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.

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Further-line treatment

2 Review question

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

7 Introduction

- 8 This review was concerned with further-line treatment for those with depression, and
- 9 included people with coexisting personality disorders, psychotic depression, and chronic
- depression. The committee recognised that these were overlapping populations in the
- 11 context of further-line treatment, and agreed that a broader evidence base would more
- 12 accurately reflect the complexities that may be associated with non-response to initial
- 13 treatment.
- 14 Further-line treatments for depression may be required when people with depression have
- 15 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.

17 Failure or intolerance of first-line treatment

- 18 First-line treatments for depression do not lead to remission in approximately two-thirds of
- 19 people and therefore the choice of further-line treatment is a common clinical dilemma for
- 20 patients and professionals. In addition, there will be people who cannot tolerate the original
- 21 choice of first-line treatment, and these people will also require selection of an appropriate
- 22 second-line option.
- 23 Further-line treatment strategies can include switching to a different medication or
- 24 psychological therapy, switching from medication to a psychological therapy, or vice versa,
- 25 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
- 27 previous history of treatment response, type of depressive syndrome and comorbidities can
- 28 be helpful in guiding the choice.
- 29 For the people who remain depressed despite second-line treatment, the terms 'treatment
- resistance' or 'treatment resistant depression' (TRD) are often used.

31 Treatment resistant depression

- 32 Treatment resistant depression (TRD) is usually defined as a failure to respond to 2
- 33 adequate courses of antidepressants within a specified episode of depression. There does
- 34 not appear to be a similarly accepted definition of failure to 2 adequate courses of
- 35 psychological therapy.
- 36 Recent models of TRD (such as the Massachusetts General Hospital and the Maudsley
- 37 Staging Method) consider the duration of depression, the severity of the illness and the
- 38 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.
- 40 However, all of these staging methods remain limited through their focus on assessing
- resistance to treatments within the current episode.
- 42 Recent clinical trials and functional neuroimaging studies have suggested that some types of
- 43 psychotherapy may have an important place in overcoming treatment resistance, and further

- 1 clarifying this role, particularly at later stages of treatment failure, may help in developing
- 2 fuller models of treatment resistance and likelihood of future remission.
- 3 Alongside efforts to more clearly delineate treatment resistance there has been greater
- 4 acknowledgement of so-called 'pseudo-resistance', where lack of response relates to
- 5 misdiagnosis (for example, of bipolar depression) or under-treatment (for example, through
- 6 inadequate dosage or length of treatment), rather than true treatment resistance.
- 7 Understanding this problem of 'pseudo-resistance' (and avoiding incorrectly labelling an
- 8 individual as genuinely treatment resistant) should remain a significant concern in day-to-day
- 9 clinical practice in order to improve treatment outcomes.
- 10 Genuine treatment resistance has been linked to a number of demographic and illness
- 11 characteristics, including: living alone; lower income; unemployment; male gender; lower
- 12 education; higher complexity through associated physical or psychiatric disorder; and a
- 13 longer, more severe current episode.
- 14 Several approaches to overcoming treatment resistant depression have been evaluated,
- including pharmacology, physical interventions and psychological therapy. Pharmacological
- 16 next-step options include switching within a class of antidepressants (for example, different
- 17 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
- 20 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
- 22 antidepressants may come through 'pharmacogenomics', indicating the genetic factors that
- 23 may make people differentially liable to the beneficial or adverse effects of particular
- 24 pharmacological agents.
- 25 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
- 27 resistant at one year. After a period of treatment resistance there is some evidence that
- 28 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.
- 31 The aim of this review is to identify the most effective interventions for people who have had
- 32 no or limited response to previous treatment(s) for the current episode of depression, have
- 33 not tolerated previous treatment(s) for the current episode of depression, or who have
- 34 treatment-resistant depression.

35 Summary of the protocol

- 36 See Table 1 for a summary of the Population, Intervention, Comparison and Outcome
- 37 (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 furtherline 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 lifePersonal, social, and occupational functioning
DCM. Diagnostic and statistical manual of m	pental disorders: FCT: electroconvulsive therapy: ICD: international

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

1 For further details see the review protocol in appendix A.

2 Methods and processes

- 3 This evidence review was developed using the methods and process described in
- 4 <u>Developing NICE guidelines: the manual</u>. Methods specific to this review question are
- 5 described in the review protocol in appendix A.
- 6 Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy
- 7 until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to
- 8 NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were
- 9 reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

10 Clinical evidence

11 Included studies

- 12 125 RCTs were included in this review (Appelberg 2001; Baert 2010 study 2; Barbee 2011;
- 13 Bauer 2009; Bauer 2013; Bauer 2019; Baumann 1996; Berman 2007; Berman 2009; Bose
- 14 2012; Carpenter 2002; Chan 2012; Cheon 2017; Chiesa 2015; Corya 2006; Dai 2019;
- 15 Danielsson 2014; Doree 2007; Dornseif 1989; Dozois 2009; Dunn 1979; Dunner 2007;
- 16 Durgam 2016; Earley 2018; Eisendrath 2016; El-Khalili 2010; Embling 2002; Fang 2010;
- 17 Fang 2011; Fava 1994a; Fava 2002; Fava 2012/Mischoulon 2012 [1 study reported across 2
- 18 papers]; Fava 2018; Fava 2019; Ferreri 2001; Folkerts 1997; Fonagy 2015; Girlanda 2014;
- 19 GlaxoSmithKline 2009; Gulrez 2012; Haghighi 2013; Ho 2014; Hobart 2018a; Hobart 2018b;
- 20 Jahangard 2018; Joffe 1993; Kamijima 2013; Kamijima 2018; Kato 2018; Keitner 2009;
- 21 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;
- 23 Li 2013; Li 2015; Licht 2002; Lynch 2007_study 2; Mahmoud 2007; Mantani 2017; Marcus
- 24 2008; Mather 2002; McIntyre 2007; Mohamed 2017; Moica 2018; Mota-Pereira 2011; Mowla
- 25 2011; Mozaffari-Khosravi 2013; Murray 2010; Nakagawa 2017; Nakajima 2011; Nakao 2018;
- 26 Nan 2017; Navarro 2019a; Navarro 2019b; Nemets 2002; Nierenberg 2003a; Nierenberg
- 27 2006; Ostacoli 2018; Otsuka Pharmaceutical 2015; Otsuka Pharmaceutical 2016;
- Papakostas 2015; Patkar 2006; Paykel 1999/Scott 2000 [1 study reported across 2 papers];
- 29 Peet 2002; Poirier 1999; Ravindran 2008a; Reeves 2008; Reynolds 2010; Rocca 2002b;
- 30 Ruhe 2009; Rush 2006; Salehi 2016; Santos 2008; Schindler 2007; Schlogelhofer 2014;
- 31 Schramm 2007; Schweizer 1990; Schweizer 2001; Sharma 2017; Shelton 2005; Song 2007;
- 32 Souery 2011a; Souza 2016; Stein 1993; Strauss 2012; Thase 2007; Thase 2015a; Thase
- 33 2015b; Town 2017/2020; Trivedi 2006; Uebelacker 2017; Wang 2012a; Watkins 2011a;
- 34 Wiles 2008; Wiles 2013/2016; Xiao 2020; Yang 2016; Yoshimura 2014; Zhang 2016). There
- 35 was evidence for 67 comparisons.
- The included studies are summarised in Table 2 to Table 68.
- 37 See the literature search strategy in appendix B and study selection flow chart in appendix C.

38 Excluded studies

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

41 Summary of studies included in the evidence review

- 42 Summaries of the studies that were included in this review are presented in Table 2 to Table
- 43 68.

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

waitlis	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 antidepressan t Intensity: 10x 90-min sessions	Waitlist + any antidepressan t	Inadequate response: participants met inclusion criteria despite all receiving antidepress ants at baseline	Treatment length (weeks): 10 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n 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 antidepressan t Intensity: 8x 2-hour weekly sessions	Attention- placebo (psychoeduca tional control group) + any antidepressan t Intensity: 8x 2-hour weekly sessions	Inadequate response (failure to achieve remission, HAMD score≥8) to treatment with antidepress ants at adequate dosages for at least 8 weeks before study beginning	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy at: Endpoint 2-month follow-up 4-month follow-up Depression symptomatolo gy change score Discontinuatio n due to any reason	
Dozois 2009 RCT Canada	N=48 Mean age (years): 46.5 Gender (% female): 74 Ethnicity (% BME): 2	CBT individual + any antidepressan t Intensity: 15x 1-hour sessions	Waitlist + any antidepressan t	Inadequate response: participants met inclusion criteria despite all receiving antidepress ants at baseline	Treatment length (weeks): 15 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score	

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

St. d.	Domulation	Intervention	Comparison	Details of inadequate response /treatment	Comments
Study	Population II 31 (more severe)	intervention	Comparison	resistance	
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 psychotherap y (CBASP) + any antidepressan t Intensity: 16- 20 sessions	Any antidepressan t	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 antidepress ant medication according to a pharmacoth erapy algorithm	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Remission Discontinuatio n 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 antidepressan t Intensity: 24x individual sessions + 24x group sessions	Any antidepressan t	Inadequate response (HAMD score>10) to 8 weeks of prospective treatment with physician choice of SSRI	Treatment length (weeks): 24 Outcomes: Depression symptomatolo gy endpoint Remission Discontinuation due ato any reason
Nakagawa 2017 RCT Japan	N=80 Mean age (years): 40.6 Gender (% female): 36	CBT individual + any antidepressan t Intensity: 16x 50-min sessions (+4 additional	Any antidepressan t	Inadequate response: at least a minimal degree of treatment- resistant depression (Maudsley Staging	Treatment length (weeks): 16 Outcomes: • Depression symptomatolo gy at: • Endpoint

				Details of	Comments
				inadequate response	
Study	Population	Intervention	Comparison	/treatment resistance	
	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 antidepress ant 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 symptomatolo gy change score Remission at: Endpoint 3-month follow-up 6-month follow-up Response at: Endpoint 3-month follow-up Response at: Endpoint 3-month follow-up 12-month follow-up Discontinuation n due ato any reason Quality of life physical component score at: Endpoint 3-month follow-up 6-month follow-up 12-month follow-up G-month follow-up Response at: Endpoint 3-month follow-up 12-month follow-up 12-month follow-up 12-month follow-up 12-month follow-up

				Details of inadequate	Comments
				response	
Charden	Denviotion	Intomiontion	Camananiaan	/treatment	
Study Nakaa 2019	Population	Intervention	Comparison Weitliet + ony	resistance	Trootmont
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 antidepressan t Intensity: 12 online modules + 12x 45-min face-to-face sessions	Waitlist + any antidepressan t	Inadequate response: HAMD score ≥14 despite having received adequate therapy with ≥1 antidepress ant medications for at least 6 weeks as part of their routine care	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n 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 antidepressan t Intensity: 16 sessions	Any antidepressan t	Inadequate response (HAMD≥8 and BDI≥9) to antidepress ant medication for at least the previous 8 weeks, with at least 4 weeks at an adequate dose	Treatment length (weeks): 20 Outcomes: Depression symptomatolo gy at: Endpoint G-month follow-up T1-month follow-up Depression symptomatolo gy change score Remission Discontinuation due ato any reason Functional impairment at: Endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Study	Population	intervention	Companson	resistance	o 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 antidepressan t Intensity: 12x 90-min sessions	Any antidepressan t	Inadequate response: met inclusion criteria despite requirement to have been on stable antidepress ant treatment for at least 3 months	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n 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 antidepress ant medication taken at a therapeutic dose as recommend ed by the BNF and/or equivalent to 125 mg of amitriptyline for at least 8 weeks continuousl y during the current episode and within the past 2 months	Treatment length (weeks): 26 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n 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 antidepress ant medication	Treatment length (weeks): 17 Outcomes: Response

Overt a	Paradation.			Details of inadequate response /treatment	Comments
Wiles	Population Ethnicity (% BME): NR Baseline severity: BDI- II 29.21 (less severe) N=469	CBT individual	Any	for at least 6 weeks at recommend ed (BNF) doses	Discontinuation due ato any reason Treatment
2013/2016 RCT UK	Mean age (years): 49.6 Gender (% female): 72 Ethnicity (% BME): 2 Baseline severity: BDI-II 31.8 (more severe)	+ any antidepressan t Intensity: 12x 50-60min sessions (+6 sessions if judged to be clinically appropriate)	antidepressant	response (BDI-II≥14) to an adhered to, adequate dose of antidepress ant medication (based on BNF and advice from psychophar macology experts) for at least 6 weeks	length (weeks): 26 Outcomes: Depression symptomatolo gy at: Endpoint 6-month follow-up 40-month follow-up Remission at: Endpoint 6-month follow-up A0-month follow-up Response at: Endpoint 6-month follow-up Quality of life physical component score at: Endpoint 6-month follow-up Quality of life physical component score at: Endpoint 6-month follow-up Quality of life physical component score at: Endpoint 6-month follow-up Quality of life mental component score at: Endpoint 6-month follow-up

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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

cogiii	tive benaviour	ai tilei apies ve	sus augmenti	ing with count	Sening
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 psychotherap y (CBASP) + any antidepressan t (algorithm- based) Intensity: 16- 20 sessions	Brief Supportive Psychotherap y + any antidepressan t (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 antidepress ant medication according to a pharmacoth erapy algorithm	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Remission Discontinuatio n due to any reason Discontinuatio n due to side effects Functional impairment endpoint

⁹ BME: black and minority ethnic; DSM: diagnostic statistical manual; HAMD: Hamilton depression scale; MDD: major depressive disorder; RCT: randomised controlled trial

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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 Psychotherap y + any antidepressan t (algorithm- based) Intensity: 16- 20 sessions	Any antidepressan t (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 antidepress ant medication according to a pharmacoth erapy algorithm	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Remission Discontinuatio n due to any reason Discontinuatio n 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 antidepressan t Intensity: 16x 90-min sessions	Any antidepressan t	TRD: Mean 2.95 (SD=1.1) failed medication trials	Treatment length (weeks): 16 Outcomes: • Depression symptomatolo gy change score • Remission • Response

Charalter.	Donulation	Intervention	Comparison	Details of inadequate response /treatment	Comments
Study	Population Baseline severity: NR (unclear severity)	intervention	Comparison	resistance	Discontinuatio n 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 escitalopra m	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 symptomatolo gy at: Endpoint 3-month follow-up 12-month follow-up Depression symptomatolo gy 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 antidepressan t	Inadequate response to 1 trial of	Treatment length (weeks): 19

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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)	antidepressan t Intensity: 16x 40-min weekly sessions		antidepress ant medication in adequate dose (defined as the equivalent of at least 75mg of amitriptyline) and duration (at least 4 weeks)	Outcomes: Depression symptomatolo gy at: Endpoint Temorth follow-up Depression symptomatolo gy change score Remission Response Discontinuatio n 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

psyci	lodynamic psy	chotherapy vei	rsus continuin	g with antide	pressant
Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Town 2017/2020 RCT	N=60 Mean age (years): 41.6	Intensive short-term dynamic psychotherap y + any	Any antidepressan t	Inadequate response to treatment (HAMD score ≥16)	Treatment length (weeks): 26
Canada	Gender (% female): 63 Ethnicity (% BME): 3 Baseline severity: HAMD 23.77 (more severe)	antidepressan t Intensity: 20 sessions		to at least 1 trial of antidepress ants at the adequate recommend ed therapeutic dose. 34% 2 or more failed antidepress ants for current episode	Outcomes: Depression symptomatolo gy at: Endpoint 3-month follow-up 6-month follow-up 12-month follow-up Depression symptomatolo gy change score Remission at: Endpoint

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

¹ 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 psychodynami c psychotherap y (following manual by Taylor 2015) + any antidepressan t Intensity: 60x 50-min weekly sessions	Any antidepressan t	TRD: Inadequate response to least 2 different treatments (mean of 3.7 previously failed treatment attempts)	Treatment length (weeks): 78 Outcomes: Depression symptomatolo gy at: Endpoint G-month follow-up 12-month follow-up Remission at: Endpoint Sendpoint Discontinuatio n 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)

voices continuing with the antidoprocedure (17 attention placess)							
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 antidepressan t	Inadequate response: met inclusion	Treatment length (weeks): 1.4		

Chudu	Donulation.	Intervention	Compositore	Details of inadequate response /treatment resistance	Comments
Study Belgium & Netherlands	Population Gender (% female): 64 Ethnicity (% BME): NR Baseline severity: HAMD 23.19 (more severe)	Intervention antidepressan t 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 symptomatolo gy endpoint • Depression symptomatolo gy 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 antidepressan t Intensity: 10 sessions (daily over 10 days)	Attention- placebo + any antidepressan t Intensity: 10 sessions (daily over 10 days)	Inadequate response (HAMD score≥20) despite at least 6 weeks of adequate antidepress ant treatment	Treatment length (weeks): 1.4 Outcomes: Depression symptomatolo gy at: Endpoint 1-month follow-up Depression symptomatolo gy change score Discontinuatio n 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 antidepressan t Intensity: 1 monitoring session	Any antidepressan t	Inadequate response (not achieving full remission, HAMD score 10-19) to at least 1 course of a recommend ed dose of an antidepress ant medication for at least 4 weeks (the median treatment	Treatment length (weeks): 6 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n due to any reason

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				duration with antidepress ant 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 antidepress ants at an adequate dosage for at least 4 weeks	Treatment length (weeks): 9 Outcomes: • Depression symptomatolo gy endpoint • Depression symptomatolo gy change score • Remission • Response • Discontinuatio n 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	N=106 Mean age (years): 45.1	Clay art therapy + any antidepressan t	Attention- placebo (non- directive visual art	Inadequate response (BDI-II≥10) after taking	Treatment length (weeks): 6
China	,		control group)	1 or more	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 antidepressan t Intensity: 6x 2.5-hour sessions	antidepress ants at an adequate dosage for at least 4 weeks	 Depression symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n 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

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 Desensitizatio n Reprocessing (EMDR), following the DeprEnd protocol (Hofmann et al. 2016) + any antidepressan t Intensity: 12- 18 sessions	CBT individual (Beck, 1979) + any antidepressan t Intensity: 12-18 sessions	Inadequate response (BDI-II≥10) after taking 1 or more antidepress ants at an adequate dosage for at least 4 weeks	Treatment length (weeks): 13-26 Outcomes: Depression symptomatolo gy endpoint Remission at: Endpoint G-month follow-up Discontinuation due to any reason Global functioning at: Endpoint G-month follow-up		

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

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

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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 escitalopra m per day	Treatment length (weeks): 6 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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% improvemen t on HAMD) to 6 weeks of openlabel 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% improvemen t on HAMD) to 6 weeks, open-label paroxetine treatment (20 mg/day)	Treatment length (weeks): 6 Outcomes: Depressionsy mptomatology endpoint Remission Response Discontinuatio n due to any reason Discontinuatio n 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% improvemen t on HAMD) to 3-week open-label prospective treatment with fluoxetine 20mg/day. 74% previous antidepress ant 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

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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

versus switching to SNN							
Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments		
Bose 2012 RCT	N=484 Mean age	Escitalopram (dose increase)	Duloxetine 60mg/day	Inadequate response (<50%	Treatment length (weeks): 8		
US	(years): 42.3 Gender (% female): 59 Ethnicity (% BME): 22 Baseline severity: MADRS 34.8 (more severe)	20mg/day		improvement on MADRS) to 2 weeks of single-blind escitalopram (10mg/day)	Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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	N=27	Fluoxetine 40- 60mg/day	Desipramine 25-50mg/day	Inadequate response	Treatment length (weeks):
RCT	Mean age (years): NR		+ fluoxetine 20mg/day	(defined as failure to	4
US	,			achieve a 50% or	Outcomes:

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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 symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n 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 symptomatolo gy endpoint Depression symptomatolo

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: HAMD 18.3 (more severe)				gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

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 symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n 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

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% improvemen t 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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		

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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% improvemen t on MADRS) to nortriptyline (25-175mg/day; mean modal dose 104.6mg/da y) during a 7-week open-label treatment phase	Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

versus continuing same 55Ki							
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 improvemen t <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

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% improvemen t 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	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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	judgment) 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% improvemen t on MADRS) to nortriptyline (25- 175mg/day; mean modal dose 104.6mg/da y) during a 7-week open-label	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects	

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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

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% improvemen t 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy change score Remission Response		

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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/da y) 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 symptomatolo gy 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	N=189	Desipramine minimum	Citalopram minimum	Inadequate response to	Treatment length (weeks):
RCT	Mean age (years): 51.4	dose 150mg/day	dose 40mg/day	treatment with at least	4
Austria, Belgium,		(mean final dose	(mean final dose 43.06mg/day)	antidepress ant (except	Outcomes:

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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 symptomatolo gy endpoint Remission Response Discontinuatio n 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	N=112 Mean age (years): 55.5	Imipramine target plasma level 175-300 ng/mL	Mirtazapine 30mg/day + Venlafaxine 225- 300mg/day	Inadequate response (non- remission HAMD>7) to	Treatment length (weeks): 10 Outcomes:
Spain	Gender (% female): 67 Ethnicity (% BME): NR Baseline severity: HAMD 28.22 (more severe)			10 weeks of treatment with venlafaxine	 Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n 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	N=72	Mianserin 60mg/day	Fluoxetine 20mg/day	Inadequate response to	Treatment length (weeks):
RCT	Mean age (years): 46.4			previous fluoxetine	6
France	· ·			treatment after at least	Outcomes:

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

versu	versus continuing with antidepressant (+/- piacebo)							
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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects			
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% improvemen t on HAMD) to 6 weeks of openlabel treatment with sertraline	Treatment length (weeks): 5 Outcomes: Remission Response Discontinuation due to any reason			

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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

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
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% improvemen t on HAMD) to 6 weeks of openlabel 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 symptomatolo gy change score Remission

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR				ResponseDiscontinuatio n due to any reason
	severity: HAMD 27.39 (more severe)				 Discontinuatio n 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

Versu	versus continuing office at the same dose								
Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments				
Kornstein 2008 RCT	N=255 Mean age (years): 45.5	Duloxetine 120mg/day	Duloxetine 60mg/day	Inadequate response (HAMD score >7) to 5-week	Treatment length (weeks): 8				
US	Gender (% female): 61 Ethnicity (% BME): 19			prospective treatment with duloxetine 60mg/day	 Outcomes: Depression symptomatolo gy change score Remission Response 				
	Baseline severity: HAMD 14.3 (less severe)				 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	N=95	Venlafaxine extended	Paroxetine 20mg/day	TRD: Inadequate	Treatment length (weeks):
RCT	Mean age (years): NR	release 225mg/day		response to 2 or more	8
China	G ,			adequate treatments	Outcomes:

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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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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

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 monotherap y 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:		

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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 symptomatolo gy change score • Remission • Response

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: QIDS 13.2 (more severe)				Discontinuatio n 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

Switching to mirtuzupine							
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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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

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

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
GlaxoSmithKli ne 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

versu	s switching to	anotner antide	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 symptomatolo gy change score • Remission • Response • Discontinuatio n due to side effects					

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

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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

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		

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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

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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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 symptomatolo gy at: Endpoint 4-month follow-up Remission		

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: PHQ-9 12.8 (less severe)				ResponseDiscontinuatio n 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 symptomatolo gy endpoint Depression symptomatolo gy endpoint Response Remission Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ant monotherap y at maximum recommend ed or tolerated doses	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					 Discontinuatio n 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 symptomatolo gy at: Endpoint A-month follow-up Remission at: Endpoint A-month follow-up Response at endpoint Discontinuatio n 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 antidepress ant at an adequate dose for at least 6 weeks	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Remission Response Discontinuatio n due to any reason Quality of life endpoint Quality of life physical component score Quality of life mental component score

