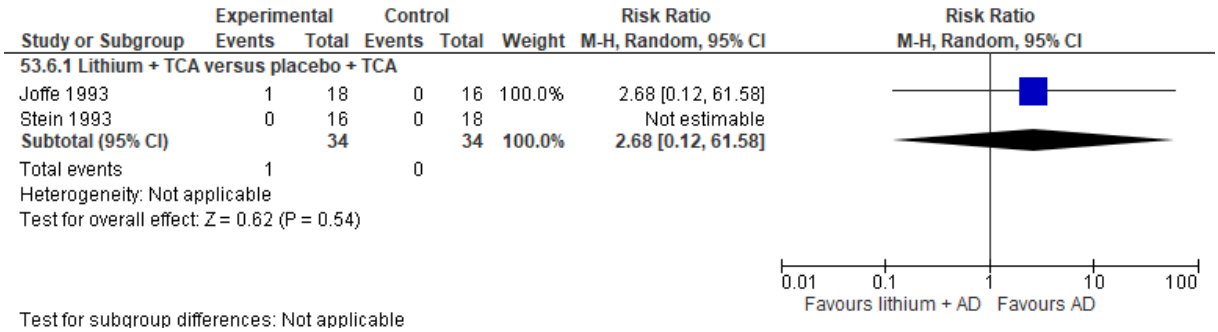
AD: antidepressant

Figure 324: Discontinuation due to any reason



AD: antidepressant

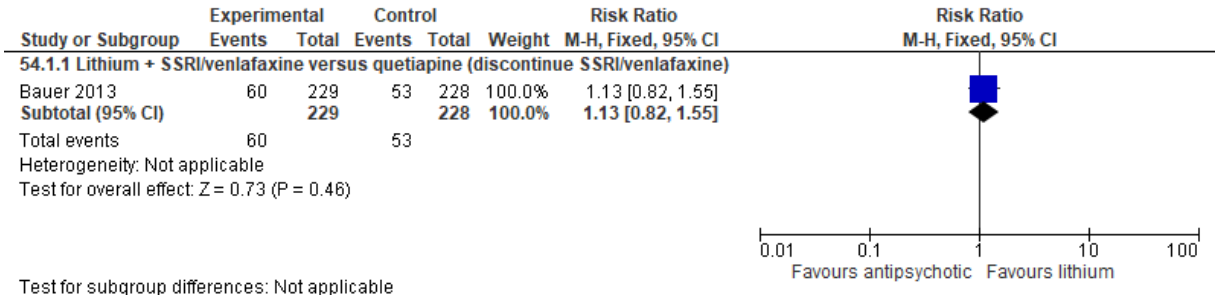
Figure 325: Discontinuation due to side effects



AD: antidepressant

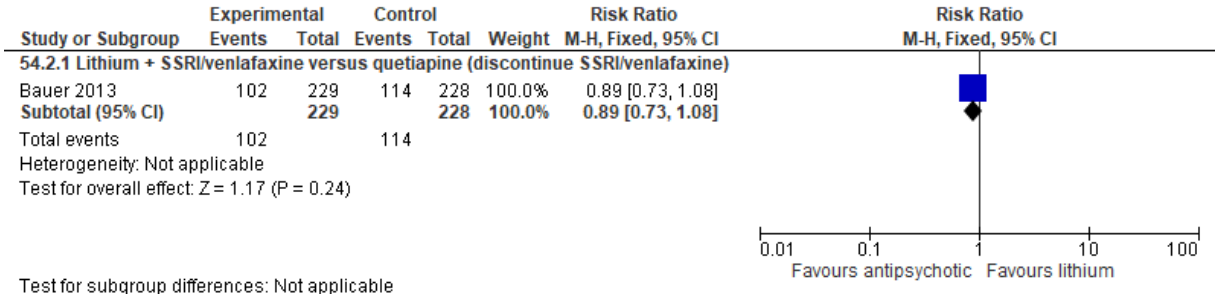
Comparison 54. Augmenting with lithium versus switch to antipsychotic

Figure 326: Remission (ITT)



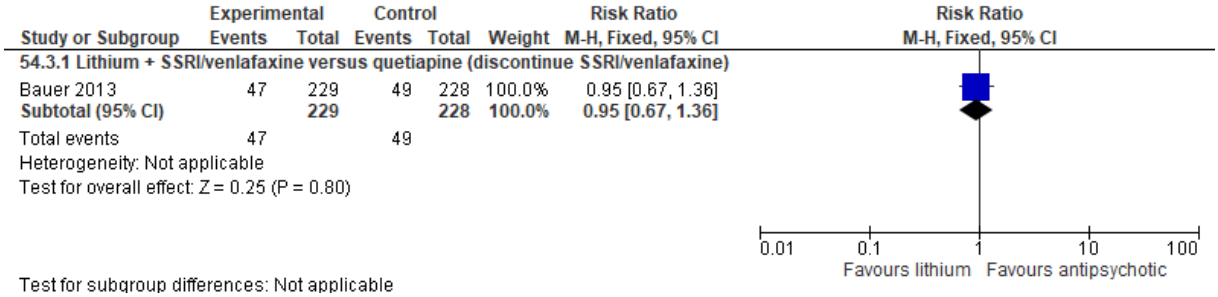
Test for subgroup differences: Not applicable

Figure 327: Response (ITT)



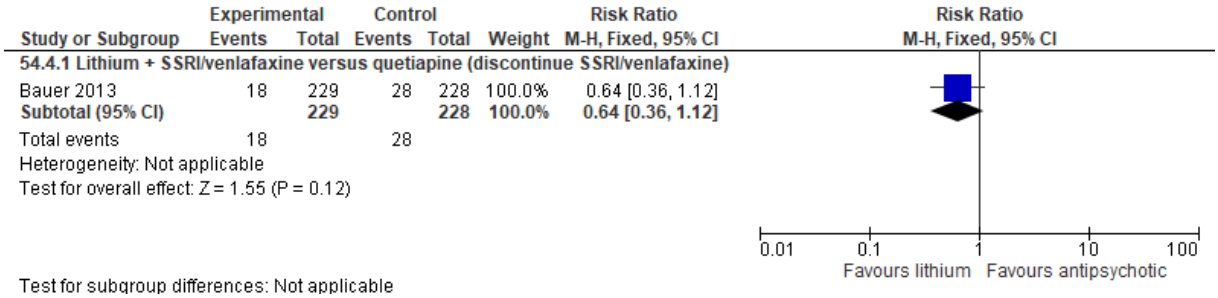
Test for subgroup differences: Not applicable

Figure 328: Discontinuation due to any reason



Test for subgroup differences: Not applicable

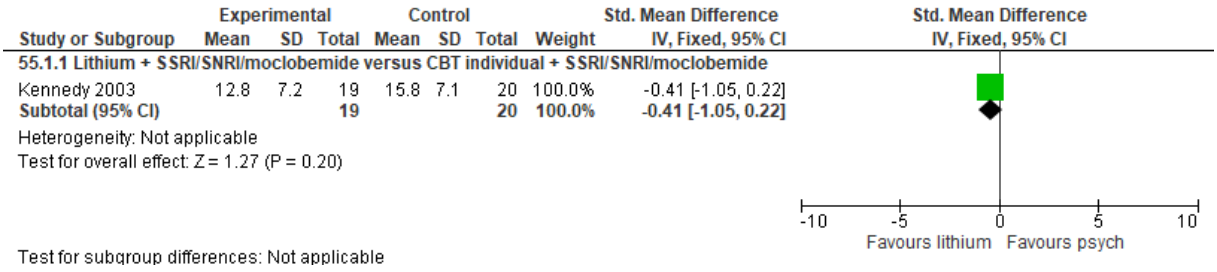
Figure 329: Discontinuation due to side effects



Test for subgroup differences: Not applicable

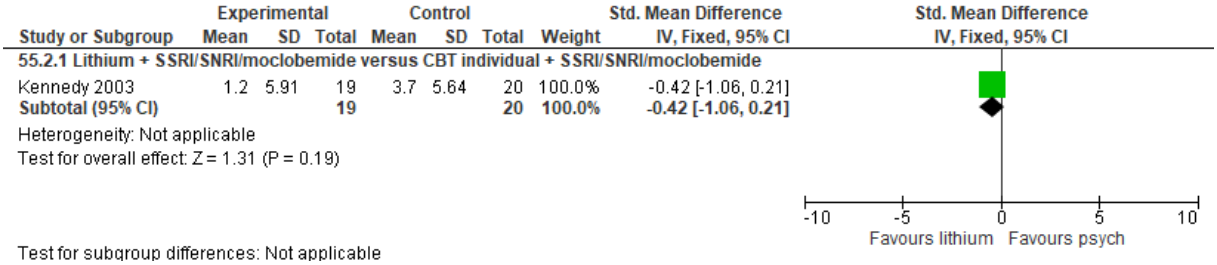
Comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

Figure 330: Depression symptomatology endpoint



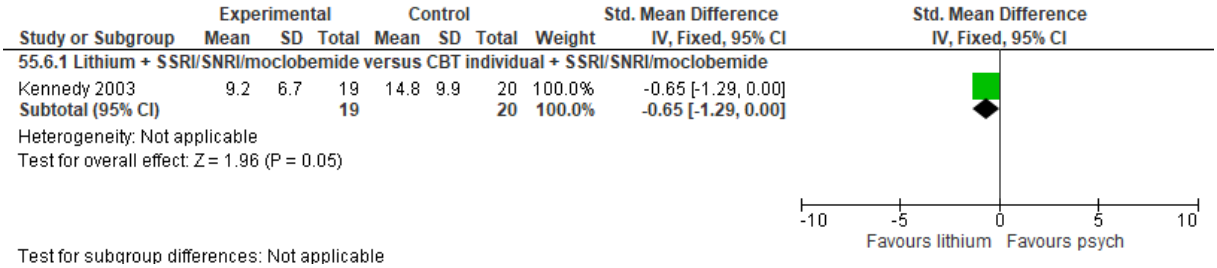
Test for subgroup differences: Not applicable

Figure 331: Depression symptomatology change score



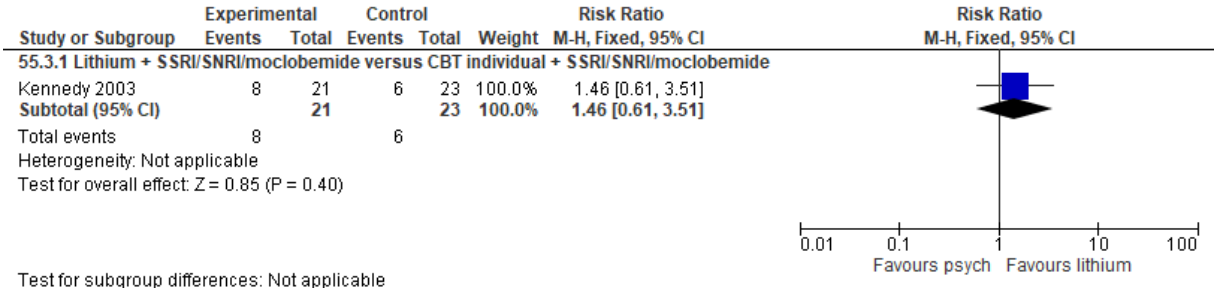
Test for subgroup differences: Not applicable

Figure 332: Depression symptomatology at 1-month follow-up



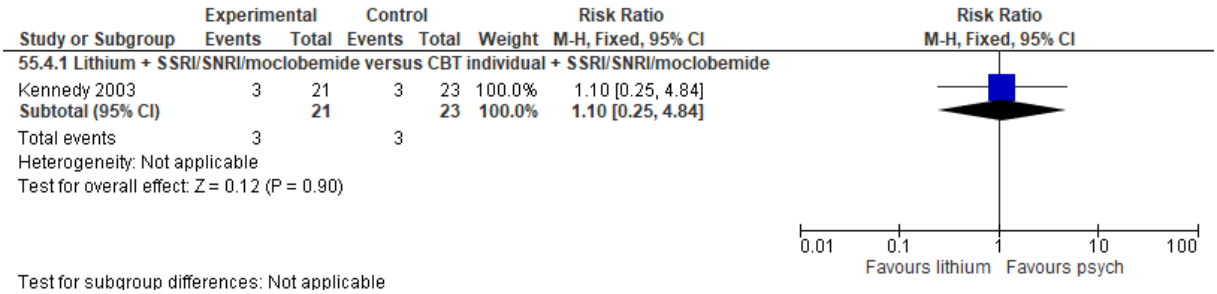
Test for subgroup differences: Not applicable

Figure 333: Remission (ITT)



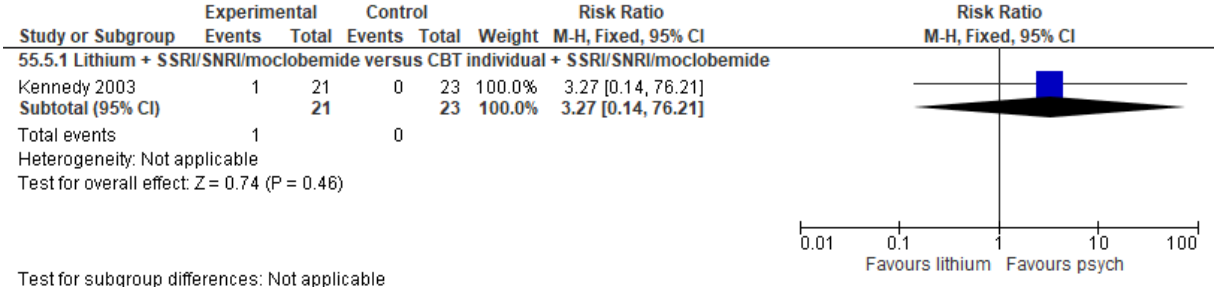
Test for subgroup differences: Not applicable

Figure 334: Discontinuation due to any reason



Test for subgroup differences: Not applicable

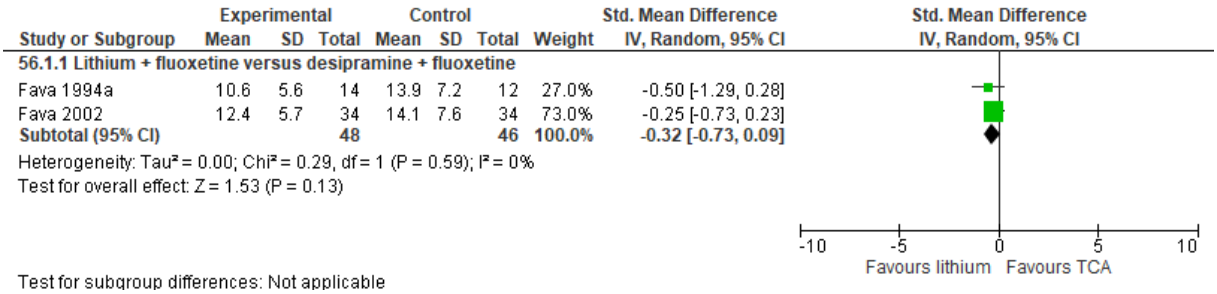
Figure 335: Discontinuation due to side effects



Test for subgroup differences: Not applicable

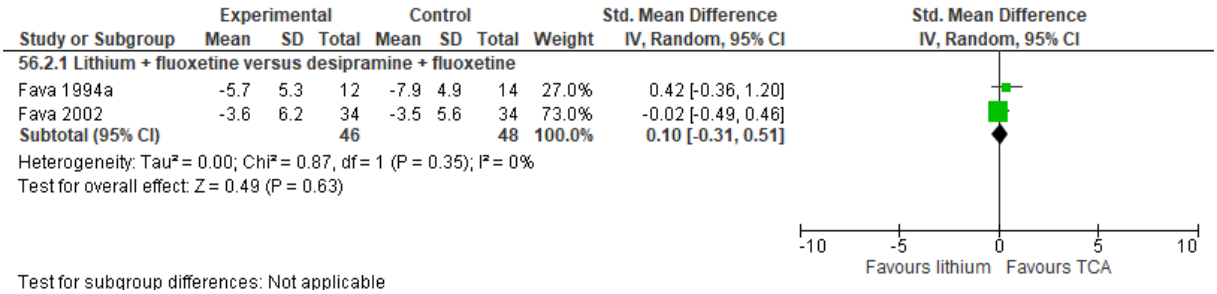
Comparison 56. Augmenting with lithium versus augmenting with TCA

Figure 336: Depression symptomatology endpoint



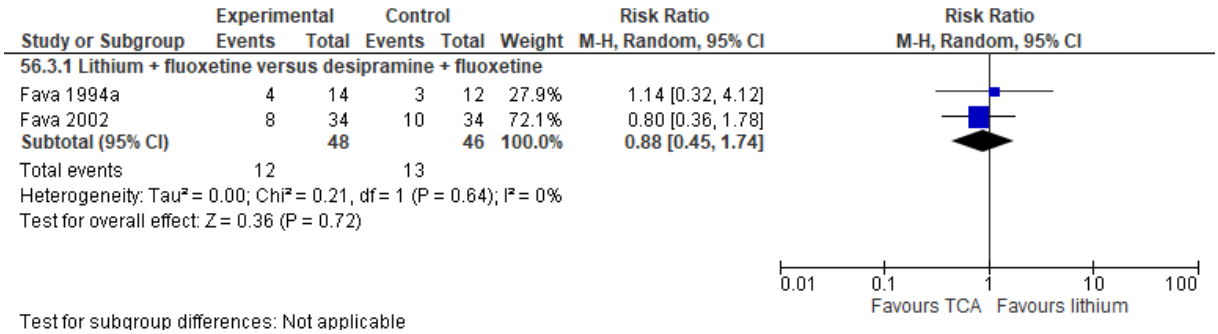
Test for subgroup differences: Not applicable

Figure 337: Depression symptomatology change score



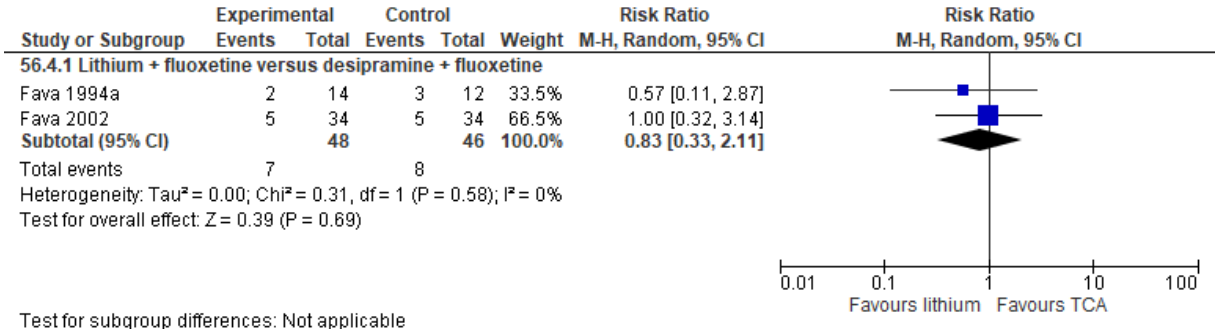
Test for subgroup differences: Not applicable

1197 **Figure 338: Remission (ITT)**



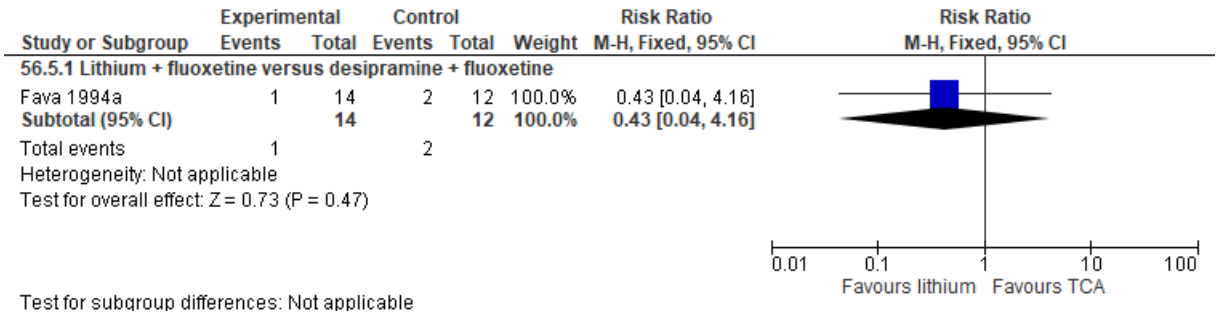
1198 Test for subgroup differences: Not applicable

1199 **Figure 339: Discontinuation due to any reason**



1200 Test for subgroup differences: Not applicable

1201 **Figure 340: Discontinuation due to side effects**

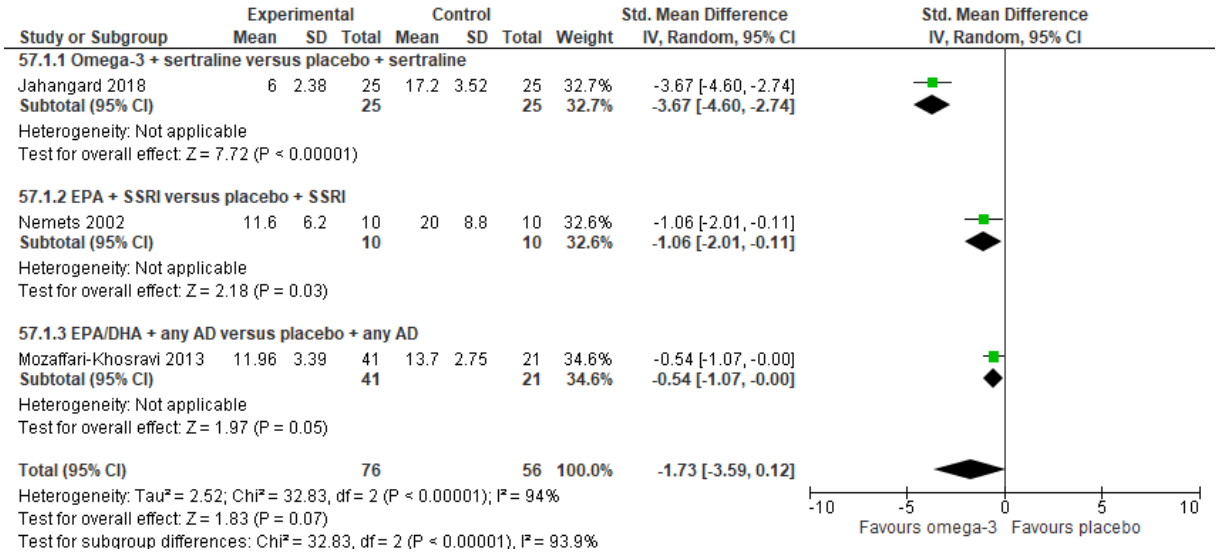


1202 Test for subgroup differences: Not applicable

1203

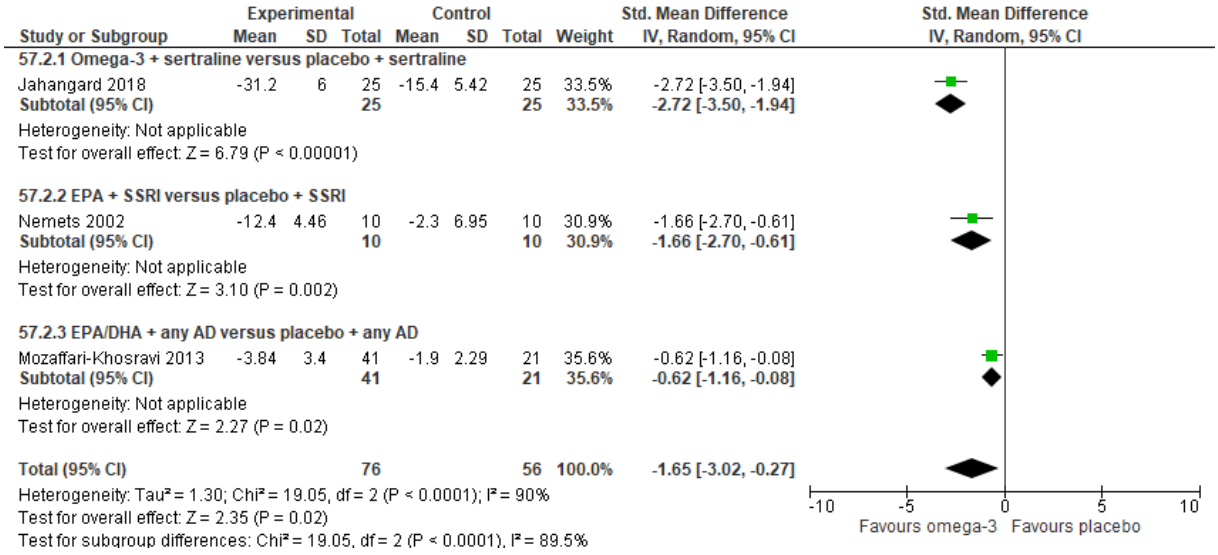
1204 ***Comparison 57. Augmenting with omega-3 fatty acids versus placebo***

1205 **Figure 341: Depression symptomatology endpoint**



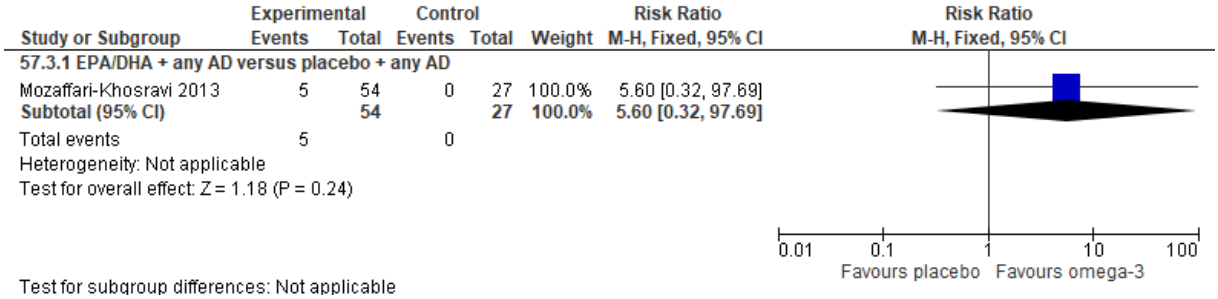
1206

1207 **Figure 342: Depression symptomatology change score**



1208

1209 **Figure 343: Remission (ITT)**



1210 Test for subgroup differences: Not applicable

Figure 344: Response (ITT)