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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 symptomatolo gy endpoint Depression symptomatolo gy endpoint Response Remission Response Discontinuatio n due to any reason Discontinuatio n 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

VCISU	s switching to	iiiii tazapiiie			
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 symptomatolo gy at: Endpoint A-month follow-up Remission at: Endpoint A-month follow-up Response at endpoint

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
					 Discontinuatio n 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 symptomatolo gy endpoint Depression symptomatolo gy endpoint Response Remission Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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)

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/par oxetine CR	Placebo + paroxetine/par oxetine CR	TRD: History of failure of ≥1 adequate trial of a US FDA- approved antidepress ant 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 symptomatolo gy endpoint Depression symptomatolo gy change score Response Discontinuatio n due to any reason Discontinuatio n 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	

				Details of	Comments
				inadequate response /treatment	
Study	Population	Intervention	Comparison	resistance	
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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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 antidepress ant treatment trials with adequate dose and duration)	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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 antidepress ant treatment trials with adequate dose and duration)	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Response

				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance	
	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	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	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n due to any
Santos 2008	(more severe)	Lamotrigine	Placeho + any	sertraline)	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 antidepressan t	Placebo + any antidepressan t	TRD: Inadequate response to treatment with at least 2 antidepress ants of different classes at the maximum- tolerated dose for at least 6 weeks	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ant treatment trials of adequate dose and duration	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Response

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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 antidepress ant treatment trials of adequate dose and duration	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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 antidepress ant treatment trials of adequate dose and duration	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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 antidepressan t	Lithium target plasma level 0.6–0.8mmol/l (mean final plasma level 0.71mmol/l) + any antidepressan t	TRD: Inadequate response (<50% reduction of initial HAMD) to at least 2 trials of different classes of	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): NR Baseline severity: HAMD 22.1 (More severe)			antidepress ants for a duration of at least 6 weeks	 Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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% improvemen t in MADRS score) to 7 weeks of venlafaxine 75—375mg/day	Treatment length (weeks): 12 Outcomes: • Depression symptomatolo gy change score • Remission • Response • Discontinuatio n due to any reason • Discontinuatio n 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 symptomatolo gy change score Remission Response

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Study	Population Baseline severity: MADRS 28.53 (more severe)	Intervention	Comparison	Details of inadequate response /treatment resistance 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: Documente d history of failure to achieve a satisfactory response (based on investigator' s clinical judgement) to an antidepress ant (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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy change score Remission

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Baseline severity: NR (more severe)			response (<30% improvemen t 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% improvemen t on MADRS) to 7 weeks of nortriptyline 25- 175mg/day	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

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% improvemen t in MADRS score) to 7 weeks of	Treatment length (weeks): 12 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason			

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
				venlafaxine 75– 375mg/day	Discontinuatio n 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% improvemen t on MADRS) to 7 weeks of nortriptyline 25- 175mg/day	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

antipsychotic versus antidepressant-only or antidepressant + piacebo						
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 amtitriptylin e, bupropion, citalopram, duloxetine, escitalopra m, 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	

2				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance (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 antidepress ants (including the treatment a patient was taking at screening) for the current MDE; and insufficient response (defined as <50% improvemen t in MADRS; MADRS score ≥18; CGI-I score ≥3) to openlabel antidepress ants and double-blind augmentation during the 8 week prospective treatment phase	Treatment length (weeks): 24 Outcomes: Remission Discontinuatio n due to any reason Discontinuatio n 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 antidepress ant trials (>6 weeks duration at adequate doses) at	Treatment length (weeks): 6 Outcomes: • Remission • Response

				Details of	Comments
				inadequate	Comments
				response	
Study	Population	Intervention	Comparison	/treatment resistance	
	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-l≥3) to prospective treatment phase (8-week treatment with escitalopra m [10/20mg/d ay], fluoxetine [20/40mg/d ay], 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 antidepress ant (as defined by <50% reduction in severity of depressive symptoms- determined by the MGH ATRQ) in 1-3 antidepress ant trials of at least 6 weeks duration at	Treatment length (weeks): 6 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 escitalopra m [10/20mg/d ay], fluoxetine [20/40mg/d ay], fluoxetine [20/40mg/d ay], paroxetine CR [37.5/50mg/day; paroxetine CR [37.5/50mg/day; 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 symptomatolo gy change score • Remission • Response

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				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance	
	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 openlabel prospective treatment phase with sertraline	 Discontinuation due to any reason Discontinuation due to side effects
Durgam 2016	N=819	Cariprazine 1- 2mg/day or 2-	Placebo + SSRI/SNRI	Inadequate response	Treatment length (weeks):
RCT	Mean age (years): 45.7	4.5mg/day + SSRI/SNRI	GOIN/GIVIN	during the current	8
US & Europe	Gender (% female): 71 Ethnicity (%			episode to antidepress ant treatment for at least 6 weeks at	Outcomes: • Depression symptomatolo gy change score
	BME): 13			recommend ed doses	RemissionResponseDiscontinuatio
	severity: MADRS 29.1				n due to any reason
	(more severe)				 Discontinuation n due to side effects
					 Functional impairment change score
Earley 2018	N=527	Cariprazine 1.5-4.5mg/day	Placebo + any antidepressan	TRD: previously	Treatment length (weeks):
RCT	Mean age (years): 44.0	+ any antidepressan	t t	failed to respond to	8
US	() - /	t		1 or 2 adequate	Outcomes:
	Gender (% female): 65			antidepress ant trials, and	 Depression symptomatolo gy change score
	Ethnicity (% BME): 28			inadequate response	• Remission

				Details of	Comments
				inadequate	
				response /treatment	
Study	Population	Intervention	Comparison	resistance	
Otady	1 opaiation	intervention	Companison		- Doonongo
	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 antidepress ant	 Response Discontinuation due to any reason Discontinuation due to side effects
				treatment	
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 antidepress ants: amitriptyline , bupropion, citalopram, duloxetine, escitalopra m, 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	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
Study Fang 2011 RCT China	Population 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	resistance TRD: Inadequate response to ≥2 adequate treatments from different classes of antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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 antidepress ant trials with an adequate dose of SSRIs/SNRIs during the current episode for ≥8 weeks	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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:

				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance	
	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% improvemen t in HAMD, HAMD score >14, or CGI-I score ≥3) to 8-week prospective open-label antidepress ant treatment phase	 Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects
Fava 2019	N=207	Pimavanserin	Placebo + SSRI/SNRI	Inadequate	Treatment
RCT	Mean age (years): NR Gender (% female): 73 Ethnicity (% BME): 28 Baseline severity: HAMD 22.23 (more severe)	34mg/day + SSRI/SNRI	JORI/JINKI	response to 1 or 2 antidepress ant treatments (including SSRI/SNRI) during the current depression episode	length (weeks): 5 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy change score

				Details of	Comments
				inadequate response	
Study	Population	Intervention	Comparison	/treatment resistance	
	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% improvemen t in HAMD and MADRS, HAMD score >14, and CGI-I score ≥3) to 8-week prospective open-label antidepress ant 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 antidepress ants 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

				Details of inadequate response	Comments
Study	Population	Intervention	Comparison	/treatment resistance	
				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 antidepress ant 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 antidepress ant 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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	Treatment length (weeks): 6
				antidepress ant	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 antidepress ant 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ant monotherap y (the particular antidepress ant 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

				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance	
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 antidepress ant trial during the present episode	Treatment length (weeks): 12 Outcomes: Remission Discontinuatio n 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 (antidepressa nt switch)	Venlafaxine 225mg/day (antidepressa nt switch)	TRD: Inadequate response (<50% reduction of initial HAMD and HAMD score ≥20) to ≥2 different antidepress ant therapies with clinically-appropriate dosage and time-course	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects
Mahmoud 2007 RCT US	N=274 Mean age (years): 46.1 Gender (% female): 74	Risperidone 0.25-2mg/day + any antidepressan t	Placebo + any antidepressan t	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
Study	Ethnicity (% BME): 24 Baseline severity: HAMD 24.6 (more severe)	mervention	Comparison	score≥20) to a 4-week prospective open-label run-in period with current antidepress ant monotherap y at the dosages recommend ed in product labelling	 Depression symptomatolo gy endpoint Remission Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ant 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

Otrodo.	Paradatian	Indonesia in	O	Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	8-week single-blind prospective treatment phase with standard antidepress ant 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/venlaf axine 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 antidepress ant 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 symptomatolo gy endpoint Depression symptomatolo gy change score
Otsuka Pharmaceutic al 2015 RCT US	N=372 Mean age (years): 43.5 Gender (% female): 68	Brexpiprazole 1-3mg/day + any antidepressan t	Placebo + any antidepressan t	TRD: history for the current depressive episode of an inadequate response to 1-3 adequate	Treatment length (weeks): 6 Outcomes: • Depression symptomatolo gy change score

				Details of inadequate response /treatment	Comments
Study	Population	Intervention	Comparison	resistance	
	Ethnicity (% BME): NR Baseline severity: NR (unclear severity)			antidepress ant treatments; incomplete response to prospective open-label treatment with commerciall y available antidepress ant for 8 weeks at maximally tolerated doses	 Remission Response Discontinuation due to any reason Discontinuation due to side effects Functional impairment change score
Otsuka Pharmaceutic al 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 antidepress ant treatments; incomplete response to prospective open-label treatment with a commerciall y available antidepress ant for 8 weeks at maximally tolerated doses	Treatment length (weeks): 6 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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 symptomatolo gy change score Remission

				Details of inadequate response	Comments
Study	Population	Intervention	Comparison	/treatment resistance	
	Baseline severity: HAMD 20 (more severe)			phase of escitalopra m treatment. Mean number of past unsuccessf ul trials of antidepress ants 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 antidepressan t	Placebo + any antidepressan t	Inadequate response to 1-2 antidepress ants for 3 or more weeks	Treatment length (weeks): 8 Outcomes: Depression symptomatolo gy change score Response Discontinuatio n due to any reason Discontinuatio n 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 antidepress ants at adequate dose	Treatment length (weeks): 6 Outcomes: • Depression symptomatolo gy endpoint
Thase 2007 RCT	N=406 Mean age (years): 44.5	Olanzapine 6, 12 or 18mg/day +	Fluoxetine 50mg/day	TRD: Documente d history of failure to achieve a	Treatment length (weeks): 8

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				Details of inadequate	Comments
				response	
Study	Population	Intonvention	Composicon	/treatment	
Study US & Canada	Population	Intervention fluoxetine	Comparison	resistance satisfactory	Outcomes:
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 antidepress ant (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	Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects Quality of life physical component score Quality of life mental component score
Thase 2015a	N=379	Brexpiprazole	Placebo +	lead-in Inadequate	Treatment
RCT US, Poland, France, & Slovakia	Mean age (years): 44.7 Gender (% female): 70 Ethnicity (% BME): 13 Baseline severity: MADRS 26.85 (more severe)	0.5-2mg/day + SSRI/SNRI	SSRI/SNRI	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 antidepress ants including the most recent drug treatment. During the current episode, 82% had 1 prior antidepress ant failure	length (weeks): 6 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects Functional impairment score

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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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n due to side effects

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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

antipsychotic versus ittilium							
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		

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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	Discontinuatio n 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 antidepressan t	Lithium 600mg/day (target plasma levels 0.8–1.2 mmol/L) + any antidepressan t	Inadequate response after 4 weeks of treatment with an antidepress ant at the maximal recommend ed 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	N=459	Quetiapine extended-	Quetiapine monotherapy	Stage I (failure to	Treatment length (weeks):
RCT	Mean age (years): NR	release (XR) 200- 300mg/day + SSRI/SNRI	200- 300mg/day	achieve remission after ≥1 adequate	6 Outcomes:

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Otrodo.	Paradetian	ludamandian	O-maria an	Details of inadequate response /treatment	Comments
Australia, Austria, Belgium, Bulgaria, Germany, Hungary, Italy, Portugal, Romania, Slovakia, Spain & UK	Population Gender (% female): NR Ethnicity (% BME): NR Baseline severity: MADRS 33.45 (more severe)	Intervention	Comparison	resistance trial of 1 major class of antidepress ants) or stage II (failure of adequate trials of 2 different classes of antidepress ants) 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: Documente d history of failure to achieve a satisfactory response (based on investigator' s clinical judgement) to an antidepress ant (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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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

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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 (%	Buspirone 20- 60mg/day + citalopram or fluoxetine	Placebo + citalopram or fluoxetine	Inadequate response (as judged by the psychiatrist in charge of	Treatment length (weeks): 6 Outcomes: Response
Filliand	female): 63 Ethnicity (% BME): NR			treatment) to ≥ 6 weeks of treatment with fluoxetine (at a dose of	• Response

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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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants 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):

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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 symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n 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

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)	Methylphenid ate extended release formulation 18-54mg/day + any antidepressan t	Placebo + any antidepressan t	Inadequate response to ≥1 antidepress ant at study entry, defined as ≥ 6-week trial of an antidepress ant at an acceptable therapeutic dose. 70% had failed multiple antidepress ant trials for the current MDD episode	Treatment length (weeks): 4 Outcomes: • Remission • Response • Discontinuatio n due to side effects		
Ravindran 2008a RCT Canada	N=145 Mean age (years): 43.8 Gender (% female): 65	Methylphenid ate extended release formulation 18-54mg/day + any antidepressan t	Placebo + any antidepressan t	Inadequate response to 1-3 previous antidepress ant monotherap ies (including current AD	Treatment length (weeks): 5 Outcomes: Depression symptomatolo gy change score		

Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	Ethnicity (% BME): 2 Baseline severity: MADRS 26.7 (more severe)			antidepress ant of adequate dose and duration and at entry were taking an adequate dose of an antidepress ant 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)

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 (improveme nt<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 antidepressan t	TRD: Inadequate response to ≥2 antidepress ants given sequentially at an adequate dose for an adequate time for the current	Treatment length (weeks): 52 Outcomes: • Depression symptomatolo gy change score • Discontinuatio n due to any reason	

Otrodo.	Paradetian		O	Details of inadequate response /treatment	Comments
Study	Population Baseline severity: QIDS 18.3 (more severe)	Intervention antidepressan t	Comparison	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 hydrochlorid e (90%) or imipramine hydrochlorid e (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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 antidepress ants 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 improvemen t) to treatment with ≥3 weeks of TCA at an adequate dose	Treatment length (weeks): 3 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
	MADRS 29.9 (more severe)				 Discontinuatio n due to any reason Discontinuatio n 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

10.00	5 Switch to ant	.poyonono			
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 antidepress ant) or stage II (failure of adequate trials of 2 different classes of antidepress ant) 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:

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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 antidepress ant medications (moclobemi de, paroxetine, sertraline, or venlafaxine) to maximum tolerated doses for 8- 14 weeks	Depression symptomatolo gy at: Endpoint 1-month follow-up Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n 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

versu	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% improvemen t in HAMD score and HAMD≥10) to 8 weeks of fluoxetine 20mg/day	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n 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 (%			t in HAMD score and	Outcomes: • Depression
	female): NR			HAMD≥10) to 8 weeks	symptomatolo gy endpoint
	Ethnicity (% BME): NR			of fluoxetine 20mg/day	 Depression symptomatolo gy change score
	severity:				 Remission
	HAMD 16.75 (more severe)				 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

ratty acids versus piacebo							
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 symptomatolo gy endpoint Depression symptomatolo gy change score Discontinuatio n due to any reason Discontinuatio n due to side effects Sleeping difficulties endpoint		
Mozaffari- Khosravi 2013 RCT Iran	N=81 Mean age (years): 35.1 Gender (% female): 61	Eicosapentae noic acid (EPA) or docosahexae noic acid (DHA) 1 g/day + any antidepressan t	Placebo + any antidepressan t	Inadequate response to current antidepress ant treatment (met DSM- IV criteria for MDD	Treatment length (weeks): 12 Outcomes: • Depression symptomatolo gy 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 antidepress ant treatment: 3.9 months)	 Depression symptomatolo gy change score Remission Response Discontinuatio n due to any reason Discontinuatio n 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)	Eicosapentae noic 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 symptomatolo gy endpoint Depression symptomatolo gy endpoint Response Response Discontinuatio n due to any reason Discontinuatio n 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- eicosapemtae noate 1g/day, 2g/day or 4g/day + any antidepressan t	Placebo + any antidepressan t	Inadequate response (HAMD≥15) to ongoing treatment with antidepress ant 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)

hormone versus continuing with antidepressant (+/- placebo)							
Churchy	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments		
Study	Population				T ()		
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 antidepress ants in the current depressive episode (adequate dosages of antidepress ants with ≥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		
lo#e 4000	N-22	Liathuranina	Diagona	Paroxetine 1-week lead-in	Tractment		
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 (triiodothyroni ne, T3) 37.5µg + desipramine/imipramine	Placebo + desipramine/ imipramine	Inadequate response (HAMD≥16) to a previous adequate trial of desipramine hydrochlorid e (90%) or imipramine hydrochlorid e (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n due to side effects		

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

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

normone versus augmenting with numum							
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 (triiodothyroni ne, 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 hydrochlorid e (90%) or imipramine hydrochlorid e (10%) ≥5 weeks	Treatment length (weeks): 2 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Discontinuatio n due to any reason Discontinuatio n 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 antidepressan t	Lithium 225- 900mg/day + any antidepressan t	TRD: Inadequate response (not achieved remission or who were intolerant) to an initial prospective treatment with citalopram and a second switch or augmentatio n trial	Treatment length (weeks): 14 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission Response Discontinuatio n 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

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

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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 antidepress ants (including ≥1 TCA) over a total period of 8 weeks	Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Response Discontinuatio n due to any reason Discontinuatio n 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

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Study	Population	Intervention	Comparison	Details of inadequate response /treatment resistance	Comments
Haghighi 201 RCT Iran	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 recommend ed by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score

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

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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 recommend ed by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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

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 recommend ed by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy change score Remission		

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

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

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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 antidepress ants, of at least 6 weeks duration	Treatment length (weeks): 10 Outcomes: Depression symptomatolo gy change score Remission Response Discontinuatio n 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 antidepressan t Intensity: 15x thrice-weekly 40-min sessions	Any antidepressan t	Inadequate response: met inclusion criteria despite being on antidepress ant at baseline	Treatment length (weeks): 3 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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	N=73 Mean age	Tai Chi + escitalopram 10-20mg/day	Attention- placebo (health education) +	Inadequate response to 4 weeks prospective	Treatment length (weeks): 10
US	(years): 70.6 Gender (% female): 62	Intensity: 10x 2-hour sessions	escitalopram 10-20mg/day	treatment with escitalopra m	Outcomes: • Depression symptomatolo gy 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 antidepressan t Intensity: 20x twice-weekly 45-min sessions	Attention- placebo (health education talks) + any antidepressan t Intensity: 20x twice-weekly 30-40 min sessions	Inadequate response: all participants had been in receipt of a therapeutic dose of antidepress ant 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 antidepressan t Intensity: 60 sessions/12x 30-45min sessions supervised	Attention- placebo (social interaction with study staff and peers) + any antidepressan t 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 symptomatolo gy change score Remission Response Discontinuatio n due to any reason Global functioning change score

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

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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 recommend ed by 2 independent psychiatrists	Treatment length (weeks): 4 Outcomes: Depression symptomatolo gy endpoint Depression symptomatolo gy 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)

continuing with antidepressant (+/- waithst 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 antidepressan t Intensity: 12 sessions	Waitlist + any antidepressan t	Inadequate response: met inclusion criteria despite having received a stable dose of antidepress ant treatment for at least 8 weeks	Treatment length (weeks): 8 Outcomes: • Depression symptomatolo gy change score • Remission • Response • Discontinuatio n due to any reason
Uebelacker 2017 RCT US	N=122 Mean age (years): 46.5 Gender (% female): 84	Hatha yoga group + any antidepressan t Intensity: 10- 20x 80-min sessions	Attention- placebo (health living workshop) + any antidepressan t	Inadequate response: met inclusion criteria despite currently taking an antidepress ant 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 demonstrat ed effectivenes s 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

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- 4 See the full evidence tables in appendix D and the forest plots in appendix E.
- 5 Quality assessment of studies included in the evidence review
- 6 See the evidence profiles in appendix F.

7 Economic evidence

8 Included studies

- 9 A single economic search was undertaken for all topics included in the scope of this
- 10 guideline. See the literature search strategy in appendix B and economic study selection flow
- 11 chart in appendix G. Details on the hierarchy of inclusion criteria for economic studies are
- 12 provided in supplement 1 (methods supplement).
- 13 The systematic search of the economic literature identified 3 UK studies that assessed the
- 14 cost-effectiveness of psychological interventions (Hollinghurst 2014, Phillips 2014, Scott
- 15 2003), 3 UK studies that assessed the cost-effectiveness of pharmacological interventions
- 16 (Benedict 2010, Edwards 2013, Kessler 2018a/2018b) and 1 UK study that assessed the
- 17 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
- 20 2017/2020) that assessed the cost-effectiveness of short term psychodynamic
- 21 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
- 23 2018) that assessed the cost effectiveness of pharmacological interventions, and 1 US study
- 24 (Ross 2018) that assessed the cost-effectiveness of ECT in adults with depression that failed
- 25 to respond to previous treatment were also included in the review, because they assessed
- 26 interventions or made comparisons that had not been covered in UK studies.
- 27 Economic evidence tables are provided in appendix H. Economic evidence profiles are
- shown in appendix I.

1 Excluded studies

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

4 Summary of studies included in the economic evidence review

5 Computerised cognitive behavioural therapy with support following inadequate

6 response to antidepressants

- 7 Phillips 2014 undertook an economic analysis alongside a RCT (N=637; for the clinical
- 8 analysis, completion was 56% at 6 weeks and 36% at 12 weeks; for the cost analysis,
- 9 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
- 11 with depression, who were already under psychotropic medication, in the UK. The
- 12 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,
- 14 counsellor, occupational health providers, other providers) and medication. The outcome
- 15 measures were the change in Work and Social Adjustment Scale (WSAS) scores and the
- 16 QALY, estimated based on EQ-5D (UK tariff). The time horizon of the analysis was 12 weeks
- 17 for the outcomes and 6 weeks for costs.
- 18 The time horizon of the analysis was very short and different for costs and outcomes, with
- 19 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
- 21 characterised by inadequate reporting of results; no incremental analysis was conducted
- 22 (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
- 26 not further considered when formulating recommendations.