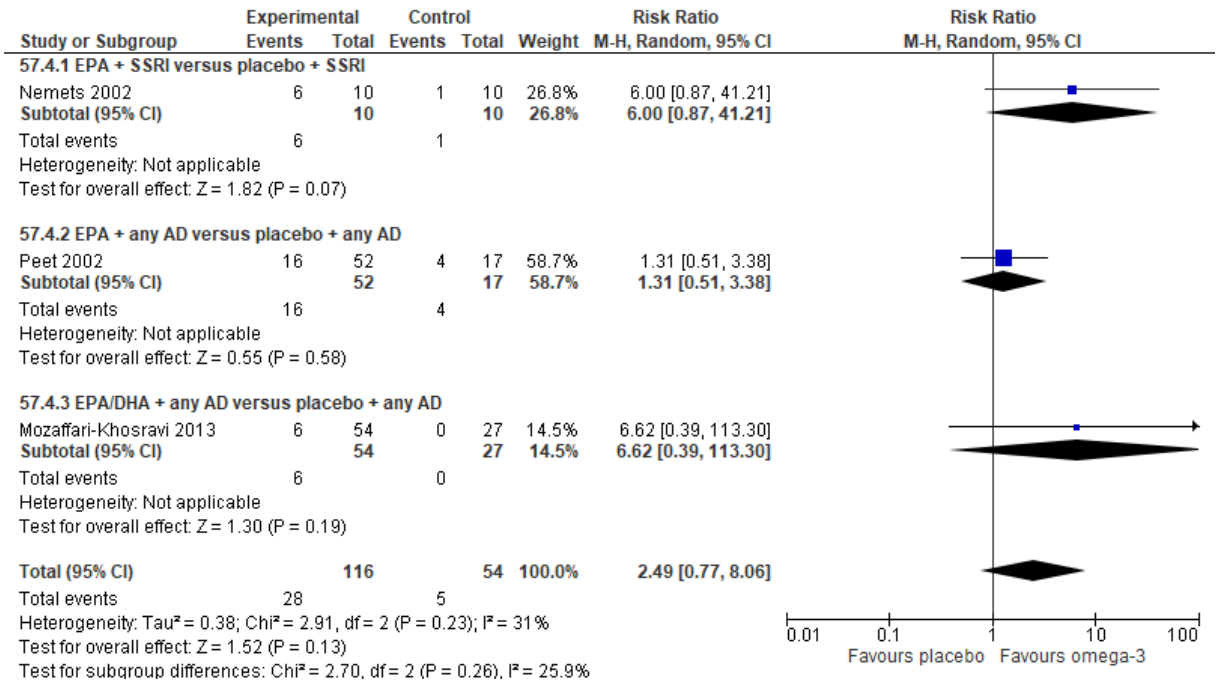


Figure 345: Discontinuation due to any reason

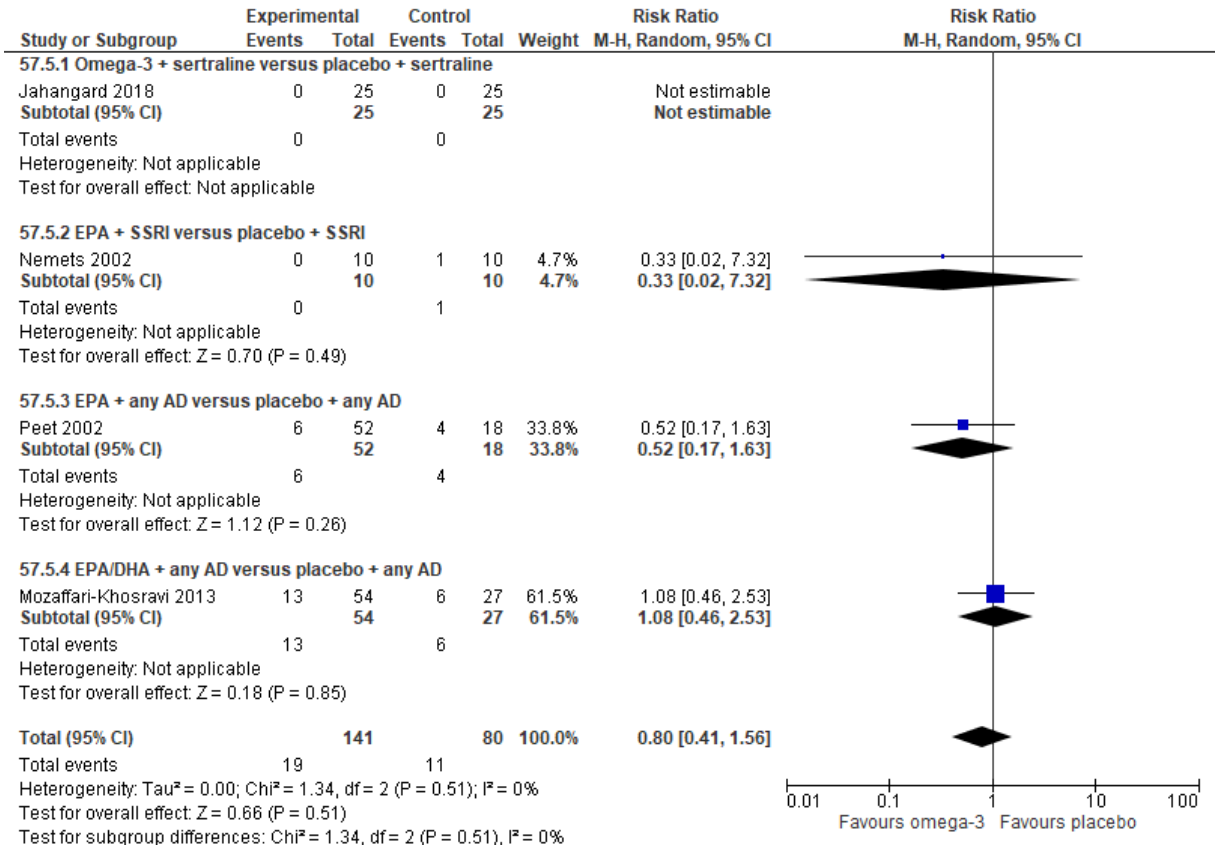


Figure 346: Discontinuation due to side effects

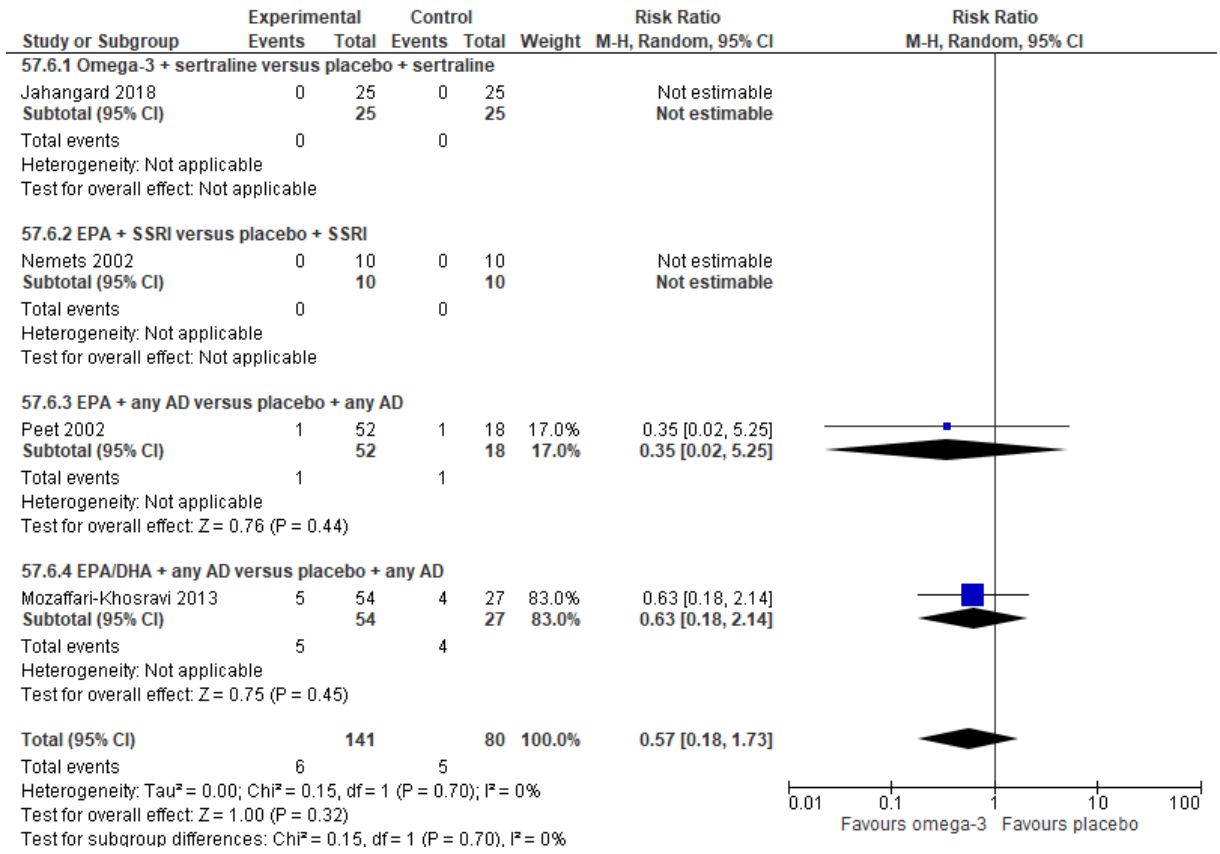
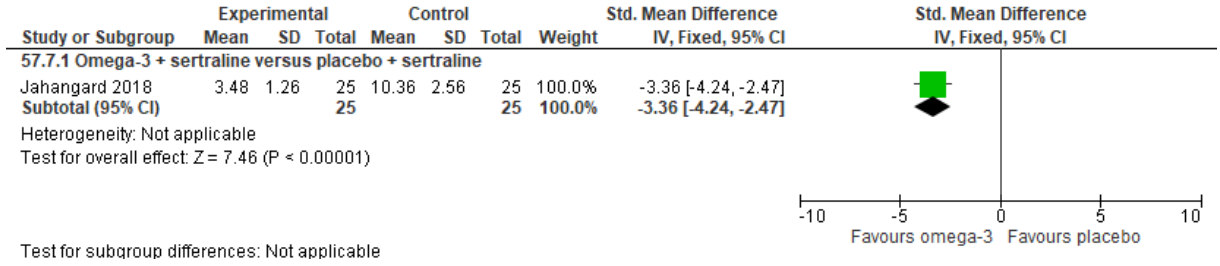
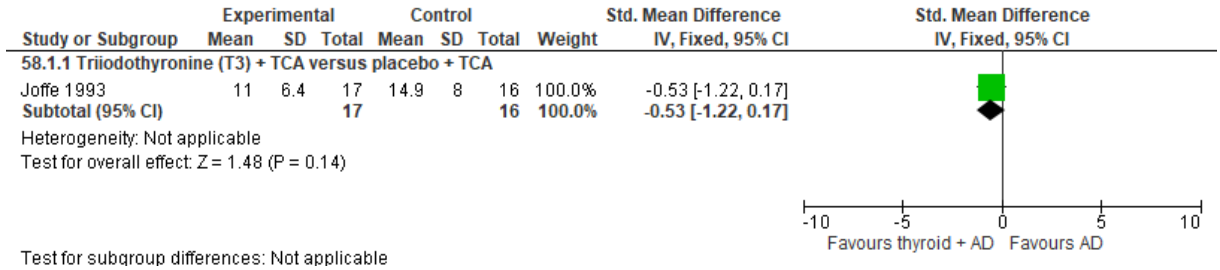


Figure 347: Sleeping difficulties endpoint



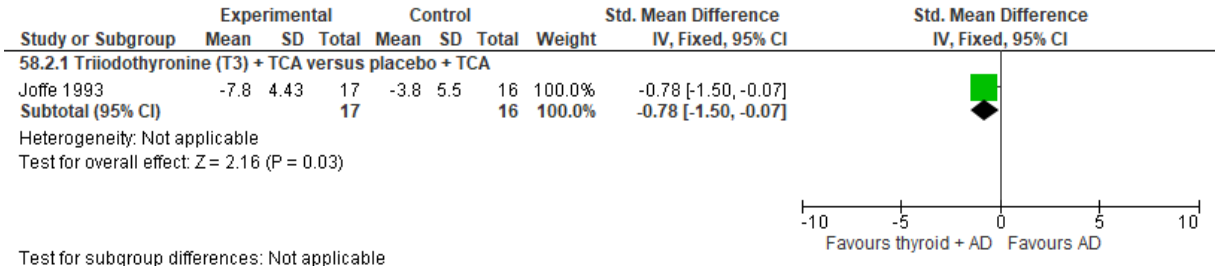
Comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

Figure 348: Depression symptomatology endpoint



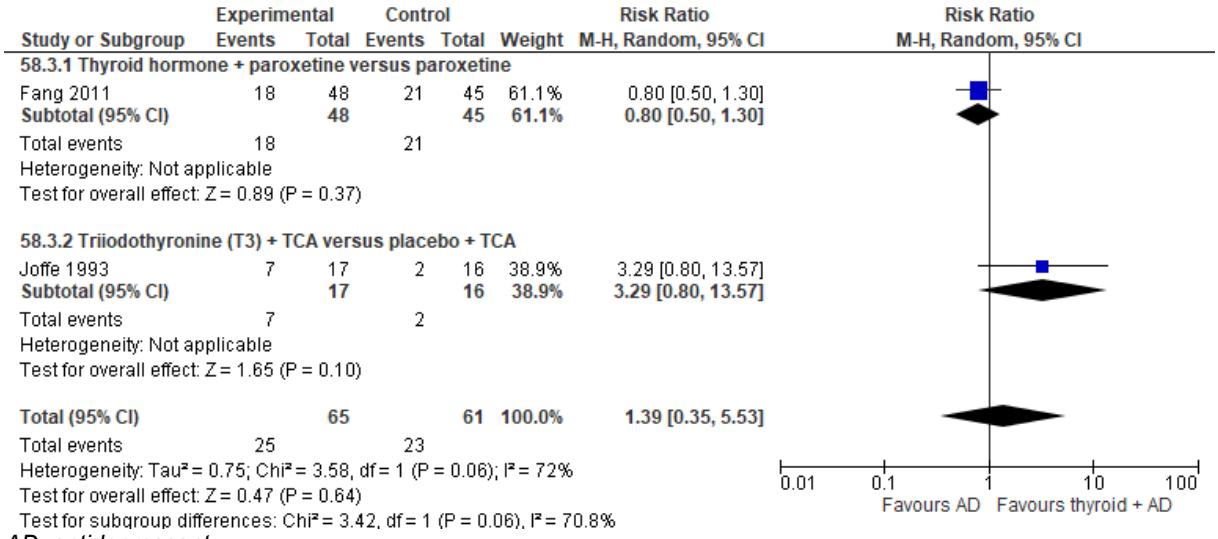
AD: antidepressant

Figure 349: Depression symptoms change score



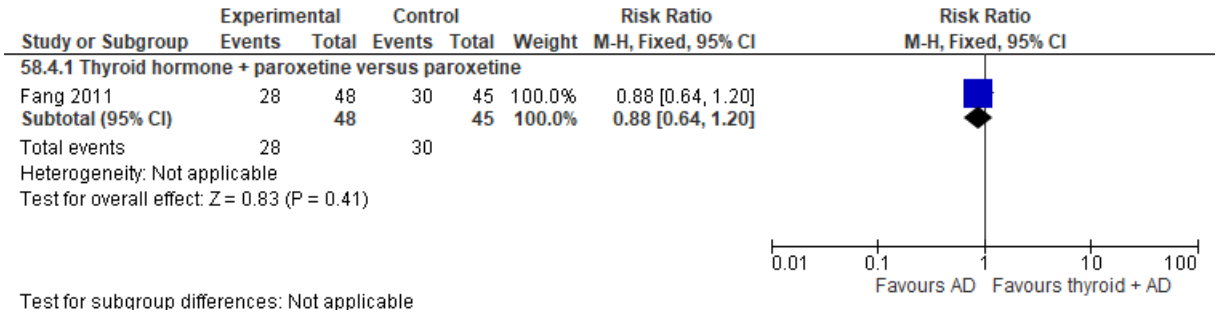
AD: antidepressant

Figure 350: Remission (ITT)



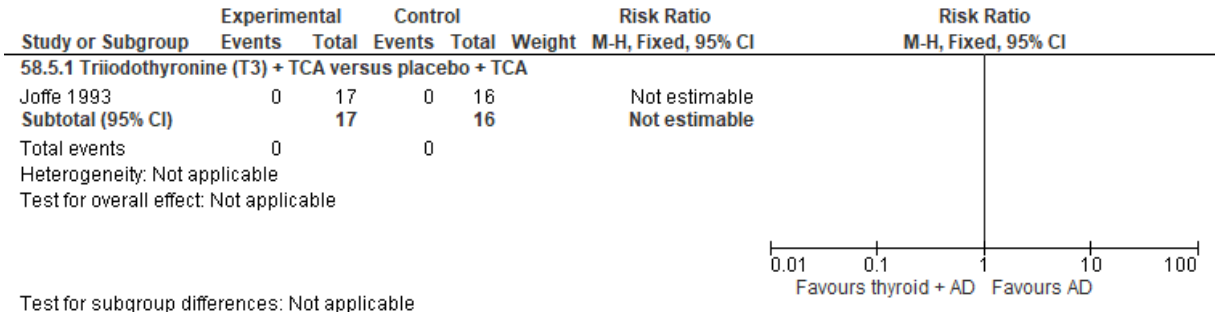
AD: antidepressant

Figure 351: Response (ITT)



AD: antidepressant

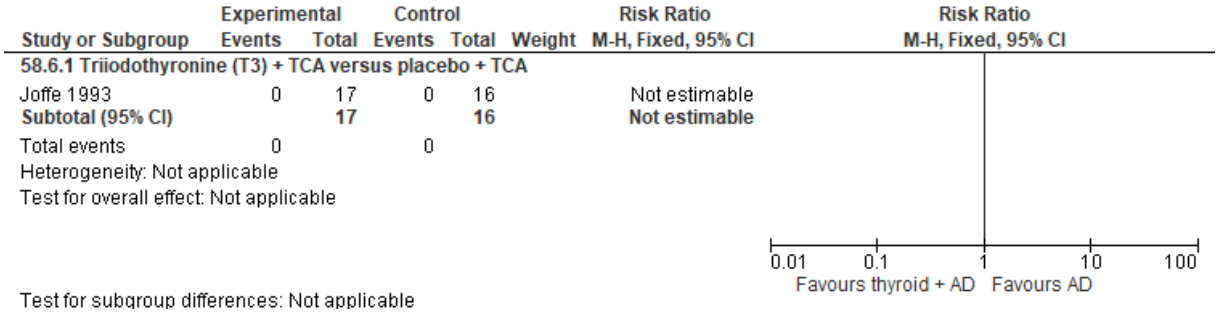
Figure 352: Discontinuation due to any reason



Test for subgroup differences: Not applicable

AD: antidepressant

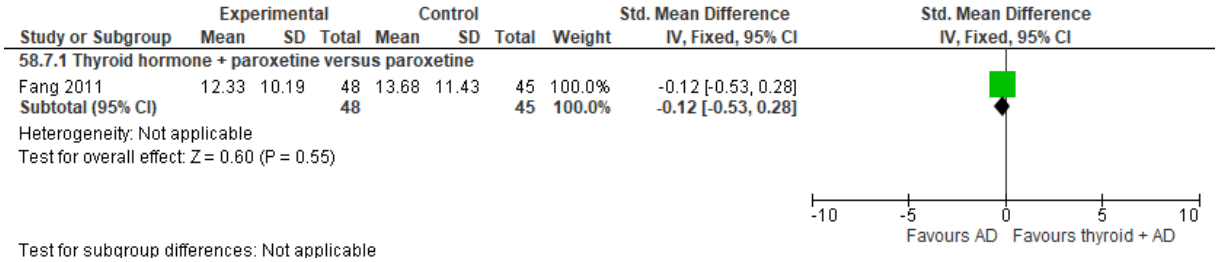
Figure 353: Discontinuation due to side effects



Test for subgroup differences: Not applicable

AD: antidepressant

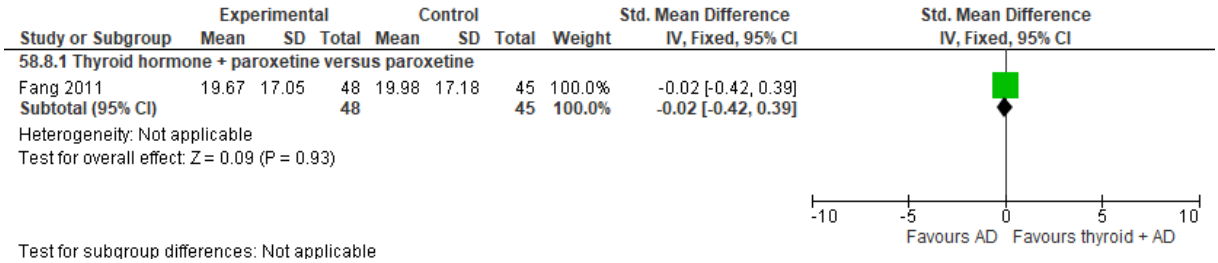
Figure 354: Quality of life physical component score (PCS) change score



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 355: Quality of life mental component score (MCS) change score

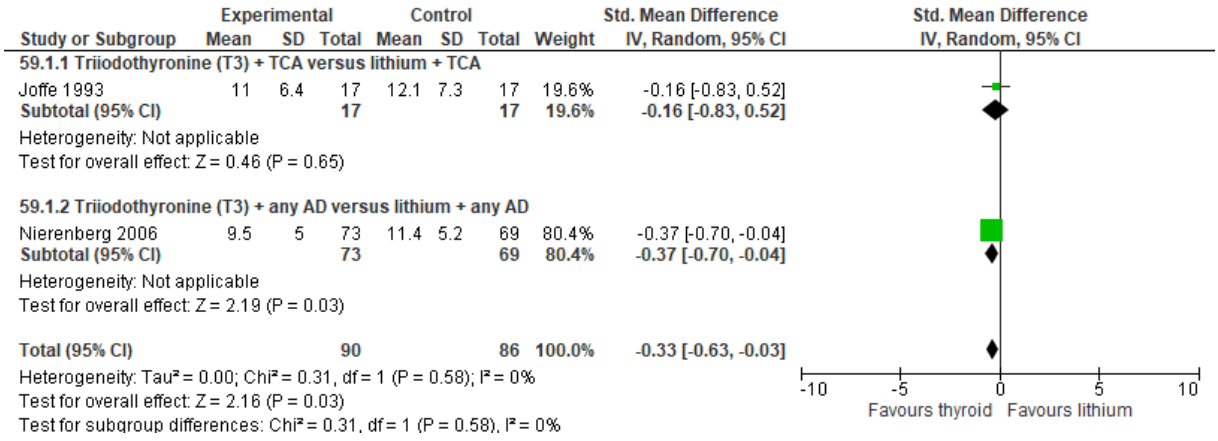


Test for subgroup differences: Not applicable

AD: antidepressant

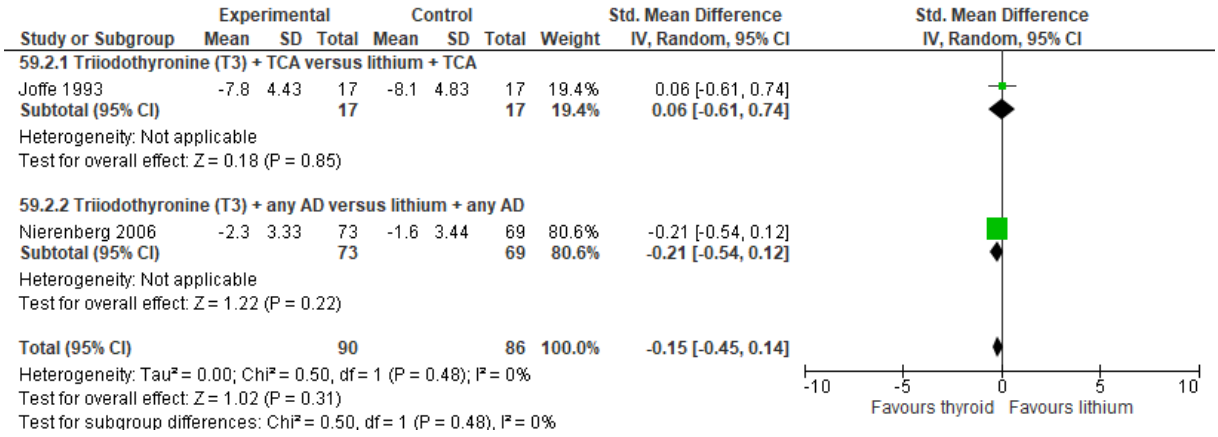
1254 ***Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium***

1255 **Figure 356: Depression symptomatology endpoint**



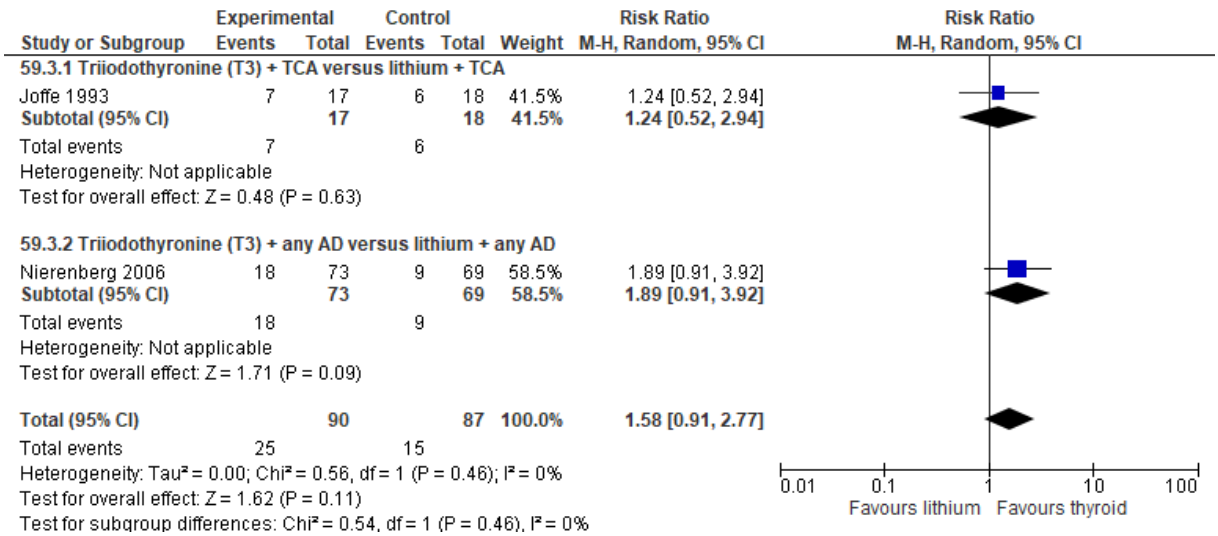
1256

1257 **Figure 357: Depression symptomatology change score**



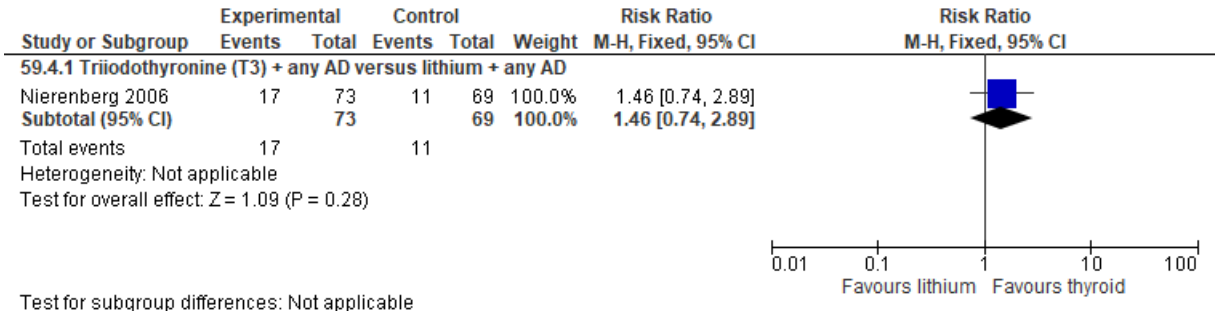
1258

1259 **Figure 358: Remission (ITT)**



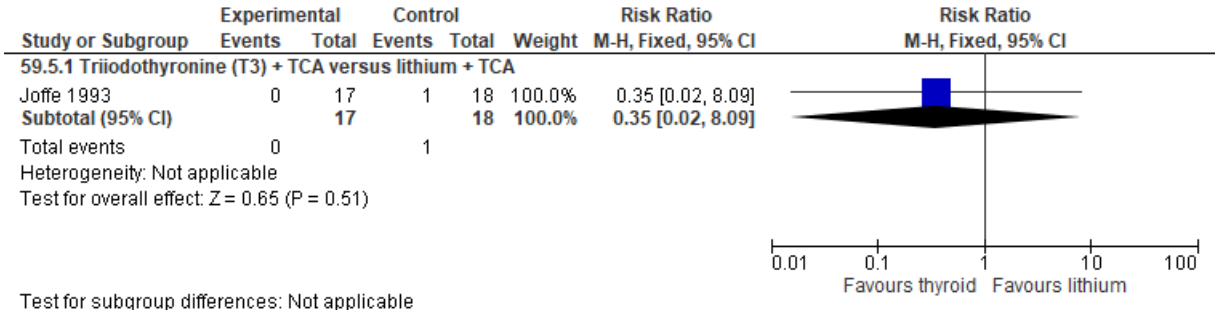
1260

Figure 359: Response (ITT)



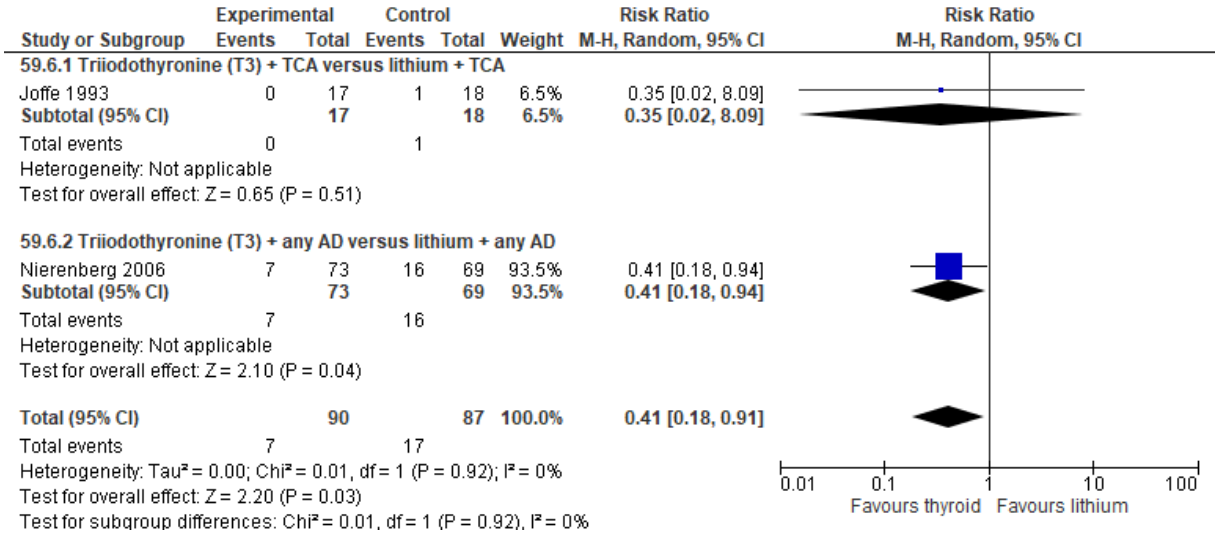
Test for subgroup differences: Not applicable

Figure 360: Discontinuation due to any reason



Test for subgroup differences: Not applicable

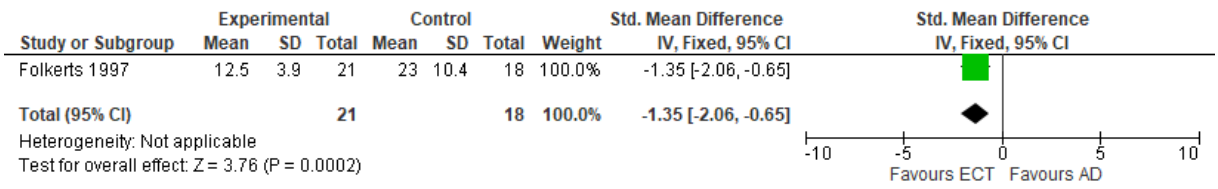
Figure 361: Discontinuation due to side effects



Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%

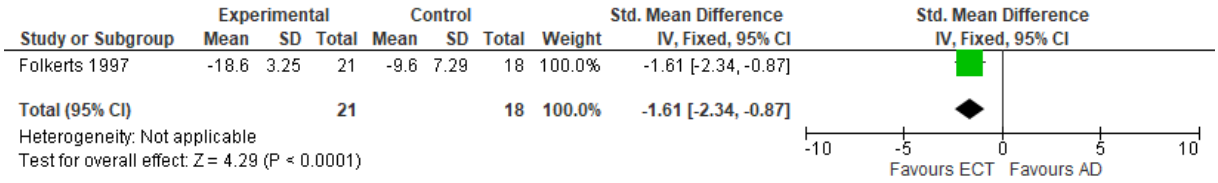
Comparison 60. Switching to ECT versus switching to paroxetine

Figure 362: Depression symptomatology endpoint



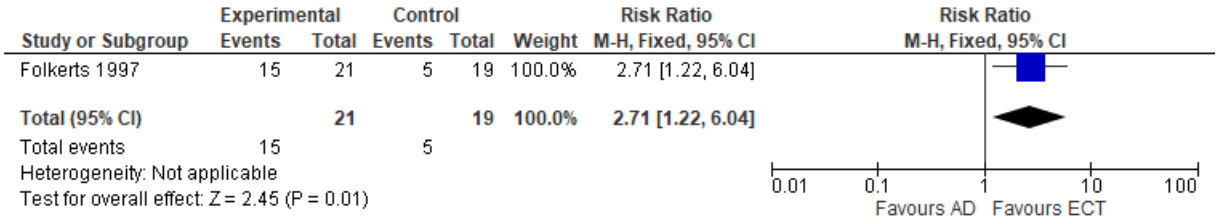
AD: antidepressant

Figure 363: Depression symptomatology change score



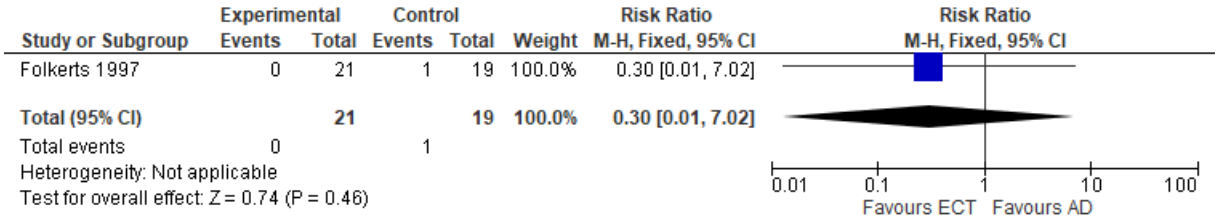
AD: antidepressant

Figure 364: Response (ITT)



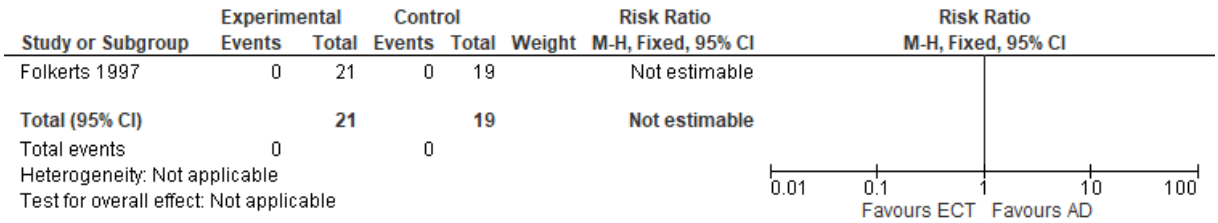
AD: antidepressant

Figure 365: Discontinuation due to any reason



AD: antidepressant

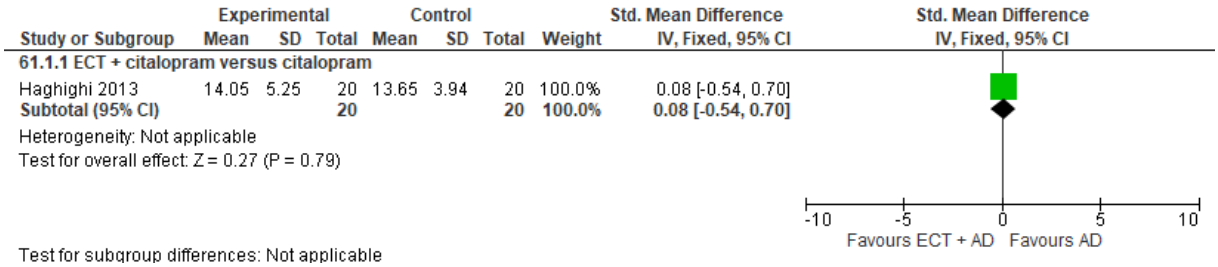
Figure 366: Discontinuation due to side effects