27 Cognitive therapy or cognitive behavioural therapy in addition to antidepressants

28 versus antidepressants alone

- 29 Scott 2003 conducted a cost effectiveness analysis alongside a RCT (Paykel1999/Scott
- 30 2000; N=158) that compared cognitive therapy in addition to antidepressant therapy and
- 31 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
- 33 months, and who had residual symptoms over at least 8 weeks (HAMD \geq 8 and BDI \geq 9). The
- perspective of the analysis was that of the NHS and personal social services (PSS).
- 35 Healthcare cost elements consisted of interventions (cognitive therapy, medication, clinical
- 36 management), inpatient care, day hospital, staff time (GP, social worker, community
- 37 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
- 39 prevented. The duration of the analysis was 17 months.
- 40 Cognitive therapy in addition to antidepressants and clinical management was significantly
- 41 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
- 43 (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
- 45 conducted. The probability of cognitive therapy in addition to antidepressant being cost-
- 46 effective was 0.60 and 0.80 at a willingness to pay (WTP) of £10,500 and £15,000 per
- 47 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
- 49 not use the QALY as the measure of outcome and interpretation of the results requires

Further-line treatment

- 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.
- 3 Hollinghurst 2014 conducted a cost consequence and cost-utility analysis alongside a RCT
- 4 (Wiles 2013/2016; N=469) to assess the cost effectiveness of cognitive behavioural therapy
- 5 (CBT) in addition to TAU versus TAU alone, in adults with major depression who had
- 6 adhered to antidepressant medication for at least 6 weeks in primary care, but who continued
- 7 to have significant depressive symptoms (BDI-II score ≥14 and ICD-10 diagnosis of
- 8 depression), in the UK; TAU comprised GP care, including antidepressant treatment as
- 9 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
- 11 cost-utility analysis was that of the NHS and PSS, with cost elements comprising intervention
- 12 (CBT), medication, primary and community mental and general health care, and specialist
- 13 (secondary) mental health care. National unit costs were used. A number of outcomes were
- 14 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-
- 16 6D ratings being used for the estimation of QALYs in a sensitivity analysis.
- 17 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
- 19 SF-12 mental sub-scale score and the QALY, both at 12 months and at the 3-5 year follow
- 20 up. At 12 months, the ICER of CBT plus TAU versus TAU alone was £17,639/QALY (2020
- 21 prices). The probability of CBT being cost-effective was 0.74 and 0.91 at the NICE lower and
- 22 upper cost effectiveness threshold of £20,000 and £30,000/QALY, respectively. Results were
- 23 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
- 30 directly applicable to the NICE decision-making context and is characterised by minor
- 31 limitations.

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Intensive short-term psychodynamic psychotherapy

- Town 2017/2020 assessed the cost-utility of intensive short-term psychodynamic
- 34 psychotherapy versus secondary care TAU, comprising community mental health teams
- delivering pharmacotherapy and clinical management, supportive or structured activities
- 36 focused around symptom management and in some cases individual or group
- 37 psychotherapy, in adults with depression who were non-remitting following at least one
- 38 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
- 41 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
- 44 £15,000/QALY was 0.65. Therefore the study was not further considered when formulating
- 45 recommendations.

Mirtazapine as an adjunct treatment to SSRIs or SNRIs

- 47 Kessler 2018a/2018b undertook a cost-utility analysis alongside a RCT (Kessler
- 48 2018a/2018b; N=480, with 75% of cost and effectiveness data available for the economic
- 49 analysis) to assess the cost effectiveness of mirtazapine added to a SSRI or SNRs versus
- 50 pill placebo added to a SSRI or SNRI, in adults with major depression who had used an
- 51 SSRI or SNRI for at least six weeks but were still depressed, in the UK. The time horizon of

- 1 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
- 4 care (e.g. GP or nurse contacts, CBT, counselling or other talking therapies, mental health
- 5 clinic, prescribed exercise programmes, NHS Direct, NHS walk-in centres), personal social
- 6 services (mental health nurse home visits, occupational therapy, social worker, day centre
- 7 use, etc.) National unit costs were used. The primary measure of outcome was the QALY,
- 8 estimating using the 5-level EQ-5D (UK tariff).
- 9 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
- 15 characterised by minor limitations.

28

16 Continuation of current pharmacological treatment (citalopram) versus switching to 17 another antidepressant (venlafaxine, sertraline) or augmentation with bupropion

- 18 Olgiati 2013 compared the cost-effectiveness of different strategies for adults with
- depression that did not remit following pharmacological treatment (citalogram), comprising
- 20 continuation of current treatment (citalogram), switching to sertraline or venlafaxine, or
- 21 augmentation of citalogram with bupropion in the US. The study reported that both switching
- and augmentation strategies were more cost-effective than continuation of current treatment
- with citalogram. However, efficacy data for the 3 strategies were taken from different studies
- 24 without using a common comparator, thus breaking randomisation rules. The study is
- 25 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

- 29 Soini 2017 assessed the relative cost-effectiveness of a number of antidepressants
- 30 (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
- 32 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
- 36 source of efficacy data for the 3 interventions of interest was a RCT (Rush 2006; n=727 at
- 37 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.
- 39 According to the results, sertraline was dominated by both venlafaxine and bupropion.
- 40 Bupropion was more effective and more costly than venlafaxine, with an ICER of
- 41 £2,249/QALY in 2020 prices. The study is partially applicable to the UK as it was conducted
- 42 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
- 45 this guideline (and thus were not of interest) and assessed uncertainty, in the form of
- 46 probability of cost-effectiveness, after making pairwise comparisons (so that vortioxetine was
- 47 compared with one intervention at a time); therefore, it was not possible to extract the
- 48 uncertainty associated with the 3 interventions of interest (in terms of probability of cost-
- 49 effectiveness of each intervention out of the 3) from the study.

- 1 Singh 2017 assessed the relative cost-effectiveness of sertraline, venlafaxine and bupriopion
- 2 for adults with depression that required further treatment after inadequate response to
- 3 previous treatment with SSRIs. The study was conducted alongside a RCT (Rush 2006;
- 4 n=727) and was conducted from the perspective of the US government as a payer. Costs
- 5 included medication, outpatient and A&E visits, as well as hospitalisation. National unit costs
- 6 were used. Two measures of outcome were used: response and remission. The time horizon
- 7 of the analysis was 9 weeks.
- 8 According to the results, there were no statistically significant differences in costs or in
- 9 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
- 12 highest net health benefit in terms of remission and a probability of being the most cost-
- 13 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
- 16 horizon.

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Duloxetine versus venlafaxine versus mirtazapine following inadequate response to

18 previous SSRI treatment

- 19 Benedict 2010 constructed an economic model to evaluate the cost effectiveness of
- 20 duloxetine, venlafaxine and mirtazapine in adults with severe major depression who failed
- 21 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).
- 26 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
- 28 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-
- 30 making context, it is characterised by potentially serious limitations, including the methods for
- 31 meta-analysis and evidence synthesis (selective use of RCTs and synthesis that appears to
- 32 have potentially broken randomisation) and the fact that it was funded by industry, which may
- 33 have introduced bias in the analysis.

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

36 Nordström 2010 developed an economic model to evaluate the cost effectiveness of

37 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,

42 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

45 remission (defined as a MADRS total score ≤ 12) achieved after 8 weeks of treatment and

46 sustained until the end of 6 months; and the QALY estimated based on EQ-5D ratings (UK

47 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

49 duloxetine and venlafaxine were pooled together. Considering only healthcare costs,

50 escitalopram was found to dominate both duloxetine and venlafaxine and to have a

51 probability of being cost-effective of more than 0.98 at the NICE lower cost effectiveness

52 threshold of £20,000/QALY. The study is only partially applicable to the NICE decision-

- 1 making context and is characterised by potentially serious limitations, including the methods
- 2 for evidence synthesis (selective use of RCTs and data pooling for two of the assessed
- 3 interventions) and the fact that it was funded by industry, which may have introduced bias in
- 4 the analysis.
- 5 Generic SSRIs (citalopram, fluoxetine, paroxetine) versus escitalopram versus
- 6 paroxetine controlled release versus sertraline versus venlafaxine following
- 7 inadequate response to previous SSRI treatment
- 8 Malone 2007 compared different SSRIs (including escitalopram, paroxetine controlled
- 9 release, sertraline and venlafaxine) in adults with major depression who failed to achieve
- 10 remission with previous treatment with SSRIs in the US. Efficacy estimates were based on a
- 11 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
- 13 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
- 17 context and is characterised by very serious limitations. Therefore, it has not been
- 18 considered further when formulating recommendations.

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

- 20 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
- 22 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
- 24 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
- 29 people with treatment-resistant depression and 1 RCT comparing lithium plus fluoxetine
- 30 versus fluoxetine alone in people who had failed at least one antidepressant; a common
- 31 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
- 33 not from people with treatment-resistant depression) due to lack of more relevant data. In
- 34 order to estimate the effect of each intervention, a fixed baseline MADRS score was
- 35 assumed for both arms; the change in MADRS scores at endpoint was assumed to have a
- 36 normal distribution, which was used to estimate proportions of people in the remission,
- 37 response and no response states.
- 38 Resource use estimates were mainly based on clinical expert opinion, with the exception of
- 39 the length of hospitalisation, which was based on national hospital episode statistics. In order
- 40 to estimate medication costs in each arm of the model, it was assumed, based on expert
- 41 advice, that antipsychotic use comprised 30% aripiprazole, 30% olanzapine, 20% quetiapine,
- 42 and 20% risperidone; and SSRI use comprised 20% citalogram, 20% escitalogram, 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
- 45 analysis was 12 months.
- 46 Augmentation of SSRIs with lithium was found to dominate augmentation of SSRIs with an
- 47 atypical antipsychotic; the probability of lithium being dominant versus antipsychotics (both
- 48 as adjuncts to an SSRI) was 1. Results were sensitive to the efficacy of augmentation
- 49 strategies and discontinuation rates; they were robust under different assumptions regarding
- 50 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,

- 1 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
- 3 baseline and endpoint MADRS scores, and the fact that all resource use was based on
- 4 expert opinion.

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

- 7 Yoon 2018 assessed the cost-effectiveness of aripiprazole adjunct to an antidepressant
- 8 versus bupropion adjunct to an antidepressant versus switching to bupropion in adult
- 9 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
- 11 conducted alongside a RCT (Mohamed 2017; N=1522, completers n=1131). The study used
- 12 a healthcare perspective and included medication and mental health (inpatient, outpatient)
- 13 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
- 17 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
- 20 outcome, switching to bupropion was dominated by bupropion adjunct. The ICER of
- 21 aripiprazole adjunct vs bupropion adjunct was £3,791/ remission (2020 prices). Using the
- 22 QALY as the outcome, the ICER of aripiprazole adjunct vs bupropion switch was
- 23 £348,428/QALY; the ICER of bupropion switch vs bupropion adjunct was £21,614/QALY. At
- 24 a cost-effectiveness threshold of £15,000/remission, the probability of cost-effectiveness was
- 25 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
- 27 characterised by potentially serious limitations, including its short time horizon, the unclear
- 28 method of estimation of QALYs from EQ-5D, and the potential conflicts of interest due to
- 29 relations with pharmaceutical industry.

Various antipsychotics adjunct to antidepressants versus antidepressant treatment alone

- Taneja 2012 compared the cost-effectiveness of different antipsychotics (aripiprazole,
- 33 quetiapine and olanzapine) as adjuncts to antidepressants versus antidepressant treatment
- 34 alone, in adults with major depression who had responded inadequately to previous
- antidepressant therapy in the US, from a healthcare perspective, using decision-analytic
- 36 modellling. The measure of outcome was response. Efficacy data were derived from a meta-
- 37 analysis of published phase III clinical trials and indirect comparison using placebo as
- 38 baseline comparator. The time horizon was too short (only 6 weeks) to allow assessment of
- 39 the cost effectiveness of interventions over the duration of the depressive episode; moreover,
- 40 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
- 42 limitations (as the time horizon was not adequate to measure effects) and was therefore not
- 43 considered further.
- 44 Sussman 2017 also compared the cost-effectiveness of different antipsychotics
- 45 (brexpiprazole, quetiapine 150 and 300mg/day, olanzapine/fluoxetine) as adjuncts to
- antidepressants versus antidepressant treatment alone, in adults with major depression who
- 47 had responded inadequately to previous antidepressant therapy in the US, from a payer's
- 48 perspective, using decision-analytic modelling. The measures of outcome were response
- and remission. Efficacy data were derived from various trials and meta-analyses, using
- 50 indirect comparisons for evidence synthesis. The time horizon was 48 weeks. The study
- 51 found that guetiapine was dominated by olanzapine/fluoxetine. Brexpiprazole was the most

- 1 effective and most costly intervention. Its ICER versus olanzapine/fluoxetine was
- 2 £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
- 4 partially applicable to the UK context and is characterised by potentially serious limitations,
- 5 mainly that is was funded by industry, which may have introduced bias in the analysis.

6 ECT versus TCAs, SSRIs, SNRIs and lithium augmentation

- 7 Greenhalgh 2005 developed an economic model to assess the cost effectiveness of
- 8 electroconvulsive therapy (ECT) compared with various pharmacological treatments such as
- 9 TCAs, SSRIs, SNRIs and lithium augmentation in adults with major depressive disorder who
- 10 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
- 12 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).
- 17 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,
- 20 psychiatrist and psychiatric nurse). Resource use data were based on published literature
- 21 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.
- 24 The most effective and cost-effective strategy appeared to be a sequence of ECT SSRI –
- 25 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
- 27 were modestly sensitive to use of alternative utility values and robust to small changes in
- 28 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
- 30 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.
- 32 Ross 2018 also constructed an economic model to assess the cost effectiveness of ECT
- 33 being used as 1st-6th line treatment following 0-5 lines of pharmacological and/or
- 34 psychological treatment, compared with no ECT (antidepressants and/or psychological
- 35 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
- 37 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
- 40 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
- 44 generation of QALYs was not consistent with NICE recommendations and is characterised
- 45 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
- 47 available data was undertaken. Therefore this study was not considered further.

48 Economic model

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

1 Evidence statements

2 Clinical evidence statements

- 3 Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus 4 continuing with antidepressant (+/ waitlist or attention-placebo)
- 5 Critical outcomes:

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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

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- 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 antidepressantsonly 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

16 Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus 17 augmenting with counselling

18 Critical outcomes:

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19 **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

33 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

1 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

8 Important outcomes:

9 Quality of life

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10 No evidence was identified for this outcome.

11 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

18 Comparison 3. Augmenting with counselling versus continuing with antidepressant

19 Critical outcomes:

20 **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

3 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

10 Important outcomes:

11 Quality of life

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12 No evidence was identified for this outcome.

13 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

20 Comparison 4. Augmenting with IPT versus continuing with antidepressant

21 Critical outcomes:

22 **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

1 Remission

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 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

7 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

18 Discontinuation due to side effects

- 19 No evidence was identified for this outcome.
- 20 Important outcomes:
- 21 Quality of life
- No evidence was identified for this outcome.

23 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

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

36 Critical outcomes:

37 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

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- 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.
- 36 **Important outcomes:**
- 37 Quality of life
- 38 No evidence was identified for this outcome.
- 39 Personal, social, and occupational functioning
- 40 No evidence was identified for this outcome.

1 Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus 2 continuing with antidepressant

3 Critical outcomes:

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4 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 longterm 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

22 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

33 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 longterm 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

1 Important outcomes:

2 Quality of life

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- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.

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

9 Critical outcomes:

10 **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

29 Remission

30 No evidence was identified for this outcome.

31 Response

32 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

1 Important outcomes:

- 2 Quality of life
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 8. Augmenting with self-help and switching to SSRI versus switching to 7 SSRI-only
- 8 Critical outcomes:

9 **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

16 Remission

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 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

22 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.
- 35 **Important outcomes:**
- 36 Quality of life
- No evidence was identified for this outcome.

1 Personal, social, and occupational functioning

- 2 No evidence was identified for this outcome.
- 3 Comparison 9. Augmenting with art therapy versus attention-placebo
- 4 Critical outcomes:
- 5 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
- 12 Remission

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- No evidence was identified for this outcome.
- 14 Response
- No evidence was identified for this outcome.
- 16 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
- 21 Discontinuation due to side effects
- No evidence was identified for this outcome.
- 23 Important outcomes:
- 24 Quality of life
- No evidence was identified for this outcome.
- 26 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 28 Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR)
- 29 versus augmenting with cognitive behavioural therapy
- 30 Critical outcomes:
- 31 **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

3 Remission

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- 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

16 Response

17 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

23 Discontinuation due to side effects

No evidence was identified for this outcome.

25 **Important outcomes:**

26 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

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

36 Critical outcomes:

37 **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

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39 40 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

21 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

41 Personal, social, and occupational functioning

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

2 Critical outcomes:

3 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

13 Remission

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 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

18 **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

23 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

33 Important outcomes:

34 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

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

2 Critical outcomes:

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3 **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

20 Response

21 No evidence was identified for this outcome.

22 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

27 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:

33 Quality of life

No evidence was identified for this outcome.

35 Personal, social, and occupational functioning

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

2 Critical outcomes:

3 **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

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• 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

14 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

32 Important outcomes:

33 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

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

6 Critical outcomes:

7 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

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29 30 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

19 Response

20 No evidence was identified for this outcome.

21 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

26 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

31 **Important outcomes:**

- 32 Quality of life
- No evidence was identified for this outcome.
- 34 Personal, social, and occupational functioning
- 35 No evidence was identified for this outcome

1 Comparison 16. Switching to SSRI versus continuing with antidepressant

2 Critical outcomes:

3 **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

10 Remission

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 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

16 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:

35 Quality of life

36 No evidence was identified for this outcome.

Personal, social, and occupational functioning

38 No evidence was identified for this outcome.

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

- 2 Critical outcomes:
- 3 Depression symptomatology
- 4 No evidence was identified for this outcome.
- 5 Remission

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- 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
- 10 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
- 15 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
- 20 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
- 26 Important outcomes:
- 27 Quality of life
- No evidence was identified for this outcome.
- 29 Personal, social, and occupational functioning
- 30 No evidence was identified for this outcome.
- 31 Comparison 18. Switching to SSRI versus antipsychotic
- 32 Critical outcomes:
- 33 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

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

Remission

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 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

21 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

26 **Important outcomes**:

- 27 Quality of life
- No evidence was identified for this outcome.
- 29 Personal, social, and occupational functioning
- 30 No evidence was identified for this outcome.

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

34 Critical outcomes:

35 **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

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 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

9 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

29 Important outcomes:

30 Quality of life

31 No evidence was identified for this outcome.

32 Personal, social, and occupational functioning

No evidence was identified for this outcome.

35 Comparison 20. Augmenting with SSRI versus augmenting with lithium

36 Critical outcomes:

37 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

4 Remission

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- 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
- 9 Response
- 10 No evidence was identified for this outcome.
- 11 Discontinuation due to any reason
- 12 No evidence was identified for this outcome.
- 13 Discontinuation due to side effects
- 14 No evidence was identified for this outcome.
- 15 **Important outcomes:**
- 16 Quality of life
- 17 No evidence was identified for this outcome.
- 18 Personal, social, and occupational functioning
- 19 No evidence was identified for this outcome.
- 20 Comparison 21. Switching to TCA versus SSRI
- 21 Critical outcomes:
- 22 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
- 28 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

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 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

7 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
- 13 Discontinuation due to side effects
- 14 No evidence was identified for this outcome.
- 15 **Important outcomes:**
- 16 Quality of life
- 17 No evidence was identified for this outcome.
- 18 Personal, social, and occupational functioning
- 19 No evidence was identified for this outcome.
- 20 Comparison 22. Switching to TCA versus augmenting with mirtazapine
- 21 Critical outcomes:
- 22 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
- 28 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
- 33 Response
- No evidence was identified for this outcome.
- 35 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

1 2 3	mirtazapine for the further-line treatment of depression, however this effect is not statistically significant
4	Discontinuation due to side effects
5	No evidence was identified for this outcome.
6	Important outcomes:
7	Quality of life
8	No evidence was identified for this outcome.
9	Personal, social, and occupational functioning
10	No evidence was identified for this outcome.
11	Comparison 23. Switching to mianserin versus continuing with antidepressant
12	Critical outcomes:
13	Depression symptomatology
14 15 16 17	 Very low quality evidence from 1 RCT (N=71) shows neither a clinically important not 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
19	Remission
20 21 22 23	 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
24	Response
25 26 27 28	 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
29	Discontinuation due to any reason
30 31 32 33 34	 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
35	Discontinuation due to side effects
36 37	 Very low quality evidence from 1 RCT (N=72) shows significantly higher discontinuation due to side effects associated with switching to mianserin, relative to

- 1 continuing with fluoxetine for an additional 6 weeks, for adults with depression who 2 have failed to respond to 6 weeks of treatment with fluoxetine 3 Important outcomes: Quality of life 4 5 No evidence was identified for this outcome. 6 Personal, social, and occupational functioning 7 No evidence was identified for this outcome. Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/-8 9 placebo) 10 **Critical outcomes:** 11 **Depression symptomatology** Very low quality evidence from 1 RCT (N=70) shows a clinically important and 12 statistically significant benefit of augmenting fluoxetine with mianserin, relative to 13 14 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 15 of treatment with fluoxetine 16 17 Remission 18 Very low quality evidence from 2 RCTs (N=267) shows a clinically important but not 19 statistically significant benefit of augmenting a SSRI with mianserin, relative to 20 continuing with SSRI-only, on the rate of remission for adults with depression who 21 had failed to respond to at least 6 weeks of SSRI treatment 22 Response 23 Very low quality evidence from 2 RCTs (N=267) shows neither a clinically important nor statistically significant difference between augmenting a SSRI with mianserin 24 relative to continuing with SSRI-only, on the rate of response for adults with 25 depression who had failed to respond to at least 6 weeks of SSRI treatment 26 27 Discontinuation due to any reason 28 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 29 with SSRI-only, for adults with depression who have failed to respond to at least 6 30 weeks of SSRI treatment, however this effect is not statistically significant 31 32 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

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1 Important outcomes:

- 2 Quality of life
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant
- 7 Critical outcomes:
- 8 Depression symptomatology
- 9 No evidence was identified for this outcome.
- 10 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
- 15 Response

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- 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
- 20 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
- 26 Discontinuation due to side effects
- No evidence was identified for this outcome.
- 28 Important outcomes:
- 29 Quality of life
- 30 No evidence was identified for this outcome.
- 31 Personal, social, and occupational functioning
- 32 No evidence was identified for this outcome.

1 Comparison 26. Augmenting with mianserin versus switch to mianserin

2 Critical outcomes:

3 **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

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 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

21 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:

34 Quality of life

No evidence was identified for this outcome.

36 Personal, social, and occupational functioning

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

2 Critical outcomes:

3 **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

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 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

14 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

19 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

24 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:

- 31 Quality of life
- 32 No evidence was identified for this outcome.
- 33 Personal, social, and occupational functioning
- No evidence was identified for this outcome.

1 Comparison 28. Switching to SNRI versus continuing with antidepressant

2 Critical outcomes:

3 Depression symptomatology

4 No evidence was identified for this outcome.

5 Remission

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 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

17 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

23 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

36 Personal, social, and occupational functioning

1 Comparison 29. Switching to SNRI versus switching to another antidepressant from 2 same class

3 Critical outcomes:

4 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 withinclass 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

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 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

16 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

34 Important outcomes:

35 Quality of life

36 No evidence was identified for this outcome.

37 Personal, social, and occupational functioning

1 Comparison 30. Switching to SNRI versus switching to bupropion

2 Critical outcomes:

3 **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

8 Remission

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23 24 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 citalogram

13 **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 citalogram

18 **Discontinuation due to any reason**

19 No evidence was identified for this outcome.

20 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

25 **Important outcomes:**

- 26 Quality of life
- No evidence was identified for this outcome.
- 28 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 30 Comparison 31. Switching to SNRI versus switching to mirtazapine
- 31 Critical outcomes:
- 32 Depression symptomatology
- No evidence was identified for this outcome.

1 Remission

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 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

19 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

25 **Important outcomes:**

26 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.