AD: antidepressant

Comparison 61. Augmenting with ECT versus continuing with antidepressant

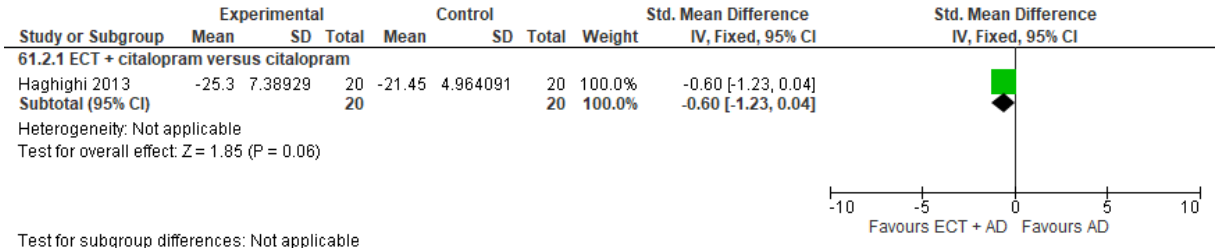
Figure 367: Depression symptomatology endpoint



Test for subgroup differences: Not applicable

AD: antidepressant

Figure 368: Depression symptomatology change score

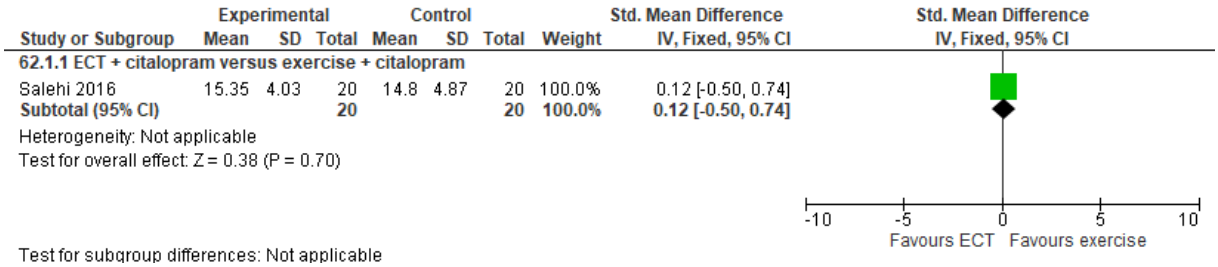


Test for subgroup differences: Not applicable

AD: antidepressant

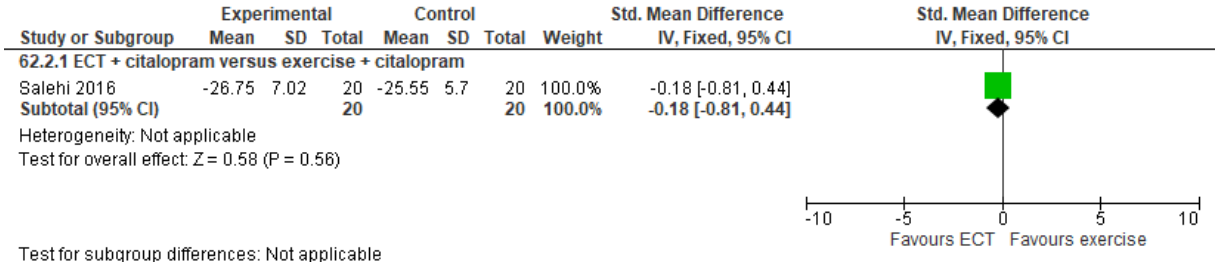
Comparison 62. Augmenting with ECT versus augmenting with exercise

Figure 369: Depression symptomatology endpoint



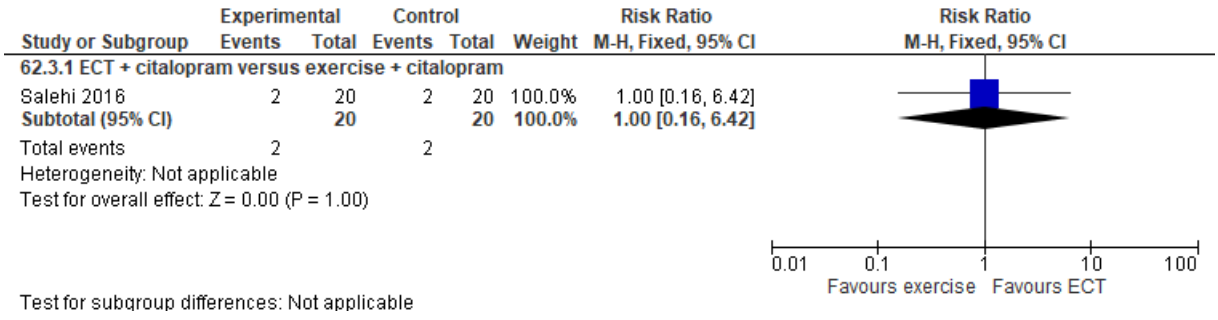
Test for subgroup differences: Not applicable

Figure 370: Depression symptomatology change score



Test for subgroup differences: Not applicable

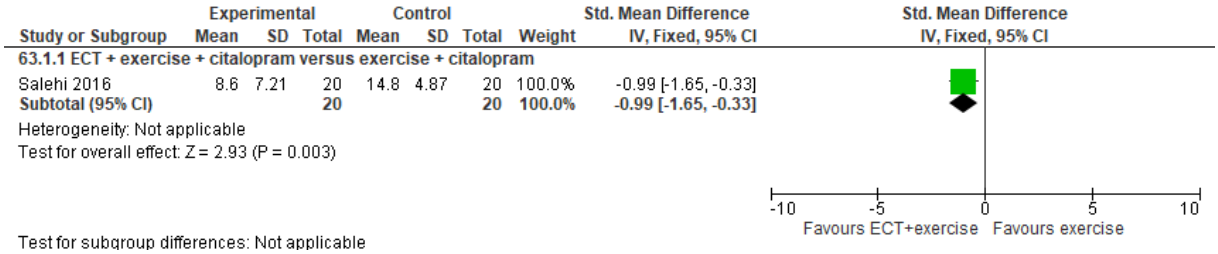
Figure 371: Remission (ITT)



Test for subgroup differences: Not applicable

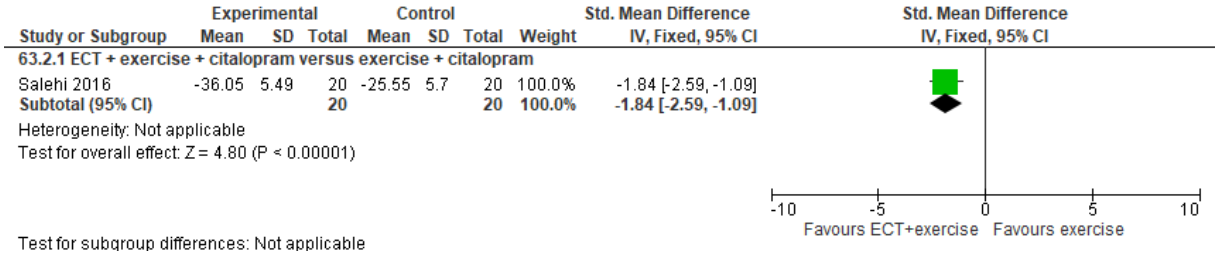
Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Figure 372: Depression symptomatology endpoint



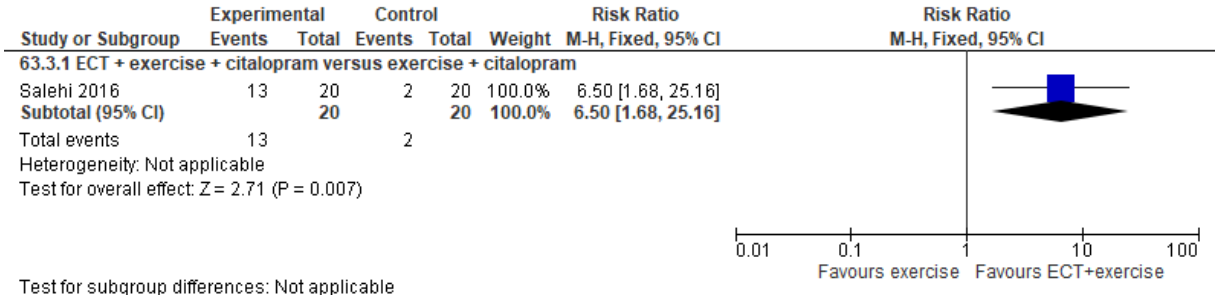
Test for subgroup differences: Not applicable

Figure 373: Depression symptomatology change score



Test for subgroup differences: Not applicable

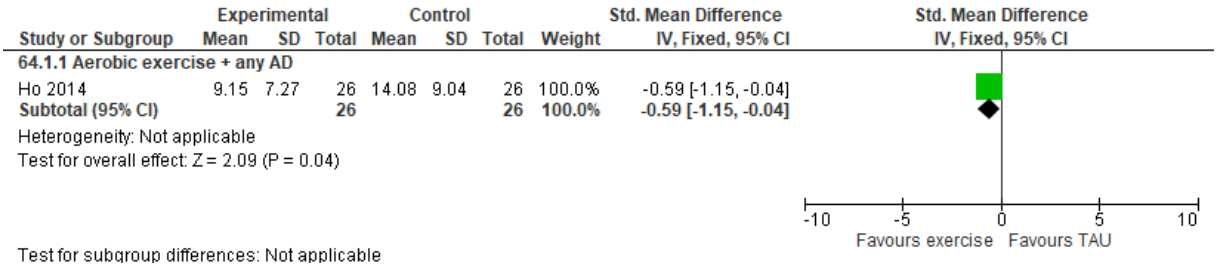
Figure 374: Remission (ITT)



Test for subgroup differences: Not applicable

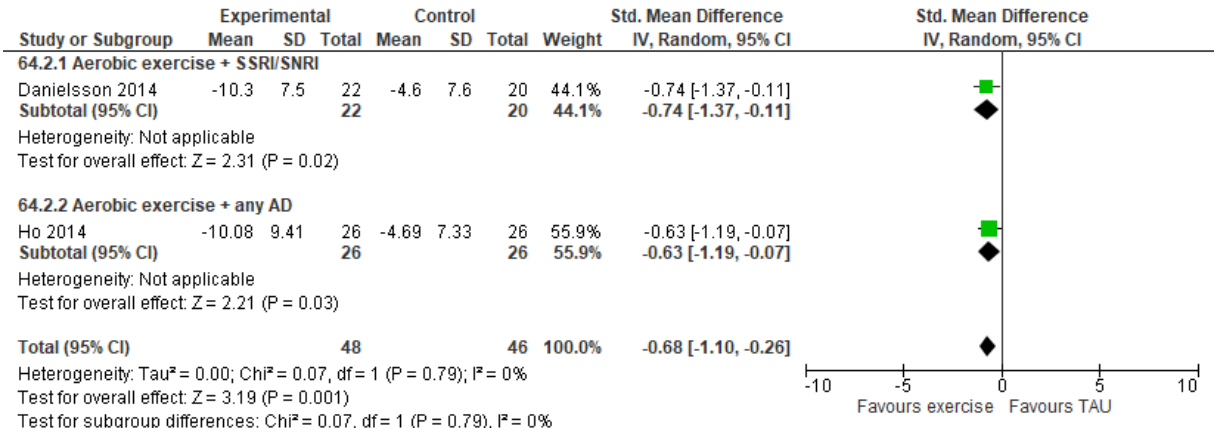
1316 ***Comparison 64. Augmenting with exercise versus TAU***

1317 **Figure 375: Depression symptomatology endpoint**



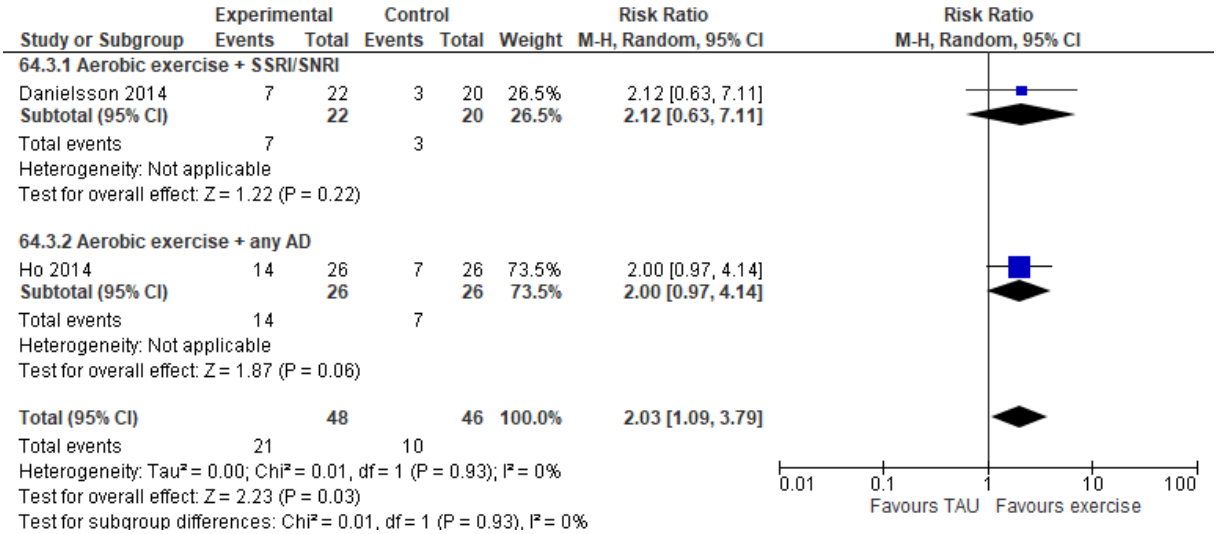
1318 Test for subgroup differences: Not applicable

1319 **Figure 376: Depression symptomatology change score**



1320 Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%

1321 **Figure 377: Remission (ITT)**



1322 Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Figure 378: Response (ITT)

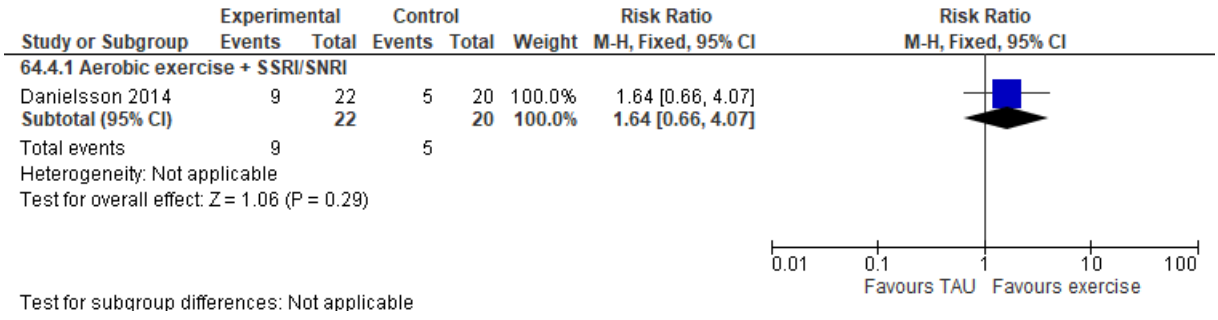
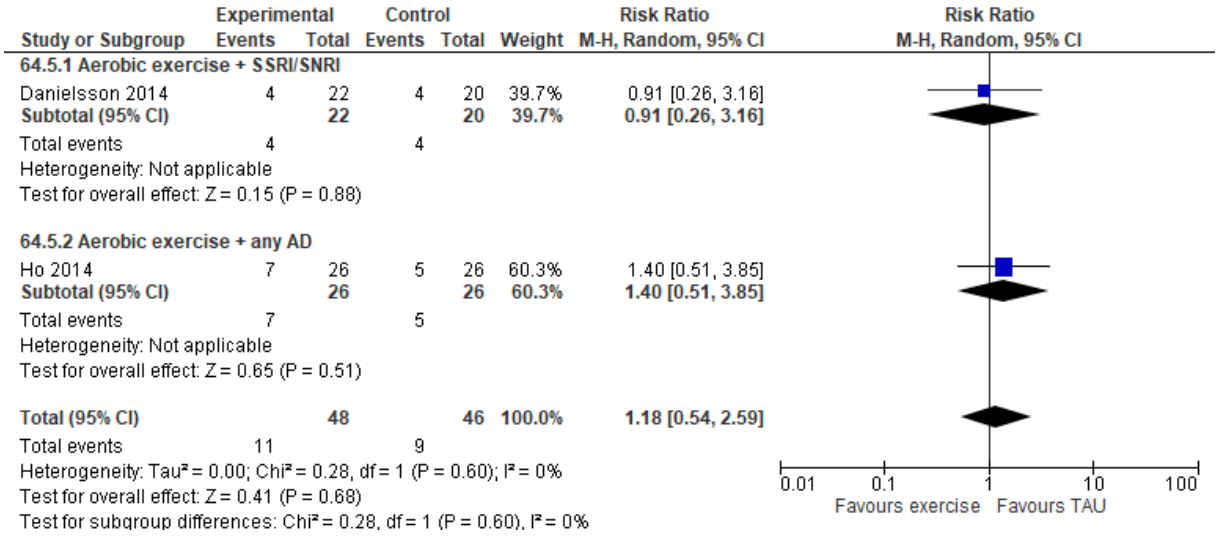


Figure 379: Discontinuation due to any reason



Comparison 65. Augmenting with exercise versus attention-placebo

Figure 380: Depression symptomatology endpoint

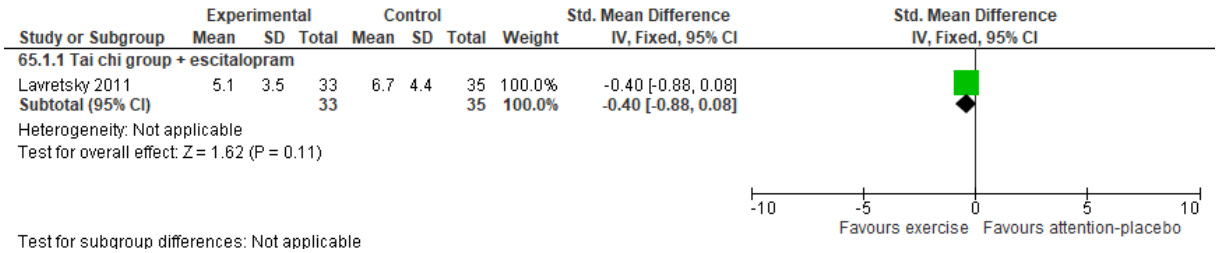
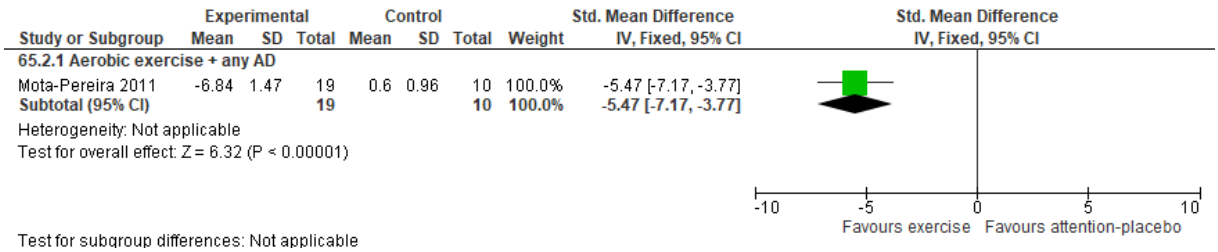
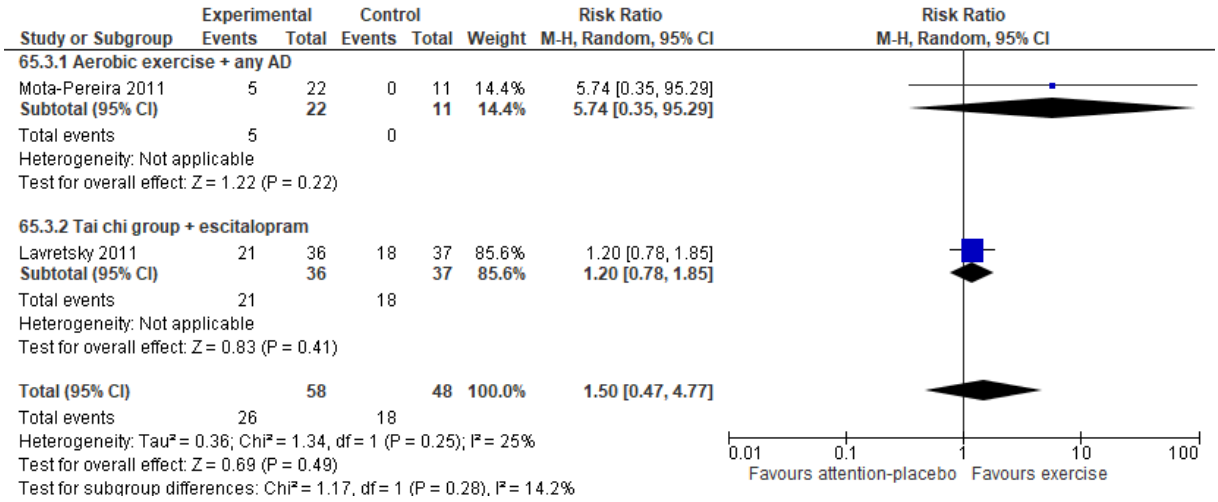


Figure 381: Depression symptomatology change score

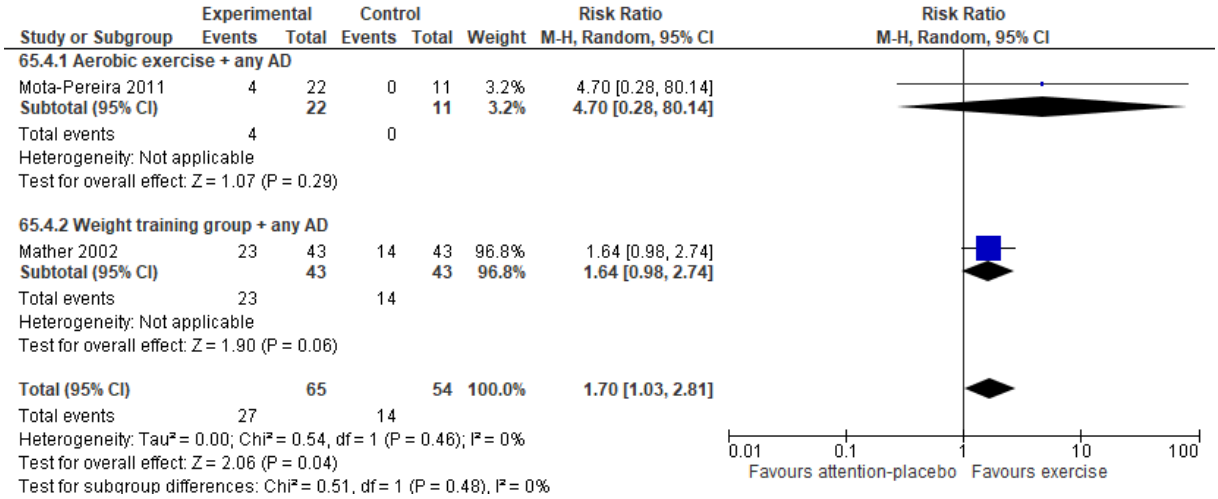


1333 **Figure 382: Remission (ITT)**



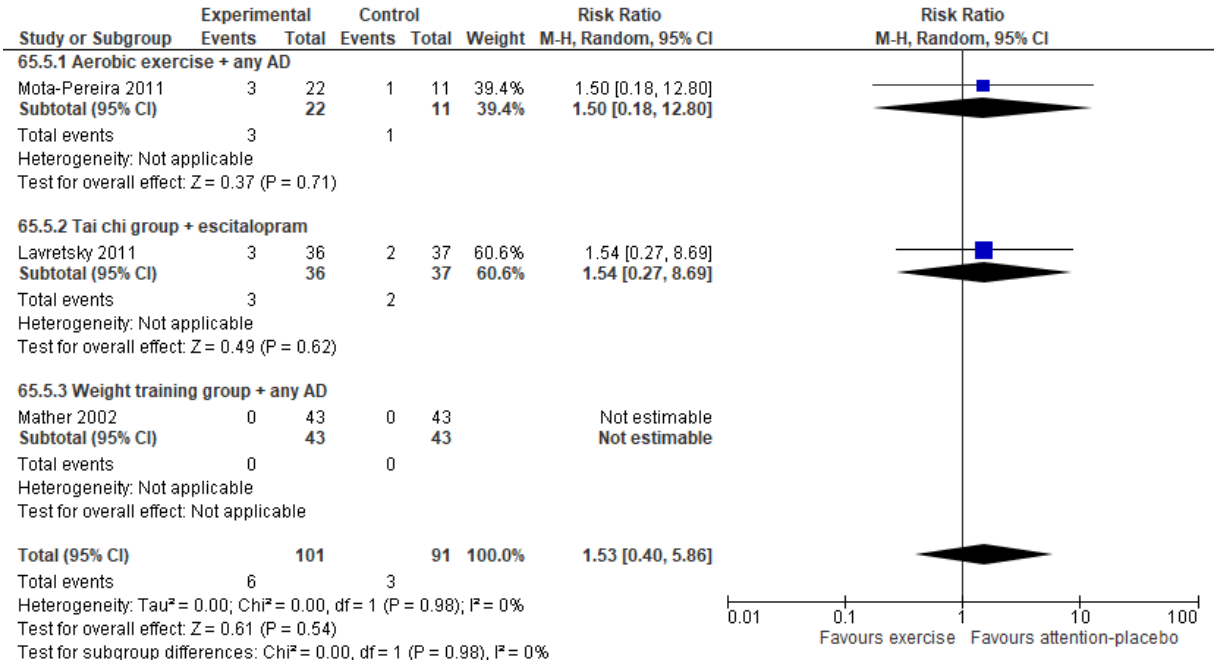
1334

1335 **Figure 383: Response (ITT)**



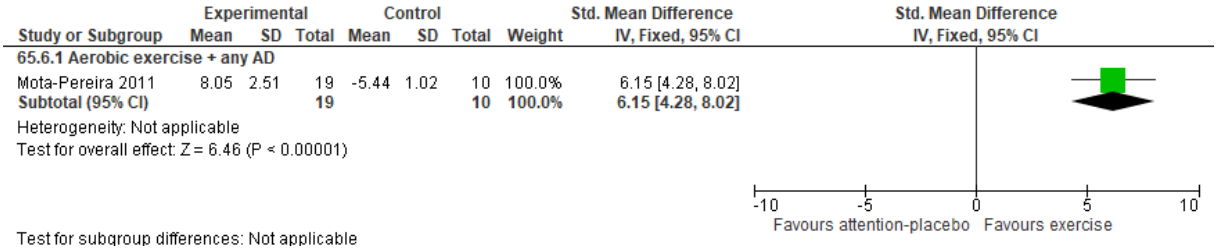
1336

1337 **Figure 384: Discontinuation due to any reason**



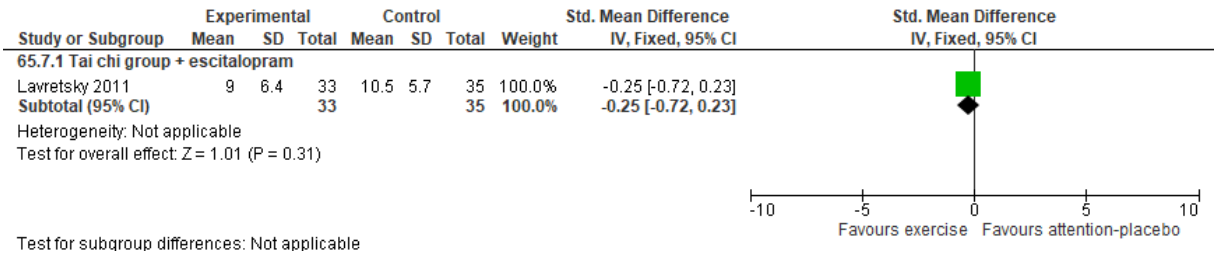
1338

1339 **Figure 385: Global functioning change score**



1340 Test for subgroup differences: Not applicable

1341 **Figure 386: Sleeping difficulties endpoint**



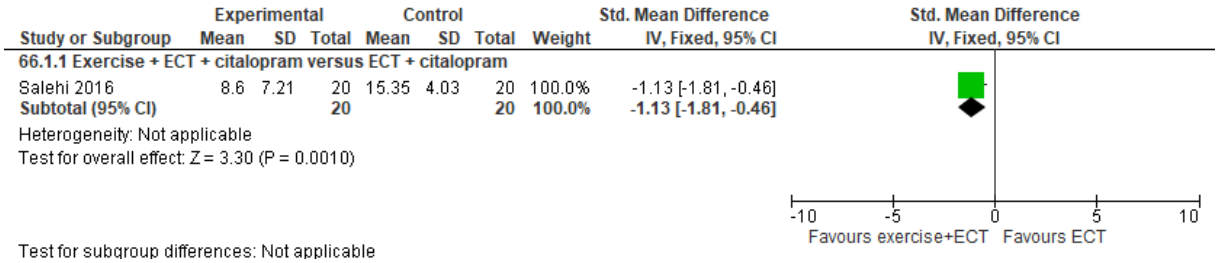
1342 Test for subgroup differences: Not applicable

1343

1344

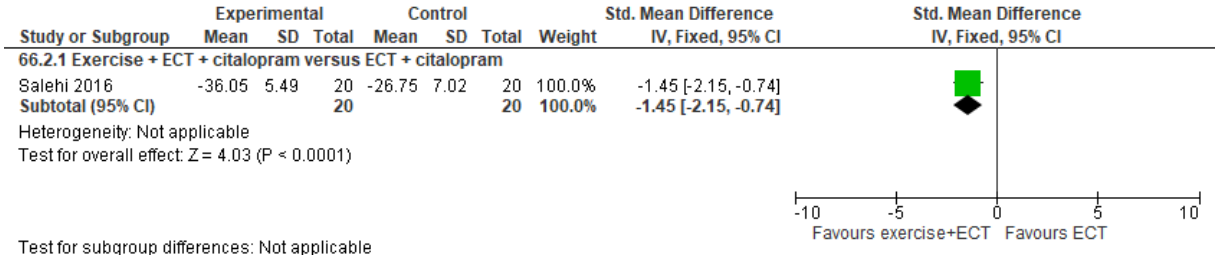
Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Figure 387: Depression symptomatology endpoint



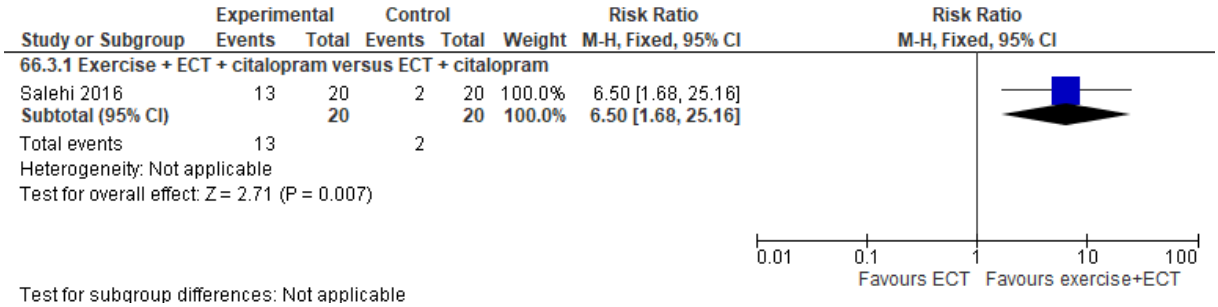
Test for subgroup differences: Not applicable

Figure 388: Depression symptomatology change score



Test for subgroup differences: Not applicable

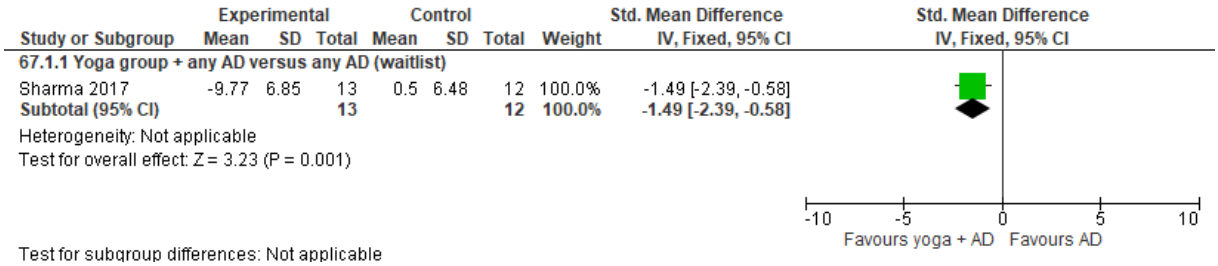
Figure 389: Remission (ITT)



Test for subgroup differences: Not applicable

Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

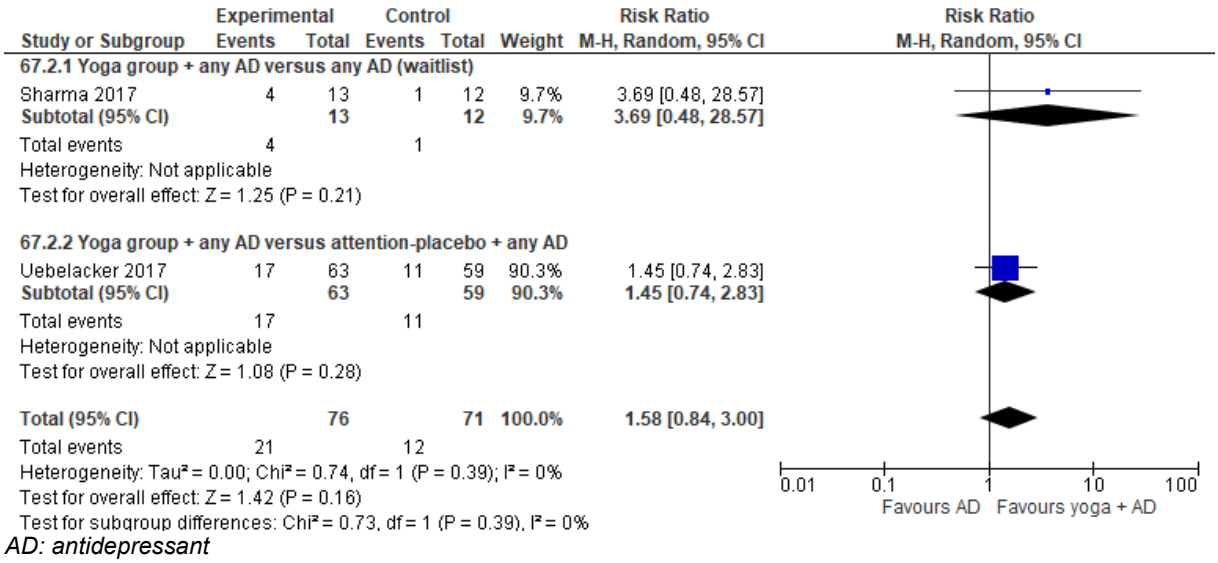
Figure 390: Depression symptomatology change score



Test for subgroup differences: Not applicable

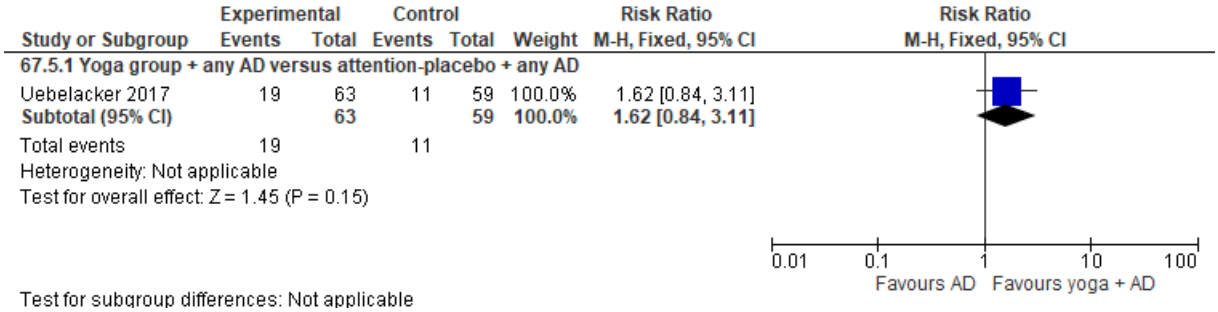
AD: antidepressant

Figure 391: Remission (ITT)



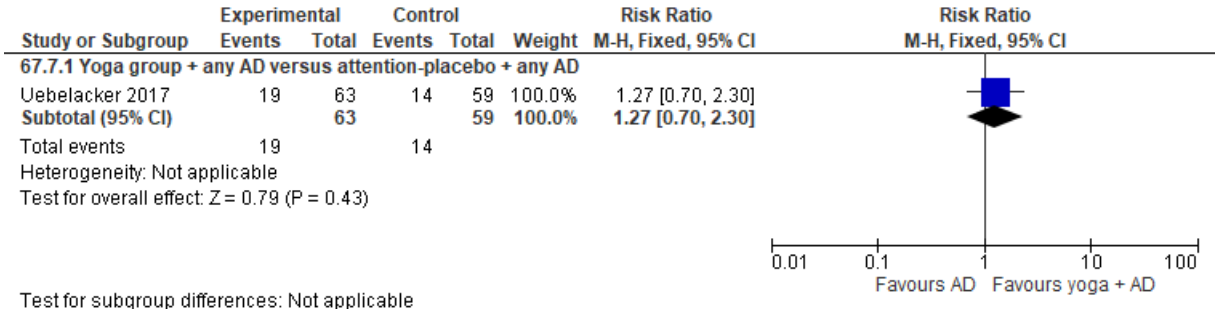
AD: antidepressant

Figure 392: Remission (ITT) at 3-month follow-up



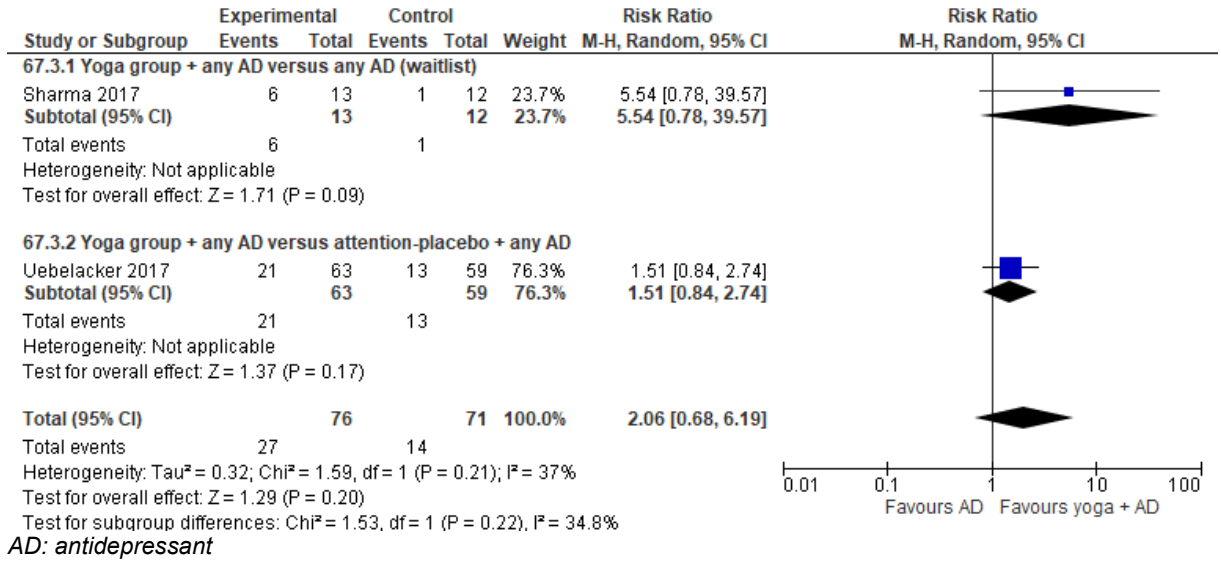
AD: antidepressant

Figure 393: Remission (ITT) at 6-month follow-up



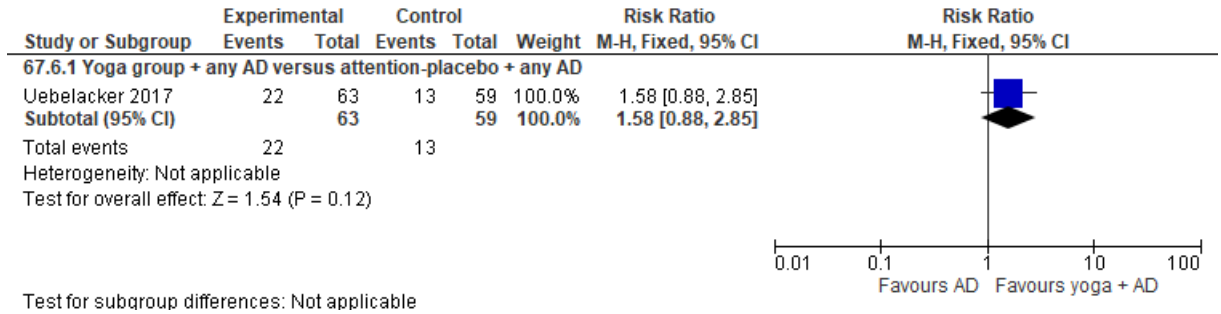
AD: antidepressant

Figure 394: Response (ITT)



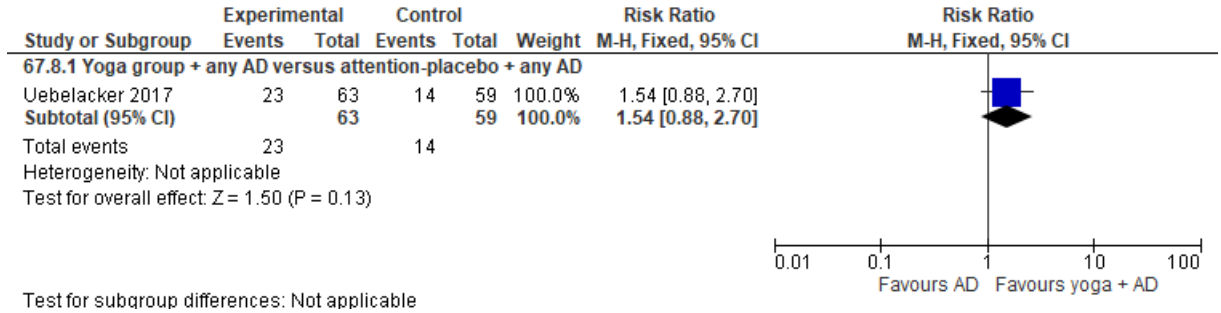
AD: antidepressant

Figure 395: Response (ITT) at 3-month follow-up



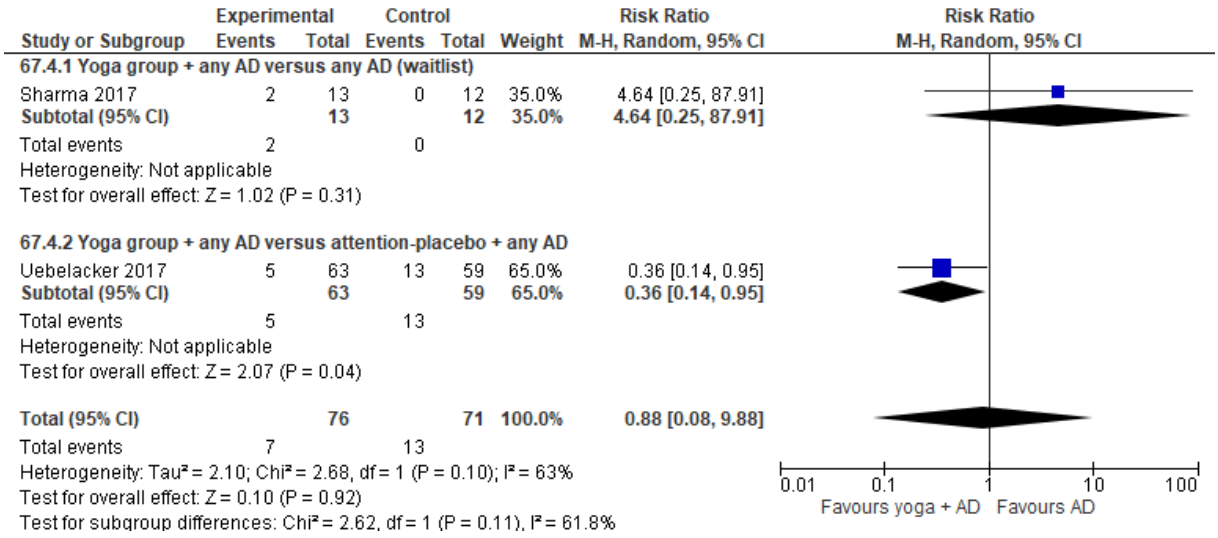
AD: antidepressant

Figure 396: Response (ITT) at 6-month follow-up



AD: antidepressant

Figure 397: Discontinuation due to any reason



AD: antidepressant

Appendix F – GRADE tables

GRADE tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 70: Clinical evidence profile for comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with cognitive and cognitive behavioural therapies	Continuing with antidepressant (+/ waitlist or attention-placebo)	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up 8-26 weeks; measured with: Beck Depression Inventory (BDI/BDI-II) or Hamilton Rating Scale for Depression (HAMD); Better indicated by lower values)												
13 (Chan 2012, Chiesa 2015, Dozois 2009, Dunn 1979, Embling 2002, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a, Wiles 2013/2016)	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	666	558	-	SMD 0.74 lower (1.03 to 0.45 lower)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up 8-26 weeks; measured with: Beck Depression Inventory (BDI/BDI-II) or Hamilton Rating Scale for Depression (HAMD) change from baseline to endpoint; Better indicated by lower values)												
10 (Chan 2012, Chiesa 2015, Dozois 2009, Dunn 1979, Embling 2002, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a)	randomised trials	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	none	265	259	-	SMD 1.36 lower (1.87 to 0.86 lower)	VERY LOW	CRITICAL
Depression symptomatology at 2-3 month follow-up (follow-up 8-16 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

2 (Chiesa 2015, Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	63	60	-	SMD 0.51 lower (0.87 to 0.15 lower)	MODERATE	CRITICAL
Depression symptomatology at 4-6 month follow-up (follow-up mean 4-6 months; measured with: Hamilton Rating Scale for Depression (HAM-D)/Beck Depression Inventory (BDI/BDI-II); Better indicated by lower values)												
5 (Chiesa 2015, Dunn 1979, Nakagawa 2017, Paykel 1999/ Scott 2000, Wiles 2013/2016)	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	350	346	-	SMD 0.51 lower (0.77 to 0.24 lower)	LOW	CRITICAL
Depression symptomatology at 11-12 month follow-up (follow-up 11-12 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Nakagawa 2017, Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	serious[3]	none	120	118	-	SMD 0.3 lower (0.93 lower to 0.33 higher)	VERY LOW	CRITICAL
Depression symptomatology at 40-month follow-up (follow-up mean 40 months; measured with: Beck Depression Inventory (BDI-II); Better indicated by lower values)												
1 (Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	136	112	-	SMD 0.31 lower (0.56 to 0.06 lower)	LOW	CRITICAL
Remission (ITT) (follow-up 8-26 weeks; assessed with: Number of people scoring =<7/10 on Hamilton Rating Scale for Depression (HAM-D) or <10 on Beck Depression Inventory (BDI-II))												
8 (Eisendrath 2016, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Watkins 2011a, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/703 (30.6%)	101/590 (17.1%)	RR 1.76 (1.32 to 2.36)	130 more per 1000 (from 55 more to 233 more)	MODERATE	CRITICAL
Remission (ITT) at 3-month follow-up (follow-up mean 3 months; assessed with: Number of people scoring =<7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	20/40 (50%)	12/40 (30%)	RR 1.67 (0.95 to 2.93)	201 more per 1000 (from 15 fewer to 579 more)	MODERATE	CRITICAL
Remission (ITT) at 6-month follow-up (follow-up mean 6 months; assessed with: Number of people scoring <10 on Beck Depression Inventory (BDI-II)/≤7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Nakagawa 2017, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/274 (38.7%)	52/275 (18.9%)	RR 1.99 (1.52 to 2.62)	187 more per 1000 (from 98 more to 306 more)	MODERATE	CRITICAL

Remission (ITT) at 12-month follow-up (follow-up mean 12 months; assessed with: Number of people scoring =<7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	29/40 (72.5%)	17/40 (42.5%)	RR 1.71 (1.13 to 2.56)	302 more per 1000 (from 55 more to 663 more)	MODERATE	CRITICAL
Remission (ITT) at 40-month follow-up (follow-up mean 40 months; assessed with: Number of people scoring <10 on Beck Depression Inventory (BDI-II))												
1 (Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38/234 (16.2%)	20/235 (8.5%)	RR 1.91 (1.15 to 3.18)	77 more per 1000 (from 13 more to 186 more)	LOW	CRITICAL
Response (ITT) (follow-up 8-26 weeks; assessed with: Response: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D)/Beck Depression Inventory (BDI-II))												
6 (Eisendrath 2016, Nakagawa 2017, Nakao 2018, Watkins 2011a, Wiles 2008, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/416 (45.4%)	81/413 (19.6%)	RR 2.27 (1.83 to 2.83)	249 more per 1000 (from 163 more to 359 more)	MODERATE	CRITICAL
Response (ITT) at 3-month follow-up (follow-up mean 3 months; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	28/40 (70%)	17/40 (42.5%)	RR 1.65 (1.09 to 2.49)	276 more per 1000 (from 38 more to 633 more)	MODERATE	CRITICAL
Response (ITT) at 6-month follow-up (follow-up mean 6 months; assessed with: Number of people showing at least 50% improvement on Beck Depression Inventory (BDI-II)/Hamilton Rating Scale for Depression (HAM-D))												
2 (Nakagawa 2017, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/274 (52.2%)	86/275 (31.3%)	RR 1.6 (1.27 to 2.01)	188 more per 1000 (from 84 more to 316 more)	MODERATE	CRITICAL
Response (ITT) at 12-month follow-up (follow-up mean 12 months; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	33/40 (82.5%)	20/40 (50%)	RR 1.65 (1.17 to 2.32)	325 more per 1000 (from 85 more to 660 more)	MODERATE	CRITICAL
Response (ITT) at 40-month follow-up (follow-up mean 40 months; assessed with: Number of people showing at least 50% improvement on Beck Depression Inventory (BDI-II))												

1 (Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/234 (25.2%)	30/235 (12.8%)	RR 1.98 (1.32 to 2.95)	125 more per 1000 (from 41 more to 249 more)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up 8-26 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
13 (Chan 2012, Chiesa 2015, Dozois 2009, Eisendrath 2016, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a, Wiles 2008, Wiles 2013/2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	111/807 (13.8%)	103/687 (15%)	RR 0.95 (0.74 to 1.21)	7 fewer per 1000 (from 39 fewer to 31 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	2/200 (1%)	2/96 (2.1%)	RR 0.48 (0.07 to 3.36)	11 fewer per 1000 (from 19 fewer to 49 more)	LOW	CRITICAL
Quality of life endpoint (follow-up mean 12 weeks; measured with: European Quality of Life Questionnaire-5 Dimensions (EQ-5D); Better indicated by higher values)												
1 (Nakao 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	20	20	-	SMD 0 higher (0.62 lower to 0.62 higher)	LOW	IMPORTANT
Quality of life physical component score (PCS) endpoint (follow-up 12-26 weeks; measured with: 12-item/36-item Short-Form Survey (SF-12/SF-36): Physical component score; Better indicated by higher values)												
3 (Nakagawa 2017, Nakao 2018, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	261	269	-	SMD 0.04 higher (0.17 lower to 0.26 higher)	MODERATE	IMPORTANT
Quality of life mental component score (MCS) endpoint (follow-up 12-26 weeks; measured with: 12-item/36-item Short-Form Survey (SF-12/SF-36): Mental component score; Better indicated by higher values)												
3 (Nakagawa 2017, Nakao 2018, Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	261	269	-	SMD 0.26 higher (0.03 lower to 0.55 higher)	LOW	IMPORTANT
Quality of life physical component score (PCS) at 3-month follow-up (follow-up mean 3 months; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Nakagawa 2017)	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[3]	none	40	40	-	SMD 0.17 lower (0.61	MODERATE	IMPORTANT

		risk of bias								lower to 0.27 higher)		
Quality of life mental component score (MCS) at 3-month follow-up (follow-up mean 3 months; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Nakagawa 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	40	40	-	SMD 0.15 lower (0.58 lower to 0.29 higher)	MODERATE	IMPORTANT
Quality of life physical component score (PCS) at 6-month follow-up (follow-up mean 6 months; measured with: 12-item/36-item Short-Form Survey (SF-12/SF-36): Physical component score; Better indicated by higher values)												
2 (Nakagawa 2015, Wiles 2013/2016)	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	234	235	-	SMD 0.07 higher (0.37 lower to 0.52 higher)	VERY LOW	IMPORTANT
Quality of life mental component score (MCS) at 6-month follow-up (follow-up mean 6 months; measured with: 12-item/36-item Short-Form Survey (SF-12/SF-36): Mental component score; Better indicated by higher values)												
2 (Nakagawa 2015, Wiles 2013/2016)	randomised trials	serious[1]	very serious[4]	no serious indirectness	very serious[5]	none	234	235	-	SMD 0.01 higher (0.56 lower to 0.58 higher)	VERY LOW	IMPORTANT
Quality of life physical component score (PCS) at 12-month follow-up (follow-up mean 12 months; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Nakagawa 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	SMD 0.05 higher (0.39 lower to 0.49 higher)	HIGH	IMPORTANT
Quality of life mental component score (MCS) at 12-month follow-up (follow-up mean 12 months; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Nakagawa 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	40	40	-	SMD 0.2 lower (0.64 lower to 0.24 higher)	MODERATE	IMPORTANT
Quality of life physical component score (PCS) at 40-month follow-up (follow-up mean 40 months; measured with: 12-item Short-Form Survey (SF-12): Physical component score; Better indicated by higher values)												
1 (Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	132	110	-	SMD 0.22 higher (0.03 lower to 0.47 higher)	MODERATE	IMPORTANT
Quality of life mental component score (MCS) at 40-month follow-up (follow-up mean 40 months; measured with: 12-item Short-Form Survey (SF-12): Mental component score; Better indicated by higher values)												
1 (Wiles 2013/2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	132	110	-	SMD 0.34 higher (0.09	LOW	IMPORTANT

										to 0.6 higher)		
Functional impairment endpoint (follow-up 12-20 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT)/Social Adjustment Scale (SAS); Better indicated by lower values)												
2 (Kocsis 2009/ Klein 2011, Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	252	153	-	SMD 0.36 lower (0.67 to 0.05 lower)	LOW	IMPORTANT
Functional impairment at 11-month follow-up (follow-up mean 11 months; measured with: Social Adjustment Scale (SAS); Better indicated by lower values)												
1 (Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	80	78	-	SMD 0.3 lower (0.61 lower to 0.01 higher)	MODERATE	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Substantial heterogeneity
[3] 95% CI crosses threshold for both clinically important benefit and no effect
[4] Considerable heterogeneity
[5] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[6] 95% CI crosses threshold for both clinically important harm and no effect

Table 71: Clinical evidence profile for comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with cognitive and cognitive behavioural therapies**	**Augmenting with counselling**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	174	168	-	SMD 0.18 lower (0.39 lower to 0.04 higher)	HIGH	CRITICAL
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) AND responding (≥50% improvement on HAM-D))												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67/200 (33.5%)	52/195 (26.7%)	RR 1.26 (0.93 to 1.7)	69 more per 1000 (from 19 fewer to 187 more)	MODERATE	CRITICAL

Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25/200 (12.5%)	27/195 (13.8%)	RR 0.9 (0.54 to 1.5)	14 fewer per 1000 (from 64 fewer to 69 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/200 (1%)	1/195 (0.51%)	RR 1.95 (0.18 to 21.33)	5 more per 1000 (from 4 fewer to 104 more)	LOW	CRITICAL
Functional impairment endpoint (follow-up mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT); Better indicated by lower values)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	172	162	-	SMD 0.15 lower (0.36 lower to 0.07 higher)	HIGH	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] 95% CI crosses threshold for no effect and thresholds for both clinically important benefit and harm

Table 72: Clinical evidence profile for comparison 3. Augmenting with counselling versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with counselling**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	168	76	-	SMD 0.06 higher (0.21 lower to 0.33 higher)	HIGH	CRITICAL
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) AND responding (≥50% improvement on HAM-D))												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	52/195 (26.7%)	30/96 (31.3%)	RR 0.85 (0.59 to 1.24)	47 fewer per 1000 (from 128 fewer to 75 more)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/195 (13.8%)	16/96 (16.7%)	RR 0.83 (0.47 to 1.47)	28 fewer per 1000 (from 88 fewer to 78 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/195 (0.51%)	2/96 (2.1%)	RR 0.25 (0.02 to 2.68)	16 fewer per 1000 (from 20 fewer to 35 more)	LOW	CRITICAL
Functional impairment endpoint (follow-up mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT); Better indicated by lower values)												
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	162	75	-	SMD 0.07 lower (0.34 lower to 0.21 higher)	HIGH	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important harm and no effect
[2] 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 73: Clinical evidence profile for comparison 4. Augmenting with IPT versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with IPT**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up 5-19 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Schramm 2007, Souza 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	79	79	-	SMD 0.36 lower (0.68 to 0.05 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up 5-19 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
3 (Murray 2010, Schramm 2007, Souza 2016)	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[2]	none	106	106	-	SMD 0.73 lower (1.38 to 0.08 lower)	LOW	CRITICAL
Depression symptomatology at 1-3 month follow-up (follow-up 1-3 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Schramm 2007, Souza 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66	65	-	SMD 0.31 lower (0.79 lower to 0.16 higher)	LOW	CRITICAL
Depression symptomatology at 12-month follow-up (follow-up mean 12 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

1 (Schramm 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	SMD 0.54 lower (0.94 to 0.13 lower)	LOW	CRITICAL
Remission (ITT) (follow-up 5-19 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
4 (Murray 2010, Reynolds 2010, Schramm 2007, Souza 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83/176 (47.2%)	57/182 (31.3%)	RR 1.44 (1.12 to 1.86)	138 more per 1000 (from 38 more to 269 more)	LOW	CRITICAL
Response (ITT) (follow-up 5-19 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
3 (Murray 2010, Schramm 2007, Souza 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62/116 (53.4%)	40/118 (33.9%)	RR 1.51 (1.14 to 1.99)	173 more per 1000 (from 47 more to 336 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 5-19 weeks; assessed with: Number of participants who dropped out for any reason)												
4 (Murray 2010, Reynolds 2010, Schramm 2007, Souza 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	31/176 (17.6%)	23/182 (12.6%)	RR 1.35 (0.81 to 2.23)	44 more per 1000 (from 24 fewer to 155 more)	LOW	CRITICAL
Global functioning endpoint (follow-up mean 5 weeks; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Schramm 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	63	61	-	SMD 0.32 higher (0.03 lower to 0.68 higher)	LOW	IMPORTANT
Global functioning at 3-month follow-up (follow-up mean 3 months; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Schramm 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	SMD 0.44 higher (0.03 to 0.84 higher)	LOW	IMPORTANT
Global functioning at 12-month follow-up (follow-up mean 12 months; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Schramm 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	47	-	SMD 0.47 higher (0.06 to 0.87 higher)	LOW	IMPORTANT

CI: confidence interval; IPT: interpersonal therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Substantial heterogeneity
[4] 95% CI crosses thresholds for both clinically important harm and no effect

Table 74: Clinical evidence profile for comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with short-term psychodynamic psychotherapy	Continuing with antidepressant	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 26 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	SMD 0.56 lower (1.07 to 0.04 lower)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 26 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	SMD 0.71 lower (1.23 to 0.19 lower)	MODERATE	CRITICAL
Depression symptomatology at 3-month follow-up (follow-up mean 3 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	SMD 0.58 lower (1.1 to 0.07 lower)	MODERATE	CRITICAL
Depression symptomatology at 6-month follow-up (follow-up mean 6 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	SMD 0.56 lower (1.08 to 0.05 lower)	MODERATE	CRITICAL
Depression symptomatology at 12-month follow-up (follow-up mean 12 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	30	-	SMD 0.62 lower (1.14 to 0.1 lower)	MODERATE	CRITICAL
Remission (ITT) (follow-up mean 26 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/30 (36.7%)	1/30 (3.3%)	RR 11 (1.51 to 79.96)	333 more per 1000 (from 17 more to 1000 more)	HIGH	CRITICAL
Remission (ITT) at 12-month follow-up (follow-up mean 12 months; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Town 2017/2020)	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2]	none	12/30 (40%)	9/30 (30%)	RR 1.33 (0.66 to 2.69)	99 more per 1000 (from 102	LOW	CRITICAL

		risk of bias								fewer to 507 more)		
Response (ITT) at 12-month follow-up (follow-up mean 12 months; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/30 (50%)	12/30 (40%)	RR 1.25 (0.71 to 2.2)	100 more per 1000 (from 116 fewer to 480 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 26 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/30 (16.7%)	3/30 (10%)	RR 1.67 (0.44 to 6.36)	67 more per 1000 (from 56 fewer to 536 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 75: Clinical evidence profile for comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with long-term psychodynamic psychotherapy**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 78 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	53	46	-	SMD 0.23 lower (0.63 lower to 0.16 higher)	VERY LOW	CRITICAL
Depression symptomatology at 6-month follow-up (follow-up mean 6 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	49	47	-	SMD 0.34 lower (0.75 lower to 0.06 higher)	VERY LOW	CRITICAL
Depression symptomatology at 12-month follow-up (follow-up mean 12 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	49	49	-	SMD 0.38 lower (0.78 lower to 0.02 higher)	VERY LOW	CRITICAL

Depression symptomatology at 24-month follow-up (follow-up mean 2 years; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	47	45	-	SMD 0.68 lower (1.1 to 0.26 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 78 weeks; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	6/67 (9%)	4/62 (6.5%)	RR 1.39 (0.41 to 4.69)	25 more per 1000 (from 38 fewer to 238 more)	VERY LOW	CRITICAL
Remission (ITT) at 24-month follow-up (follow-up mean 2 years; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fonagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	10/67 (14.9%)	3/62 (4.8%)	RR 3.08 (0.89 to 10.69)	101 more per 1000 (from 5 fewer to 469 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 78 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Fornagy 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	10/67 (14.9%)	8/62 (12.9%)	RR 1.16 (0.49 to 2.74)	21 more per 1000 (from 66 fewer to 225 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Statistically significant group difference at baseline
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Study partially funded by the International Psychoanalytic Association
[4] 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 76: Clinical evidence profile for comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/- attention-placebo)

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with self-help**	**Continuing with the antidepressant (+/- attention-placebo)**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up 1.4-6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Beck Depression Inventory (BDI-II); Better indicated by lower values)												
3 (Baert 2010_study 2, Dai 2019,	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	80	77	-	SMD 0.29 lower (0.61	MODERATE	CRITICAL