34 Comparison 32. Switching to bupropion versus placebo

35 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

1 Remission

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 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

6 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

11 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

16 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

21 Important outcomes:

- 22 Quality of life
- No evidence was identified for this outcome.
- 24 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 26 Comparison 33. Switching to bupropion versus switching to another antidepressant from same class

29 **Depression symptomatology**

Critical outcomes:

• 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 citalogram

34 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

1 Response

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 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 citalogram

6 **Discontinuation due to any reason**

7 No evidence was identified for this outcome.

8 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
- 13 **Important outcomes:**
- 14 Quality of life
- No evidence was identified for this outcome.
- 16 Personal, social, and occupational functioning
- 17 No evidence was identified for this outcome.
- 18 Comparison 34. Augmenting with bupropion versus placebo
- 19 **Critical outcomes:**
- 20 **Depression symptomatology**
- 21 No evidence was identified for this outcome.
- 22 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
- 26 Response
- No evidence was identified for this outcome.
- 28 Discontinuation due to any reason
- 29 No evidence was identified for this outcome.
- 30 Discontinuation due to side effects
- 31 No evidence was identified for this outcome.

1 Important outcomes:

- 2 Quality of life
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 35. Augmenting with bupropion versus switching to bupropion
- 7 Critical outcomes:
- 8 Depression symptomatology
- 9 No evidence was identified for this outcome.
- 10 Remission

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- 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
- 16 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
- 22 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
- 28 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
- 32 Important outcomes:
- 33 Quality of life
- No evidence was identified for this outcome.

1 Personal, social, and occupational functioning

- 2 No evidence was identified for this outcome.
- 3 Comparison 36. Switching to mirtazapine versus continuing with antidepressant
- 4 Critical outcomes:

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5 **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

21 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 followup, 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

1 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:

8 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

14 Personal, social, and occupational functioning

No evidence was identified for this outcome.

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17 Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/18 placebo)

19 Critical outcomes:

20 **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

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43 44 • 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

3 Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

4 Critical outcomes:

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5 **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 followup for adults with depression who have failed to respond to 2 weeks of treatment with sertraline

21 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 1 2 2 weeks of treatment with paroxetine, however this effect is not statistically significant 3 Important outcomes: Quality of life 4 5 No evidence was identified for this outcome. 6 Personal, social, and occupational functioning 7 No evidence was identified for this outcome. Comparison 39. Augmenting with trazodone versus continuing with antidepressant 9 **Critical outcomes:** 10 **Depression symptomatology** No evidence was identified for this outcome. 11 12 Remission 13 Very low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with trazodone and 14 continuing with paroxetine-only on the rate of remission, for adults with depression 15 who have shown an inadequate response to at least 2 previous courses of 16 17 antidepressant treatment for the current episode 18 Response 19 Very low quality evidence from 1 RCT (N=92) shows neither a clinically important nor statistically significant difference between augmenting paroxetine with trazodone and 20 21 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 22 23 antidepressant treatment for the current episode 24 Discontinuation due to any reason 25 No evidence was identified for this outcome. Discontinuation due to side effects 26 27 No evidence was identified for this outcome. 28 Important outcomes: 29 Quality of life 30 Low quality evidence from 1 RCT (N=92) shows neither a clinically important nor 31 statistically significant difference between augmenting paroxetine with trazodone and continuing with paroxetine-only on quality of life physical and mental component 32

scores, for adults with depression who have shown an inadequate response to at

least 2 previous courses of antidepressant treatment for the current episode

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1 Personal, social, and occupational functioning

- 2 No evidence was identified for this outcome.
- 3 Comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/- placebo)
- 5 Critical outcomes:

6 **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

14 Remission

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 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

20 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

1 Important outcomes:

2 Quality of life

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• 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

8 Personal, social, and occupational functioning

9 No evidence was identified for this outcome.

10 Comparison 41. Augmenting with anticonvulsant versus lithium

11 Critical outcomes:

12 **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

23 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

 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

7 Important outcomes:

8 Quality of life

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- 9 No evidence was identified for this outcome.
- 10 Personal, social, and occupational functioning
- 11 No evidence was identified for this outcome.
- 12 Comparison 42. Switching to antipsychotic versus continuing with antidepressant
- 13 **Critical outcomes:**

14 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

20 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

 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

7 Important outcomes:

8 Quality of life

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 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

14 Personal, social, and occupational functioning

No evidence was identified for this outcome.

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

17 *antidepressant*

18 Critical outcomes:

19 **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

26 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

11 Important outcomes:

12 Quality of life

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No evidence was identified for this outcome.

14 Personal, social, and occupational functioning

15 No evidence was identified for this outcome.

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

17 Critical outcomes:

18 **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

25 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

4 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

10 Important outcomes:

11 Quality of life

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12 No evidence was identified for this outcome.

13 Personal, social, and occupational functioning

14 No evidence was identified for this outcome.

15 Comparison 45. Augmenting with antipsychotic versus antidepressant-only or

16 antidepressant + placebo

17 Critical outcomes:

18 **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 1

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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

12 Comparison 46. Augmenting with antipsychotic versus bupropion

13 **Critical outcomes:**

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14 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

20 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

1 Important outcomes:

- 2 **Quality of life**
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 47. Augmenting with antipsychotic versus lithium
- 7 Critical outcomes:
- 8 **Depression symptomatology**
- 9 No evidence was identified for this outcome.
- Remission 10

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- Low quality evidence from 3 RCTs (N=510) shows a higher rate of remission associated with augmenting antidepressant treatment with an antipsychotic relative to 12 augmentation with lithium for adults with depression who have shown an inadequate 13 response to at least 1 previous course of antidepressant treatment for the current 14 15 episode, however this effect is not statistically significant
- 16 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
- 22 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
- 34 Important outcomes:
- 35 **Quality of life**
- 36 No evidence was identified for this outcome.

1 Personal, social, and occupational functioning

- 2 No evidence was identified for this outcome.
- 3 Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic
- 4 Critical outcomes:

5 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

12 Remission

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• 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

18 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:

38 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 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

10 Personal, social, and occupational functioning

11 No evidence was identified for this outcome.

12 Comparison 49. Augmenting with antipsychotic versus switch to bupropion

13 Critical outcomes:

14 Depression symptomatology

No evidence was identified for this outcome.

16 Remission

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 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

22 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

1 Important outcomes:

- 2 Quality of life
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/- placebo)
- 8 Critical outcomes:
- 9 Depression symptomatology
- 10 No evidence was identified for this outcome.
- 11 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
- 17 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
- 23 Discontinuation due to any reason
- No evidence was identified for this outcome.
- 25 Discontinuation due to side effects
- No evidence was identified for this outcome.
- 27 Important outcomes:
- 28 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
- 35 Personal, social, and occupational functioning
- No evidence was identified for this outcome.

1 Comparison 51. Augmenting with buspirone versus bupropion

2 Critical outcomes:

3 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

9 Remission

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• 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

14 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

19 Discontinuation due to any reason

No evidence was identified for this outcome.

21 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

26 Important outcomes:

- 27 Quality of life
- No evidence was identified for this outcome.
- 29 Personal, social, and occupational functioning
- 30 No evidence was identified for this outcome.
- 31 Comparison 52. Augmenting with methylphenidate versus placebo
- 32 Critical outcomes:
- 33 **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

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 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

22 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

28 **Important outcomes:**

- 29 Quality of life
- 30 No evidence was identified for this outcome.
- 31 Personal, social, and occupational functioning
- 32 No evidence was identified for this outcome.
- 33 Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/- placebo)
- 35 Critical outcomes:

36 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

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• 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

19 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

25 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

30 Important outcomes:

- 31 Quality of life
- No evidence was identified for this outcome.
- 33 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 35 Comparison 54. Augmenting with lithium versus switch to antipsychotic
- 36 Critical outcomes:
- 37 Depression symptomatology
- 38 No evidence was identified for this outcome.

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• 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

7 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

20 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

26 **Important outcomes:**

- 27 Quality of life
- No evidence was identified for this outcome.
- 29 Personal, social, and occupational functioning
- 30 No evidence was identified for this outcome.
- 31 Comparison 55. Augmenting with lithium versus augmenting with a psychological
- 32 intervention
- 33 Critical outcomes:

34 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 1month follow-up for adults with depression who have shown a partial response to 8-14 weeks of antidepressant treatment

Remission

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 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

12 Response

No evidence was identified for this outcome.

14 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

20 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

26 **Important outcomes:**

27 Quality of life

No evidence was identified for this outcome.

29 Personal, social, and occupational functioning

30 No evidence was identified for this outcome.

31 Comparison 56. Augmenting with lithium versus augmenting with TCA

32 Critical outcomes:

33 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

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35 36 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

6 Response

7 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

13 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

18 **Important outcomes:**

- 19 Quality of life
- No evidence was identified for this outcome.
- 21 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 23 Comparison 57. Augmenting with omega-3 fatty acids versus placebo
- 24 Critical outcomes:

25 **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

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 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

19 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

25 **Important outcomes:**

26 Quality of life

No evidence was identified for this outcome.

28 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)

35 Critical outcomes:

36 **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

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39 40 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 antidepressantonly, 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

41 Personal, social, and occupational functioning

42 No evidence was identified for this outcome.

1 Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

2 Critical outcomes:

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3 **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

21 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

39 **Important outcomes:**

40 Quality of life

No evidence was identified for this outcome.

1 Personal, social, and occupational functioning

- 2 No evidence was identified for this outcome.
- 3 Comparison 60. Switching to ECT versus switching to paroxetine
- 4 Critical outcomes:
- 5 **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
- 11 Remission

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- 12 No evidence was identified for this outcome.
- 13 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
- 19 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
- 25 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
- 31 **Important outcomes:**
- 32 Quality of life
- No evidence was identified for this outcome.
- 34 Personal, social, and occupational functioning
- 35 No evidence was identified for this outcome.

1 Comparison 61. Augmenting with ECT versus continuing with antidepressant

2 Critical outcomes:

3 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

13 Remission

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- 14 No evidence was identified for this outcome.
- 15 **Response**
- 16 No evidence was identified for this outcome.
- 17 Discontinuation due to any reason
- 18 No evidence was identified for this outcome.
- 19 Discontinuation due to side effects
- 20 No evidence was identified for this outcome.
- 21 Important outcomes:
- 22 Quality of life
- No evidence was identified for this outcome.
- 24 Personal, social, and occupational functioning
- No evidence was identified for this outcome.
- 26 Comparison 62. Augmenting with ECT versus augmenting with exercise
- 27 Critical outcomes:
- 28 **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

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- 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
- 6 Response
- 7 No evidence was identified for this outcome.
- 8 Discontinuation due to any reason
- 9 No evidence was identified for this outcome.
- 10 Discontinuation due to side effects
- 11 No evidence was identified for this outcome.
- 12 **Important outcomes:**
- 13 Quality of life
- 14 No evidence was identified for this outcome.
- 15 Personal, social, and occupational functioning
- 16 No evidence was identified for this outcome.
- 17 Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise
- 18 Critical outcomes:
- 19 **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
- 25 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
- 30 Response
- No evidence was identified for this outcome.
- 32 Discontinuation due to any reason
- No evidence was identified for this outcome.

- 2 No evidence was identified for this outcome.
- 3 Important outcomes:
- 4 Quality of life
- 5 No evidence was identified for this outcome.
- 6 Personal, social, and occupational functioning
- 7 No evidence was identified for this outcome.
- 8 Comparison 64. Augmenting with exercise versus TAU
- 9 Critical outcomes:

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10 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

23 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

- 2 No evidence was identified for this outcome.
- 3 Important outcomes:
- 4 Quality of life
- 5 No evidence was identified for this outcome.
- 6 Personal, social, and occupational functioning
- 7 No evidence was identified for this outcome.
- 8 Comparison 65. Augmenting with exercise versus attention-placebo
- 9 Critical outcomes:

10 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

22 Remission

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• 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

28 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

- 2 No evidence was identified for this outcome.
- 3 Important outcomes:
- 4 Quality of life

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5 No evidence was identified for this outcome.

6 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
- 18 Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT
- 19 Critical outcomes:
- 20 **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
- 26 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
- 31 Response
- 32 No evidence was identified for this outcome.
- 33 Discontinuation due to any reason
- No evidence was identified for this outcome.
- 35 Discontinuation due to side effects
- No evidence was identified for this outcome.

1 Important outcomes:

- 2 Quality of life
- 3 No evidence was identified for this outcome.
- 4 Personal, social, and occupational functioning
- 5 No evidence was identified for this outcome.
- 6 Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/7 waitlist or attention-placebo)
- 8 Critical outcomes:

9 **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

16 Remission

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- 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

1 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

8 Discontinuation due to side effects

- 9 No evidence was identified for this outcome.
- 10 **Important outcomes:**
- 11 Quality of life

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- 12 No evidence was identified for this outcome.
- 13 Personal, social, and occupational functioning
- 14 No evidence was identified for this outcome.

15 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.
- 21 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 22 23 people with depression who have responded inadequately to previous treatment and have residual depressive symptoms, as the outcome measure was not the QALY and 24 interpretation of the results depends on the willingness to pay in order to avoid an 25 26 additional relapse. This evidence, although it was conducted in the UK, is only partially 27 applicable to the NICE decision-making context (due to lack of QALY estimation) and it 28 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 costeffective 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 costeffective 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 costeffective 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.

4 The committee's discussion of the evidence

5 Interpreting the evidence

6 The outcomes that matter most

- 7 The aim of this review was to identify the most effective treatments for depression that has
- 8 not responded to previous therapies, so the committee prioritised depression
- 9 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.
- 12 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
- 14 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
- 17 on decision-making.

18 The quality of the evidence

- 19 The quality of evidence was assessed using GRADE and was generally rated as low to very
- 20 low, reflecting the high risk of bias associated with the studies. This included high risk of bias
- 21 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
- 23 number of studies for each comparator, small numbers of participants in most trials and
- 24 imprecision in most of the results.

25 **Benefits and harms**

- 26 In developing recommendations for people with depression that has not responded or where
- 27 there has been a limited response to treatment, the committee drew on their knowledge and
- 28 experience that a significant number of people with depression may not adhere to the
- 29 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.
- 31 They therefore agreed that a review of these factors should be considered before initiating
- 32 any additional treatment options. Based on the expert opinion of the committee, it was noted
- 33 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
- 37 when the initial treatment has not worked, and may need reassurance that alternative or
- 38 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
- 40 worked and providing some explanation about how the further-line treatment works
- 41 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
- 44 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
- 47 people who respond to pharmacological interventions will have have shown some response

- 1 within 4 weeks of initiation of treatment. Response curves are similar for psychological
- 2 interventions but response to psychological interventions may initially be slower than to
- 3 medication with people typically responding to treatment within 4 to 6 weeks.
- 4 In developing their recommendations, the committee considered three main scenarios: first
- 5 where a person had not responded to initial psychological therapy, secondly where a person
- 6 had not responded to initial antidepressant medication, and thirdly where a person had not
- 7 responded to initial treatment with a combination of antidepressant medication and
- 8 psychological therapy.
- 9 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
- 12 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
- 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
- 20 treatments particularly in more severe depression where combination treatment was more
- 21 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
- 24 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,
- 29 individuals could switch to a psychological intervention, or antidepressant medication could
- 30 be continued but with an alternative drug or an increased dose. There was some evidence
- 31 from randomised controlled trials for clinical benefits associated with augmenting
- 32 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
- 38 pragmatic, trials of cognitive-behavioural therapies (including CBASP and rumination-
- 39 focused CBT) as further-line treatment or treatment for residual depression, which replicated
- 40 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;
- 42 Hvenegaard 2020; Moore and Blackburn 1997; Segal 2020; Teissman 2014). The committee
- 43 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
- This introduction to an intervention. There were
- 45 no evidence that specifically examined switching to a psychological intervention for those
- 46 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
- 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
- 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
- 53 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

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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.

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- 1 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
- 3 modalities of ECT treatment, comparing ECT with other neuromodulatory therapies, and into
- 4 possible adverse effects. However the remit of the original review of ECT for the guideline
- 5 had a focus on sham-controlled randomised trials and so had not taken account of this wider
- 6 evidence base. The committee was also aware of the PRIDE study of continuation ECT in
- 7 depression in older people (Kellner 2016) which had reported a positive finding based on
- 8 odds ratios.
- 9 The committee considered the short-term and long-term harms associated with medication,
- 10 for example, side effects associated with SSRIs include drowsiness, nausea, insomnia,
- agitation, restlessness and sexual problems. For the TCAs there is the potential for
- 12 cardiotoxicity and associated increased risk in overdose, although this is much greater for
- 13 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
- 15 '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
- 17 lithium there were concerns about renal toxicity and thyroid and parathyroid function. For the
- 18 antipsychotics concerns with weight gain and hyperlipidaemia and raised blood glucose were
- 19 also considered. The committee took these factors into consideration and in particular the
- 20 increased burden of harms that may arise with the use of a combination of medications. In
- 21 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
- 23 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
- 27 prescribers, including GPs, would not feel competent to initiate such combination treatment
- and therefore also recommended that combination therapy should be initiated in specialist
- 29 settings or after consulting a specialist.

Longer-term follow-up

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- 31 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
- 33 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
- 39 years). The committee agreed that the effects on depression outcomes at follow-up were
- 40 generally in line with the effects observed at endpoint, and this strengthened their confidence
- 41 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
- 46 life associated with increasing the dose of an SSRI (versus same dose), some evidence for a
- 47 benefit on global functioning or functional impairment of antipsychotic augmentation (relative
- 48 to increasing SSRI dose, or continuing with the antidepressant at the same dose) or
- 49 augmenting antidepressants with exercise, and of omega-3 augmentation on sleeping
- 50 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
- 2 functioning outcomes.

3 Cost effectiveness and resource use

- 4 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
- 6 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
- 8 healthcare system.

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- 9 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
- 12 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
- 14 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
- 17 previous treatment with SSRIs. Evidence from Sweden suggests that escitalopram is more
- 18 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
- 22 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
- 24 committee noted that economic evidence on psychological interventions is overall
- 25 characterised by minor limitations, whereas evidence on pharmacological interventions is
- 26 characterised by minor to potentially serious limitations. Other available non-UK evidence
- 27 was not considered as it was characterised by very serious limitations and/or high
- 28 uncertainty. Finally, there was some UK evidence that ECT may be cost-effective as part of a
- 29 sequence of treatments that includes ECT SSRI lithium augmentation in adults with
- 30 major depression that requires hospitalisation. The committee considered this evidence
- 31 when formulating separate ECT recommendations in the guideline.
- 32 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
- 34 treatments of a new depressive episode that was undertaken for the guideline (See Evidence
- 35 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
- 39 populations with more severe depression, the combination of individual CBT with an
- 40 antidepressant was likely to be the most cost-effective option for the treatment of new
- 41 episodes, followed by pharmacological treatments, group exercise and individual
- 42 psychological interventions (such as CBT, IPT or STPP). All these options were found to be
- 43 more cost-effective than GP care.

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- 44 Considering the available economic evidence, the committee decided to recommend further-
- 45 line treatment options among those that were found to be cost-effective versus TAU (which
- 46 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

psychological intervention alone, and the possibility of changing the components of

- treatment for people who have responded inadequately to medication alone or to

- 1 combination therapy in people who are already on a combination of medication and a psychological therapy.
- 3 The committee considered that offering an SSRI or mirtagapine as an alternative or as an
- 4 adjunct to psychological treatment to people whose symptoms have not adequately
- 5 responded to an initial psychological intervention would have minor resource implications as
- 6 the intervention cost of providing antidepressant treatment is overall lower than that of an
- 7 individual psychological intervention. Moreover, the committee noted that switching from a
- 8 psychological therapy that led to inadequate response to a different type of psychological
- 9 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
- 11 further care costs.

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- 12 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
- 14 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
- 16 generic form, although there are costs associated with the necessary clinical review of dose
- 17 escalations or switching. Switching from a drug that is causing side effects to another drug of
- 18 the same or different class may lead to cost-savings and better outcomes for the person, if
- 19 the new drug is better tolerated.
- The committee noted that, according to existing evidence, offering psychological therapy to
- 21 people who have limited response to previous pharmacological treatment may be cost-
- 22 effective. They also considered that adding a group exercise intervention to people with
- 23 inadequate response to previous antidepressant treatment has been shown to be beneficial
- to the person and is likely to have minor resource implications.
- 25 The committee acknowledged the additional costs associated with combined medication
- therapy, for example combined antidepressant treatment or provision of lithium or
- 27 antipsychotics in addition to antidepressant treatment, which should take place in specialist
- 28 settings or after consultation with a specialist. These costs relate to specialist staff time but
- 29 also to monitoring costs and costs associated with side effects. The committee considered
- the available UK evidence according to which adding mirtagapine to SSRI treatment is cost-
- 31 effective. They also noted that lithium dominates antipsychotics as an adjunct to SSRIs in the
- 32 treatment of adults with depression that has not responded to treatment, but noted that this
- 33 evidence was characterised by potentially serious limitations. Based on the above
- 34 considerations, the committee recommended combining different antidepressants (for
- example mirtazapine with a SSRI) or combining antidepressants with an antipsychotic or
- 36 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
- 39 accept the possibility of an increased side-effect burden. In this population, alternative
- 40 effective treatment options are limited and the committee expressed the view that the
- 41 benefits of combined medication treatment are likely to outweigh costs associated with its
- 42 provision to this group.

13 Other factors the committee took into account

- When reviewing the evidence for further line treatment the committee had originally decided
- 45 to separately examine the evidence base for treatment resistant depression (usually defined
- 46 as no or limited response to two adequate courses of an antidepressant) from no or limited
- 47 response to treatment. However, after carefully reviewing the trial populations and the
- 48 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
- 50 between the two populations and therefore decided to use the same data sets for both
- 51 questions to inform the development of recommendations for no or limited response.

DRAFT FOR CONSULTATION Further-line treatment

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

9 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
- 11 recommendations in the NICE guideline.
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23

Appendices

2 Appendix A – Review protocol

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

6 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 areas
	Other agents
	• Lithium
	Omega-3 fatty acids Thyraid harmons ³
	• Thyroid hormone ³
	Physical interceptions
	Physical interventions
	Acupuncture ECT
	• Exercise
	• Yoga
	Light therapy (for depression, not SAD)
	Light therapy (for depression, flot 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 HAMP
	• 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

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
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
Update of CG90 (2009)
For details please see the guideline in development web site.
For details please see section 4.5 of Developing NICE guidelines: the manual 2014
For details please see appendix B.
A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
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/.
For details please see section 6.4 of Developing NICE guidelines: the manual 2014
For details please see the methods chapter.
For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
For details please see the introduction to the evidence review.
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.