Schlogelhofer 2014)		risk of bias								lower to 0.03 higher)		
Depression symptomatology change score (follow-up 1.4-6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Beck Depression Inventory (BDI-II) change from baseline to endpoint; Better indicated by lower values)												
3 (Baert 2010_study 2, Dai 2019, Schlogelhofer 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80	77	-	SMD 0.39 lower (0.71 to 0.08 lower)	MODERATE	CRITICAL
Depression symptomatology at 1-month follow-up (follow-up mean 1 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Dai 2019)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	16	-	SMD 1.37 lower (2.15 to 0.59 lower)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up 1.4-6 weeks; assessed with: Number of participants who dropped out for any reason)												
2 (Dai 2019, Schlogelhofer 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15/69 (21.7%)	10/61 (16.4%)	RR 1.32 (0.64 to 2.74)	52 more per 1000 (from 59 fewer to 285 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] Risk of bias is high or unclear across multiple domains
[3] 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 77: Clinical evidence profile for comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with self-help and switching to SSRI**	**Switching to SSRI-only**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 9 weeks; measured with: Patient Health Questionnaire (PHQ-9); Better indicated by lower values)												
1 (Mantani 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	81	83	-	SMD 1.13 lower (1.46 to 0.8 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 9 weeks; measured with: Patient Health Questionnaire (PHQ-9) change from baseline to endpoint; Better indicated by lower values)												
1 (Mantani 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	81	83	-	SMD 0.76 lower (1.08 to 0.44 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 9 weeks; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9))												

1 (Mantani 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	25/81 (30.9%)	15/83 (18.1%)	RR 1.71 (0.97 to 3)	128 more per 1000 (from 5 fewer to 361 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 9 weeks; assessed with: Number of people showing at least 50% improvement on Patient Health Questionnaire (PHQ-9))												
1 (Mantani 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	34/81 (42%)	18/83 (21.7%)	RR 1.94 (1.19 to 3.14)	204 more per 1000 (from 41 more to 464 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 9 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Mantani 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	1/81 (1.2%)	0/83 (0%)	RR 3.07 (0.13 to 74.35)	-	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] Study partially funded by pharmaceutical companies
[3] 95% CI crosses thresholds for both clinically important benefit and no effect
[4] 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 78: Clinical evidence profile for comparison 9. Augmenting with art therapy versus attention-placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with art therapy**	**Attention-placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Beck Depression Inventory (BDI-II); Better indicated by lower values)												
1 (Nan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	48	-	SMD 0.56 lower (0.96 to 0.16 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Beck Depression Inventory (BDI-II) change from baseline to endpoint; Better indicated by lower values)												
1 (Nan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	48	-	SMD 1.22 lower (1.64 to 0.79 lower)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Nan 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/53 (1.9%)	5/53 (9.4%)	RR 0.2 (0.02 to 1.65)	75 fewer per 1000 (from 92 fewer to 61 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] *Risk of bias is high or unclear across multiple domains*
[2] *95% CI crosses thresholds for both clinically important benefit and no effect*
[3] *95% CI crosses thresholds for no effect and both clinically important benefit and harm*

Table 79: Clinical evidence profile for comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with eye movement desensitization reprocessing (EMDR)	Augmenting with cognitive behavioural therapy	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up 13-26 weeks; measured with: Beck Depression Inventory (BDI-II); Better indicated by lower values)												
1 (Ostacoli 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	31	35	-	SMD 0.65 lower (1.14 to 0.15 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 13-26 weeks; assessed with: Number of people scoring <13 on Beck Depression Inventory (BDI-II))												
1 (Ostacoli 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	22/40 (55%)	17/42 (40.5%)	RR 1.36 (0.86 to 2.16)	146 more per 1000 (from 57 fewer to 470 more)	VERY LOW	CRITICAL
Remission (ITT) at 6-month follow-up (follow-up mean 6 months; assessed with: Number of people scoring <13 on Beck Depression Inventory (BDI-II))												
1 (Ostacoli 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17/40 (42.5%)	15/42 (35.7%)	RR 1.19 (0.69 to 2.05)	68 more per 1000 (from 111 fewer to 375 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 13-26 weeks; assessed with: Number of participants who dropped out for any reason)												
1 (Ostacoli 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	9/40 (22.5%)	7/42 (16.7%)	RR 1.35 (0.56 to 3.28)	58 more per 1000 (from 73 fewer to 380 more)	VERY LOW	CRITICAL
Global functioning at endpoint (follow-up 13-26 weeks; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Ostacoli 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	31	35	-	SMD 0.22 higher (0.27 lower to 0.7 higher)	VERY LOW	IMPORTANT
Global functioning at 6-month follow-up (follow-up mean 6 months; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												

1 (Ostacoli 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	31	35	-	SMD 0.24 higher (0.24 lower to 0.73 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Potential conflict of interest as study funded by the EMDR Research Foundation
[4] 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 80: Clinical evidence profile for comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Increasing the dose of SSRI**	**Continuing SSRI at the same dose**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Ruhe 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	27	-	SMD 0.63 higher (0.1 to 1.17 higher)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up 5-6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Dornseif 1989, Kim 2019)	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	reporting bias[5]	205	211	-	SMD 0.33 lower (0.73 lower to 0.07 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 5-6 weeks; assessed with: Number of people scoring <=7/<=8 on Hamilton Rating Scale for Depression (HAM-D) or <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
5 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer 2001)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	116/372 (31.2%)	112/381 (29.4%)	RR 1.1 (0.84 to 1.45)	29 more per 1000 (from 47 fewer to 132 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 5-6 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D)/Montgomery Asberg Depression Rating Scale (MADRS) or rated as much or very much improved on Clinical Global Impressions scale (CGI-I))												
6 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	reporting bias[5]	195/408 (47.8%)	195/422 (46.2%)	RR 1.1 (0.86 to 1.39)	46 more per 1000 (from 65	VERY LOW	CRITICAL

1990, Schweizer 2001)										fewer to 180 more)		
Discontinuation due to any reason (follow-up 5-6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
5 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer 2001)	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[6]	reporting bias[5]	66/372 (17.7%)	77/381 (20.2%)	RR 0.77 (0.4 to 1.48)	46 fewer per 1000 (from 121 fewer to 97 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
4 (Dornseif 1989, Kim 2019, Ruhe 2009, Schweizer 1990)	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[6]	reporting bias[5]	27/272 (9.9%)	16/286 (5.6%)	RR 1.59 (0.42 to 6.03)	33 more per 1000 (from 32 fewer to 281 more)	VERY LOW	CRITICAL
Quality of life physical component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Ruhe 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30	27	-	SMD 0.6 lower (1.13 to 0.06 lower)	MODERATE	IMPORTANT
Quality of life mental component score (MCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Ruhe 2009)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	27	-	SMD 1.55 higher (0.95 to 2.14 higher)	HIGH	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor
[1] 95% CI crosses thresholds for both clinically important harm and no effect
[2] Risk of bias is high or unclear across multiple domains
[3] Substantial heterogeneity
[4] 95% CI crosses thresholds for both clinically important benefit and no effect
[5] Funding from pharmaceutical companies
[6] 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 81: Clinical evidence profile for comparison 12. Increasing the dose of SSRI versus switching to SNRI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Switching to SNRI	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 8 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS); Better indicated by lower values)												

1 (Bose 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	229	243	-	SMD 0.21 lower (0.39 to 0.03 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
1 (Bose 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	229	243	-	SMD 0.16 lower (0.35 lower to 0.02 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Bose 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	124/238 (52.1%)	102/246 (41.5%)	RR 1.26 (1.04 to 1.52)	108 more per 1000 (from 17 more to 216 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Bose 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	167/238 (70.2%)	170/246 (69.1%)	RR 1.02 (0.9 to 1.14)	14 more per 1000 (from 69 fewer to 97 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Bose 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	56/238 (23.5%)	53/246 (21.5%)	RR 1.09 (0.78 to 1.52)	19 more per 1000 (from 47 fewer to 112 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Bose 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	13/238 (5.5%)	13/246 (5.3%)	RR 1.03 (0.49 to 2.18)	2 more per 1000 (from 27 fewer to 62 more)	VERY LOW	CRITICAL
Quality of life endpoint (follow-up mean 8 weeks; measured with: Quality of Life Enjoyment and Satisfaction Questionnaire-short form (Q-LES-Q-SF); Better indicated by higher values)												
1 (Bose 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	229	243	-	SMD 0.11 higher (0.08 lower to 0.29 higher)	LOW	IMPORTANT

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

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

[2] Funding from pharmaceutical company

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

[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 82: Clinical evidence profile for comparison 13. Increasing the dose of SSRI versus augmenting with TCA

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with TCA	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	46	-	SMD 0.67 lower (1.28 to 0.05 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	46	-	SMD 0.44 lower (0.9 lower to 0.01 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/48 (45.8%)	13/46 (28.3%)	RR 1.6 (0.91 to 2.81)	170 more per 1000 (from 25 fewer to 512 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 4 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Fava 1994a, Fava 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/48 (10.4%)	8/46 (17.4%)	RR 0.58 (0.21 to 1.64)	73 fewer per 1000 (from 137 fewer to 111 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 4 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Fava 1994a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	0/15 (0%)	2/12 (16.7%)	RR 0.16 (0.01 to 3.09)	140 fewer per 1000 (from 165 fewer to 348 more)	VERY LOW	CRITICAL

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

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

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

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

[4] *Study partially funded by pharmaceutical company*

Table 83: Clinical evidence profile for comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with antipsychotic	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 13 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	32	-	SMD 0.1 higher (0.41 lower to 0.6 higher)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 13 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	32	-	SMD 0.07 higher (0.43 lower to 0.58 higher)	MODERATE	CRITICAL
Remission (ITT) (follow-up mean 13 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/28 (32.1%)	14/32 (43.8%)	RR 0.73 (0.38 to 1.43)	118 fewer per 1000 (from 271 fewer to 188 more)	LOW	CRITICAL
Response (ITT) (follow-up mean 13 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/28 (53.6%)	18/32 (56.3%)	RR 0.95 (0.6 to 1.51)	28 fewer per 1000 (from 225 fewer to 287 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 13 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/28 (14.3%)	5/32 (15.6%)	RR 0.91 (0.27 to 3.08)	14 fewer per 1000 (from 114 fewer to 325 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 13 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/28 (7.1%)	2/32 (6.3%)	RR 1.14 (0.17 to 7.59)	9 more per 1000 (from 52 fewer to 412 more)	LOW	CRITICAL
Functional remission (follow-up mean 13 weeks; assessed with: Number of people scoring =>71 on Global Assessment of Function (GAF))												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/28 (39.3%)	22/32 (68.8%)	RR 0.57 (0.34 to 0.96)	296 fewer per 1000 (from 28 fewer to 454 fewer)	MODERATE	IMPORTANT
Global functioning endpoint (follow-up mean 13 weeks; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	32	-	SMD 0.67 lower (1.19 to 0.15 lower)	MODERATE	IMPORTANT

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

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

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

Table 84: Clinical evidence profile for comparison 15. Increasing the dose of SSRI versus augmenting with lithium

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with lithium	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	48	-	SMD 0.34 lower (0.75 lower to 0.06 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	48	-	SMD 0.31 lower (0.72 lower to 0.09 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/48 (45.8%)	12/48 (25%)	RR 1.83 (1.03 to 3.25)	208 more per 1000 (from 7 more to 562 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 4 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Fava 1994a, Fava 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/48 (10.4%)	7/48 (14.6%)	RR 0.72 (0.24 to 2.11)	41 fewer per 1000 (from 111 fewer to 162 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 4 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Fava 1994a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	0/15 (0%)	1/14 (7.1%)	RR 0.31 (0.01 to 7.09)	49 fewer per 1000 (from 71 fewer to 435 more)	VERY LOW	CRITICAL

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

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

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

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

[4] *Study partially funded by pharmaceutical company*

Table 85: Clinical evidence profile for comparison 16. Switching to SSRI versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SSRI**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												

2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	reporting bias[3]	198	126	-	SMD 0.03 higher (0.31 lower to 0.38 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	29/202 (14.4%)	25/127 (19.7%)	RR 0.76 (0.46 to 1.24)	47 fewer per 1000 (from 106 fewer to 47 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	60/202 (29.7%)	50/127 (39.4%)	RR 0.78 (0.54 to 1.12)	87 fewer per 1000 (from 181 fewer to 47 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[5]	reporting bias[3]	40/202 (19.8%)	23/127 (18.1%)	RR 1.13 (0.54 to 2.38)	24 more per 1000 (from 83 fewer to 250 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	7/202 (3.5%)	3/127 (2.4%)	RR 1.43 (0.38 to 5.47)	10 more per 1000 (from 15 fewer to 106 more)	VERY LOW	CRITICAL

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

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

[2] *Substantial heterogeneity*

[3] *Funding from pharmaceutical companies*

[4] *95% CI crosses thresholds for both clinically important harm and no effect*

[5] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

Table 86: Clinical evidence profile for comparison 17. Switching to a different SSRI versus continuing same SSRI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to a different SSRI	Continuing same SSRI	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												

1 (Nakajima 2011)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	12/20 (60%)	3/21 (14.3%)	RR 4.2 (1.39 to 12.71)	457 more per 1000 (from 56 more to 1000 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Nakajima 2011)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	15/20 (75%)	4/21 (19%)	RR 3.94 (1.57 to 9.85)	560 more per 1000 (from 109 more to 1000 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Nakajima 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	2/20 (10%)	5/21 (23.8%)	RR 0.42 (0.09 to 1.92)	138 fewer per 1000 (from 217 fewer to 219 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Nakajima 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	0/20 (0%)	0/21 (0%)	not pooled	not pooled	LOW	CRITICAL

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

[1] *Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug in switch arm*

[2] *Study partially funded by pharmaceutical company*

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

Table 87: Clinical evidence profile for comparison 18. Switching to SSRI versus antipsychotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SSRI**	**Antipsychotic**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	198	203	-	SMD 0.27 lower (0.5 to 0.03 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	29/202 (14.4%)	27/206 (13.1%)	RR 1.1 (0.67 to 1.79)	13 more per 1000 (from 43 fewer to 104 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	60/202 (29.7%)	43/206 (20.9%)	RR 1.42 (1.01 to 2)	88 more per 1000 (from 2 more to 209 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	40/202 (19.8%)	50/206 (24.3%)	RR 0.82 (0.56 to 1.18)	44 fewer per 1000 (from 107 fewer to 44 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	7/202 (3.5%)	19/206 (9.2%)	RR 0.39 (0.16 to 0.91)	56 fewer per 1000 (from 8 fewer to 77 fewer)	LOW	CRITICAL

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

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

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

[3] Funding from pharmaceutical companies

[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 88: Clinical evidence profile for comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to combined SSRI + antipsychotic**	**Switching to antipsychotic-only**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	reporting bias[4]	376	203	-	SMD 0.44 lower (0.91 lower to 0.03 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	94/389 (24.2%)	27/206 (13.1%)	RR 1.63 (0.97 to 2.73)	83 more per 1000 (from 4 fewer to 227 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	140/389 (36%)	43/206 (20.9%)	RR 1.53 (1.12 to 2.1)	111 more per 1000 (from 25 more to 230 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	90/389 (23.1%)	50/206 (24.3%)	RR 0.89 (0.65 to 1.21)	27 fewer per 1000 (from 85 fewer to 51 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[4]	39/389 (10%)	19/206 (9.2%)	RR 0.98 (0.48 to 2.03)	2 fewer per 1000 (from 48 fewer to 95 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] Considerable heterogeneity
[3] 95% CI crosses thresholds for both clinically important benefit and no effect
[4] Funding from pharmaceutical companies
[5] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 89: Clinical evidence profile for comparison 20. Augmenting with SSRI versus augmenting with lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with SSRI**	**Augmenting with lithium**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Navarro 2019b)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	52	-	SMD 0.56 lower (0.95 to 0.16 lower)	LOW	CRITICAL
Remission (ITT) (follow-up mean 10 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Navarro 2019b)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/52 (40.4%)	11/52 (21.2%)	RR 1.91 (1.03 to 3.55)	193 more per 1000 (from 6 more to 539 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 90: Clinical evidence profile for comparison 21. Switching to TCA versus SSRI

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to TCA	SSRI	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Souery 2011a)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	67	85	-	SMD 0.2 lower (0.52 lower to 0.12 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Souery 2011a)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	21/84 (25%)	16/105 (15.2%)	RR 1.64 (0.92 to 2.94)	98 more per 1000 (from 12 fewer to 296 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 4 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Souery 2011a)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	37/84 (44%)	46/105 (43.8%)	RR 1.01 (0.73 to 1.39)	4 more per 1000 (from 118 fewer to 171 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 4 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Souery 2011a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17/84 (20.2%)	20/105 (19%)	RR 1.06 (0.6 to 1.9)	11 more per 1000 (from 76 fewer to 171 more)	VERY LOW	CRITICAL

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

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

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

[3] *Study partially funded by pharmaceutical company*

[4] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

Table 91: Clinical evidence profile for comparison 22. Switching to TCA versus augmenting with mirtazapine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to TCA**	**Augmenting with mirtazapine**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Navarro 2019a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	56	-	SMD 1.13 lower (1.53 to 0.73 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Navarro 2019a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	56	-	SMD 1.47 lower (1.88 to 1.05 lower)	LOW	CRITICAL
Remission (ITT) (follow-up mean 10 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												

1 (Navarro 2019a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/56 (71.4%)	22/56 (39.3%)	RR 1.82 (1.26 to 2.62)	322 more per 1000 (from 102 more to 636 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 10 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Navarro 2019a)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/56 (8.9%)	2/56 (3.6%)	RR 2.5 (0.51 to 12.35)	54 more per 1000 (from 18 fewer to 405 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

[1] Risk of bias is high or unclear across multiple domains and rapid tapering of failed drug in switch arm

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

Table 92: Clinical evidence profile for comparison 23. Switching to mianserin versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to mianserin**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	33	38	-	SMD 0.24 lower (0.71 lower to 0.23 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12/34 (35.3%)	7/38 (18.4%)	RR 1.92 (0.85 to 4.3)	169 more per 1000 (from 28 fewer to 608 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	16/34 (47.1%)	14/38 (36.8%)	RR 1.28 (0.74 to 2.21)	103 more per 1000 (from 96 fewer to 446 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Ferreri 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	12/34 (35.3%)	7/38 (18.4%)	RR 1.92 (0.85 to 4.3)	169 more per 1000 (from 28 fewer to 608 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Ferreri 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[3]	8/34 (23.5%)	0/38 (0%)	RR 18.94 (1.13 to 316.35)	-	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] *Risk of bias is high or unclear across multiple domains and abrupt tapering for the switch arm*
[2] *95% CI crosses thresholds for both clinically important benefit and no effect*
[3] *Study funded by pharmaceutical company*
[4] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*
[5] *95% CI crosses thresholds for both clinically important harm and no effect*

Table 93: Clinical evidence profile for comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mianserin	Continuing with antidepressant (+/- placebo)	Relative (95% CI)	Absolute		
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Ferreri 2001)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32	38	-	SMD 0.66 lower (1.14 to 0.17 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 5-6 weeks; assessed with: Number of people scoring <=7/<=8 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Ferreri 2001, Licht 2002)	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[5]	reporting bias[3]	57/130 (43.8%)	44/137 (32.1%)	RR 1.53 (0.78 to 2.99)	170 more per 1000 (from 71 fewer to 639 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 5-6 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
2 (Ferreri 2001, Licht 2002)	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[5]	reporting bias[3]	86/130 (66.2%)	83/137 (60.6%)	RR 1.22 (0.7 to 2.13)	133 more per 1000 (from 182 fewer to 685 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 5-6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Ferreri 2001, Licht 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	23/130 (17.7%)	17/137 (12.4%)	RR 1.43 (0.79 to 2.56)	53 more per 1000 (from 26 fewer to 194 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Ferreri 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	2/32 (6.3%)	0/38 (0%)	RR 5.91 (0.29 to 118.78)	-	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] *Risk of bias is high or unclear across multiple domains*
[2] *95% CI crosses thresholds for both clinically important benefit and harm*

[3] *Funding from pharmaceutical company*
[4] *Substantial heterogeneity*
[5] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

Table 94: Clinical evidence profile for comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mianserin	Increasing dose of antidepressant	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 5 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Licht 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	43/98 (43.9%)	28/98 (28.6%)	RR 1.54 (1.05 to 2.26)	154 more per 1000 (from 14 more to 360 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 5 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Licht 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	66/98 (67.3%)	54/98 (55.1%)	RR 1.22 (0.98 to 1.53)	121 more per 1000 (from 11 fewer to 292 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 5 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Licht 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	17/98 (17.3%)	15/98 (15.3%)	RR 1.13 (0.6 to 2.14)	20 more per 1000 (from 61 fewer to 174 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
[1] *Risk of bias is high or unclear across multiple domains*
[2] *95% CI crosses thresholds for both clinically important benefit and no effect*
[3] *Study funded by pharmaceutical company*
[4] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

Table 95: Clinical evidence profile for comparison 26. Augmenting with mianserin versus switch to mianserin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mianserin	Switch to mianserin	Relative (95% CI)	Absolute		
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												

1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	32	33	-	SMD 0.41 lower (0.91 lower to 0.08 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	14/32 (43.8%)	12/34 (35.3%)	RR 1.24 (0.68 to 2.26)	85 more per 1000 (from 113 fewer to 445 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Ferreri 2001)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	20/32 (62.5%)	16/34 (47.1%)	RR 1.33 (0.85 to 2.08)	155 more per 1000 (from 71 fewer to 508 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Ferreri 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[3]	6/32 (18.8%)	12/34 (35.3%)	RR 0.53 (0.23 to 1.25)	166 fewer per 1000 (from 272 fewer to 88 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Ferreri 2001)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	2/32 (6.3%)	8/34 (23.5%)	RR 0.27 (0.06 to 1.16)	172 fewer per 1000 (from 221 fewer to 38 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains and abrupt tapering for the switch arm
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Study funded by pharmaceutical company
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 96: Clinical evidence profile for comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Increasing the dose of SNRI**	**Continuing SNRI at the same dose**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Kornstein 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	118	130	-	SMD 0.01 higher (0.24 lower to 0.26 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Kornstein 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	36/124 (29%)	39/131 (29.8%)	RR 0.98 (0.67 to 1.43)	6 fewer per 1000 (from 98 fewer to 128 more)	VERY LOW	CRITICAL

Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Kornstein 2008)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	48/124 (38.7%)	58/131 (44.3%)	RR 0.87 (0.65 to 1.17)	58 fewer per 1000 (from 155 fewer to 75 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Kornstein 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	34/124 (27.4%)	26/131 (19.8%)	RR 1.38 (0.88 to 2.16)	75 more per 1000 (from 24 fewer to 230 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Kornstein 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	7/124 (5.6%)	6/131 (4.6%)	RR 1.23 (0.43 to 3.57)	11 more per 1000 (from 26 fewer to 118 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

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

[2] *Study funded by pharmaceutical company*

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

[4] *95% CI crosses thresholds for both clinically important harm and no effect*

Table 97: Clinical evidence profile for comparison 28. Switching to SNRI versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SNRI**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/50 (42%)	21/45 (46.7%)	RR 0.9 (0.57 to 1.41)	47 fewer per 1000 (from 201 fewer to 191 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	32/50 (64%)	30/45 (66.7%)	RR 0.96 (0.72 to 1.29)	27 fewer per 1000 (from 187 fewer to 193 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Fang 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/50 (18%)	8/45 (17.8%)	RR 1.01 (0.43 to 2.4)	2 more per 1000 (from 101 fewer to 249 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												

1 (Fang 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/50 (0%)	1/45 (2.2%)	RR 0.3 (0.01 to 7.2)	16 fewer per 1000 (from 22 fewer to 138 more)	VERY LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	45	-	SMD 0.02 higher (0.38 lower to 0.42 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	50	45	-	SMD 0.14 higher (0.26 lower to 0.54 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[3] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 98: Clinical evidence profile for comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SNRI**	**Switching to another antidepressant from same class**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 4-14 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
2 (Poirier 1999, Rush 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	302	293	-	SMD 0.05 higher (0.11 lower to 0.21 higher)	MODERATE	CRITICAL
Remission (ITT) (follow-up 4-14 weeks; assessed with: Number of people scoring <=4/<10 on Hamilton Rating Scale for Depression (HAM-D) or <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
3 (Lenox-Smith 2008, Poirier 1999, Rush 2006)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	reporting bias[4]	145/511 (28.4%)	107/506 (21.1%)	RR 1.48 (0.86 to 2.56)	102 more per 1000 (from 30 fewer to 330 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 4-14 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) AND much/very much improved on CGI-I (score 1-2) or at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												

2 (Poirier 1999, Rush 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	97/311 (31.2%)	81/300 (27%)	RR 1.21 (0.85 to 1.7)	57 more per 1000 (from 40 fewer to 189 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 4-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Lenox-Smith 2008, Poirier 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[4]	58/261 (22.2%)	50/268 (18.7%)	RR 1.19 (0.85 to 1.67)	35 more per 1000 (from 28 fewer to 125 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-14 weeks; assessed with: Number of participants who dropped out due to adverse events)												
3 (Lenox-Smith 2008, Poirier 1999, Rush 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	69/511 (13.5%)	64/506 (12.6%)	RR 1.04 (0.76 to 1.41)	5 more per 1000 (from 30 fewer to 52 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

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

[2] Considerable heterogeneity

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

[4] Funding from pharmaceutical companies

[5] 95% CI crosses thresholds for both clinically important harm and no effect

[6] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 99: Clinical evidence profile for comparison 30. Switching to SNRI versus switching to bupropion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SNRI**	**Switching to bupropion**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 14 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	239	-	SMD 0.01 lower (0.19 lower to 0.17 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 14 weeks; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	62/250 (24.8%)	61/239 (25.5%)	RR 0.97 (0.72 to 1.32)	8 fewer per 1000 (from 71 fewer to 82 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 14 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												

1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	70/250 (28%)	62/239 (25.9%)	RR 1.08 (0.81 to 1.45)	21 more per 1000 (from 49 fewer to 117 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 14 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Rush 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	53/250 (21.2%)	65/239 (27.2%)	RR 0.78 (0.57 to 1.07)	60 fewer per 1000 (from 117 fewer to 19 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[3] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 100: Clinical evidence profile for comparison 31. Switching to SNRI versus switching to mirtazapine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to SNRI**	**Switching to mirtazapine**	**Relative (95% CI)**	**Absolute**		
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/50 (42%)	20/55 (36.4%)	RR 1.15 (0.72 to 1.86)	55 more per 1000 (from 102 fewer to 313 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32/50 (64%)	32/55 (58.2%)	RR 1.1 (0.81 to 1.49)	58 more per 1000 (from 111 fewer to 285 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Fang 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/50 (18%)	10/55 (18.2%)	RR 0.99 (0.44 to 2.24)	2 fewer per 1000 (from 102 fewer to 225 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Fang 2010)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	0/55 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	50	55	-	SMD 0.29 higher (0.09 lower to 0.68 higher)	VERY LOW	IMPORTANT

Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	50	55	-	SMD 0.3 higher (0.08 lower to 0.69 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[3] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 101: Clinical evidence profile for comparison 32. Switching to bupropion versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to bupropion**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (GlaxoSmithKline 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	165	157	-	SMD 0.02 higher (0.19 lower to 0.24 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (GlaxoSmithKline 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	40/166 (24.1%)	39/159 (24.5%)	RR 0.98 (0.67 to 1.44)	5 fewer per 1000 (from 81 fewer to 108 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 12 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (GlaxoSmithKline 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	63/166 (38%)	58/159 (36.5%)	RR 1.04 (0.78 to 1.38)	15 more per 1000 (from 80 fewer to 139 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (GlaxoSmithKline 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	67/166 (40.4%)	47/159 (29.6%)	RR 1.37 (1.01 to 1.85)	109 more per 1000 (from 3 more to 251 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (GlaxoSmithKline 2009)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	39/166 (23.5%)	31/159 (19.5%)	RR 1.21 (0.79 to 1.83)	41 more per 1000 (from 41 fewer to 162 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Rapid tapering of previous treatment
[2] Study run and funded by pharmaceutical company
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[4] 95% CI crosses thresholds for both clinically important harm and no effect

Table 102: Clinical evidence profile for comparison 33. Switching to bupropion versus switching to another antidepressant from same class

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to bupropion**	**Switching to another antidepressant from same class**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 14 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	-	SMD 0.12 higher (0.06 lower to 0.3 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 14 weeks; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	61/239 (25.5%)	63/238 (26.5%)	RR 0.96 (0.71 to 1.31)	11 fewer per 1000 (from 77 fewer to 82 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 14 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Rush 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	62/239 (25.9%)	63/238 (26.5%)	RR 0.98 (0.73 to 1.32)	5 fewer per 1000 (from 71 fewer to 85 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 14 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Rush 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	65/239 (27.2%)	50/238 (21%)	RR 1.29 (0.94 to 1.79)	61 more per 1000 (from 13 fewer to 166 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[3] 95% CI crosses thresholds for both clinically important harm and no effect

Table 103: Clinical evidence profile for comparison 34. Augmenting with bupropion versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with bupropion	Placebo	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Gulrez 2012)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/30 (60%)	7/30 (23.3%)	RR 2.57 (1.26 to 5.24)	366 more per 1000 (from 61 more to 989 more)	MODERATE	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
[1] Risk of bias is high or unclear across multiple domains

Table 104: Clinical evidence profile for comparison 35. Augmenting with bupropion versus switching to bupropion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with bupropion	Switching to bupropion	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	136/506 (26.9%)	114/511 (22.3%)	RR 1.2 (0.97 to 1.5)	45 more per 1000 (from 7 fewer to 112 more)	MODERATE	CRITICAL
Response (ITT) (follow-up mean 12 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	332/506 (65.6%)	319/511 (62.4%)	RR 1.05 (0.96 to 1.15)	31 more per 1000 (from 25 fewer to 94 more)	HIGH	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	128/506 (25.3%)	158/511 (30.9%)	RR 0.82 (0.67 to 1)	56 fewer per 1000 (from 102 fewer to 0 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	37/506 (7.3%)	51/511 (10%)	RR 0.73 (0.49 to 1.1)	27 fewer per 1000 (from 51 fewer to 10 more)	MODERATE	CRITICAL

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

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

Table 105: Clinical evidence profile for comparison 36. Switching to mirtazapine versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to mirtazapine	Continuing with antidepressant	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Patient Health Questionnaire (PHQ-9) or Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	618	605	-	SMD 0.21 lower (0.58 lower to 0.17 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Xiao 2020)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[4]	68	68	-	SMD 0.19 lower (0.53 lower to 0.15 higher)	VERY LOW	CRITICAL
Depression symptomatology at 4-month follow-up (follow-up mean 4 months; measured with: Patient Health Questionnaire (PHQ-9); Better indicated by lower values)												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	540	538	-	SMD 0.01 higher (0.11 lower to 0.13 higher)	HIGH	CRITICAL
Remission (ITT) (follow-up 6-8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) or <=4 on Patient Health Questionnaire (PHQ-9))												
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	232/681 (34.1%)	185/664 (27.9%)	RR 1.22 (1.04 to 1.43)	61 more per 1000 (from 11 more to 120 more)	LOW	CRITICAL
Remission (ITT) at 4-month follow-up (follow-up mean 4 months; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9))												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	262/558 (47%)	245/551 (44.5%)	RR 1.06 (0.93 to 1.2)	27 more per 1000 (from 31 fewer to 89 more)	HIGH	CRITICAL
Response (ITT) (follow-up 6-8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) or Patient Health Questionnaire (PHQ-9))												
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	357/681 (52.4%)	306/664 (46.1%)	RR 1.1 (0.95 to 1.28)	46 more per 1000 (from 23 fewer to 129 more)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up 6-8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[7]	30/681 (4.4%)	34/664 (5.1%)	RR 0.85 (0.54 to 1.36)	8 fewer per 1000 (from 24 fewer to 18 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 6-8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Fang 2010, Xiao 2020)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[7]	3/123 (2.4%)	2/113 (1.8%)	RR 1.19 (0.12 to 11.73)	3 more per 1000 (from 16 fewer to 190 more)	VERY LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	55	45	-	SMD 0.28 lower (0.67 lower to 0.12 higher)	VERY LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2010)	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	55	45	-	SMD 0.17 lower (0.56 lower to 0.22 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] *Substantial heterogeneity*
[2] *95% CI crosses thresholds for both clinically important benefit and no effect*
[3] *Risk of bias is high across multiple domains*
[4] *Study partially funded by pharmaceutical company*
[5] *Statistically significant difference between groups at baseline*
[6] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*
[7] *Funding from pharmaceutical companies*
[8] *Risk of bias is high or unclear across multiple domains*
[9] *95% CI crosses thresholds for both clinically important harm and no effect*