14 15

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—Asberg 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-

1 Appendix B – Literature search strategies

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

7 Clinical search

- 8 Database(s): Embase 1974 to 2019 Week 19, Emcare 1995 to present, Ovid MEDLINE(R)
- 9 and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May
- 10 14, 2019, PsycINFO 1806 to May Week 1 2019
- 11 Date of Search: 16/05/2019
- 12 Search updated: 04/06/2020

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 illnealth*)).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 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

# 28	Searches Artidenyseeine Agente Trievelie/ use pro-
29	Antidepressive Agents, Tricyclic/ use ppez 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 40	lamotrigine/ or (lamotrigine or anticonvul* or anti-convul*).tw. 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 48	anxiolytic agent/ use oemezd,emcr 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 58	or/53-56 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. 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 74	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Walking/) use ppez (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 84	(befriend* or friend* or mentor* or peer group* or peer support or (communit* adj (navigat* or support*))).tw. or/79-83
85	or/15,35,40,46,52,57,67,78,84
33	50, 10,000, 10, 10,000,01,101,10,00T

#	Searches
86 87	6 and 85 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 96	Comment/ use ppez 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 99 not 102
103 104	(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
111 112	exp animal experiment/ use oemezd,emcr 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
119 120	exp rodents/ use psyh (rat or rats or mouse or mice).ti.
120	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
129 130	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti. 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/
137 138	(meta analy* or metanaly* or metaanaly*).ti,ab. ((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 psychinfo or psychinfo or cinahl or science citation
144	index or bids or cancerlit).ab. cochrane.jw.
144	((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

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 "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric i		
#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 sensitization" 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 nanspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centered 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		
#40			
#42	MeSH descriptor: [Lofepramine] this term only		
#42	MeSH descriptor: [Minteranginal this term only		
	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	for #10-#89}		
#91	#9 and #90 with Cochrane Library publication date Between Jan 2016 and May 2019, in Cochrane Reviews, Cochrane Protocols, Trials		

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

Searcl	h 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/
02	notati oconomico,

#	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 euroqol* or euroquol* or euroquol* or euroquol5d* or euroquol5d* or euroqol* or euroqol5d* or euroqual5d* or europasconscipling* or europasconscipling		
86	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5 dimension* or 5 domain* or 5 domain*)).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 expectano*)).tw.		
98	"costs and cost analysis"/ use psyh and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.		
99	*quality of life/ and (quality of life or qol).ti.		
100	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.		
101	quality of life/ and health-related quality of life.tw.		
102	Models, Economic/ use ppez		
103	economic model/ use oemezd		
104	or/74-101		
105	73 or 104		
106	41 and 105		
107	limit 106 to english language		
108	limit 107 to yr="2016 -Current"		

- Database(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA) 1
- 2
- 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

- Database(s): CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature) 1937-current, EBSCO Host 1
- 2
- 3 Date of search: 26/02/2019
- Search updated: 02/03/2020

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 euroquol* or euroquol* or euroquol* or euroquol5d* or euroquol5d* or eur qol* or euroqol5d* or euroquol5d* or euroqul5d* or euroqul5d* or euroqul5d* or euroqul5d* or euroqul5d* or euroqul5d* 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

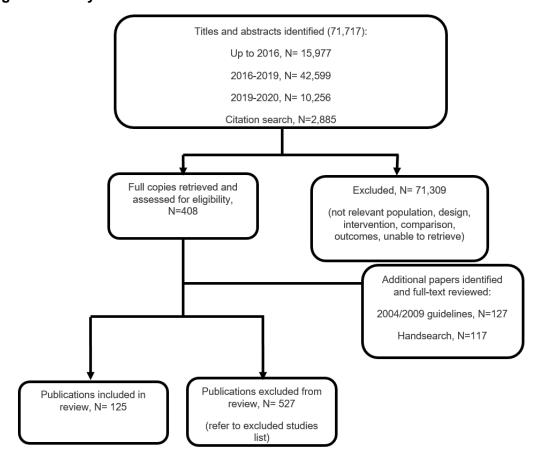
#	Query	Limiters/Expanders
S1	(MH "Depression+") OR (MH "Premenstrual Dysphoric Disorder") OR	Search modes - Boolean/Phrase
	(MH "Seasonal Affective Disorder")	

1

1 Appendix C - Clinical evidence study selection

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

7 Figure 1: Study selection flow chart



10

1 Appendix D – Clinical evidence tables

- 2 Evidence tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial,
- 3 pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate
- 4 response to at least one previous intervention for the current episode?
- 5 Please refer to the clinical evidence tables in supplement D Clinical evidence tables for Evidence review D Further-line treatment.

8 Appendix E – Forest plots

- 9 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 11

inadequate response to at least one previous intervention for the current

13 episode?

14 Comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus

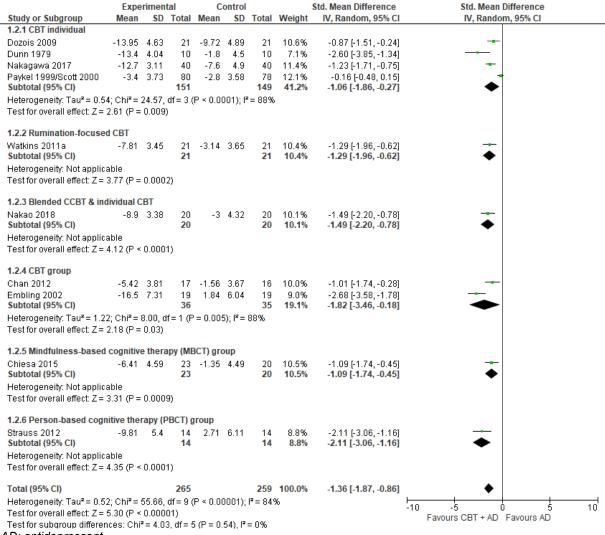
15 continuing with antidepressant (+/ waitlist or attention-placebo)

16 Figure 2: Depression symptomatology endpoint

Study or Subgroup	Expe Mean	eriment		C Mean	ontrol	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
Study or Subgroup 1.1.1 CBT individual	Weali	30	Total	Weall	30	Total	weight	IV, Kalluolli, 55% Cl	IV, Raildolli, 93% CI
Dozois 2009	6.43	6.95	21	9.33	7.21	21	7.7%	-0.40 [-1.01, 0.21]	-
Dunn 1979		4.81	10		6.18	10	4.4%	-1.87 [-2.96, -0.78]	
Nakagawa 2017	8.2	4.7	40	13.2	6.9	40	9.0%	-0.84 [-1.30, -0.38]	
Paykel 1999/Scott 2000	8.7	5.3	80	9.4	5.2	78	10.3%	-0.13 [-0.44, 0.18]	+
Wiles 2013/2016 Subtotal (95% CI)	18.9	14.2	206 357	24.5	13.1	213 362	11.1% 42.5 %	-0.41 [-0.60, -0.22] - 0.54 [-0.88 , - 0.20]	•
Heterogeneity: Tau² = 0.09 Test for overall effect: Z = 3				(P = 0.0	1); l²=	70%			
1.1.2 Rumination-focused	CBT								
Watkins 2011a Subtotal (95% CI)	5.48	5.15	21 21	9.05	5.25	21 21	7.6% 7.6 %	-0.67 [-1.30, -0.05] - 0.67 [-1.30 , - 0.05]	<u>→</u>
Heterogeneity: Not applica Test for overall effect: Z = 2		0.03)							
1.1.3 Cognitive behavioral	l analysi	is syste	em of	osycho	therap	v (CBA	SP)		
Kocsis 2009/Klein 2011	11.29	8.3		12.28		76	10.6%	-0.12 [-0.39, 0.15]	4
Subtotal (95% CI)	20	0.0	174	0	2	76	10.6%	-0.12 [-0.39, 0.15]	
Heterogeneity: Not applica Test for overall effect: Z = 0		0.39)							
1.1.4 Dialectical behaviou	r therap	y (DBT)						
Lynch 2007_study 2 Subtotal (95% CI)	7.88	4.35	21 21	11.26	9.22	10 10	6.4% 6.4 %	-0.52 [-1.29, 0.24] - 0.52 [-1.29, 0.24]	-
Heterogeneity: Not applica Test for overall effect: Z = 1		0.18)							
1.1.5 Blended CCBT & indi	ividual (BT							
Nakao 2018 Subtotal (95% CI)	9.4	5.1	20 20	15.5	6.3	20 20	7.2% 7.2 %	-1.04 [-1.71, -0.38] - 1.04 [-1.71 , - 0.38]	→
Heterogeneity: Not applica Test for overall effect: $Z = 3$		0.002)	ı						
1.1.6 CBT group									
Chan 2012	6.82	5.73	17	10	4.41	16	6.9%	-0.60 [-1.30, 0.10]	-
Embling 2002	15.17			32.17		19	5.7%	-2.47 [-3.34, -1.61]	
Subtotal (95% CI)			36			35	12.6%	-1.52 [-3.35, 0.31]	•
Heterogeneity: Tau² = 1.58 Test for overall effect: Z = 1	-		df= 1 ((P = 0.0	01); l² =	91%			
1.1.7 Mindfulness-based	cognitiv	e thera	ру (МЕ	BCT) gr	oup				
Chiesa 2015 Subtotal (95% CI)		7.35	23 23		7.32	20 20	7.7% 7.7 %	-0.53 [-1.14, 0.08] - 0.53 [-1.14, 0.08]	-
Heterogeneity: Not applica Test for overall effect: Z= 1		0.09)							
1.1.8 Person-based cogni	itive the	rany (D	BCT)	TOUR					
Strauss 2012	27.93		14	43.19	8.58	14	5.4%	-1.83 [-2.73, -0.92]	_
Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 3		0.0001	14 1)			14	3.4%	-1.83 [-2.73, -0.92]	
Total (95% CI)			666			558	100.0%	-0.74 [-1.03, -0.45]	•
Heterogeneity: Tau ² = 0.18 Test for overall effect: Z = 5 Test for subgroup different AD: antidepressant	5.06 (P <	0.000	df = 12 01)			; = 7	7%		-10 -5 0 5 10 Favours CBT + AD Favours AD

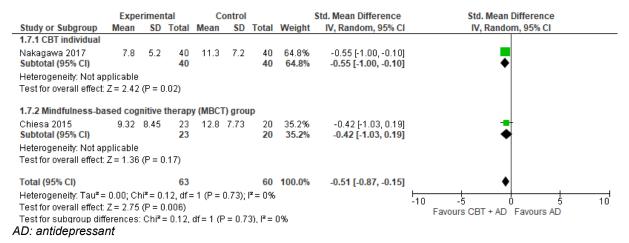
17 18

20 Figure 3: Depression symptomatology change score



21 22 AD: antidepressant

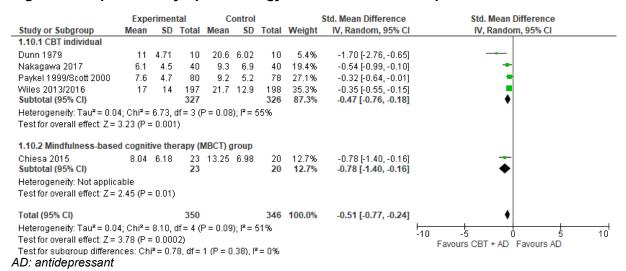
24 Figure 4: Depression symptomatology at 2-3 month follow-up



25 26

23

28 Figure 5: Depression symptomatology at 4-6 month follow-up

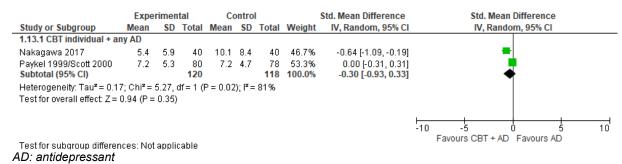


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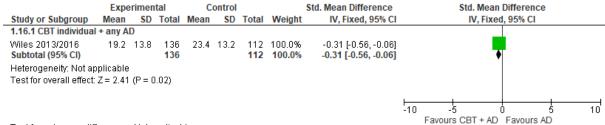
32 Figure 6: Depression symptomatology at 11-12 month follow-up



33 34

35

36 Figure 7: Depression symptomatology at 40-month follow-up

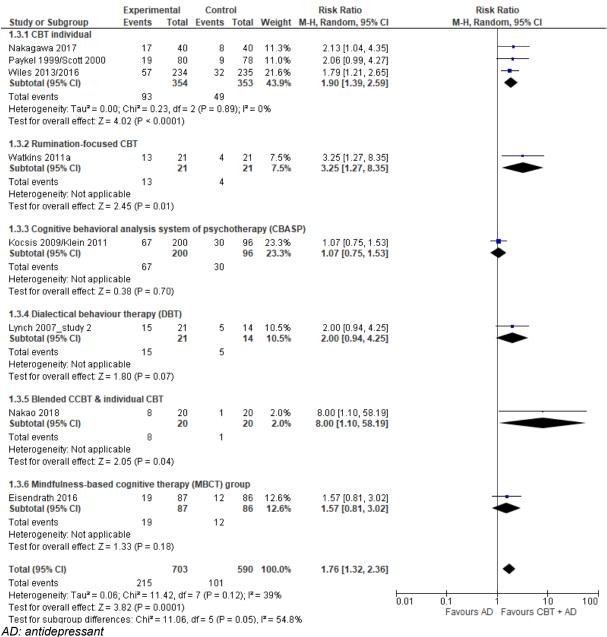


37

Test for subgroup differences: Not applicable

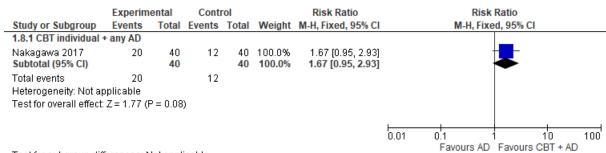
AD: antidepressant

40 Figure 8: Remission (ITT)



43

44 Figure 9: Remission (ITT) at 3-month follow-up



Test for subgroup differences: Not applicable AD: antidepressant

47 48

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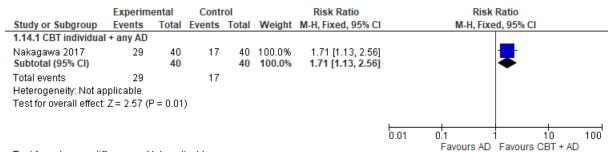
Figure 10: Remission (ITT) at 6-month follow-up

	Experime	ental	Conti	rol		Risk Ratio		Ris	sk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rar	ndom, 95%	CI	
1.11.1 CBT individua	I + any AD										
Nakagawa 2017	28	40	16	40	39.9%	1.75 [1.14, 2.69]			-		
Wiles 2013/2016	78	234	36	235	60.1%	2.18 [1.53, 3.09]			-		
Subtotal (95% CI)		274		275	100.0%	1.99 [1.52, 2.62]			•		
Total events	106		52								
Heterogeneity: Tau ² :	= 0.00; Chi²	= 0.62,	df = 1 (P	= 0.43); I ^z = 0%						
Test for overall effect	Z = 4.98 (F	° < 0.00	001)								
							0.01	0.1	+	10	100
							0.01		D Favours		

50 Test for subgroup differences: Not applicable 51 AD: antidepressant

52

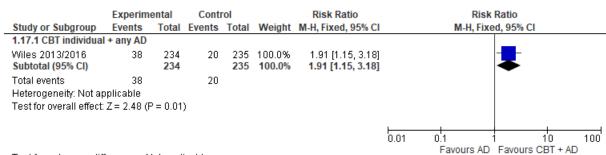
53 Figure 11: Remission (ITT) at 12-month follow-up



Test for subgroup differences: Not applicable AD: antidepressant

56

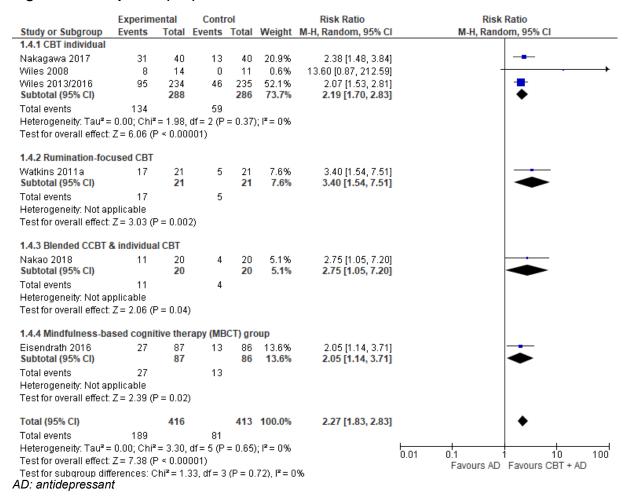
57 Figure 12: Remission (ITT) at 40-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

61 Figure 13: Response (ITT)



62 63 64

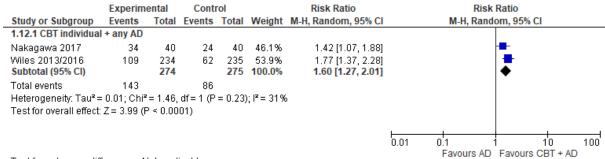
65 Figure 14: Response (ITT) at 3-month follow-up

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95%	6 CI	
1.9.1 CBT individual	+ any AD									
Nakagawa 2017 Subtotal (95% CI)	28	40 40	17	40 40	100.0% 100.0%	1.65 [1.09, 2.49] 1.65 [1.09, 2.49]		•		
Total events Heterogeneity: Not a Test for overall effec		P = 0.02	17							
							0.01	0.1 1 Favours AD Favou	10 10 urs CBT + AD)O

66 67 Test for subgroup differences: Not applicable

AD: antidepressant

69 Figure 15: Response (ITT) at 6-month follow-up



Test for subgroup differences: Not applicable AD: antidepressant

72

70 71

73 Figure 16: Response (ITT) at 12-month follow-up

	Experim	ental	Conti	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
1.15.1 CBT individua	ıl + any AD									
Nakagawa 2017 Subtotal (95% CI)	33	40 40	20	40 40	100.0% 100.0 %	1.65 [1.17, 2.32] 1.65 [1.17, 2.32]			•	
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	20							
							0.01	0.1 Favours AD		0 100 BT + AD

Test for subgroup differences: Not applicable AD: antidepressant

76

74 75

77 Figure 17: Response (ITT) at 40-month follow-up

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
1.18.1 CBT individual	+ any AD									
Wiles 2013/2016 Subtotal (95% CI)	59	234 234	30	235 235	100.0% 100.0 %	1.98 [1.32, 2.95] 1.98 [1.32, 2.95]			.	
Total events Heterogeneity: Not ap Test for overall effect:	•	° = 0.00	30							
							0.01	0.1 favours AD	10 Favours CBT	100 + AD

Test for subgroup differences: Not applicable AD: antidepressant

81 Figure 18: Discontinuation due to any reason

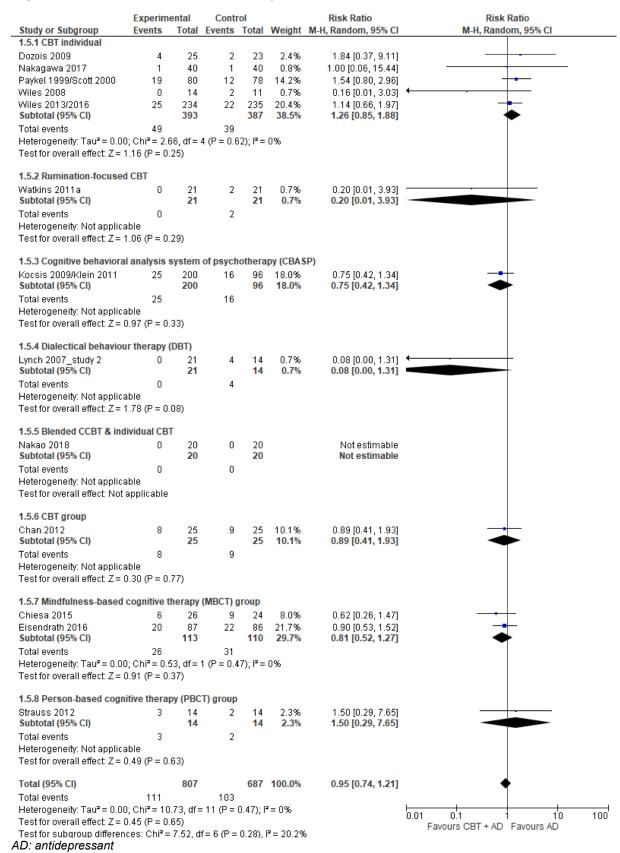
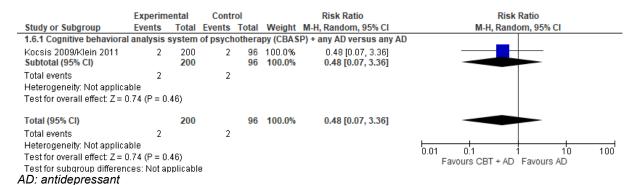


Figure 19: Discontinuation due to side effects

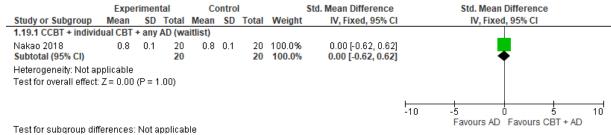


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87 88

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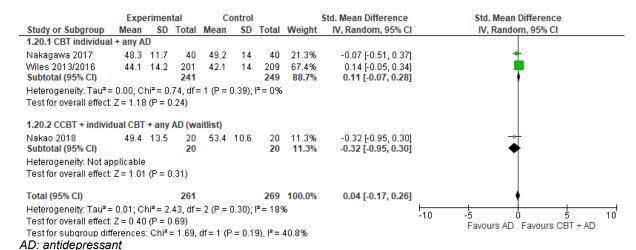
90 Figure 20: Quality of life endpoint



91 Test for subgroup differences: AD: antidepressant

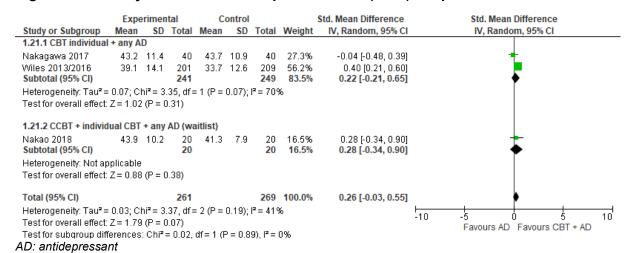
93

94 Figure 21: Quality of life physical component score (PCS) endpoint



95 96

Figure 22: Quality of life mental component score (MCS) endpoint

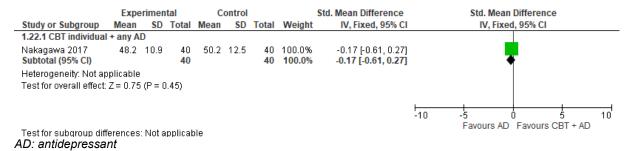


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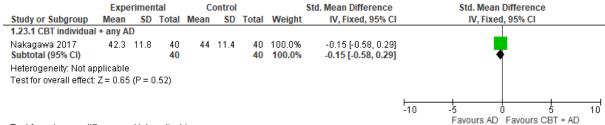
Figure 23: Quality of life physical component score (PCS) at 3-month follow-up



103 104

105

106 Figure 24: Quality of life mental component score (MCS) at 3-month follow-up

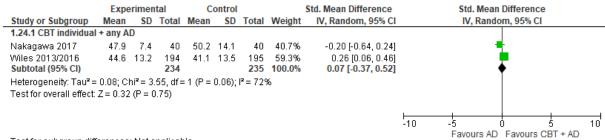


107 108

Test for subgroup differences: Not applicable

AD: antidepressant

110 Figure 25: Quality of life physical component score (PCS) at 6-month follow-up



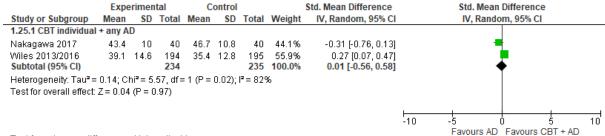
111 Test for subgroup differences: Not applicable AD: antidepressant

113

Figure 26: Quality of life mental component score (MCS) at 6-month follow-up

115

114



116 Test for subgroup differences: Not applicable AD: antidepressant

118

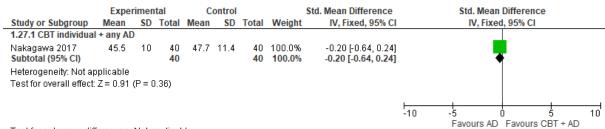
119 Figure 27: Quality of life physical component score (PCS) at 12-month follow-up

	Expe	rimen	tal	C	ontrol								
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed			
1.26.1 CBT individua	I + any AD)											
Nakagawa 2017 Subtotal (95% CI)	50.8	11.8	40 40	50.2	11.9	40 40	100.0% 100.0 %	0.05 [-0.39, 0.49] 0.05 [-0.39, 0.49]					
Heterogeneity: Not ap Test for overall effect	•	(P = 0).82)										
									-10	-5 Favours AD	0 5 Favours CBT +	10 - AD	

120 Test for subgroup differences: Not applicable AD: antidepressant

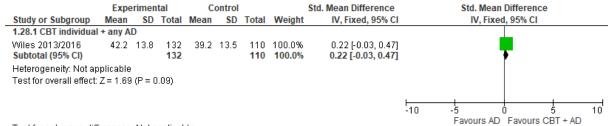
122

123 Figure 28: Quality of life mental component score (MCS) at 12-month follow-up



124 Test for subgroup differences: Not applicable AD: antidepressant

127 Figure 29: Quality of life physical component score (PCS) at 40-month follow-up



128 129 Test for subgroup differences: Not applicable

AD: antidepressant

130

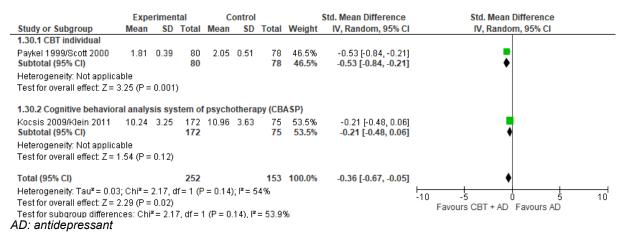
134

Figure 30: Quality of life mental component score (MCS) at 40-month follow-up 131

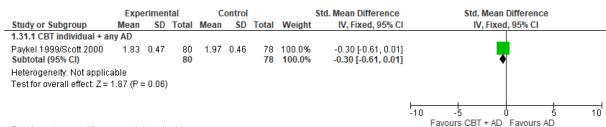
	Expe	erimen	tal					Std. Mean Difference		Std. Mean Difference	:e
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.29.1 CBT individua	l + any A	D									
Wiles 2013/2016 Subtotal (95% CI)	38.7	12.1	132 132	34.6	11.8		100.0% 100.0%	0.34 [0.09, 0.60] 0.34 [0.09, 0.60]		.	
Heterogeneity: Not as	oplicable										
Test for overall effect:	Z = 2.63	(P = 0).009)								
									-10	-5 0	
									-10	Favours AD Favours	

132 133 Test for subgroup differences: Not applicable AD: antidepressant

135 Figure 31: Functional impairment endpoint



139 Figure 32: Functional impairment at 11-month follow-up



Test for subgroup differences: Not applicable

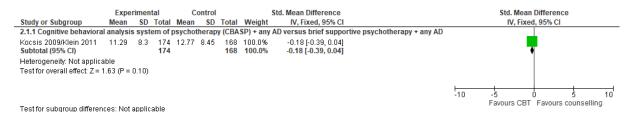
AD: antidepressant

136 137

143

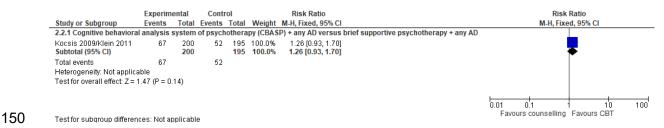
144 Comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus 145 augmenting with counselling

146 Figure 33: Depression symptomatology endpoint



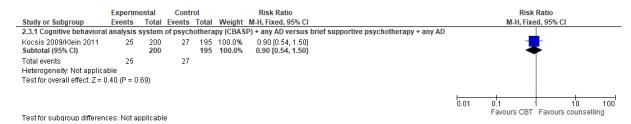
147148

149 Figure 34: Remission (ITT)



151

152 Figure 35: Discontinuation due to any reason

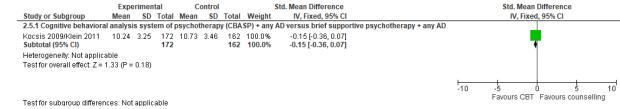


153154

155 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

	Expe	erimen	ital	Control Std. Mean Differen				Std. Mean Difference	Std. Mean Di	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 9	95% CI
3.1.1 Brief supportive psy	chother	ару +	any AD)						
Kocsis 2009/Klein 2011 Subtotal (95% CI)	12.77	8.45	168 168	12.28	8.44	76 76	100.0% 100.0 %	0.06 [-0.21, 0.33] 0.06 [-0.21, 0.33]	•	
Heterogeneity: Not applica Test for overall effect: Z = I		0.68)								
Test for subaroup differen	ices: Not	annlio	:ahle						-10 -5 0 Favours counselling + AD	5 10 Favours AD

163 164 AD: antidepressant

165

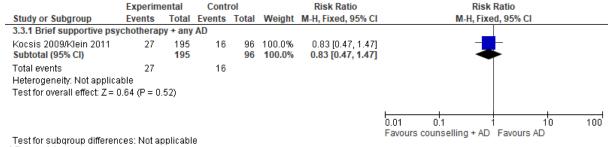
166 Figure 39: Remission (ITT)

	Experime	ental	Contr	ol	Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	i, 95% CI		
3.2.1 Brief supportive psy	/chotherap	y + any	AD								
Kocsis 2009/Klein 2011 Subtotal (95% CI)	52	195 195	30	96 96	100.0% 100.0 %	0.85 [0.59, 1.24] 0.85 [0.59, 1.24]		-	•		
Total events Heterogeneity: Not applica Test for overall effect: Z = 0		41)	30								
T16							0.01	0.1 1 Favours AD		l O Inselling	100 3 + AD

167 168 Test for subgroup differences: Not applicable AD: antidepressant

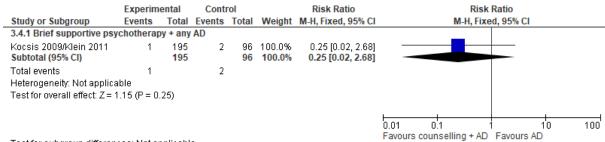
169

170 Figure 40: Discontinuation due to any reason



AD: antidepressant

174 Figure 41: Discontinuation due to side effects



175 Test for subgroup differences: Not applicable 176 AD: antidepressant

177

178 Figure 42: Functional impairment endpoint

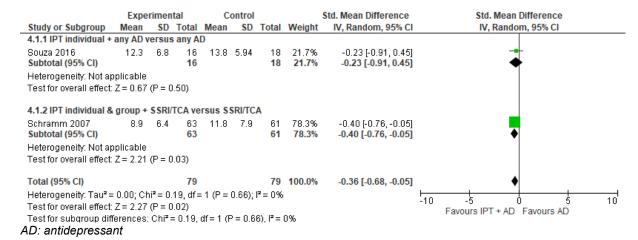
	Expe	erimen	nental Control					Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
3.5.1 Brief supportive psy	chother	ару +	any AD							
Kocsis 2009/Klein 2011 Subtotal (95% CI)	10.73	3.46	162 162	10.96	3.63	75 75	100.0% 100.0 %	-0.07 [-0.34, 0.21] - 0.07 [-0.34, 0.21]		
Heterogeneity: Not applicate Test for overall effect: Z =		0.64)								
Test for subgroup differen	ices: Not	annlio	able:						-10 -5 0 5 Favours counselling + AD Favours AD	10

179 Test for subgroup differences: Not applicable 180 AD: antidepressant

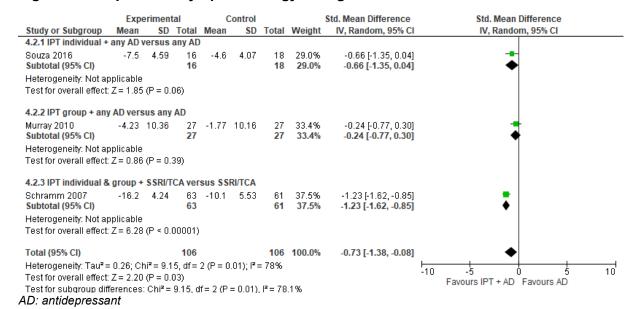
181

182 Comparison 4. Augmenting with IPT versus continuing with antidepressant

183 Figure 43: Depression symptomatology endpoint



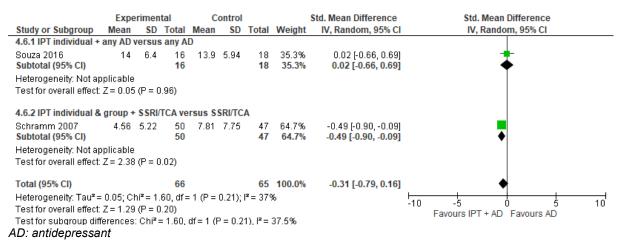
187 Figure 44: Depression symptomatology change score



188 189

190

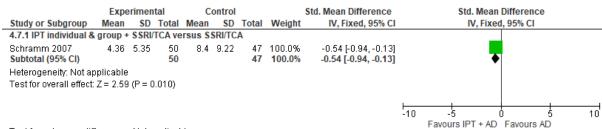
191 Figure 45: Depression symptomatology at 1-3 month follow-up



192 193

194

195 Figure 46: Depression symptomatology at 12-month follow-up

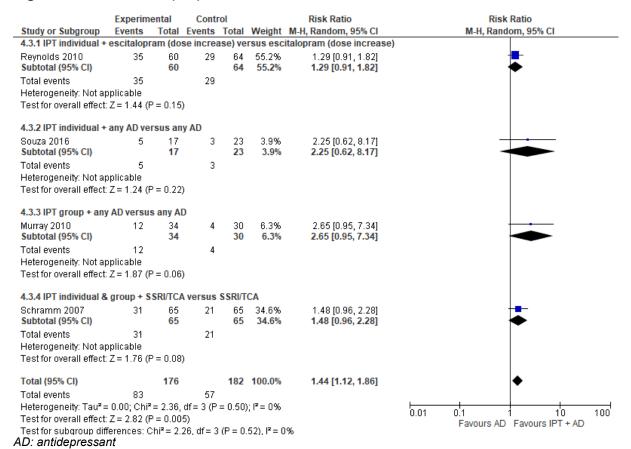


196

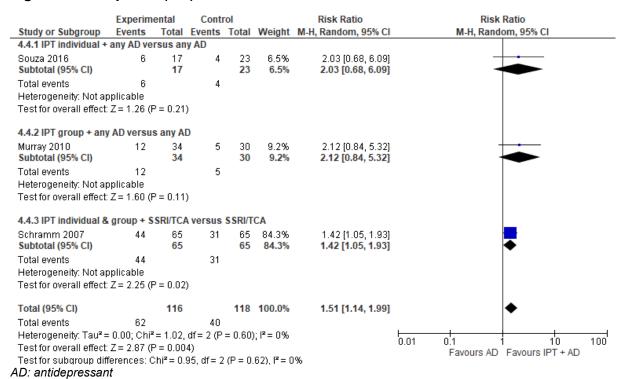
Test for subgroup differences: Not applicable

AD: antidepressant

199 Figure 47: Remission (ITT)



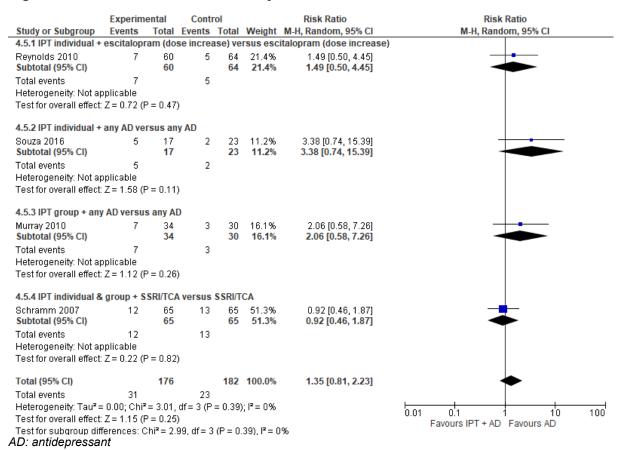
203 Figure 48: Response (ITT)



204 205

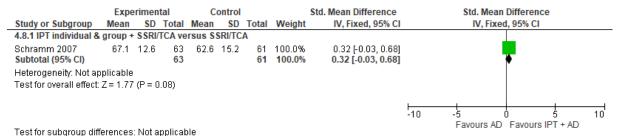
206

207 Figure 49: Discontinuation due to any reason



210

211 Figure 50: Global functioning endpoint



214

212 AD: antidepressant

AD: antidepressant

215 Figure 51: Global functioning at 3-month follow-up

	Expe	tal	C	ontrol			Std. Mean Difference	Sto	d. Mean Differe	ence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% (CI	
4.9.1 IPT individual &	group +	SSRI/T	CA ver	sus SSI	RI/TCA							
Schramm 2007 Subtotal (95% CI)	78.37	12.34	50 50	72.5	14.37	47 47	100.0% 100.0 %	0.44 [0.03, 0.84] 0.44 [0.03, 0.84]		•		
Heterogeneity: Not ap Test for overall effect:			03)									
Test for subgroup diff	ferences:	· Not ar	nlicahl	ρ.					-10 -5 Favo	0 ours AD Favou	5 Irs IPT + AD	10

216

218

219 Figure 52: Global functioning at 12-month follow-up

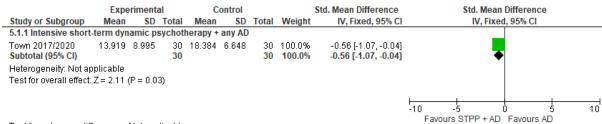
	Exp	eriment	tal	Control				Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95% (CI	
4.10.1 IPT individual	& group	+ SSRI/	TCA ve	ersus S	SRI/TCA	١							
Schramm 2007 Subtotal (95% CI)	79.08	11.29	50 50	72.17	17.49	47 47	100.0% 100.0%	0.47 [0.06, 0.87] 0.47 [0.06, 0.87]			•		
Heterogeneity: Not ap Test for overall effect:	•		02)										
Test for subgroup dif	ferences	: Not ap	plicabl	e					-10	-5 Favou	0 rs AD Favou	5 Irs IPT + AE	10 D

AD: antidepressant

222

223 Comparison 5. Augmenting with short-term psychodynamic psychotherapy versus 224 continuing with antidepressant

225 Figure 53: Depression symptomatology endpoint

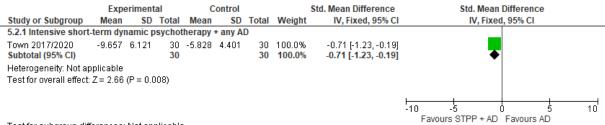


Test for subgroup differences: Not applicable AD: antidepressant

228

229

Figure 54: Depression symptomatology change score



230 Test for subgroup differences: Not applicable AD: antidepressant

232

233 Figure 55: Depression symptomatology at 3-month follow-up

	Expe	riment	al	C	ontrol			Std. Mean Difference	Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	i, 95% CI	
5.5.1 Intensive short	term dyn	amic p	sychot	herapy ·	+ any A	D					
Town 2017/2020 Subtotal (95% CI)	13.284	7.358	30 30	18	8.514	30 30		-0.58 [-1.10, -0.07] - 0.58 [-1.10 , - 0.07]	•		
Heterogeneity: Not ap Test for overall effect:		(P = 0.0	3)								
Test for subgroup dif	foroncoc:	Not ann	licable						-10 -5 Favours STPP + AD	5 Favours AD	10

234 Test for subgroup differe 235 AD: antidepressant

236

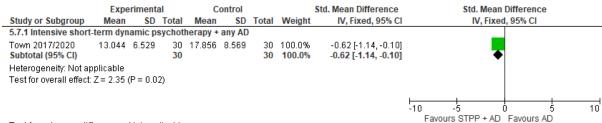
237 Figure 56: Depression symptomatology at 6-month follow-up

	Expe	riment	al	C	ontrol			Std. Mean Difference	Std. Mea	n Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixe	ed, 95% CI	
5.6.1 Intensive short	t-term dyn	amic p	sychot	herapy +	any AD)			_		
Town 2017/2020 Subtotal (95% CI)	13.098	7.959	30 30	17.889	8.782	30 30	100.0% 100.0%	-0.56 [-1.08, -0.05] - 0.56 [-1.08, -0.05]		>	
Heterogeneity: Not a Test for overall effect		(P = 0.0	3)								
									-10 -5	0 5	10
Tact for cubarous dit	foroncoc:	Not ann	dicable						Favours STPP + AD) Favours AD	

238 239 Test for subgroup differences: Not applicable AD: antidepressant

240

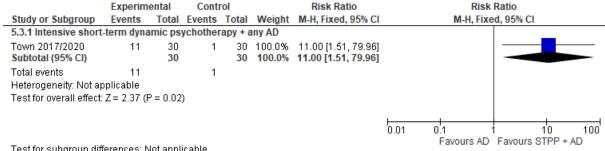
241 Figure 57: Depression symptomatology at 12-month follow-up



242 243 Test for subgroup differences: Not applicable

AD: antidepressant

245 Figure 58: Remission (ITT)



Test for subgroup differences: Not applicable AD: antidepressant

248

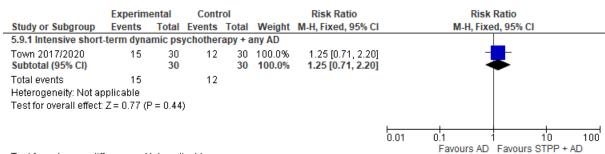
249 Figure 59: Remission (ITT) at 12-month follow-up

	Experim	ental	Conti	rol		Risk Ratio		Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI			
5.8.1 Intensive short-term dynamic psychotherapy + any AD												
Town 2017/2020 Subtotal (95% CI)	12	30 30	9	30 30	100.0% 100.0 %	1.33 [0.66, 2.69] 1.33 [0.66, 2.69]		-				
Total events Heterogeneity: Not a Test for overall effect		P = 0.42	9									
							0.01	0.1 Favours AD	1 Favours S	10 TPP +	100 AD	

250 Test for subgroup differences: Not applicable 251 AD: antidepressant

252

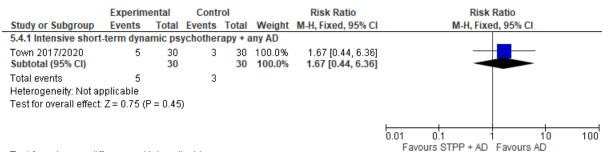
253 Figure 60: Response (ITT) at 12-month follow-up



254 Test for subgroup differences: Not applicable 255 AD: antidepressant

256

257 Figure 61: Discontinuation due to any reason



258 Test for subgroup differences: Not applicable

259 AD: antidepressant

260

261 Comparison 6. Augmenting with long-term psychodynamic psychotherapy versus 262 continuing with antidepressant

263 Figure 62: Depression symptomatology endpoint

	Expe	rimen	ıtal	Co	ontro	I		Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
6.1.1 Augmenting an	y AD									
Fonagy 2015 Subtotal (95% CI)	16.4	6.2	53 53	17.9	6.5	46 46	100.0% 100.0%	-0.23 [-0.63, 0.16] - 0.23 [-0.63, 0.16]		•
Heterogeneity: Not ap Test for overall effect:			0.25)							
									-10	-5 0 5 10
Test for subgroup dif	ferences:	: Not a	pplicat	ole						Favours LTPP + AD Favours continuing AD

264 265 AD: antidepressant

266

267 Figure 63: Depression symptomatology at 6-month follow-up

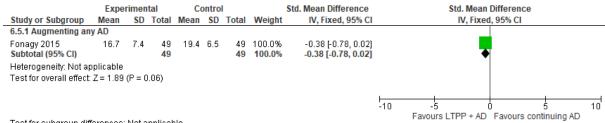
	Expe	rimer	ıtal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
6.4.1 Augmenting an	y AD								
Fonagy 2015 Subtotal (95% CI)	15.4	6.6	49 49	17.6	6.1	47 47	100.0% 100.0%	-0.34 [-0.75, 0.06] - 0.34 [-0.75, 0.06]	•
Heterogeneity: Not as	oplicable								
Test for overall effect	Z=1.67	(P = 0	0.10)						
									-10 -5 0 5 10
Test for subgroup dif	ferences:	Not a	applicat	ole					Favours LTPP + AD Favours continuing AD

268 269

270

271

272 Figure 64: Depression symptomatology at 1-year follow-up



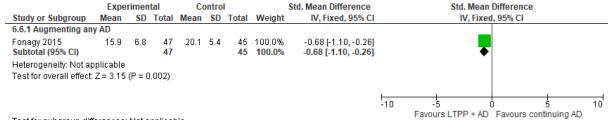
275

Test for subgroup differences: Not applicable

AD: antidepressant

AD: antidepressant

276 Figure 65: Depression symptomatology at 2-year follow-up



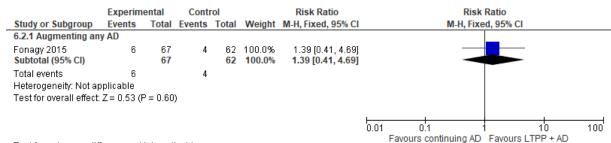
277 278 Test for subgroup differences: Not applicable AD: antidepressant

279

283

287

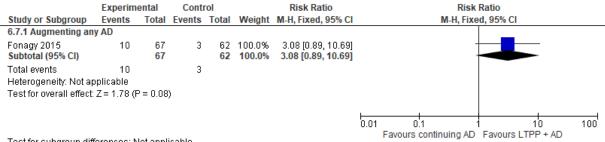
280 Figure 66: Remission (ITT)



281 282 Test for subgroup differences: Not applicable

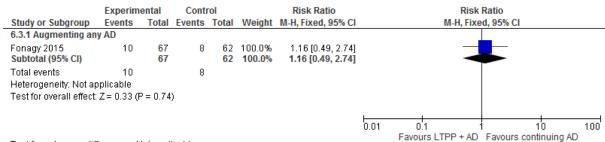
AD: antidepressant

284 Figure 67: Remission (ITT) at 2-year follow-up



Test for subgroup differences: Not applicable AD: antidepressant

288 Figure 68: Discontinuation due to any reason

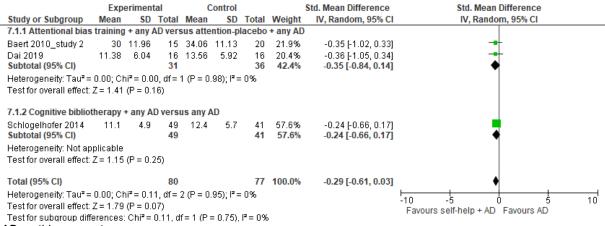


289 Test for subgroup differences: Not applicable

290 291 AD: antidepressant 292

293 Comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/-294 attention-placebo)

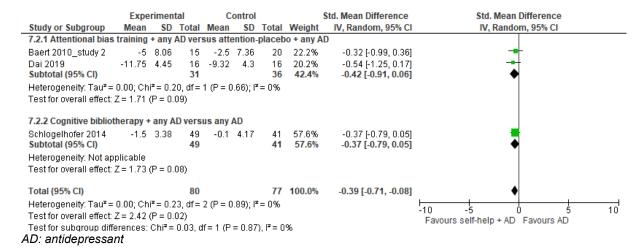
295 Figure 69: Depression symptomatology endpoint



297 AD: antidepressant

298

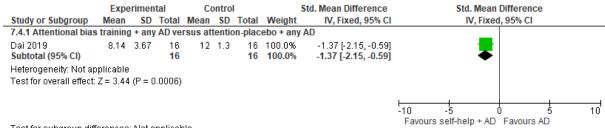
299 Figure 70: Depression symptomatology change score