Table 106: Clinical evidence profile for comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/- placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mirtazapine	Continuing with antidepressant (+/- placebo)	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Patient Health Questionnaire (PHQ-9) or Beck Depression Inventory (BDI-II); Better indicated by lower values)												

4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	820	837	-	SMD 0.26 lower (0.44 to 0.09 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up 4-6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
2 (Carpenter 2002, Xiao 2020)	randomised trials	very serious[1]	very serious[3]	no serious indirectness	serious[4]	reporting bias[5]	79	83	-	SMD 0.52 lower (1.53 lower to 0.48 higher)	VERY LOW	CRITICAL
Depression symptomatology at 4-month follow-up (follow-up mean 4 months; measured with: Patient Health Questionnaire (PHQ-9); Better indicated by lower values)												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	520	538	-	SMD 0.07 lower (0.19 lower to 0.05 higher)	HIGH	CRITICAL
Remission (ITT) (follow-up 4-12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) or <=4 on Patient Health Questionnaire (PHQ-9) or <10 on Beck Depression Inventory (BDI-II))												
4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	290/857 (33.8%)	219/873 (25.1%)	RR 1.3 (1.04 to 1.61)	75 more per 1000 (from 10 more to 153 more)	LOW	CRITICAL
Remission (ITT) at 4-month follow-up (follow-up mean 4 months; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9))												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	263/537 (49%)	245/551 (44.5%)	RR 1.1 (0.97 to 1.25)	44 more per 1000 (from 13 fewer to 111 more)	MODERATE	CRITICAL
Response (ITT) (follow-up 4-12 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) or Patient Health Questionnaire (PHQ-9) or Beck Depression Inventory (BDI-II))												
4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	422/857 (49.2%)	357/873 (40.9%)	RR 1.19 (1.06 to 1.34)	78 more per 1000 (from 25 more to 139 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 4-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	47/857 (5.5%)	50/873 (5.7%)	RR 0.95 (0.65 to 1.4)	3 fewer per 1000 (from 20 fewer to 23 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Carpenter 2002, Xiao 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	reporting bias[5]	3/79 (3.8%)	2/83 (2.4%)	RR 1.69 (0.29 to 9.93)	17 more per 1000 (from 17 fewer to 215 more)	VERY LOW	CRITICAL

Quality of life endpoint (follow-up mean 12 weeks; measured with: European Quality of Life Questionnaire-5 Dimensions (EQ-5D); Better indicated by higher values)												
1 (Kessler 2018a/2018b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	213	216	-	SMD 0.04 lower (0.23 lower to 0.15 higher)	LOW	IMPORTANT
Quality of life physical component score (PCS) endpoint (follow-up mean 12 weeks; measured with: 12-item Short-Form Survey (SF-12): Physical component score; Better indicated by higher values)												
1 (Kessler 2018a/2018b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	208	210	-	SMD 0.14 lower (0.33 lower to 0.05 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) endpoint (follow-up mean 12 weeks; measured with: 12-item Short-Form Survey (SF-12): Mental component score; Better indicated by higher values)												
1 (Kessler 2018a/2018b)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	208	210	-	SMD 0.29 higher (0.1 to 0.48 higher)	LOW	IMPORTANT
Global functioning endpoint (follow-up mean 4 weeks; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												
1 (Carpenter 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	11	15	-	SMD 0.92 higher (0.1 to 1.75 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Substantial heterogeneity
[3] Considerable heterogeneity
[4] 95% CI crosses thresholds for both clinically important benefit and no effect
[5] Funding from pharmaceutical companies
[6] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 107: Clinical evidence profile for comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with mirtazapine**	**Switching to mirtazapine**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Patient Health Questionnaire (PHQ-9) or Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	595	618	-	SMD 0.01 lower (0.12 lower to 0.1 higher)	HIGH	CRITICAL
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Xiao 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	68	68	-	SMD 0.12 higher (0.22 lower to 0.45 higher)	VERY LOW	CRITICAL
Depression symptomatology at 4-month follow-up (follow-up mean 4 months; measured with: Patient Health Questionnaire (PHQ-9); Better indicated by lower values)												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	520	540	-	SMD 0.08 lower (0.2 lower to 0.04 higher)	HIGH	CRITICAL
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9) or <=7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	222/605 (36.7%)	212/626 (33.9%)	RR 1.04 (0.85 to 1.29)	14 more per 1000 (from 51 fewer to 98 more)	MODERATE	CRITICAL
Remission (ITT) at 4-month follow-up (follow-up mean 4 months; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9))												
1 (Kato 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	263/537 (49%)	262/558 (47%)	RR 1.04 (0.92 to 1.18)	19 more per 1000 (from 38 fewer to 85 more)	HIGH	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Patient Health Questionnaire (PHQ-9) or Hamilton Rating Scale for Depression (HAM-D))												
2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	321/605 (53.1%)	325/626 (51.9%)	RR 1.01 (0.91 to 1.12)	5 more per 1000 (from 47 fewer to 62 more)	HIGH	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	19/605 (3.1%)	20/626 (3.2%)	RR 0.95 (0.52 to 1.73)	2 fewer per 1000 (from 15 fewer to 23 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Xiao 2020)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	2/68 (2.9%)	3/68 (4.4%)	RR 0.67 (0.12 to 3.86)	15 fewer per 1000 (from 39 fewer to 126 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] Risk of bias is high across multiple domains

[2] Study partially funded by pharmaceutical company

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

[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 108: Clinical evidence profile for comparison 39. Augmenting with trazodone versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with trazodone	Continuing with antidepressant	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/47 (42.6%)	21/45 (46.7%)	RR 0.91 (0.58 to 1.44)	42 fewer per 1000 (from 196 fewer to 205 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/47 (61.7%)	30/45 (66.7%)	RR 0.93 (0.68 to 1.26)	47 fewer per 1000 (from 213 fewer to 173 more)	VERY LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	47	45	-	SMD 0.26 lower (0.67 lower to 0.15 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	47	45	-	SMD 0.2 higher (0.21 lower to 0.61 higher)	LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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

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

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

[4] *95% CI crosses thresholds for both clinically important benefit and no effect*

Table 109: Clinical evidence profile for comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with anticonvulsant	Continuing with antidepressant (+/- placebo)	Relative (95% CI)	Absolute		

Depression symptomatology endpoint (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS); Better indicated by lower values)												
8 (Barbee 2011, Li 2009, Li 2015, Mowla 2011, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	301	298	-	SMD 1.39 lower (2.33 to 0.46 lower)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
8 (Barbee 2011, Li 2009, Li 2015, Mowla 2011, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	301	298	-	SMD 1.97 lower (3.07 to 0.87 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	19/39 (48.7%)	21/45 (46.7%)	RR 1.04 (0.67 to 1.63)	19 more per 1000 (from 154 fewer to 294 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 4-12 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS))												
8 (Barbee 2011, Fang 2011, Li 2009, Li 2015, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised trials	serious[1]	serious[5]	no serious indirectness	serious[3]	none	149/320 (46.6%)	105/321 (32.7%)	RR 1.44 (0.93 to 2.24)	144 more per 1000 (from 23 fewer to 406 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-10 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
3 (Barbee 2011, Mowla 2011, Santos 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[6]	23/91 (25.3%)	26/92 (28.3%)	RR 0.89 (0.55 to 1.43)	31 fewer per 1000 (from 127 fewer to 122 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-10 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Barbee 2011, Santos 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[6]	9/65 (13.8%)	10/65 (15.4%)	RR 1.12 (0.21 to 5.94)	18 more per 1000 (from 122 fewer to 760 more)	VERY LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												

1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	39	45	-	SMD 0.21 lower (0.64 lower to 0.22 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39	45	-	SMD 0.19 higher (0.24 lower to 0.62 higher)	LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Considerable heterogeneity
[3] 95% CI crosses thresholds for both clinically important benefit and no effect
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[5] Substantial heterogeneity
[6] Funding from pharmaceutical companies
[7] 95% CI crosses thresholds for both clinically important harm and no effect

Table 110: Clinical evidence profile for comparison 41. Augmenting with anticonvulsant versus lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with anticonvulsant	Lithium	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Schindler 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	SMD 0.31 lower (0.99 lower to 0.36 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Schindler 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	SMD 0.81 lower (1.51 to 0.11 lower)	LOW	CRITICAL
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Schindler 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/17 (23.5%)	3/17 (17.6%)	RR 1.33 (0.35 to 5.08)	58 more per 1000 (from 115 fewer to 720 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												

1 (Schindler 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/17 (52.9%)	7/17 (41.2%)	RR 1.29 (0.62 to 2.65)	119 more per 1000 (from 156 fewer to 679 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Schindler 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/17 (11.8%)	2/17 (11.8%)	RR 1 (0.16 to 6.3)	0 fewer per 1000 (from 99 fewer to 624 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Schindler 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/17 (0%)	not pooled	not pooled	HIGH	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 111: Clinical evidence profile for comparison 42. Switching to antipsychotic versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to antipsychotic**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	reporting bias[4]	400	329	-	SMD 0.22 higher (0.12 lower to 0.56 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8/<=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	56/405 (13.8%)	59/333 (17.7%)	RR 0.79 (0.56 to 1.1)	37 fewer per 1000 (from 78 fewer to 18 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	94/405 (23.2%)	110/333 (33%)	RR 0.68 (0.48 to 0.96)	106 fewer per 1000 (from 13 fewer to 172 fewer)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	122/405 (30.1%)	63/333 (18.9%)	RR 1.67 (1.26 to 2.23)	127 more per 1000 (from 49 more to 233 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	51/405 (12.6%)	8/333 (2.4%)	RR 5.34 (2.57 to 11.09)	104 more per 1000 (from 38 more to 242 more)	MODERATE	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	197	203	-	SMD 0.15 lower (0.35 lower to 0.04 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[4]	197	203	-	SMD 0.05 lower (0.25 lower to 0.15 higher)	LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Substantial heterogeneity
[3] 95% CI crosses thresholds for both clinically important harm and no effect
[4] Funding from pharmaceutical companies

Table 112: Clinical evidence profile for comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to combined antipsychotic + SSRI**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	376	126	-	SMD 0.09 lower (0.3 lower to 0.11 higher)	LOW	CRITICAL

Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	94/389 (24.2%)	25/127 (19.7%)	RR 1.15 (0.77 to 1.71)	30 more per 1000 (from 45 fewer to 140 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	140/389 (36%)	50/127 (39.4%)	RR 0.85 (0.67 to 1.09)	59 fewer per 1000 (from 130 fewer to 35 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	90/389 (23.1%)	23/127 (18.1%)	RR 1.22 (0.69 to 2.16)	40 more per 1000 (from 56 fewer to 210 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	39/389 (10%)	3/127 (2.4%)	RR 3.48 (1.06 to 11.44)	59 more per 1000 (from 1 more to 247 more)	LOW	CRITICAL

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

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

[2] *Funding from pharmaceutical companies*

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

[4] *95% CI crosses thresholds for both clinically important harm and no effect*

Table 113: Clinical evidence profile for comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching to combined antipsychotic + SSRI**	**Switch to SSRI-only**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	376	198	-	SMD 0.12 lower (0.35 lower to 0.1 higher)	LOW	CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												

2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	94/389 (24.2%)	29/202 (14.4%)	RR 1.46 (0.97 to 2.19)	66 more per 1000 (from 4 fewer to 171 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Corya 2006, Shelton 2005)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[2]	140/389 (36%)	60/202 (29.7%)	RR 1.1 (0.81 to 1.5)	30 more per 1000 (from 56 fewer to 149 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[2]	90/389 (23.1%)	40/202 (19.8%)	RR 1.12 (0.78 to 1.59)	24 more per 1000 (from 44 fewer to 117 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[2]	39/389 (10%)	7/202 (3.5%)	RR 2.41 (1.07 to 5.42)	49 more per 1000 (from 2 more to 153 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor
[1] Risk of bias is high or unclear across multiple domains
[2] Funding from pharmaceutical companies
[3] 95% CI crosses thresholds for both clinically important benefit and no effect
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[5] 95% CI crosses thresholds for both clinically important harm and no effect

Table 114: Clinical evidence profile for comparison 45. Augmenting with antipsychotic versus antidepressant-only or antidepressant + placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with antipsychotic**	**Antidepressant-only or antidepressant + placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up 4-8 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
5 (Fava 2012/ Mischoulon 2012, Li 2013, Mahmoud 2007, Moica 2018, Song 2007)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	295	411	-	SMD 0.78 lower (1.24 to	VERY LOW	CRITICAL

										0.32 lower)		
Depression symptomatology change score (follow-up 4-8 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
20 (Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Li 2013, Moica 2018, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	reporting bias[5]	3784	2932	-	SMD 0.33 lower (0.44 to 0.23 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 4-24 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS) or <=7 on Hamilton Rating Scale for Depression (HAM-D))												
28 (Bauer 2009, Bauer 2019, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fang 2011, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Li 2013, Lenze 2015, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	1494/5653 (26.4%)	839/4425 (19%)	RR 1.37 (1.23 to 1.52)	70 more per 1000 (from 44 more to 99 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 4-8 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D))												
28 (Bauer 2009, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fang 2011, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Li 2013, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015,	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	1912/5190 (36.8%)	1025/3964 (25.9%)	RR 1.37 (1.27 to 1.49)	96 more per 1000 (from 70 more to 127 more)	LOW	CRITICAL

Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Song 2007, Thase 2007, Thase 2015a, Thase 2015b)												
Discontinuation due to any reason (follow-up 4-24 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
28 (Bauer 2009, Bauer 2019, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Lenze 2015, Li 2013, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[5]	825/5620 (14.7%)	525/4392 (12%)	RR 1.26 (1.13 to 1.4)	31 more per 1000 (from 16 more to 48 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-24 weeks; assessed with: Number of participants who dropped out due to adverse events)												
27 (Bauer 2009, Bauer 2019, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Li 2013, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	346/5608 (6.2%)	70/4381 (1.6%)	RR 3.07 (2.36 to 3.99)	33 more per 1000 (from 22 more to 48 more)	MODERATE	CRITICAL
Quality of life endpoint (follow-up mean 6 weeks; measured with: Quality of Life Enjoyment and Satisfaction Questionnaire-short form (Q-LES-Q-SF); Better indicated by higher values)												
1 (Mahmoud 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	101	101	-	SMD 0.47 higher (0.19 to 0.75 higher)	VERY LOW	IMPORTANT
Quality of life change score (follow-up mean 6 weeks; measured with: Quality of Life Enjoyment and Satisfaction Questionnaire-short form (Q-LES-Q-SF) change from baseline to endpoint; Better indicated by higher values)												

2 (Berman 2009, Otsuka Pharmaceutical 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	446	281	-	SMD 0.17 higher (0 to 0.34 higher)	MODERATE	IMPORTANT
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
2 (Fang 2011, Thase 2007)	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	reporting bias[5]	243	248	-	SMD 0.04 higher (0.33 lower to 0.41 higher)	VERY LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
2 (Fang 2011, Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	243	248	-	SMD 0.05 higher (0.19 lower to 0.3 higher)	LOW	IMPORTANT
Global functioning change score (follow-up mean 6 weeks; measured with: Social Adaptation Self-evaluation Scale (SASS) change from baseline to endpoint; Better indicated by higher values)												
1 (Kamijima 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	164	149	-	SMD 0.58 higher (0.36 to 0.81 higher)	LOW	IMPORTANT
Functional remission (follow-up mean 24 weeks; assessed with: Number of people scoring <=6 total score on Sheehan Disability Scale (SDS) and all SDS domain scores <=2)												
1 (Bauer 2019)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	reporting bias[5]	68/444 (15.3%)	73/442 (16.5%)	RR 0.93 (0.68 to 1.26)	12 fewer per 1000 (from 53 fewer to 43 more)	VERY LOW	IMPORTANT
Functional impairment endpoint (follow-up mean 6 weeks; measured with: Sheehan Disability Scale (SDS); Better indicated by lower values)												
1 (Mahmoud 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	100	101	-	SMD 0.62 lower (0.9 to 0.34 lower)	VERY LOW	IMPORTANT
Functional impairment change score (follow-up 5-8 weeks; measured with: Sheehan Disability Scale (SDS) change from baseline to endpoint; Better indicated by lower values)												
10 (Berman 2009, Durgam 2016, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	2710	1844	-	SMD 0.17 lower (0.24 to 0.11 lower)	LOW	IMPORTANT

2016, Thase 2015a, Thase 2015b)													

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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

[2] *Considerable heterogeneity*

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

[4] *Substantial heterogeneity*

[5] *Funding from pharmaceutical companies*

[6] *95% CI crosses thresholds for both clinically important harm and no effect*

[7] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

Table 115: Clinical evidence profile for comparison 46. Augmenting with antipsychotic versus bupropion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Bupropion	Relative (95% CI)	Absolute		
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
1 (Cheon 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	56	47	-	SMD 0.48 lower (0.87 to 0.08 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 6-12 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS) or <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
2 (Cheon 2017, Mohamed 2017)	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[2]	none	177/561 (31.6%)	152/553 (27.5%)	RR 1.25 (0.85 to 1.85)	69 more per 1000 (from 41 fewer to 234 more)	LOW	CRITICAL
Response (ITT) (follow-up 6-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS) or Quick Inventory of Depressive Symptomatology (QIDS))												
2 (Cheon 2017, Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	409/561 (72.9%)	352/553 (63.7%)	RR 1.17 (1 to 1.38)	108 more per 1000 (from 0 more to 242 more)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up 6-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Cheon 2017, Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	113/561 (20.1%)	139/553 (25.1%)	RR 0.8 (0.64 to 1)	50 fewer per 1000 (from 90 fewer to 0 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up 6-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												

2 (Cheon 2017, Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27/561 (4.8%)	37/553 (6.7%)	RR 0.73 (0.45 to 1.18)	18 fewer per 1000 (from 37 fewer to 12 more)	MODERATE	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Funding from pharmaceutical companies
[4] Substantial heterogeneity

Table 116: Clinical evidence profile for comparison 47. Augmenting with antipsychotic versus lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Lithium	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up 4-8 weeks; assessed with: Number of people scoring <=8/<=10 on Montgomery Asberg Depression Rating Scale (MADRS) or <=7 on Hamilton Rating Scale for Depression (HAM-D))												
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	84/261 (32.2%)	65/249 (26.1%)	RR 1.35 (0.82 to 2.22)	91 more per 1000 (from 47 fewer to 318 more)	LOW	CRITICAL
Response (ITT) (follow-up 4-8 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D))												
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	135/261 (51.7%)	111/249 (44.6%)	RR 1.18 (0.98 to 1.41)	80 more per 1000 (from 9 fewer to 183 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 4-8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	36/261 (13.8%)	51/249 (20.5%)	RR 0.71 (0.48 to 1.05)	59 fewer per 1000 (from 107 fewer to 10 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	24/261 (9.2%)	20/249 (8%)	RR 1.16 (0.66 to 2.04)	13 more per 1000 (from 27 fewer to 84 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] Funding from pharmaceutical companies
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 117: Clinical evidence profile for comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Switch to antipsychotic	Relative (95% CI)	Absolute		
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
1 (Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	198	197	-	SMD 0.38 lower (0.58 to 0.18 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 6-8 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Bauer 2013, Thase 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	127/431 (29.5%)	82/427 (19.2%)	RR 1.54 (1.14 to 2.07)	104 more per 1000 (from 27 more to 205 more)	LOW	CRITICAL
Response (ITT) (follow-up 6-8 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Bauer 2013, Thase 2007)	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	serious[2]	reporting bias[3]	200/431 (46.4%)	165/427 (38.6%)	RR 1.25 (0.84 to 1.88)	97 more per 1000 (from 62 fewer to 340 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 6-8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Bauer 2013, Thase 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	87/431 (20.2%)	121/427 (28.3%)	RR 0.71 (0.56 to 0.9)	82 fewer per 1000 (from 28 fewer to 125 fewer)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 6-8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Bauer 2013, Thase 2007)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	50/431 (11.6%)	60/427 (14.1%)	RR 0.83 (0.58 to 1.17)	24 fewer per 1000 (from 59 fewer to 24 more)	LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	198	197	-	SMD 0.33 higher (0.13 to 0.53 higher)	VERY LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Thase 2007)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	198	197	-	SMD 0.18 higher (0.01 lower to 0.38 higher)	LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

[1] *Risk of bias is high or unclear across multiple domains*
[2] *95% CI crosses thresholds for both clinically important benefit and no effect*
[3] *Funding from pharmaceutical companies*
[4] *Considerable heterogeneity*

Table 118: Clinical evidence profile for comparison 49. Augmenting with antipsychotic versus switch to bupropion

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Switch to bupropion	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	146/505 (28.9%)	114/511 (22.3%)	RR 1.3 (1.05 to 1.6)	67 more per 1000 (from 11 more to 134 more)	MODERATE	CRITICAL
Response (ITT) (follow-up mean 12 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	375/505 (74.3%)	319/511 (62.4%)	RR 1.19 (1.09 to 1.29)	119 more per 1000 (from 56 more to 181 more)	MODERATE	CRITICAL
Discontinuation due to any reason (follow-up mean 12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	99/505 (19.6%)	158/511 (30.9%)	RR 0.63 (0.51 to 0.79)	114 fewer per 1000 (from 65 fewer to 152 fewer)	HIGH	CRITICAL
Discontinuation due to side effects (follow-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Mohamed 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	27/505 (5.3%)	51/511 (10%)	RR 0.54 (0.34 to 0.84)	46 fewer per 1000 (from 16 fewer to 66 fewer)	MODERATE	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
[1] *95% CI crosses thresholds for both clinically important benefit and no effect*

Table 119: Clinical evidence profile for comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/- placebo)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with buspirone	Continuing with antidepressant (+/- placebo)	Relative (95% CI)	Absolute		
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/46 (32.6%)	21/45 (46.7%)	RR 0.7 (0.42 to 1.18)	140 fewer per 1000 (from 271 fewer to 84 more)	LOW	CRITICAL
Response (ITT) (follow-up 6-8 weeks; assessed with: Number of people rated as much or very much improved on Clinical Global Impressions scale (CGI-I) or showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
2 (Appelberg 2001, Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43/97 (44.3%)	46/96 (47.9%)	RR 0.9 (0.68 to 1.19)	48 fewer per 1000 (from 153 fewer to 91 more)	LOW	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.06 lower (0.48 lower to 0.35 higher)	MODERATE	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.08 higher (0.34 lower to 0.49 higher)	MODERATE	IMPORTANT

1 *CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference*
2 *[1] Risk of bias is high or unclear across multiple domains*
3 *[2] 95% CI crosses thresholds for both clinically important harm and no effect*

4 **Table 120: Clinical evidence profile for comparison 51. Augmenting with buspirone versus bupropion**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with buspirone**	**Bupropion**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS); Better indicated by lower values)												
1 (Trivedi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	279	-	SMD 0.2 higher (0.04 to 0.37 higher)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 6 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												

1 (Trivedi 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	279	-	SMD 0.17 higher (0.01 to 0.34 higher)	MODERATE	CRITICAL
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Trivedi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	86/286 (30.1%)	83/279 (29.7%)	RR 1.01 (0.79 to 1.3)	3 more per 1000 (from 62 fewer to 89 more)	LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Trivedi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	77/286 (26.9%)	88/279 (31.5%)	RR 0.85 (0.66 to 1.1)	47 fewer per 1000 (from 107 fewer to 32 more)	MODERATE	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Trivedi 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	59/286 (20.6%)	35/279 (12.5%)	RR 1.64 (1.12 to 2.41)	80 more per 1000 (from 15 more to 177 more)	MODERATE	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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

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

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

Table 121: Clinical evidence profile for comparison 52. Augmenting with methylphenidate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with methylphenidate**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology change score (follow-up mean 5 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
1 (Ravindran 2008a)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[2]	72	72	-	SMD 0.06 higher (0.27 lower to 0.38 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Patkar 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[2]	4/30 (13.3%)	1/30 (3.3%)	RR 4 (0.47 to 33.73)	100 more per 1000 (from 18 fewer to 1000 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 4-5 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Patkar 2006, Ravindran 2008a)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[2]	46/103 (44.7%)	37/102 (36.3%)	RR 1.21 (0.87 to 1.68)	76 more per 1000 (from 47 fewer to 247 more)	VERY LOW	CRITICAL

Discontinuation due to any reason (follow-up mean 5 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Ravindran 2008a)	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[2]	11/73 (15.1%)	4/72 (5.6%)	RR 2.71 (0.91 to 8.12)	95 more per 1000 (from 5 fewer to 396 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-5 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Patkar 2006, Ravindran 2008a)	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	very serious[3]	reporting bias[2]	8/103 (7.8%)	2/102 (2%)	RR 2.92 (0.21 to 40.65)	38 more per 1000 (from 15 fewer to 777 more)	VERY LOW	CRITICAL

Abbreviations: CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Funding from pharmaceutical companies
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[4] 95% CI crosses thresholds for both clinically important benefit and no effect
[5] Statistically significant group difference at baseline
[6] 95% CI crosses thresholds for both clinically important harm and no effect
[7] Substantial heterogeneity

Table 122: Clinical evidence profile for comparison 53. Augmenting with lithium versus continuing with antidepressant (+/- placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with lithium**	**Continuing with antidepressant (+/- placebo)**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up 2-3 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS); Better indicated by lower values)												
2 (Joffe 1993, Stein 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	34	-	SMD 0.23 lower (0.71 lower to 0.25 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up 2-52 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Montgomery Asberg Depression Rating Scale (MADRS) or Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
3 (Girlanda 2014, Joffe 1993, Stein 1993)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	56	-	SMD 0.26 lower (0.76 lower to 0.23 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 3 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) AND responding (at least 50% improvement on HAM-D))												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/18 (33.3%)	2/16 (12.5%)	RR 2.67 (0.62 to 11.39)	209 more per 1000 (from 47	LOW	CRITICAL

										fewer to 1000 more)		
Response (ITT) (follow-up 1-6 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
2 (Baumann 1996, Nierenberg 2003a)	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[3]	reporting bias[5]	8/28 (28.6%)	5/31 (16.1%)	RR 1.72 (0.27 to 11.05)	116 more per 1000 (from 118 fewer to 1000 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 2-52 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
4 (Girlanda 2014, Joffe 1993, Nierenberg 2003a, Stein 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/81 (6.2%)	7/78 (9%)	RR 0.67 (0.22 to 2.03)	30 fewer per 1000 (from 70 fewer to 92 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 2-3 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Joffe 1993, Stein 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/34 (2.9%)	0/34 (0%)	RR 2.68 (0.12 to 61.58)	-	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias was high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[4] Substantial heterogeneity
[5] Funding from pharmaceutical companies

Table 123: Clinical evidence profile for comparison 54. Augmenting with lithium versus switch to antipsychotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with lithium**	**Switch to antipsychotic**	**Relative (95% CI)**	**Absolute**		
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Bauer 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	60/229 (26.2%)	53/228 (23.2%)	RR 1.13 (0.82 to 1.55)	30 more per 1000 (from 42 fewer to 128 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Bauer 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	102/229 (44.5%)	114/228 (50%)	RR 0.89 (0.73 to 1.08)	55 fewer per 1000 (from 135 fewer to 40 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

1 (Bauer 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	47/229 (20.5%)	49/228 (21.5%)	RR 0.95 (0.67 to 1.36)	11 fewer per 1000 (from 71 fewer to 77 more)	VERY LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 6 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Bauer 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	18/229 (7.9%)	28/228 (12.3%)	RR 0.64 (0.36 to 1.12)	44 fewer per 1000 (from 79 fewer to 15 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk
[1] Rapid switch from failed drug for quetiapine monotherapy arm
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] Study funded by pharmaceutical company
[4] 95% CI crosses thresholds for both clinically important harm and no effect
[5] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 124: Clinical evidence profile for comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with lithium**	**Augmenting with a psychological intervention**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19	20	-	SMD 0.41 lower (1.05 lower to 0.22 higher)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19	20	-	SMD 0.42 lower (1.06 lower to 0.21 higher)	MODERATE	CRITICAL
Depression symptomatology at 1-month follow-up (follow-up mean 1 months; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19	20	-	SMD 0.65 lower (1.29 lower to 0 higher)	MODERATE	CRITICAL
Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												

1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/21 (38.1%)	6/23 (26.1%)	RR 1.46 (0.61 to 3.51)	120 more per 1000 (from 102 fewer to 655 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 8 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/21 (14.3%)	3/23 (13%)	RR 1.1 (0.25 to 4.84)	13 more per 1000 (from 98 fewer to 501 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Kennedy 2003)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/21 (4.8%)	0/23 (0%)	RR 3.27 (0.14 to 76.21)	-	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 125: Clinical evidence profile for comparison 56. Augmenting with lithium versus augmenting with TCA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with lithium**	**Augmenting with TCA**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	46	-	SMD 0.32 lower (0.73 lower to 0.09 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	46	48	-	SMD 0.1 higher (0.31 lower to 0.51 higher)	LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Fava 1994a, Fava 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	12/48 (25%)	13/46 (28.3%)	RR 0.88 (0.45 to 1.74)	34 fewer per 1000 (from 155 fewer to 209 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 4 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Fava 1994a, Fava 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	7/48 (14.6%)	8/46 (17.4%)	RR 0.83 (0.33 to 2.11)	30 fewer per 1000 (from 117 fewer to 193 more)	LOW	CRITICAL

Discontinuation due to side effects (follow-up mean 4 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Fava 1994a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	reporting bias[5]	1/14 (7.1%)	2/12 (16.7%)	RR 0.43 (0.04 to 4.16)	95 fewer per 1000 (from 160 fewer to 527 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

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

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

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

[4] *95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

[5] *Study partially funded by pharmaceutical company*

Table 126: Clinical evidence profile for comparison 57. Augmenting with omega-3 fatty acids versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with omega-3 fatty acids**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
3 (Jahanggard 2018, Mozaffari-Khosravi 2013, Nemets 2002)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	76	56	-	SMD 1.73 lower (3.59 lower to 0.12 higher)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
3 (Jahanggard 2018, Mozaffari-Khosravi 2013, Nemets 2002)	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3]	none	76	56	-	SMD 1.65 lower (3.02 to 0.27 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Mozaffari-Khosravi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/54 (9.3%)	0/27 (0%)	RR 5.6 (0.32 to 97.69)	-	VERY LOW	CRITICAL
Response (ITT) (follow-up 4-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS) or at least 30% or 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
3 (Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	28/116 (24.1%)	5/54 (9.3%)	RR 2.49 (0.77 to 8.06)	138 more per 1000 (from 21 fewer to 654 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 4-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												