300 301

302

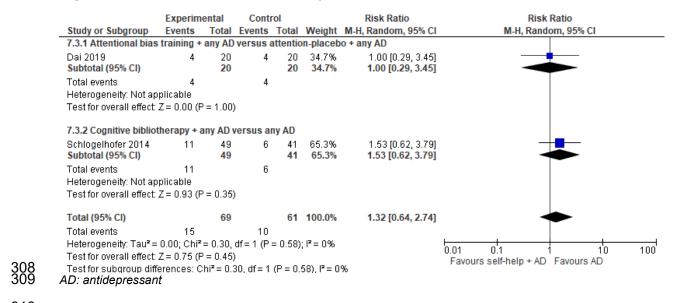
303 Figure 71: Depression symptomatology at 1-month follow-up



304 305 Test for subgroup differences: Not applicable

AD: antidepressant

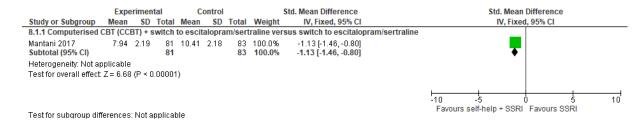
307 Figure 72: Discontinuation due to any reason



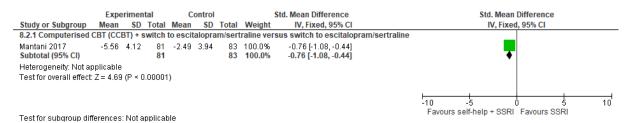
310

311 Comparison 8. Augmenting with self-help and switching to SSRI versus switching to 312 SSRI-only

313 Figure 73: Depression symptomatology endpoint



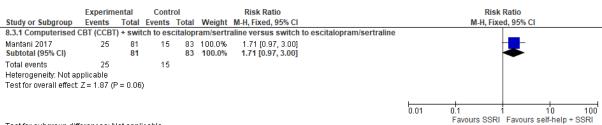
315 Figure 74: Depression symptomatology change score



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314

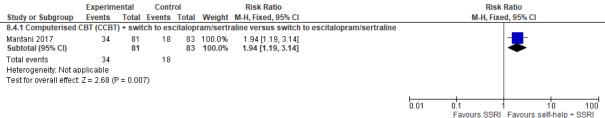
318 Figure 75: Remission (ITT)



319

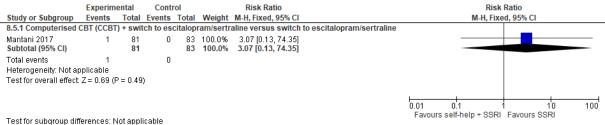
Test for subgroup differences: Not applicable

321 Figure 76: Response (ITT)



322 Test for subgroup differences: Not applicable

323 Figure 77: Discontinuation due to any reason

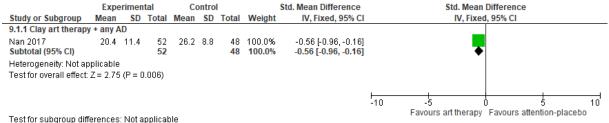


324

325

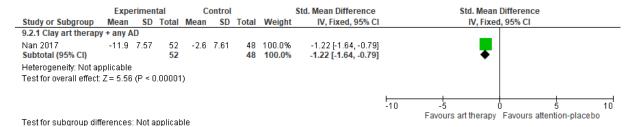
326 Comparison 9. Augmenting with art therapy versus attention-placebo

327 Figure 78: Depression symptomatology endpoint

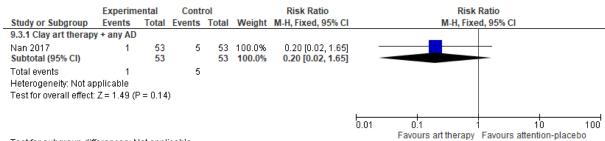


328

329 Figure 79: Depression symptomatology change score



332 Figure 80: Discontinuation due to any reason



333 Test for subgroup differences: Not applicable

334

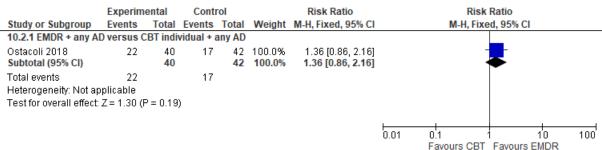
335 Comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

337 Figure 81: Depression symptomatology endpoint

	Exp	eriment	tal	(Control			Std. Mean Difference		Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	1, 95% CI		
10.1.1 EMDR + any AD versus CBT individual + any AD													
Ostacoli 2018 Subtotal (95% CI)	10.55	11.17	31 31	17.86	11.17	35 35	100.0% 100.0%	-0.65 [-1.14, -0.15] - 0.65 [-1.14, -0.15]		•			
Heterogeneity: Not a	' '		- 41										
Test for overall effect	: Z = 2.55	(P = U.	U1)										
									-10	-5	<u> </u>	5	10
										Favours EMDR	Favours C	BT	

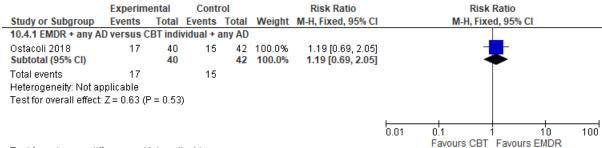
338 Test for subgroup differences: Not applicable

339 Figure 82: Remission (ITT)



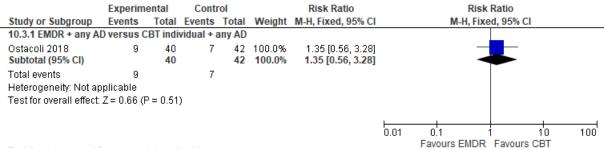
340 Test for subgroup differences: Not applicable

341 Figure 83: Remission (ITT) at 6-month follow-up



342 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

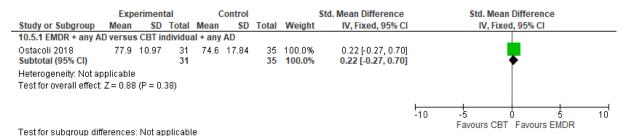
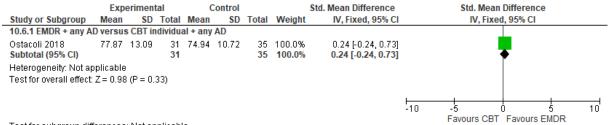


Figure 86: Global functioning at 6-month follow-up



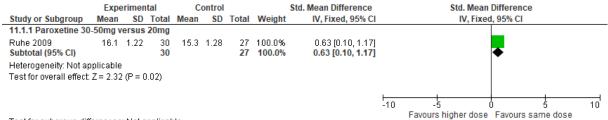
348 Test for subgroup differences: Not applicable

349

346

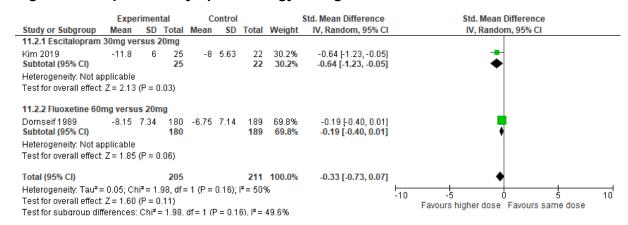
350 Comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

351 Figure 87: Depression symptomatology endpoint



352 Test for subgroup differences: Not applicable

353 Figure 88: Depression symptomatology change score



355 Figure 89: Remission (ITT)

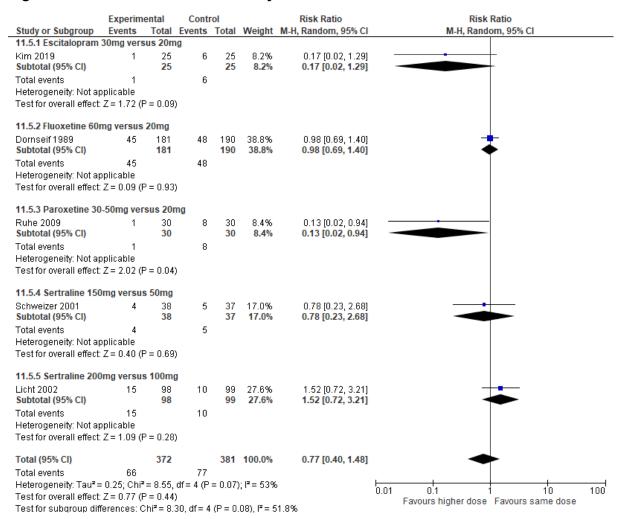
	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
11.3.1 Escitalopram	•	us 20m	ıg				
Kim 2019 Subtotal (95% CI)	15	25 25	10	25 25	17.2% 17.2 %	1.50 [0.84, 2.67] 1.50 [0.84, 2.67]	•
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.17	10				
11.3.2 Fluoxetine 60r	ng versus	20mg					
Dornseif 1989 Subtotal (95% CI)	51	181 181	51	190 190	34.7% 34.7%	1.05 [0.75, 1.46] 1.05 [0.75, 1.46]	‡
Total events Heterogeneity: Not ap Test for overall effect:		o = 0 77	51				
11.3.3 Paroxetine 30	•	,					
Ruhe 2009 Subtotal (95% CI)	4	30 30 30	2	30 30	2.8% 2.8%	2.00 [0.40, 10.11] 2.00 [0.40, 10.11]	
Total events Heterogeneity: Not ap	4		2		2.07	2.00 [0.10, 10.11]	
Test for overall effect:	•	9 = 0.40)				
11.3.4 Sertraline 150	mg versus	50mg					
Schweizer 2001 Subtotal (95% CI)	18	38 38	12	37 37	17.4% 17.4 %	1.46 [0.82, 2.59] 1.46 [0.82, 2.59]	*
Total events Heterogeneity: Not ap	18 plicable		12				
Test for overall effect:	Z = 1.30 (F	P = 0.20)				
11.3.5 Sertraline 200	mg versus	100mg	9				
Licht 2002 Subtotal (95% CI)	28	98 98	37	99 99	27.9% 27.9 %	0.76 [0.51, 1.14] 0.76 [0.51, 1.14]	-
Total events Heterogeneity: Not ap Test for overall effect:	•	P = 0.19	37				
Total (95% CI)	,	372		381	100.0%	1.10 [0.84, 1.45]	L
Total events	116	012	112	001	.00.070	1110 [0104, 1140]	T
Heterogeneity: Tau² = Test for overall effect:	0.03; Chi²		df= 4 (P	= 0.22)	; I²= 30%		0.01 0.1 1 10 1
Test for overall ellect. Test for subgroup diff	,		,	/P = 0	22) 18 - 2	0.00	Favours same dose Favours higher dose

356

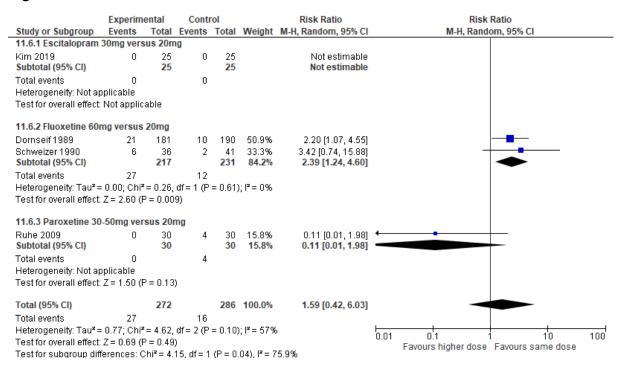
357 Figure 90: Response (ITT)

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup 11.4.1 Escitalopram	Events			Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kim 2019	20 20	25 2011	9 12	25	14.3%	1.67 [1.06, 2.62]	
Subtotal (95% CI)	20	25 25	12	25 25	14.3%	1.67 [1.06, 2.62]	•
Total events	20		12				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 2.21 (F	P = 0.03))				
11.4.2 Fluoxetine 60n	ng versus	20mg					
Dornseif 1989	63	181	62	190	20.6%	1.07 [0.80, 1.42]	+
Schweizer 1990	18	36	21	41	14.7%	0.98 [0.63, 1.52]	+
Subtotal (95% CI)		217		231	35.3%	1.04 [0.82, 1.32]	•
Total events	81		83				
Heterogeneity: Tau ² =				= 0.74	; I² = 0%		
Test for overall effect:	Z = 0.31 (F	² = 0.75)	1				
11.4.3 Paroxetine 30	-50mg ver	sus 20n	ng				
Ruhe 2009	10	30	10	30	8.2%	1.00 [0.49, 2.05]	
Subtotal (95% CI)		30		30	8.2%	1.00 [0.49, 2.05]	•
Total events	10		10				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.00 (F	P = 1.00))				
11.4.4 Sertraline 150	mg versus	s 50mg					
Schweizer 2001	30	38	21	37	19.0%	1.39 [1.00, 1.93]	
Subtotal (95% CI)		38		37	19.0%	1.39 [1.00, 1.93]	•
Total events	30		21				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 1.99 (F	° = 0.05))				
11.4.5 Sertraline 200	mg versus	s 100mg	J				
Licht 2002	54	98	69	99	23.3%	0.79 [0.63, 0.99]	*
Subtotal (95% CI)		98		99	23.3%	0.79 [0.63, 0.99]	◆
Total events	54		69				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 2.08 (F	P = 0.04)				
Total (95% CI)		408		422	100.0%	1.10 [0.86, 1.39]	•
Total events	195		195				
Heterogeneity: Tau ² =	0.05; Chi²	= 13.24	, df = 5 (f	= 0.0	2); I² = 62	%	0.01 0.1 1 10 100
Test for overall effect:							Favours same dose Favours higher dose
Test for subgroup diff	erences: C	hi² = 13	.13, df=	4 (P = I	0.01), I²=	69.5%	

359 Figure 91: Discontinuation due to any reason

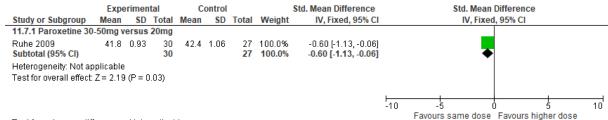


361 Figure 92: Discontinuation due to side effects



362

363 Figure 93: Quality of life physical component score (PCS) endpoint



364 Test for subgroup differences: Not applicable

365 Figure 94: Quality of life mental component score (MCS) endpoint

	Expe	erimen	tal	C	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.8.1 Paroxetine 3	0-50mg v	/ersus	20mg							
Ruhe 2009 Subtotal (95% CI)	29.6	1.37	30 30	27.3	1.57	27 27	100.0% 100.0%	1.55 [0.95, 2.14] 1.55 [0.95, 2.14]		
Heterogeneity: Not a Test for overall effect			0.00001)						
									-10	-5 0 5 10 Favours same dose Favours higher dose

366 Test for subgroup differences: Not applicable

367

370

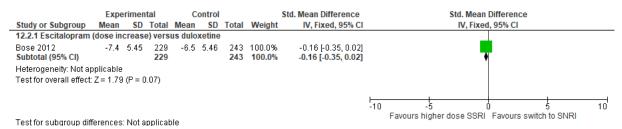
372

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

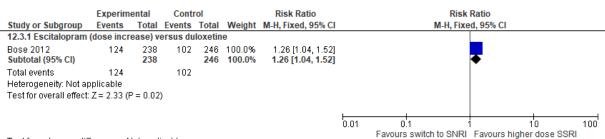
369 Figure 95: Depression symptomatology endpoint

	Expe	rimen	ital	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.1.1 Escitalopram	(dose inc	creas	e) vers	us dulo:	xetine				<u></u>
Bose 2012 Subtotal (95% CI)	7.7	5.3	229 229	8.8	5.14	243 243	100.0% 100.0 %	-0.21 [-0.39, -0.03] -0.21 [-0.39, -0.03]	•
Heterogeneity: Not a Test for overall effect		(P = 0	0.02)						
									-10 -5 0 5 10
Test for subgroup di	fferences:	Not a	pplicat	ole					Favours higher dose SSRI Favours switch to SNRI

371 Figure 96: Depression symptomatology change score

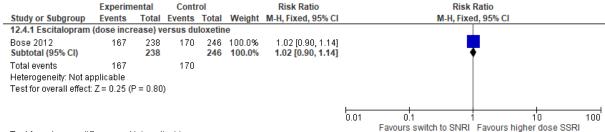


373 Figure 97: Remission (ITT)



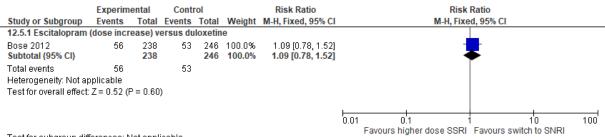
374 Test for subgroup differences: Not applicable

375 Figure 98: Response (ITT)



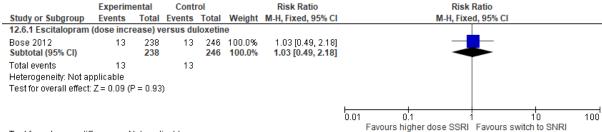
376 Test for subgroup differences: Not applicable

377 Figure 99: Discontinuation due to any reason



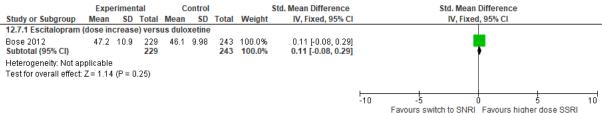
378 Test for subgroup differences: Not applicable

379 Figure 100: Discontinuation due to side effects



380 Test for subgroup differences: Not applicable

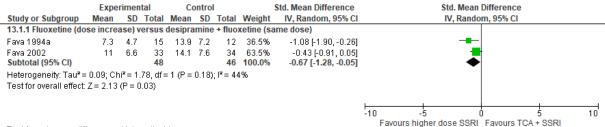
381 Figure 101: Quality of life endpoint



382 Test for subgroup differences: Not applicable

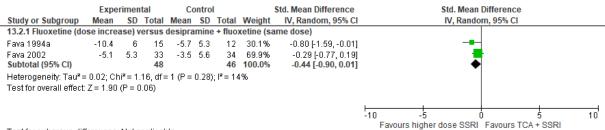
384 Comparison 13. Increasing the dose of SSRI versus augmenting with TCA

385 Figure 102: Depression symptomatology endpoint



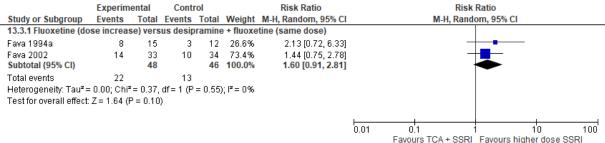
386 Test for subgroup differences: Not applicable

387 Figure 103: Depression symptomatology change score



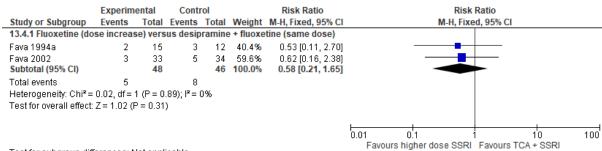
388 Test for subgroup differences: Not applicable

389 Figure 104: Remission (ITT)

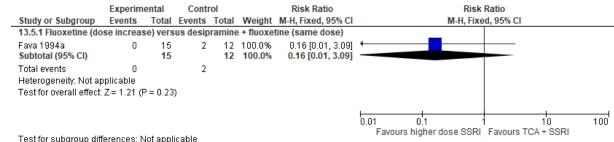


390 Test for subgroup differences: Not applicable

391 Figure 105: Discontinuation due to any reason



393 Figure 106: Discontinuation due to side effects



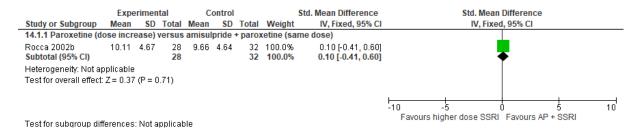
394

395

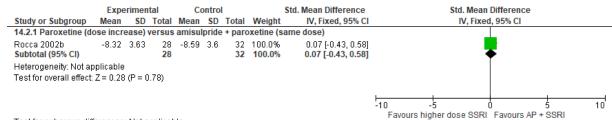
398

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

397 Figure 107: Depression symptomatology endpoint

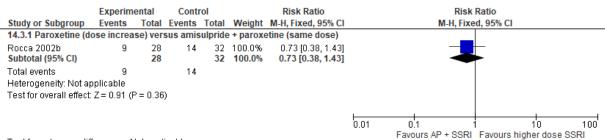


399 Figure 108: Depression symptomatology change score

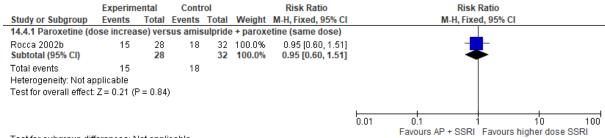


400 Test for subgroup differences: Not applicable

401 Figure 109: Remission (ITT)

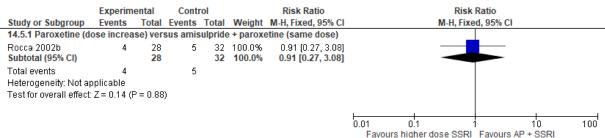


403 Figure 110: Response (ITT)



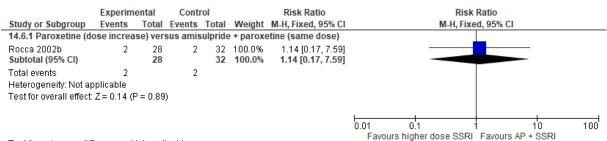
404 Test for subgroup differences: Not applicable

405 Figure 111: Discontinuation due to any reason



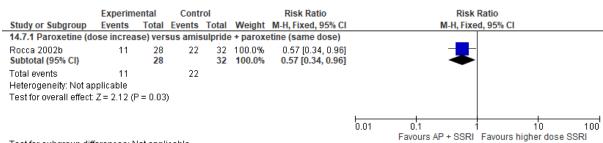
406 Test for subgroup differences: Not applicable

407 Figure 112: Discontinuation due to side effects



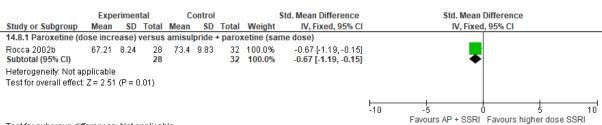
408 Test for subgroup differences: Not applicable

409 Figure 113: Functional remission (GAF score ≥71)



410 Test for subgroup differences: Not applicable

411 Figure 114: Global functioning endpoint

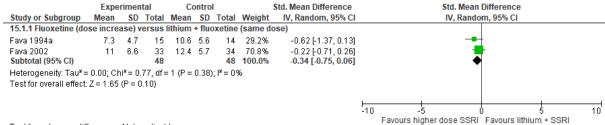


413

418

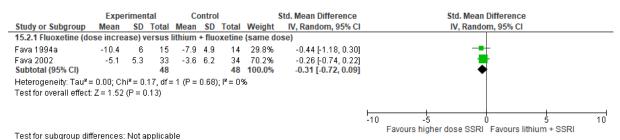
414 Comparison 15. Increasing the dose of SSRI versus augmenting with lithium