4 (Jahangard 2018, Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	19/141 (13.5%)	11/80 (13.8%)	RR 0.8 (0.41 to 1.56)	27 fewer per 1000 (from 81 fewer to 77 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 4-12 weeks; assessed with: Number of participants who dropped out due to adverse events)												
4 (Jahangard 2018, Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/141 (4.3%)	5/80 (6.3%)	RR 0.57 (0.18 to 1.73)	27 fewer per 1000 (from 51 fewer to 46 more)	LOW	CRITICAL
Sleeping difficulties endpoint (follow-up mean 12 weeks; measured with: Insomnia Severity Index (ISI); Better indicated by lower values)												
1 (Jahangard 2018)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	SMD 3.36 lower (4.24 to 2.47 lower)	HIGH	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] Considerable heterogeneity
[3] 95% CI crosses thresholds for both clinically important benefit and no effect
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 127: Clinical evidence profile for comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with thyroid hormone	Continuing with antidepressant (+/- placebo)	Relative (95% CI)	Absolute		
Depression symptoms endpoint (follow-up mean 2 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17	16	-	SMD 0.53 lower (1.22 lower to 0.17 higher)	MODERATE	CRITICAL
Depression symptoms change score (follow-up mean 2 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17	16	-	SMD 0.78 lower (1.5 to 0.07 lower)	MODERATE	CRITICAL
Remission (ITT) (follow-up 2-8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												

2 (Fang 2011, Joffe 1993)	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	25/65 (38.5%)	23/61 (37.7%)	RR 1.39 (0.35 to 5.53)	147 more per 1000 (from 245 fewer to 1000 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	28/48 (58.3%)	30/45 (66.7%)	RR 0.88 (0.64 to 1.2)	80 fewer per 1000 (from 240 fewer to 133 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 2 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/16 (0%)	not pooled	not pooled	HIGH	CRITICAL
Discontinuation due to side effects (follow-up mean 2 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/16 (0%)	not pooled	not pooled	HIGH	CRITICAL
Quality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	48	45	-	SMD 0.12 lower (0.53 lower to 0.28 higher)	LOW	IMPORTANT
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)												
1 (Fang 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	45	-	SMD 0.02 lower (0.42 lower to 0.39 higher)	MODERATE	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] Risk of bias is high or unclear across multiple domains
[3] Substantial heterogeneity
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[5] 95% CI crosses thresholds for both clinically important harm and no effect

Table 128: Clinical evidence profile for comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with thyroid hormone	Augmenting with lithium	Relative (95% CI)	Absolute		

Depression symptomatology endpoint (follow-up 2-14 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Quick Inventory of Depressive Symptomatology (QIDS); Better indicated by lower values)												
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90	86	-	SMD 0.33 lower (0.63 to 0.03 lower)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up 2-14 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	86	-	SMD 0.15 lower (0.45 lower to 0.14 higher)	LOW	CRITICAL
Remission (ITT) (follow-up 2-14 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) or <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/90 (27.8%)	15/87 (17.2%)	RR 1.58 (0.91 to 2.77)	100 more per 1000 (from 16 fewer to 305 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up mean 14 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Nierenberg 2006)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/73 (23.3%)	11/69 (15.9%)	RR 1.46 (0.74 to 2.89)	73 more per 1000 (from 41 fewer to 301 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up mean 2 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/17 (0%)	1/18 (5.6%)	RR 0.35 (0.02 to 8.09)	36 fewer per 1000 (from 54 fewer to 394 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 2-14 weeks; assessed with: Number of participants who dropped out due to adverse events)												
2 (Joffe 1993, Nierenberg 2006)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/90 (7.8%)	17/87 (19.5%)	RR 0.41 (0.18 to 0.91)	115 fewer per 1000 (from 18 fewer to 160 fewer)	LOW	CRITICAL

1 *CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference*
2 *[1] Risk of bias is high or unclear across multiple domains*
3 *[2] 95% CI crosses thresholds for both clinically important benefit and no effect*
4 *[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm*

5 **Table 129: Clinical evidence profile for comparison 60. Switching to ECT versus switching to paroxetine**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to ECT	Switching to paroxetine	Relative (95% CI)	Absolute		

Depression symptomatology endpoint (follow-up 2-4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Folkerts 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	18	-	SMD 1.35 lower (2.06 to 0.65 lower)	LOW	CRITICAL
Depression symptomatology change score (follow-up 2-4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Folkerts 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	18	-	SMD 1.61 lower (2.34 to 0.87 lower)	LOW	CRITICAL
Response (ITT) (follow-up 2-4 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Folkerts 1997)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/21 (71.4%)	5/19 (26.3%)	RR 2.71 (1.22 to 6.04)	450 more per 1000 (from 58 more to 1000 more)	VERY LOW	CRITICAL
Discontinuation due to any reason (follow-up 2-4 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
1 (Folkerts 1997)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/21 (0%)	1/19 (5.3%)	RR 0.3 (0.01 to 7.02)	37 fewer per 1000 (from 52 fewer to 317 more)	LOW	CRITICAL
Discontinuation due to side effects (follow-up 2-4 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Folkerts 1997)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/21 (0%)	0/19 (0%)	not pooled	not pooled	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains and rapid tapering of prior antidepressant treatment
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 130: Clinical evidence profile for comparison 61. Augmenting with ECT versus continuing with antidepressant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with ECT**	**Continuing with antidepressant**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Haghighi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	20	-	SMD 0.08 higher (0.54 lower to 0.7 higher)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Haghighi 2013)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	SMD 0.6 lower (1.23 lower to 0.04 higher)	LOW	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[3] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 131: Clinical evidence profile for comparison 62. Augmenting with ECT versus augmenting with exercise

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with ECT	Augmenting with exercise	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	20	20	-	SMD 0.12 higher (0.5 lower to 0.74 higher)	LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	SMD 0.18 lower (0.81 lower to 0.44 higher)	MODERATE	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	LOW	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[2] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 132: Clinical evidence profile for comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with ECT + exercise	Augmenting with exercise	Relative (95% CI)	Absolute		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20	20	-	SMD 0.99 lower (1.65 to 0.33 lower)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	SMD 1.84 lower (2.59 to 1.09 lower)	HIGH	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/20 (65%)	2/20 (10%)	RR 6.5 (1.68 to 25.16)	550 more per 1000 (from 68 more to 1000 more)	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 133: Clinical evidence profile for comparison 64. Augmenting with exercise versus TAU

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with exercise**	**TAU**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 3 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS); Better indicated by lower values)												
1 (Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	26	26	-	SMD 0.59 lower (1.15 to 0.04 lower)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up 3-10 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
2 (Danielsson 2014, Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	46	-	SMD 0.68 lower (1.1 to 0.26 lower)	MODERATE	CRITICAL
Remission (ITT) (follow-up 3-10 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												
2 (Danielsson 2014, Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/48 (43.8%)	10/46 (21.7%)	RR 2.03 (1.09 to 3.79)	224 more per 1000 (from 20 more to 607 more)	MODERATE	CRITICAL
Response (ITT) (follow-up mean 10 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))												
1 (Danielsson 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/22 (40.9%)	5/20 (25%)	RR 1.64 (0.66 to 4.07)	160 more per 1000 (from 85 fewer to 768 more)	LOW	CRITICAL

Discontinuation due to any reason (follow-up 3-10 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Danielsson 2014, Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/48 (22.9%)	9/46 (19.6%)	RR 1.18 (0.54 to 2.59)	35 more per 1000 (from 90 fewer to 311 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TAU: treatment as usual
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 134: Clinical evidence profile for comparison 65. Augmenting with exercise versus attention-placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with exercise**	**Attention-placebo**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Lavretsky 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33	35	-	SMD 0.4 lower (0.88 lower to 0.08 higher)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Mota-Pereira 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	19	10	-	SMD 5.47 lower (7.17 to 3.77 lower)	LOW	CRITICAL
Remission (ITT) (follow-up 10-12 weeks; assessed with: Number of people scoring <=7 or <7 on Hamilton Rating Scale for Depression (HAM-D))												
2 (Lavretsky 2011, Mota-Pereira 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	26/58 (44.8%)	18/48 (37.5%)	RR 1.5 (0.47 to 4.77)	188 more per 1000 (from 199 fewer to 1000 more)	LOW	CRITICAL
Response (ITT) (follow-up 10-12 weeks; assessed with: Number of people showing at least 30% or 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
2 (Mather 2002, Mota-Pereira 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	27/65 (41.5%)	14/54 (25.9%)	RR 1.7 (1.03 to 2.81)	181 more per 1000 (from 8 more to 469 more)	LOW	CRITICAL
Discontinuation due to any reason (follow-up 10-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
3 (Lavretsky 2011, Mather 2002, Mota-Pereira 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	6/101 (5.9%)	3/91 (3.3%)	RR 1.53 (0.4 to 5.86)	17 more per 1000 (from 20 fewer to 160 more)	LOW	CRITICAL
Global functioning change score (follow-up mean 12 weeks; measured with: Global Assessment of Function (GAF); Better indicated by higher values)												

1 (Mota-Pereira 2011)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	19	10	-	SMD 6.15 higher (4.28 to 8.02 higher)	LOW	IMPORTANT
Sleeping difficulties endpoint (follow-up mean 10 weeks; measured with: Pittsburgh Sleep Quality Index (PSQI); Better indicated by lower values)												
1 (Lavretsky 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33	35	-	SMD 0.25 lower (0.72 lower to 0.23 higher)	MODERATE	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect
[2] Risk of bias is high or unclear across multiple domains
[3] Study partially funded by pharmaceutical company
[4] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 135: Clinical evidence profile for comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Augmenting with exercise + ECT**	**Augmenting with ECT**	**Relative (95% CI)**	**Absolute**		
Depression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20	20	-	SMD 1.13 lower (1.81 to 0.46 lower)	MODERATE	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	SMD 1.45 lower (2.15 to 0.74 lower)	HIGH	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/20 (65%)	2/20 (10%)	RR 6.5 (1.68 to 25.16)	550 more per 1000 (from 68 more to 1000 more)	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] 95% CI crosses thresholds for both clinically important benefit and no effect

Table 136: Clinical evidence profile for comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with yoga	Continuing with antidepressant (+/- waitlist or attention-placebo)	Relative (95% CI)	Absolute		
Depression symptomatology change score (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	12	-	SMD 1.49 lower (2.39 to 0.58 lower)	HIGH	CRITICAL
Remission (ITT) (follow-up 8-10 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D) or <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
2 (Sharma 2017, Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/76 (27.6%)	12/71 (16.9%)	RR 1.58 (0.84 to 3)	98 more per 1000 (from 27 fewer to 338 more)	LOW	CRITICAL
Remission (ITT) at 3-month follow-up (follow-up mean 3 months; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/63 (30.2%)	11/59 (18.6%)	RR 1.62 (0.84 to 3.11)	116 more per 1000 (from 30 fewer to 393 more)	LOW	CRITICAL
Remission (ITT) at 6-month follow-up (follow-up mean 6 months; assessed with: Number of people scoring <=5 on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/63 (30.2%)	14/59 (23.7%)	RR 1.27 (0.7 to 2.3)	64 more per 1000 (from 71 fewer to 308 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up 8-10 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) or Quick Inventory of Depressive Symptomatology (QIDS))												
2 (Sharma 2017, Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	27/76 (35.5%)	14/71 (19.7%)	RR 2.06 (0.68 to 6.19)	209 more per 1000 (from 63 fewer to 1000 more)	VERY LOW	CRITICAL
Response (ITT) at 3-month follow-up (follow-up mean 3 months; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/63 (34.9%)	13/59 (22%)	RR 1.58 (0.88 to 2.85)	128 more per 1000 (from 26 fewer to 408 more)	LOW	CRITICAL
Response (ITT) at 6-month follow-up (follow-up mean 6 months; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))												
1 (Uebelacker 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/63 (36.5%)	14/59 (23.7%)	RR 1.54 (0.88 to 2.7)	128 more per 1000 (from 28	LOW	CRITICAL

										fewer to 403 more)		
Discontinuation due to any reason (follow-up 8-10 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))												
2 (Sharma 2017, Uebelacker 2017)	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[3]	none	7/76 (9.2%)	13/71 (18.3%)	RR 0.88 (0.08 to 9.88)	22 fewer per 1000 (from 168 fewer to 1000 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
[1] Risk of bias is high or unclear across multiple domains
[2] 95% CI crosses thresholds for both clinically important benefit and no effect
[3] 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
[4] Substantial heterogeneity

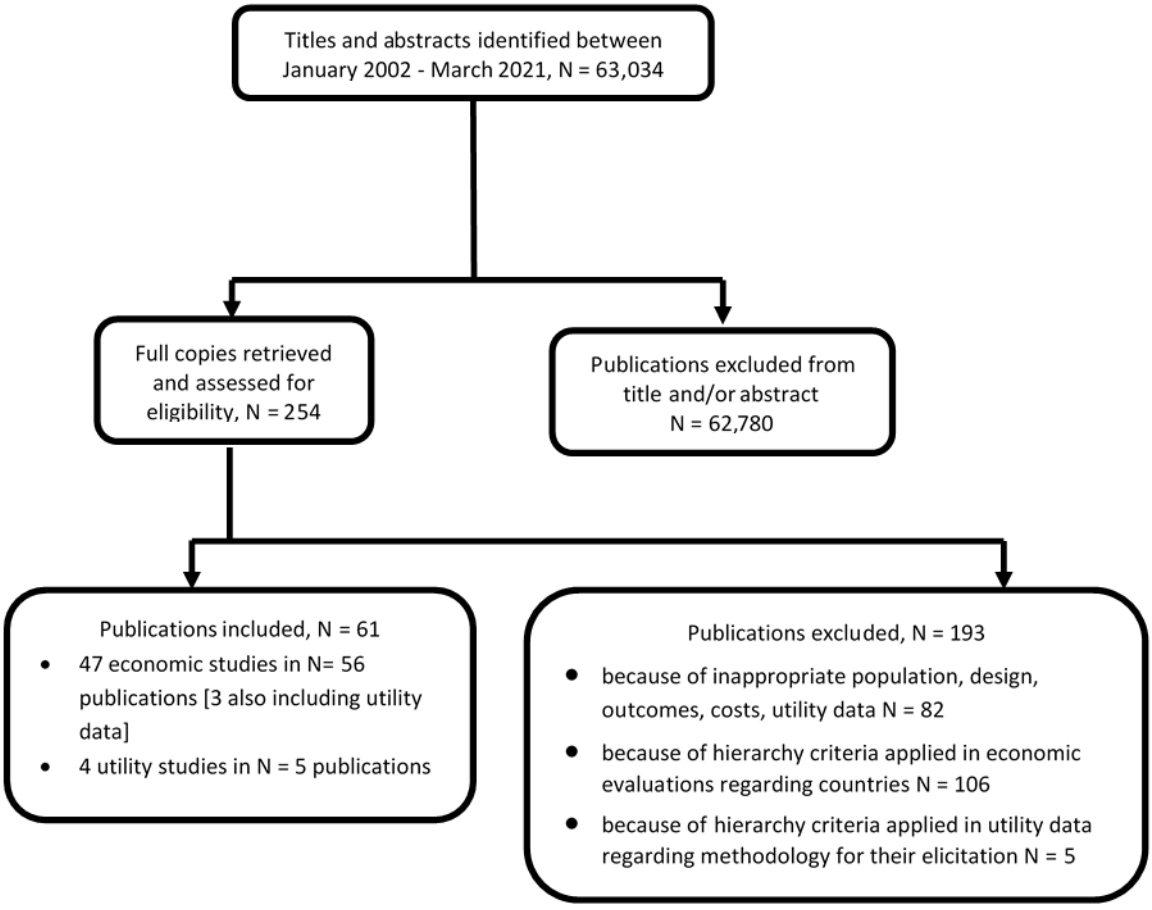
Click here to enter text.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

A global health economics search was undertaken for all areas covered in the guideline. Figure 398 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 398. 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: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 137: Economic evidence table for computerised cognitive behavioural therapy with support following inadequate response to antidepressants

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Phillips 2014 UK Cost effectiveness and cost-utility analysis	Interventions: Computerised CBT (MoodGYM) comprising 5 1hr modules, usually taken weekly, plus support in the form of telephone interviews (cCBT) Attention control (five websites with general information about mental health)	Adults with depressive symptoms, as measured by PHQ-9 responses, identified via occupational health settings Pragmatic RCT (Phillips 2014, N=637) Source of efficacy and resource use data: RCT (for clinical analysis: completion 56% at 6 weeks; 36% at 12 weeks; for cost analysis: completion rates not reported) Source of unit costs: national sources	Costs: hospital (inpatient and outpatient care), community services, staff time (GP, psychiatrist, district nurse, counsellor, occupational health providers, other providers), medication Intervention cost appears to have been omitted from analysis Productivity losses considered in societal perspective Mean total NHS cost per person (SD): cCBT: £29 (£110); Control: £38 (£125) Outcome measures: Work and Social Adjustment Scale (WSAS); QALYs estimated based on EQ-5D (UK tariff) Outcome results: WSAS difference: -0.470 (95% CI -1.837 to 0.897) QALY: cCBT: 0.082; control: 0.083 at 6 weeks cCBT: 0.167; control: 0.170 at 12 weeks	ICER of control vs cCBT: £3,667/QALY	Perspective: NHS (and societal) Currency: GBP£ Cost year: likely 2010 Time horizon: 12 weeks for outcomes; 6 weeks for costs Discounting: NA Applicability: directly applicable Quality: very serious limitations

Table 138: Economic evidence tables for cognitive therapy or cognitive behavioural therapy in addition to antidepressants versus antidepressants alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Scott 2003 UK Cost effectiveness analysis	Interventions: Cognitive therapy (16 sessions in 20 weeks plus 2 booster sessions) in addition to antidepressants (minimum dose equivalent to ≥ 125mg of amitryptiline) and clinical management (30-min appointments with a psychiatrist every 4 weeks during 20 weeks and every 8 weeks during the 48-week follow-up) (CT & AD) Antidepressants and clinical management alone (AD)	Outpatients 21-65 years that met DSM-III-R criteria for major depression, who were in an episode within the past 18 months but not in the past 2 months. At randomisation they had residual symptoms over at least 8 weeks with HAMD ≥ 8 and BDI ≥ 9. Exclusion criteria: past history of bipolar disorder; current history of significant Axis I or II comorbidity; currently receiving formal psychotherapy; having previously received CT for > 5 sessions. RCT (Paykel 1999/Scott 2000, N=158) Source of efficacy data: RCT (N=158) Source of resource use data: RCT (full data for 65% of participants) Source of unit costs: national & local inpatient cost data	Costs: CT, medication, clinical management, inpatient care, day hospital, GP, social worker, community psychiatric nurse, therapist/counsellor, group therapy, marital therapy. Mean cost per person: CT & AD: £1898 AD: £1119 Cost difference: £779 (95% CI £387 to £1170) Primary outcome measure: percentage of relapses Cumulative relapse rates: CT & AD: 29% AD: 47% Adjusted HR 0.51 (95% CI 0.32-0.93)	ICER of CT & AD vs AD: £4328 per relapse prevented £4667 using mean imputation £5028 using non-parametric multiple imputation £7056 using only the 65% of subjects in the complete case analysis Probability of CT & AD being cost-effective 0.60 and 0.80 at WTP of £6000 and £8500 per relapse prevented, respectively Probability sensitive to method of missing data imputation	Perspective: NHS/PSS Currency: GBP£ Cost year: 1999 Time horizon: 17 months Discounting: 6% Applicability: partially applicable Quality: minor limitations
Hollinghurst 2014 UK Cost consequence	Interventions: Cognitive behavioural therapy comprising 12-18 sessions lasting	Adults aged 18-75 years with major depression, who had adhered to antidepressant medication for at least 6 weeks in	Costs: medication, primary and community mental and general health care, specialist (secondary) mental health care, personal out-of-pocket expenditure such as travel costs, use of private	AT 12 MONTHS ICER of CBT vs. TAU £14,911/QALY Probability of CBT being cost-effective	Perspective: NHS/PSS for cost-utility analysis; health and

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
and cost-utility analysis	about an hour each, taking place at a GP surgery or a similar location, in addition to treatment as usual (CBT) Treatment as usual alone, comprising GP care, including antidepressant treatment as judged appropriate by the person's GP or a referral as required (TAU)	primary care, but who continued to have significant depressive symptoms; people had a BDI-II score of at least 14 or more and an ICD-10 diagnosis of depression using the Revised Clinical Interview Schedule (CIS-R) RCT (Wiles 2013/2016, N=469) Source of efficacy data and resource use data: RCT (NHS and PSS cost and QALY data available for n=368 at 12 months; follow-up data available for n= 248) Source of unit costs: national sources	therapies and over-the-counter medications; productivity losses AT 12 MONTHS Mean total cost per person (SD): NHS/PSS cost: CBT £1614 (£1100); TAU £763 (£697); difference: £850 (95%CI £683 to £1017) Personal expenditure: CBT £80 (£12), TAU £127 (£35); difference -£47 (95%CI -£120 to £25) Out-of-pocket expenses: CBT £694 (£4,824), TAU £517 (£2,464); difference £176 (95%CI -£662 to £1014) Lost productivity: CBT £1,067 (£3,887), TAU £1,102 (£3,529); difference -£36 (95%CI -£797 to £726) AT 3-5 YEARS Mean annual NHS/PSS cost (SD): CBT £885 (£938); TAU £604 (£904); difference: £281 (95%CI £32 to £531) Outcome measures: response (reduction of at least 50% in BDI-II score); BDI-II score; remission (BDI-II <10; SF-12 mental and physical subscales; EQ-5D; QALYs estimated using EQ-5D & SF-6D ratings (latter in sensitivity analysis) (UK tariff) AT 12 MONTHS Response: CBT 55.3%, TAU %31.3; OR 2.89 (95%CI 2.03 to 4.10) BDI-II score (mean, SD): CBT 17.0 (14.0), TAU 21.7 (12.9); difference -5.1 (-7.1 to -3.1)	0.74 and 0.91 at WTP of £20,000/QALY and £30,000/QALY, respectively Results robust to changes in psychologist unit costs and exclusion of hospitalisation costs. Results sensitive to use of SF-6D instead of EQ-5D, with ICER rising at £29,626/QALY Analysis of completers' data (instead of imputation of missing data): ICER £18,361/QALY AT 3-5 YEARS ICER of CBT vs. TAU £5,374/QALY Probability of CBT being cost-effective at a WTP of £20,000/QALY and £30,000/QALY: 0.92 and 0.95, respectively	social care provider for cost consequence analysis, with service user expenses and productivity losses assessed in additional analyses Currency: GBP£ Cost year: 2010 for endpoint data; 2013 for follow-up data Time horizon: 12 months; follow-up analysis 3-5 years (median 45.5 months, interquartile range 42.5 to 51.1) Discounting: 3.5% annually 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
			Remission: CBT 39.6%, TAU 18.2%; OR 2.74 (95%CI 1.82 to 4.13) SF-12 mental sub-scale (mean, SD): CBT 39.1 (14.6), TAU 35.4 (12.8); difference 4.8 (2.7 to 6.9) SF-12 physical sub-scale (mean, SD): CBT 44.6 (13.2), TAU 41.1 (13.5); difference -0.7 (95%CI -2.1 to 0.8) QALYs: CBT 0.62 (0.22), TAU 0.56 (0.25); difference 0.053 (95%CI 0.019 to 0.087) AT 3-5 YEARS Response: CBT 43%, TAU 27%; OR 2.09 (95%CI 1.19 to 3.67) BDI-II score (mean, SD): CBT 19.2 (13.8), TAU 23.4 (13.2); difference -3.6 (-6.6 to -0.6) Remission: CBT 28%, TAU 18%; OR 1.77 (95%CI 0.93 to 3.39) SF-12 mental sub-scale (mean, SD): CBT 38.7 (12.1), TAU 34.6 (11.8); difference 3.5 (0.7 to 6.3) SF-12 physical sub-scale (mean, SD): CBT 42.2 (13.8), TAU 39.2 (13.5); difference 0.9 (95%CI -0.2 to 3.8) Mean annual QALYs: CBT 0.60 (0.17), TAU 0.54 (0.20); difference 0.052 (95%CI 0.003 to 0.102)		

1

2 **Table 139: Economic evidence tables for intensive short-term psychodynamic psychotherapy versus treatment as usual (TAU)**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Town 2017/2020 Canada Cost-utility analysis	Interventions: Intensive short-term psychodynamic psychotherapy (STPP) Treatment as usual in secondary care, comprising community mental health teams delivering pharmacotherapy and clinical management, supportive or structured activities focused around symptom management and in some cases individual or group psychotherapy (TAU)	Adults (aged 18-65 years) with depression who were non-remitting following at least one antidepressant treatment course RCT (Town 2017/2020, N=60) Source of efficacy and resource use data: RCT (N=60) Source of unit costs: national cost data	Costs (only mental health related): intervention, physician visits, inpatient care, outpatient care, medication, A&D, out of pocket Mean cost per person: STPP: $4,674; TAU $5,178 Primary outcome measure: QALY based on SF-6D collected from SF-12 (UK tariff) Mean QALY per person: STPP: 0.90; TAU: 0.87	As reported by authors: STPP dominant When high volume service users were removed from analysis: ICER of STPP vs TAU: Can$19,015/QALY STPP cost-saving in 2.5% of iterations Probability of STPP being cost-effective 0.65 at WTP of $25,000/QALY	Perspective: mental health payer Currency: Canadian$ Cost year: 2017 Time horizon: 18 months Discounting: 1.5% Applicability: partially applicable Quality: very serious limitations

3 **Table 140: Economic evidence table for mirtazapine as an adjunct treatment to SSRIs or SNRIs**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kessler 2018a/2018b UK Cost-utility analysis	Interventions: Mirtazapine in addition to SSRI or SNRI treatment	Adults (aged ≥18 years) with a BDI score of ≥14 and a diagnosis of depression according to ICD-10, who had used an SSRI or SNRI	Costs: mirtazapine, other medication, hospital care related to depression or mental health (inpatient care, A&E attendances, outpatient care), primary and community care (GP or nurse contacts at the surgery, by telephone or at home, counselling or other talking therapies, face-to-face or computerised CBT, mental health clinic	INMB of mirtazapine vs. placebo: £398 (-£914 to £1709) [completer analysis] £92 (-£106 to £290) [imputed data analysis]	Perspective: NHS/PSS (personal costs and productivity losses considered in

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Pill placebo in addition to SSRI or SNRI treatment	for at least six weeks but were still depressed. RCT (Kessler 2018a/2018b, N=480) Source of efficacy data: RCT (N=368) Source of resource use data: RCT (N=369) Source of unit costs: national sources	attendances, prescribed exercise programmes, NHS Direct or 111, NHS walk-in centres), personal social services (mental health nurse home visits, occupational therapy, social worker, day centre use, self-help groups run by social services, home care worker visits, other) Costs to people with depression & their carers and productivity costs estimated separately Mean cost per person (SD): mirtazapine: £261 (£52); placebo £192 (£49) Difference: £69 (£71) Primary outcome measure: QALY based on EQ-5D-5L (UK tariff) Mean QALYs per person (SD): mirtazapine 0.734 (0.009); placebo 0.724 (0.009). Difference: 0.009 (0.013)	Probability of mirtazapine being cost-effective 0.69 and 0.71 at WTP of £20,000 and £30,000 per QALY, respectively.	additional analysis) Currency: GBP£ Cost year: 2016 Time horizon: 12 months Discounting: NA Applicability: directly applicable Quality: minor limitations

Table 141: Economic evidence table for continuation of current treatment (citalopram) versus switching to another antidepressant (venlafaxine, sertraline) or augmentation with bupropion

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Olgiati 2013 US Cost-utility analysis	Interventions: Different strategies for non-remitters: A. Continuation of current treatment (citalopram) for 13 weeks B. Choice to: a. switch to sertraline or venlafaxine for 13 weeks	Adult outpatients with chronic depression, with a HAMD17 ≥ 14, who were treated with citalopram for 13 weeks and received 2nd line treatment following no remission; exclusion criteria: indications for hospital treatment such as psychotic symptoms, suicidal risk or inpatient detoxification for alcohol / substance dependence; obsessive	Costs: medication, primary care, outpatient visits, community mental health services Mean total cost per person: Strategy A: $724 Strategy B: $800 Strategy Ba: $809 Strategy Bb: $849 Outcome measure: QALY estimated based on service	ICER of strategy B versus strategy A: Deterministic analysis: $11,481/QALY Probabilistic analysis: $10,665/QALY (95%CI: $6,498 to $14,832)	Perspective: 3rd party payer Currency: US$ Cost year: 2011 Time horizon: 26 weeks Discounting: NA Applicability: partially applicable Quality: very serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	or b. augment with bupropion for 13 weeks Remitters (HAMD17<7) continued treatment with citalopram for another 13 weeks	compulsive disorder, eating disorder Decision-analytic modelling Source of efficacy data: data for A taken from a non-RCT (Wade 2006); data for B taken from a study comprising series of RCTs (Rush2006), thus breaking randomisation rules Source of resource use data: expert opinion Source of unit costs: national sources	Canadian/US users' preferences for vignettes Incremental number of QALYs per person: Strategy B vs strategy A: 0.007 Strategy Ba vs strategy A: 0.006 Strategy Bb vs strategy A: 0.008	ICER of strategy Ba versus strategy A: $14,738/QALY ICER of strategy Bb versus strategy A: $15,458/QALY Results robust to changes in utility scores and the probability of remission after 3 months of citalopram (strategy A)	

1 **Table 142: Economic evidence table for sertraline versus venlafaxine versus bupropion**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Singh 2017 US Cost-effectiveness analysis	Interventions: Sertraline Venlafaxine Bupropion	People who require further treatment after inadequate response to a SSRI RCT (Rush 2006; N=727) Source of efficacy and resource use data: RCT Source of unit costs: national sources	Costs: medication, outpatient and A&E visits, hospitalisation Mean cost per person (SD): Sertraline: $2,232 ($3,248) Venlafaxine: $2,416 ($2,176) Bupropion: $1,972 ($1,629) Outcome measures: response and remission Response: Sertraline: 27%; Venlafaxine: 28%; Bupropion: 26% Remission: Sertraline: 27%; Venlafaxine: 25%; Bupropion: 26%	At a WTP of $30,000 / unit of effectiveness, venlafaxine had the highest net health benefit in terms of response and a probability of being the most cost-effective option around 40%; sertraline had the highest net health benefit in terms of remission and a probability of being the most cost-effective option around 45%	Perspective: payer Currency: US$ Cost year: 2014 Time horizon: 9 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Soini 2017 Finland Cost-utility analysis	Interventions: Sertraline Venlafaxine Bupropion [and vortioxetine, agomelatine, which were not included in review question]	People who require further treatment after inadequate response to a SSRI Decision-analytic modelling Source of efficacy data: RCT (Rush 2006; N=727) Source of resource use data: published evidence and expert opinion Source of unit costs: national sources	Costs: medication, GP visits, psychiatrist, psychotherapist or counsellor, psychiatric ward, outpatient visit Mean cost per person: Sertraline: €3070; Venlafaxine: €2943; Bupropion: €2961 Primary outcome measure: QALY based on EQ-5D (Finnish VAS scale) Mean QALYs per person: Sertraline: 0.7247; Venlafaxine: 0.7272; Bupropion: 0.7356	Sertraline dominated by both venlafaxine and bupropion ICER of bupropion vs venlafaxine: €2,235/QALY Probability of cost-effectiveness nor possible to estimate, as analysis included options not relevant to review question	Perspective: payer Currency: Euro (€) Cost year: 2013 Time horizon: 12 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 143: Economic evidence table for duloxetine versus venlafaxine versus mirtazapine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Benedict 2010 UK Cost-utility analysis	Interventions: Duloxetine Venlafaxine Mirtazapine	Adults with severe major depression defined by a HAMD17 score ≥25, who failed previous SSRI treatment and were referred to mental health specialists in secondary care Decision-analytic modelling Source of efficacy data: meta-analyses of clinical trials -randomisation possibly broken Source of resource use data: expert opinion Source of unit costs: national sources	Costs: medication, A&E Visits, GPs, psychiatrists, hospitalisation Mean total cost per person: Duloxetine £1,622 Venlafaxine £1,667 Mirtazapine £1,640 Outcome measure: QALY estimated based on EQ-5D ratings (UK tariff) Number of QALYs per person: Duloxetine 0.637 Venlafaxine XR 0.632 Mirtazapine 0.629	Duloxetine dominates venlafaxine XR and mirtazapine Probability of duloxetine being cost-effective at WTP £20,000/QALY: approximately 0.80 Results robust to sensitivity analysis	Perspective: Scottish NHS Currency: GBP£ Cost year: likely 2003 Time horizon: 48 weeks Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Table 144: Economic evidence table for escitalopram versus duloxetine versus venlafaxine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Nordström 2010 Sweden Cost effectiveness and cost-utility analysis	Interventions: Escitalopram Duloxetine Venlafaxine	Adults with major depression who initiated treatment with one of the assessed interventions in primary care, who had had a history of treatment with another antidepressant within the previous 6 months Decision-analytic modelling Source of efficacy data: pooled analysis of trial data, including only participants who had already received antidepressant therapy prior to randomisation – data for duloxetine and venlafaxine pooled together Source of resource use data: cohort study conducted in 56 primary care centres in Sweden over 6 months Source of unit costs: national sources	Costs: medication, staff time (GP, psychiatrist, other doctors e.g. neurologist, cardiologist, psychotherapist, counsellor, psychologist, nurse), hospitalisation, treatment of side effects, indirect costs (sick leave) Mean total healthcare cost per person: Escitalopram €973 Duloxetine €990 Venlafaxine €1,014 Outcome measures: probability of remission (defined as a MADRS total score ≤ 12) achieved after 8 weeks of treatment and sustained until the end of 6 months; QALY estimated based on EQ-5D ratings (UK tariff) Probability of remission: Escitalopram: 50.1% Duloxetine: 33.6% Venlafaxine: 33.6% Mean QALYs per person: Escitalopram 0.322 Duloxetine 0.297 Venlafaxine 0.298	Escitalopram dominant over duloxetine and venlafaxine Considering healthcare costs only: probability of escitalopram being cost-effective at WTP £20,000/QALY (€22,080/QALY) 0.981 and 0.985 compared with duloxetine and venlafaxine, respectively Results robust to changes in remission rates, relapse rates, number of GP visits, or incidence of nausea	Perspective: societal; healthcare costs reported separately Currency: Euros(€) Cost year: 2009 Time horizon: 6 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 145: Economic evidence table for generic SSRIs (citalopram, fluoxetine, paroxetine) versus escitalopram versus paroxetine controlled release versus sertraline versus venlafaxine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Malone 2007 US	Interventions:	Adults with major depression who failed to	Costs: medication, physician visits, laboratory tests, inpatient mental health care	Paroxetine CR and sertraline dominated by other options	Perspective: 3rd party payer

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Cost effectiveness analysis	Generic SSRIs (citalopram, fluoxetine, paroxetine, weighted according to market share) Escitalopram Paroxetine controlled release [CR] Sertraline Venlafaxine extended release [XR]	achieve remission with SSRIs Decision-analytic modelling Source of efficacy data: review of published trial data and further assumptions – synthesis by naïve addition of data (leading to breaking of randomisation) Source of resource use data: analysis of 1,814 persons enrolled in 10 antidepressant studies Source of unit costs: medication costs from national sources; other unit costs taken from other studies, unclear whether these were national or local	Mean total healthcare cost per person: Generic SSRIs $3,095 Escitalopram $3,127 Paroxetine CR $3,206 Sertraline $3,178 Venlafaxine $3,172 Outcome measure: probability of remission (defined as a HDRS score ≤ 7 or a MADRS total score ≤ 10) Probability of remission: Generic SSRIs 18.5% (weighted average) Escitalopram 19.4% Paroxetine CR 17.7% Sertraline 19.5% Venlafaxine XR 22.2%	ICER of venlafaxine XR vs. generic SSRIs $2,073 per person achieving remission ICER of escitalopram vs. generic SSRIs $3,566 / additional person remitting [extendedly dominated] Results of sensitivity analysis reported using primarily each intervention's CER and not ICERs.	Currency: US$ Cost year: not reported, likely 2005 Time horizon: 6 months Discounting: NA Applicability: partially applicable Quality: very serious limitations

1 **Table 146: Economic evidence table for atypical antipsychotics adjunct to a SSRI versus lithium adjunct to a SSRI**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Edwards 2013 UK Cost-utility analysis	Interventions: An atypical antipsychotic drug (AAP) as an adjunct to an SSRI Lithium as an adjunct to an SSRI	Adults with treatment-resistant depression (TRD) defined as failure to respond to at least 2 previous antidepressants in the current episode of depression Decision-analytic modelling Source of efficacy data: systematic review and indirect comparison using 6 RCTs comparing olanzapine +	Costs: medication (weighted costs according to expert opinion; it was estimated that AAP comprises 30% aripiprazole, 30% olanzapine, 20% quetiapine, and 20% risperidone; and an SSRI comprises 20% citalopram, 20% escitalopram, 30% fluoxetine, and 30% sertraline),	Augmentation with lithium dominates augmentation with AAP Probability of lithium being dominant 1 Results sensitive to efficacy of augmentation strategies and	Perspective: NHS/PSS Currency: GBP£ Cost year: 2011 Time horizon: 12 months Discounting: NA Applicability: directly applicable

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		fluoxetine vs. fluoxetine alone in people with TRD and 1 RCT comparing lithium + fluoxetine vs. fluoxetine alone in people who had failed at least one antidepressant; a common class effect was assumed for the SSRIs and the AAPs. Data on lithium taken from population that had failed to respond to 1 previous SSRI (so not a TRD population) Source of resource use data: mainly clinical expert opinion, length of hospitalisation taken from national hospital episode statistics Source of unit costs: national sources	healthcare professional time (GP, CMHT, CRHTT), hospitalisation and monitoring (laboratory testing) Mean total cost per person: AAP £5,644; Lithium £4,739 Outcome measure: QALYs estimated using EQ-5D ratings (UK tariff) Mean QALYs per person: AAP 1.225; Lithium 1.253	discontinuation rates; robust under different assumptions regarding resource use, as well as under changes in remission and relapse risk at follow-up	Quality: potentially serious limitations Other comments: a fixed baseline MADRS score was assumed; change in MADRS scores at endpoint assumed to have a normal distribution in order to estimate proportions of people in response, no response, and remission states

Table 147: Economic evidence table for aripiprazole adjunct to an antidepressant versus bupropion adjunct to an antidepressant versus switching to bupropion

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Yoon 2018 US Cost-effectiveness and cost-utility analysis	Interventions: Aripiprazole adjunct to an antidepressant Bupropion adjunct to an antidepressant Switching to bupropion	Adult veterans with treatment-resistant depression (TRD) defined as failure to respond to at least 2 previous antidepressants in the current episode of depression RCT (Mohamed 2017; N=1522) Source of efficacy data & resource	Costs: medication, mental health care (inpatient, outpatient) Mean total cost per person: Aripiprazole adjunct: $2,273; Bupropion adjunct: $2,171; Bupropion switch: $2,201 Outcome measures: Remission, defined as QIDS-C score of ≤5 in 2 consecutive follow-up visits; QALYs estimated using EQ-5D, no further details reported (e.g. if it was VAS or TTO, and, if the latter, which tariff was used). Remission:	On remission outcome: Bupropion switch dominated by bupropion adjunct ICER of aripiprazole adjunct vs bupropion adjunct: $5,094/ remission On QALY outcome: ICER of aripiprazole adjunct vs bupropion switch $468,126/QALY ICER of bupropion switch vs bupropion adjunct: $29,039/QALY	Perspective: healthcare Currency: US$ Cost year: likely 2016 Time horizon: 12 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		use data: RCT (completers n=1131) Source of unit costs: national sources	Aripiprazole adjunct: 29%; Bupropion adjunct: 27%; Bupropion switch: 22% Mean QALYs per person: Aripiprazole adjunct: 0.15; Bupropion adjunct: 0.14; Bupropion switch: 0.15	At WTP $20,000/remission, probability of cost-effectiveness: aripiprazole adjunct 76%; bupropion adjunct 23%; bupropion switch: 1%	

Table 148: Economic evidence table for aripiprazole versus quetiapine versus olanzapine/fluoxetine (all adjunct to antidepressant treatment) versus antidepressant treatment alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Taneja 2012 US Cost effectiveness analysis	Interventions: Aripiprazole 2-20 mg /day and antidepressant therapy (ARI) Quetiapine 150 mg /day or 300 mg /day and antidepressant therapy (QUE) Fixed-dose combination of olanzapine 6, 12, or 18 mg /day with fluoxetine 50 mg /day (OLZ/FLUO) Antidepressant therapy alone (AD)	Adults with major depression who responded inadequately to previous antidepressant therapy Decision-analytic modelling Source of efficacy data: meta-analysis of published phase III clinical trials and indirect comparison using placebo as baseline comparator Source of resource use data: administrative databases and assumptions Source of unit costs: national sources	Costs: medication, outpatient care for depression, treatment of adverse events Mean total healthcare cost per person: ARI $847 QUE 150 mg/day $541 QUE 300 mg/day $672 OLZ/FLUO $791; AD $192 Outcome measure: probability of response (defined as at least 50% reduction in MADRS total score) Probability of response: ARI 49% QUE 150 mg/day 34% QUE 300 mg/day 38% OLZ/FLUO 45%; AD 30%	QUE 150 & 300 mg/day and OLZ/FLUO extendedly dominated ICER of ARI vs. AD $3,447 per person responding Results sensitive to changes in relative effectiveness	Perspective: healthcare system Currency: US$ Cost year: 2011 Time horizon: 6 weeks Discounting: NA Applicability: partially applicable Quality: very serious limitations

Table 149: Economic evidence table for brexpiprazole versus quetiapine versus olanzapine/fluoxetine (all adjunct to antidepressant treatment) versus antidepressant treatment alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Sussman 2017 US Cost-effectiveness analysis	Interventions: Brexpiprazole adjunct to antidepressants [BREX] Quetiapine XR 300mg/day adjunct to antidepressants [QUET300] Quetiapine XR 150mg/day adjunct to antidepressants [QUET150] Olanzapine/ fluoxetine adjunct to antidepressants [OLZ/FLUO] Antidepressants alone [AD]	Adults aged 18–65 years with single or recurrent non-psychotic major depressive episode and inadequate response after an adequate trial of 1-3 antidepressants Decision-analytic modelling Source of efficacy data: various trials and meta-analyses, using indirect comparisons for evidence synthesis Source of resource use data: published literature Source of unit costs: published evidence and national sources	Costs: medication, standard healthcare for depression, healthcare costs relating to response, remission, relapse, treatment discontinuation, management of adverse events Mean total cost per person: BREX $11,511; QUET300 $10,072; QUET150 $9,082; OLZ/FLUO $8,256; AD $7255 Outcome measures: response and remission (different definitions across trials informing the analysis) Response / Remission: BREX 48.4% / 22.4% QUET300 41.1% / 17.1% QUET150 37.8% / 14.6% OLZ/FLUO 41.8% / 17.9% AD 32.5% / 10.4%	QUET150 and QUET300 dominated by OLZ/FLUO using both response and remission as outcomes ICER of BREX vs OLZ/FLUO: $48,745/responder and $71,839/remitter ICER of OLZ/FLUO vs AD: $10,720/responder and $13,293/remitter	Perspective: payer Currency: US$ Cost year: unclear; likely 2015 Time horizon: 48 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 150: Economic evidence table for electroconvulsive therapy versus antidepressants (TCAs, SSRIs, SNRIs, and lithium augmentation) or psychotherapy

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Greenhalgh 2005 UK Cost-utility analysis	Interventions: Electroconvulsive therapy (ECT), TCAs, SSRIs, SNRIs and lithium augmentation (Li) combined in 8 strategies of 3 lines of therapy plus maintenance therapy of SSRI unless otherwise specified: 1. SNRI, SSRI, Li 2. ECT, SSRI, Li; ECT maintenance in ECT 3. ECT, SSRI, Li; Lithium & TCA maintenance in ECT 4. SNRI, ECT, Li; Lithium & TCA maintenance in ECT 5. ECT, SSRI, Li 6. SNRI, SSRI, ECT; Lithium & TCA maintenance in ECT 7. SNRI, ECT, Li; ECT maintenance in ECT 8. SNRI, SSRI, ECT; ECT maintenance in ECT	Adults with major depressive disorder who require hospitalisation Decision-analytic modelling (decision tree) Source of efficacy data: systematic literature review of RCTs and published meta-analyses, and further assumptions. Source of resource use data: published literature and expert opinion Source of unit costs: national sources	Costs: intervention (ECT, medication, hospitalisation), continued care for non-responders (nursing home placement with psychiatric provision), maintenance treatment (laboratory testing, contacts with GP, psychiatrist and psychiatric nurse) Mean total cost per person (95% CI): Strategy 1. £11,400 (£9,349 to £13,718) Strategy 2. £15,354 (£13,445 to £17,361) Strategy 3. £10,997 (£9,080 to £13,045) Strategy 4. £10,592 (£8,874 to £12,435) Strategy 5. £11,022 (£9,016 to £13,069) Strategy 6. £13,939 (£11,161 to £17,049) Strategy 7. £12,591 (£10,678 to £14,497) Strategy 8. £14,548 (£11,680 to £17,717) Primary outcome measure: QALYs estimated based on preferences for vignettes using the McSad health state classification system valued by service users with previous depression in Canada using SG Mean total QALYs per person (95% CI): Strategy 1. 0.490 (0.453 to 0.526) Strategy 2. 0.458 (0.422 to 0.493) Strategy 3. 0.424 (0.389 to 0.459) Strategy 4. 0.470 (0.431 to 0.508) Strategy 5. 0.539 (0.498 to 0.579) Strategy 6. 0.489 (0.452 to 0.524) Strategy 7. 0.486 (0.449 to 0.522) Strategy 8. 0.494 (0.459 to 0.529)	Strategies 1, 2, 3, 6, 7, and 8 were dominated ICER of Strategy 5 vs. strategy 4: £6,232/QALY Results modestly sensitive to use of alternative utility values; results robust to small changes in costs and suicide rates	Perspective: NHS Currency: GBP£ Cost year: 2001 Time horizon: 12 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Ross 2018 US Cost-utility analysis	Interventions: Electroconvulsive therapy (ECT) as 1st, 2nd, 3rd, 4th, 5, 6th line of treatment, following 0-5 lines of antidepressants and/or psychotherapy No ECT	Adults with treatment-resistant depression Decision-analytic modelling Source of efficacy data: meta-analyses, RCTs, observational studies and further assumptions. No comparative data used and no evidence synthesis of available data undertaken. Source of resource use data: published literature Source of unit costs: published literature and national sources	Costs: ECT, medication, outpatient and inpatient care, laboratory testing Mean total cost per person: 1st line ECT $54,520, 2nd line ECT $52,000, 3rd line ECT $49,830, 4th line ECT $50,900, 5th line ECT $49,850, 6th line ECT $50,080, no ECT $42,490 Primary outcome measure: QALYs estimated based on published utility data, which are derived from RQ-5D (UK tariff) Mean total QALYs per person: 1st line ECT 2.78, 2nd line ECT 2.77, 3rd line ECT 2.77, 4th line ECT 2.76, 5th line ECT 2.76, 6th line ECT 2.75, no ECT 2.63	4th, 5th, and 6th line ECT dominated ICER of 3rd line ECT vs no ECT $54,000/QALY ICER of 2nd vs 3rd line ECT $564,000/QALY ICER of 1st vs 2nd line ECT $815,000/QALY At WTP $100,000/QALY, probability that at least 1 ECT strategy is cost-effective: 74-78%; probability of cost-effectiveness of 3rd line ECT: 56-58%. Results at the WTP robust under alternative scenarios tested	Perspective: healthcare Currency: US$ Cost year: 2013 Time horizon: 4 years Discounting: 3% annually Applicability: partially applicable Quality: very serious limitations

1
2

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 151: Economic evidence profile for cognitive therapy or cognitive behavioural therapy in addition to antidepressants versus antidepressants alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Scott 2003 UK	Minor limitations[2]	Partially applicable[3]	Intervention: cognitive therapy TAU: antidepressant and clinical management Outcome measure: percentage of relapses avoided	£1,371	18%	£7,621	ICER £8,218 using mean imputation; £8,853 using non-parametric multiple imputation; £12,425 using only the 65% of subjects in the complete case analysis Probability of cognitive therapy being cost-effective 0.60 and 0.80 at WTP of £10,500 and £15,000 per relapse prevented, respectively; probability sensitive to method of missing data imputation
Hollinghurst 2014 UK	Minor limitations[4]	Directly applicable[5]	Intervention: cognitive behavioural therapy TAU: GP management and antidepressant or referral as required Outcome measure: QALY	Endpoint: £1,006 Mean over 3-5 years: £311	Endpoint: 0.053 Mean over 3-5 years: 0.052	Endpoint: £17,639 Follow-up: £5,943	Results robust to changes in psychologist unit cost & exclusion of hospitalisation costs Using SF-6D-based QALYs: £35,045/QALY Using completers' data: £21,720/QALY Probability of CBT being cost-effective: Endpoint: 0.74 / 0.91; follow-up: 0.92 / 0.95 at WTP of £20,000/£30,000/QALY, respectively

1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 17 months; analysis conducted alongside RCT (N=158; full data for 65% of participants); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented.
3. UK study; NHS & PSS perspective; outcome measure % of relapses, no QALY used as an outcome
4. Time horizon 12 months plus 3-5 year follow-up; analysis conducted alongside RCT (N=469; NHS and PSS cost and QALY data available for n=368 at 12 months; follow-up data available for n= 248); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented

5. UK study; NHS & PSS perspective; QALYs estimated based on EQ-5D ratings (UK tariff)

Table 152: Economic evidence profile for mirtazapine in addition to SSRIs or SNRIs versus SSRIs or SNRIs alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Kessler 2018a/2018b UK	Minor limitations[2]	Directly applicable[3]	Outcome measure: QALY	£75	0.009	£430 (-£987 to £1846) [completer analysis] £99 (-£115 to £313) [imputed data analysis]	Difference in costs and QALYs not significant Probability of mirtazapine being cost-effective: 0.69 / 0.71 at WTP of £20,000/ £30,000/QALY, respectively

1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis conducted alongside RCT (N=480; full data for 75% of participants); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented.
3. UK study; NHS & PSS perspective; QALYs estimated based on EQ-5D-5L ratings (UK tariff)

Table 153: Economic evidence profile for sertraline versus venlafaxine versus bupropion following inadequate response to a SSRI

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Soini 2017 Finland	Potentially serious limitations[2]	Partially applicable[3]	Outcome measure: QALY Sertraline dominated by the other two interventions	Bupropion vs venlafaxine £15	Bupropion vs venlafaxine 0.0084	Bupropion vs venlafaxine: £2,249/QALY	Probability of cost-effectiveness nor possible to estimate, as analysis included options not relevant to review question
Singh 2017 US	Potentially serious limitations[4]	Partially applicable[5]	Outcome measures: response and remission	Vs bupropion: Sertraline: £198 Venlafaxine: £155	Response, vs bupropion: Sertraline: 1% Venlafaxine: 2% Remission, vs bupropion: Sertraline: 2% Venlafaxine: -1%	Incremental net health benefit (at WTP £23,000 /unit of effectiveness): Response, vs bupropion: Sertraline: -0.0037 Venlafaxine: 0.0062 Remission, vs bupropion: Sertraline: 0.0013 Venlafaxine: -0.0218	At a WTP of £23,000 / unit of effectiveness, venlafaxine had a probability of being the most cost-effective option around 40% (in terms of response); sertraline had a probability of being the most cost-effective option around 45% (in terms of remission)

1. Costs converted to UK pounds and uplifted to 2020 prices using Purchasing Power Parity exchange rates and the NHS cost inflation index (Curtis 2020).

2. Time horizon 12 months; analysis based on decision-analytic modelling; efficacy data from RCT (N=727); national unit costs used; CEACs presented for pairwise comparisons of vortioxetine (which was of no interest) versus each of the other interventions; funded by industry.
3. Finnish study; healthcare payer's perspective; QALYs estimated based on EQ-5D VAS ratings in Finland
4. Time horizon 9 weeks; analysis based on RCT (N=727); national unit costs used; statistical analyses conducted and CEACs presented
5. US study; government payer's perspective; response and remission used as outcome measures

Table 154: Economic evidence profile for various pharmacological interventions following inadequate response to previous antidepressant treatment

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Benedict 2010 UK	Potentially serious limitations[2]	Directly applicable[3]	Interventions: duloxetine, venlafaxine, mirtazapine Outcome: QALY	Duloxetine vs: Venlafaxine: -£67 Mirtazapine: -£27	Duloxetine versus: Venlafaxine: 0.05 Mirtazapine: 0.08	Duloxetine dominant	Probability of duloxetine being cost-effective at WTP £20,000/QALY: approximately 0.80
Nordström 2010 Sweden	Potentially serious limitations[4]	Partially applicable[5]	Interventions: escitalopram, duloxetine, venlafaxine Outcome: QALY	Escitalopram vs: Duloxetine: -£16 Venlafaxine: -£60	Escitalopram versus: Duloxetine: 0.025 Venlafaxine: 0.024	Escitalopram dominant	Probability of escitalopram being cost-effective at WTP £20,000/QALY 0.981 and 0.985 compared with duloxetine and venlafaxine, respectively

1. Costs converted to UK pounds and uplifted to 2020 prices using Purchasing Power Parity exchange rates and the NHS cost inflation index (Curtis 2020).
2. Time horizon 48 weeks; analysis based on decision-analytic modelling; efficacy data derived from meta-analyses of clinical trials with randomisation possibly broken; disutility and costs due to side effects not considered; resource use estimates based on expert opinion; national unit costs used; funded by industry
3. UK study; Scottish NHS perspective; QALYs based on EQ-5D (UK tariff)
4. Time horizon 6 months; analysis based on decision-analytic modelling; efficacy data derived from pooled analysis of trial data, including only participants who had already received antidepressant therapy prior to randomisation; data for duloxetine and venlafaxine pooled together; resource use estimates based on a cohort study conducted in 56 primary care centres in Sweden over 6 months; national unit costs used; CEACs presented for escitalopram versus each of the other drugs considered and not for all 3 options; funded by industry
5. Swedish study; societal perspective but analysis based on healthcare costs presented separately; QALYs based on EQ

Table 155: Economic evidence profile for atypical antipsychotics adjunct to a SSRI versus lithium adjunct to a SSRI

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Edwards 2013 UK	Potentially serious limitations[2]	Directly applicable[3]	Outcome: QALY	-£1,040	0.028	Lithium as an adjunct to SSRI dominant	Probability of lithium being dominant: 1.00 Results sensitive to efficacy of augmentation strategies and discontinuation rates; robust under different assumptions regarding resource use, as well as under changes in remission and relapse risk at follow-up

1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis based on decision-analytic modelling; efficacy data taken from a systematic review and indirect comparison using 6 RCTs comparing olanzapine + fluoxetine vs. fluoxetine alone in people with treatment-resistant depression and 1 RCT comparing lithium + fluoxetine vs. fluoxetine alone in people who had failed at least one antidepressant (so not from a population with treatment-resistant depression); a common class effect was assumed for the SSRIs and the AAPs; resource use estimates based on expert opinion; national unit costs used; PSA conducted.
3. UK study; NHS & PSS perspective; QALY estimates based on EQ-5D (UK tariff)

Table 156: Economic evidence profile for aripiprazole adjunct to antidepressants versus bupropion adjunct to antidepressants versus switching to bupropion

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Yoon 2018 US	Potentially serious limitations[2]	Partially applicable[3]	Outcomes: Remission QALY	Vs bupropion switch: Aripiprazole adjunct £53 Bupropion adjunct –£22	Remission vs bupropion switch: Aripiprazole adjunct 7% Bupropion adjunct 5% QALY vs bupropion switch: Aripiprazole adjunct 0.0002 Bupropion adjunct -0.001	Remission: Bupropion switch dominated by bupropion adjunct Aripiprazole adjunct vs bupropion adjunct: £3,791/ remission QALY: Aripiprazole adjunct vs bupropion switch £348,428/QALY Bupropion switch vs bupropion adjunct: £21,614/QALY	At WTP £15,000/remission, probability of cost-effectiveness: aripiprazole adjunct 76%; bupropion adjunct 23%; bupropion switch: 1%

1. Costs converted to UK pounds and uplifted to 2020 prices using purchasing power parity exchange rates and the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 weeks; analysis conducted alongside RCT (N=1522; complete data for n=1131); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented for the remission outcome. Method of estimating QALYs from EQ-5D unclear (e.g. VAS vs ratings translated into utility values); potential conflict of interest due to relations with pharma industry
3. US study; healthcare perspective; outcome measure % of remission plus QALY based on EQ-5D but unclear whether VAS or ratings translated into utility values was used

Table 157: Economic evidence profile for brexpiprazole versus quetiapine (150 and 300mg/day) versus olanzapine/fluoxetine adjunct to antidepressants versus antidepressant treatment alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Sussman 2017 US	Potentially serious limitations[2]	Partially applicable[3]	Outcomes: Response Remission	Vs AD: BREX £3,194 QUET300 £2,113 QUET150 £1,370 OLZ/FLUO £749	Response vs AD: BREX 0.16 QUET300 0.09 QUET150 0.05 OLZ/FLUO 0.09 Remission vs AD: BREX 0.12 QUET300 0.07 QUET150 0.04 OLZ/FLUO 0.08	QUET150 and QUET300 dominated by OLZ/FLUO using both response and remission as outcomes ICER of BREX vs OLZ/FLUO: £36,619/responder and £53,969/remitter ICER of OLZ/FLUO vs AD: £8,053/responder and £9,986/remitter	Not reported

1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 48 weeks; analysis based on decision-analytic modelling; efficacy data obtained from trials and meta-analyses using indirect comparisons for evidence synthesis; resource use and unit costs taken from published studies, further national unit costs used; no incremental analysis conducted but possible to undertake using reported data; no CEACs; funded by industry
3. US study; payer's perspective; no QALYs used

Table 158: Economic evidence profile for ECT versus TCAs, SSRIs, SNRIs, and lithium augmentation

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
Greenhalgh 2005 UK	Potentially serious limitations[2]	Partially applicable[3]	Population: adults with depression requiring hospitalisation Strategies: 1. SNRI, SSRI, Li 2. ECT, SSRI, Li; ECT maintenance in ECT 3. ECT, SSRI, Li; Lithium & TCA maintenance in ECT 4. SNRI, ECT, Li; Lithium & TCA maintenance in ECT 5. ECT, SSRI, Li 6. SNRI, SSRI, ECT; Lithium & TCA maintenance in ECT 7. SNRI, ECT, Li; ECT maintenance in ECT	Strategies 2-8 vs 1: £6,397 -£652 -£1,307 -£611 £4,107 £1,926 £5,093	Strategies 2-8 vs 1: -0.032 -0.066 -0.020 0.049 -0.001 -0.004 0.004	Strategies 1, 2, 3, 6, 7, and 8 dominated ICER of 5 vs. 4: £10,082 /QALY	Results modestly sensitive to use of alternative utility values; results robust to small changes in costs and suicide rates

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty[1]
			8. SNRI, SSRI, ECT; ECT maintenance in ECT Outcome: QALY				

1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis based on economic modelling, efficacy data from systematic literature review of RCTs and published meta-analyses, and further assumptions; resource use data based on published literature and expert opinion; national unit costs used; sensitivity analysis conducted including PSA (95% CI reported); impact of side effects considered only in terms of discontinuation
3. UK study; NHS perspective; QALYs estimated based on preferences for vignettes using the McSad health state classification system valued by service users with previous depression in Canada using standard gamble techniques

Appendix J – Economic analysis

Economic analysis for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Clinical studies

Please refer to the excluded studies in supplement D – Clinical evidence tables for Evidence Review D Further-line treatment.

Economic studies

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

Appendix L – Research recommendations

Research recommendations for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Research question

What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?

Why this is important

Not all people with depression respond well to first-line treatments and approximately one-third do not fully recover with first line treatment and may remain symptomatic even after a second-line treatment. Finding improved models of treatment for people who do not respond to first-line treatment is critical. We do not know what treatment options best follow inadequate response to a first-line psychological intervention, including adding antidepressant medication or switching to another psychological intervention or how to make this choice.

Table 159: Research recommendation rationale

Research question	**What are the relative benefits and risks of further psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?**
Why is this needed	
Importance to 'patients' or the population	Depression is a debilitating and highly prevalent condition in adults. Despite significant investment in 'Improving Access to Psychological Therapies' (IAPT) services, the most effective, evidence-based and well-established treatments have only modest effects on depressive symptoms. In addition, many people relapse from an episode of depression. More effective treatments for a single episode of depression are needed. The definition of 'Treatment-resistant' depression is disputed, but includes failure to respond to at least two antidepressants (ADs) from different classes and there is no consideration of response to psychological interventions.. Further research on the identification and management of treatment-resistant depression is required.

Research question	What are the relative benefits and risks of further psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?
Relevance to NICE guidance	The guidelines currently make recommendations for further-line interventions and for treatment-resistant depression but there is uncertainty as to what interventions are most effective in response to an initial psychological intervention, given that most evidence is based on initial treatment with antidepressant medication. improved evidence for effective further-line treatments following unsuccessful first line psychological treatment could lead to greater clarity in the recommendations.
Relevance to the NHS	Use of more effective and more cost-effective options may lead to reduced costs for treating people with acute depression. Evidence on the sequencing of psychological interventions may lead to improved IAPT service delivery.
National priorities	The NHS Five Year Forward plan and NHS Long Term plan make access to effective mental health services a key national priority.
Current evidence base	The current evidence base for further-line treatment is predominantly based on antidepressant medication as the first line of treatment. Treatment resistant depression (TRD) is usually defined as a failure to respond to 2 adequate courses of antidepressants within a specified episode of depression, without consideration of response to psychological interventions. With increasing access to psychological interventions (via IAPT) and many patients expressing preference for psychological interventions, increasing numbers of patients with depression may have a psychological intervention as the first-line treatment. However, there is uncertainty as to what to do next, whether to switch to antidepressants, switch to another psychological intervention, continue the psychological intervention and add antidepressant medication. Very little evidence is available which identifies what are the most effective and cost-effective interventions following an unsuccessful first-line psychological intervention.
Equality	NA - No equality concerns identified
Feasibility	This research would require a series of RCTs utilising different designs and comparisons (e.g., switching psychological interventions, switching to antidepressant medication, augmentation with

Research question	What are the relative benefits and risks of further psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to an initial psychological intervention for the current episode?
	antidepressant medication) to identify which further-line interventions are most effective. These novel treatments should then be tested in large scale RCTs against current most effective psychological treatments. This would require an extensive programme of research. Numbers of people treated for depression in primary care make this study feasible.
Other comments	NA

NA: not applicable

Table 160: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults in a depressive episode whose depression has not responded or there has been limited response for the current episode or residual depressive symptoms following initial psychological treatment(s)
Intervention	Psychological interventions: • Behavioural therapies • Cognitive and cognitive behavioural therapies • Counselling • Interpersonal psychotherapy • Psychodynamic psychotherapies • Psychoeducational interventions • Self-help with or without support (facilitation) Antidepressant medications including SSRIs, SNRIs, TCAs Physical interventions including ECT
Comparator	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	Critical: • Depression symptomatology • Remission • Response • Discontinuation due to any reason • Discontinuation due to side effects

Criterion	Explanation
	Important: • Quality of life • Personal, social, and occupational functioning
Study design	Randomised controlled trials
Timeframe	Minimum follow-up 6 months
Additional information	The randomised controlled trials can include a range of designs to test switching/augmentation such as adaptive and SMART designs. It would be helpful to collect data that supports the development of treatment decision rules.

1 *ECT: electroconvulsive therapy*

2

3