415 Figure 115: Depression symptomatology endpoint

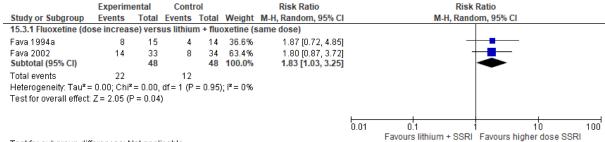


416 Test for subgroup differences: Not applicable

417 Figure 116: Depression symptomatology change score

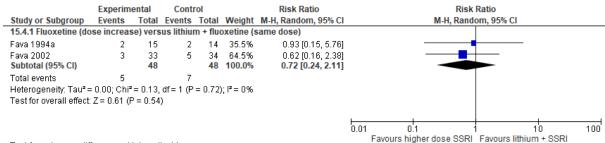


419 Figure 117: Remission (ITT)

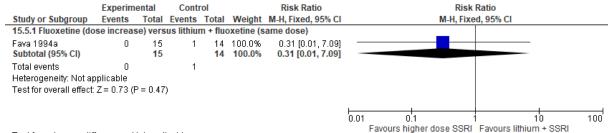


420 Test for subgroup differences: Not applicable

421 Figure 118: Discontinuation due to any reason



423 Figure 119: Discontinuation due to side effects



424 Test for subgroup differences: Not applicable

425

426 Comparison 16. Switching to SSRI versus continuing with antidepressant

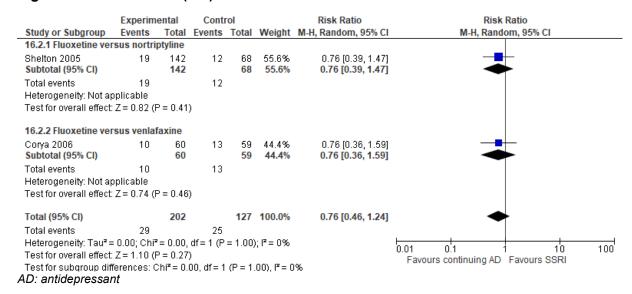
427 Figure 120: Depression symptomatology change score

	Expe	erimen	tal	Co	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
16.1.1 Fluoxetine ver	sus nor	triptyli	ne						
Shelton 2005 Subtotal (95% CI)	-8.51	8.34	142 142	-7.46	8.08	68 68	55.4% 55.4 %	-0.13 [-0.42, 0.16] - 0.13 [-0.42, 0.16]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.86	(P = 0).39)						
16.1.2 Fluoxetine ver	sus ven	lafaxir	1e						
Corya 2006 Subtotal (95% CI)	-11.7	8.83	56 56	-13.73	8.91	58 58	44.6% 44.6 %	0.23 [-0.14, 0.60] 0.23 [-0.14, 0.60]	<u> </u>
Heterogeneity: Not ap									
Test for overall effect:	Z = 1.21	(P = 0	1.23)						
Total (95% CI)			198			126	100.0%	0.03 [-0.31, 0.38]	♦
Heterogeneity: Tau² =				: 1 (P = 0	0.14); I	= 54%	5		-10 -5 0 5 10
Test for overall effect:		•	,						Favours SSRI Favours continuing AD
Test for subgroup diff		: Chi * :	= 2.19,	df = 1 (P	= 0.14	1), I*= 5	4.4%		
AD: antidepressa	ırıt								

428

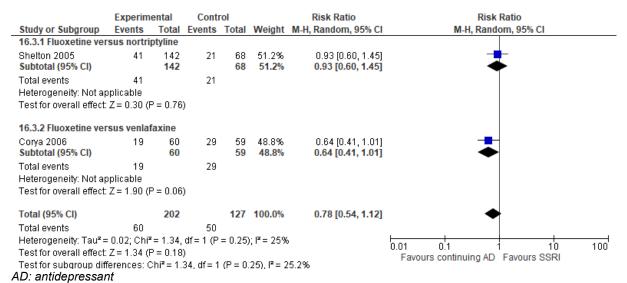
430

431 Figure 121: Remission (ITT)



432 433

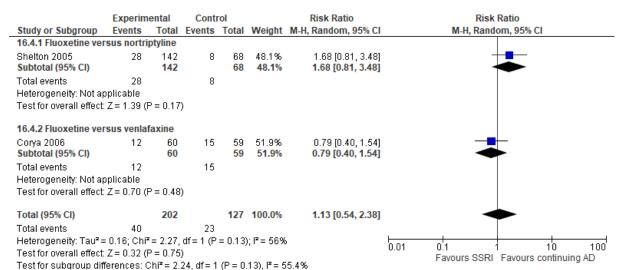
435 Figure 122: Response (ITT)



437

438

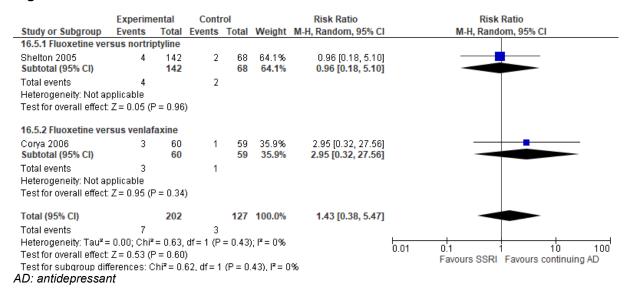
439 Figure 123: Discontinuation due to any reason



440

AD: antidepressant

443 Figure 124: Discontinuation due to side effects



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446

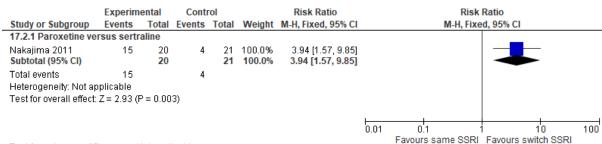
447 Comparison 17. Switching to a different SSRI versus continuing same SSRI

448 Figure 125: Remission (ITT)

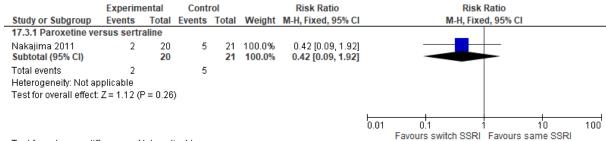
	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
17.1.1 Paroxetine ve	ersus sertr	aline								
Nakajima 2011 Subtotal (95% CI)	12	20 20	3	21 21	100.0% 100.0 %	4.20 [1.39, 12.71] 4.20 [1.39, 12.71]				
Total events Heterogeneity: Not a Test for overall effect		P = 0.01	3							
							0.01	0.1 Favours same SSRI	10 10 Favours switch SSRI	100

449 Test for subgroup differences: Not applicable

450 Figure 126: Response (ITT)

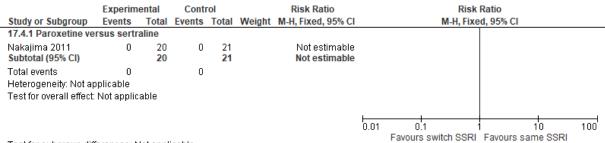


452 Figure 127: Discontinuation due to any reason



453 Test for subgroup differences: Not applicable

454 Figure 128: Discontinuation due to side effects

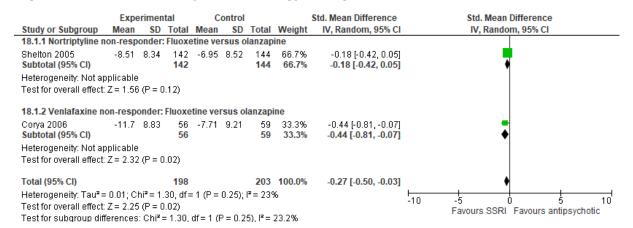


455 Test for subgroup differences: Not applicable

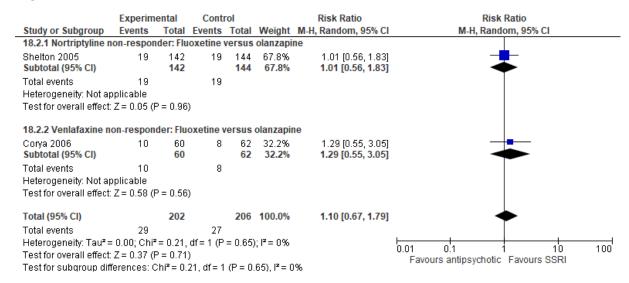
456

457 Comparison 18. Switching to SSRI versus antipsychotic

458 Figure 129: Depression symptomatology change score



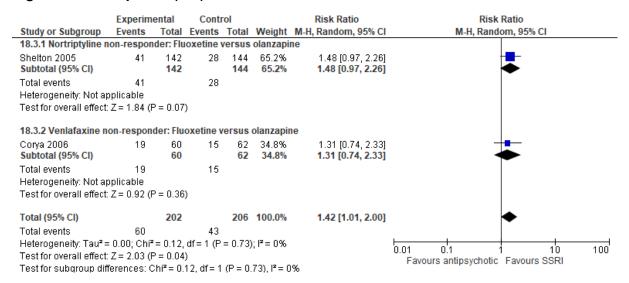
460 Figure 130: Remission (ITT)



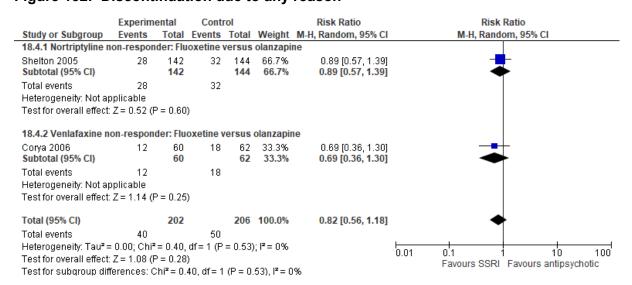
462 Figure 131: Response (ITT)

461

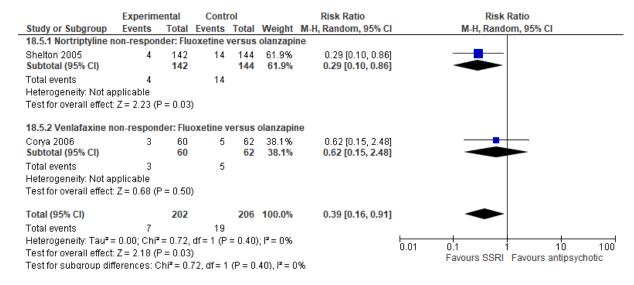
463



464 Figure 132: Discontinuation due to any reason



466 Figure 133: Discontinuation due to side effects

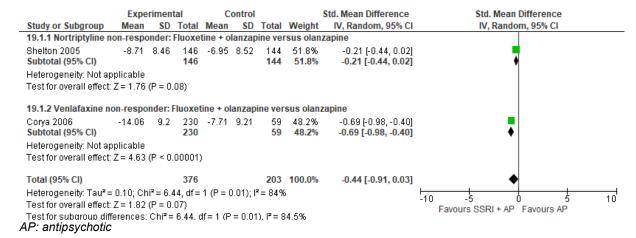


467 468

469

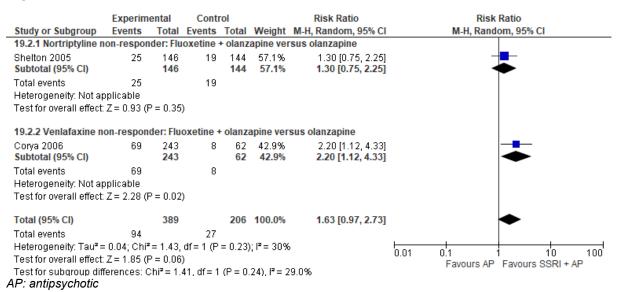
470 Comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychotic-only

472 Figure 134: Depression symptomatology change score



473 474

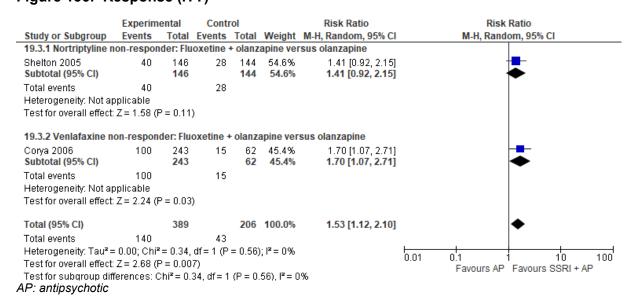
476 Figure 135: Remission (ITT)



4// 478

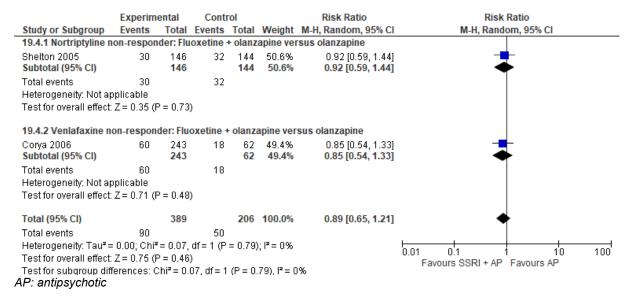
479

480 Figure 136: Response (ITT)



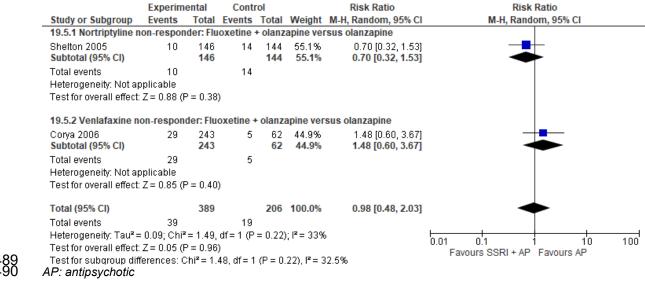
481 482

484 Figure 137: Discontinuation due to any reason



487

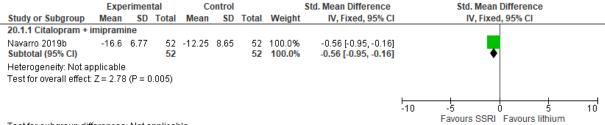
488 Figure 138: Discontinuation due to side effects



491 492

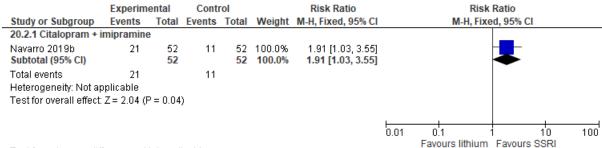
493 Comparison 20. Augmenting with SSRI versus augmenting with lithium

494 Figure 139: Depression symptomatology change score



495

496 Figure 140: Remission (ITT)



497 Test for subgroup differences: Not applicable

498

499 Comparison 21. Switching to TCA versus SSRI

500 Figure 141: Depression symptomatology endpoint

	rimen	lai	C	ontrol		S	td. Mean Difference		Std. Mean I	Difference	
Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
t study (drugs)	non-re	esponde	ers: De	esipran	nine versu	s citalopram				
14.09	8.56	67 67	15.83	8.75	85 85	100.0% 100.0%			•	ı	
plicable Z = 1.22		1.22)									
								-10	-5 0	1 5	10
ŀ	t study 14.09 olicable	t study drugs) 14.09 8.56 olicable	t study drugs) non -ro 14.09 8.56 67 67	t study drugs) non-responde 14.09 8.56 67 15.83 67 olicable	t study drugs) non-responders: De 14.09 8.56 67 15.83 8.75 67 olicable	t study drugs) non-responders: Desiprar 14.09 8.56 67 15.83 8.75 85 67 85 olicable	t study drugs) non-responders: Desipramine versu: 14.09 8.56 67 15.83 8.75 85 100.0% 67 85 100.0% olicable	t study drugs) non-responders: Desipramine versus citalopram 14.09 8.56 67 15.83 8.75 85 100.0% -0.20 [-0.52, 0.12] 67 85 100.0% -0.20 [-0.52, 0.12] olicable	t study drugs) non-responders: Desipramine versus citalopram 14.09 8.56 67 15.83 8.75 85 100.0% -0.20 [-0.52, 0.12] 67 85 100.0% -0.20 [-0.52, 0.12] olicable Z = 1.22 (P = 0.22)	t study drugs) non-responders: Desipramine versus citalopram 14.09 8.56 67 15.83 8.75 85 100.0% -0.20 [-0.52, 0.12] 67 85 100.0% -0.20 [-0.52, 0.12] olicable Z = 1.22 (P = 0.22)	t study drugs) non-responders: Desipramine versus citalopram 14.09 8.56 67 15.83 8.75 85 100.0% -0.20 [-0.52, 0.12] 67 85 100.0% -0.20 [-0.52, 0.12] olicable Z = 1.22 (P = 0.22)

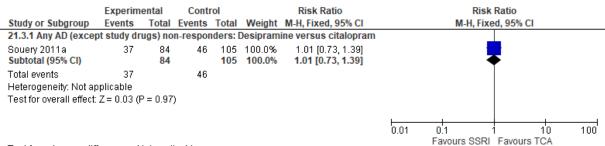
Test for subgroup differences: Not applicable

502 Figure 142: Remission (ITT)

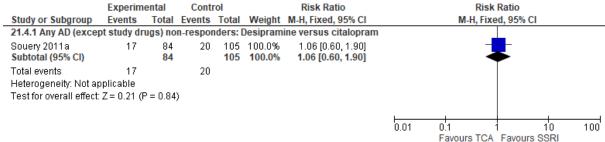
	Experim	ental	Conti	rol		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
21.2.1 Any AD (exce	pt study dr	ugs) no	n-respor	nders: l	Desipram	ine versus citalopram					
Souery 2011a Subtotal (95% CI)	21	84 84	16	105 105	100.0% 100.0%	1.64 [0.92, 2.94] 1.64 [0.92, 2.94]		,			
Total events Heterogeneity: Not a Test for overall effect		P = 0.10	16								
							0.01	0.1 Favours SSRI	•	10 CA	100

Test for subgroup differences: Not applicable

504 Figure 143: Response (ITT)



506 Figure 144: Discontinuation due to any reason



Test for subgroup differences: Not applicable

508

509 Comparison 22. Switching to TCA versus augmenting with mirtazapine

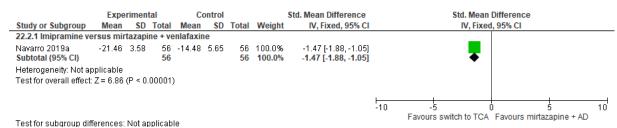
510 Figure 145: Depression symptomatology endpoint

	Expe	rimen	tal	Co	ontrol			Std. Mean Difference		Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
22.1.1 Imipramine ve	ersus mii	tazap	ine + v	enlafaxi	ine							
Navarro 2019a Subtotal (95% CI)	6.43	4.28	56 56	14.07	8.51	56 56	100.0% 100.0 %	-1.13 [-1.53, -0.73] - 1.13 [-1.53, -0.73]		•		
Heterogeneity: Not ap Test for overall effect:			.00001)								
									-10	-5	 	10

511 Test for subgroup differences: Not applicable AD: antidepressant

513

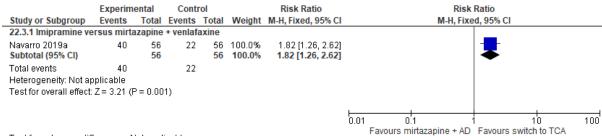
514 Figure 146: Depression symptomatology change score



515 Test for subgroup difference 516 AD: antidepressant

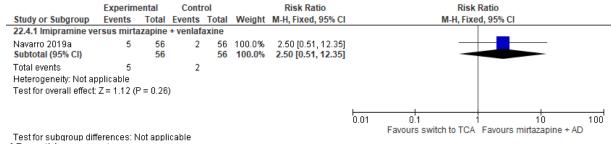
517

518 Figure 147: Remission (ITT)



519 Test for subgroup differences: Not applicable 520 AD: antidepressant

522 Figure 148: Discontinuation due to any reason



523 Test for subgroup differences: Not applicable 524 AD: antidepressant

525

526 Comparison 23. Switching to mianserin versus continuing with antidepressant

527 Figure 149: Depression symptomatology change score

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference		Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
23.1.1 versus fluoxe	etine										
Ferreri 2001 Subtotal (95% CI)	-13.1	7.3	33 33	-11.3	7.4	38 38	100.0% 100.0%	-0.24 [-0.71, 0.23] - 0.24 [-0.71, 0.23]		•	
Heterogeneity: Not a Test for overall effect		(P = 0	1.31)								
									-10	-5 0 5	5 10
Test for subgroup di	fferences:	Not a	nnlicat	nle						Favours mianserin Favours conti	nuing AD

Prest for subgroup differences: Not applicable AD: antidepressant

530

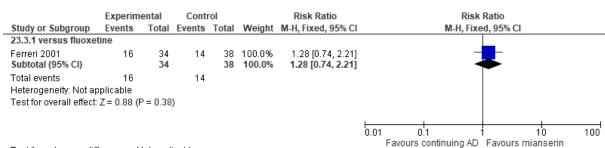
531 Figure 150: Remission (ITT)

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
23.2.1 versus fluoxe	etine									
Ferreri 2001 Subtotal (95% CI)	12	34 34	7	38 38	100.0% 100.0 %	1.92 [0.85, 4.30] 1.92 [0.85, 4.30]				
Total events Heterogeneity: Not a Test for overall effect		P = 0.12	7							
T16							0.01	0.1 1 Favours continuing AD Favours	10 mianserin	100

532 Test for subgroup differences: Not applicable AD: antidepressant

534

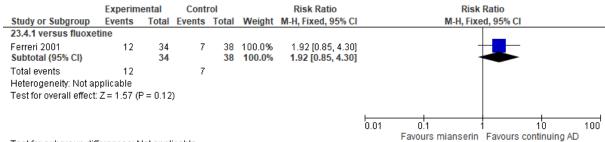
535 Figure 151: Response (ITT)



536 537 Test for subgroup differences: Not applicable

AD: antidepressant

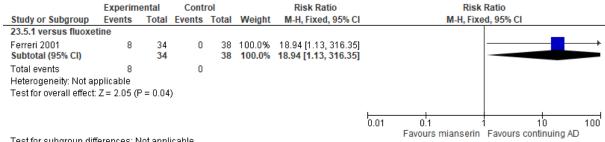
539 Figure 152: Discontinuation due to any reason



Test for subgroup differences: Not applicable AD: antidepressant

542

543 Figure 153: Discontinuation due to side effects



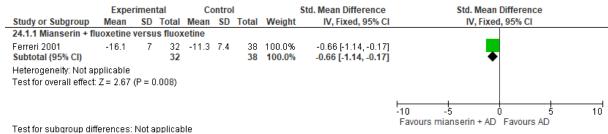
Test for subgroup differences: Not applicable AD: antidepressant

546

547

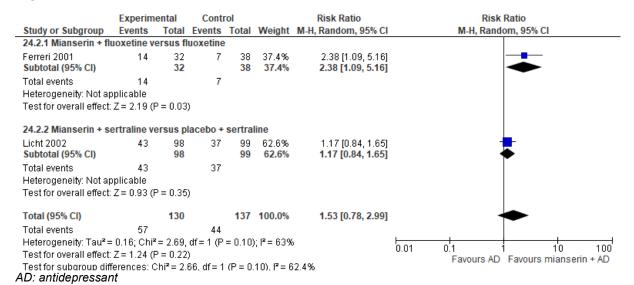
548 Comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/-549 placebo)

550 Figure 154: Depression symptomatology change score



AD: antidepressant

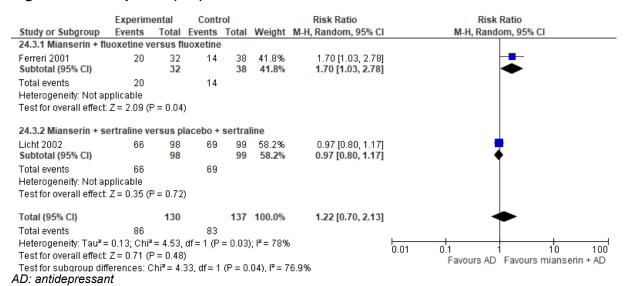
554 Figure 155: Remission (ITT)



550

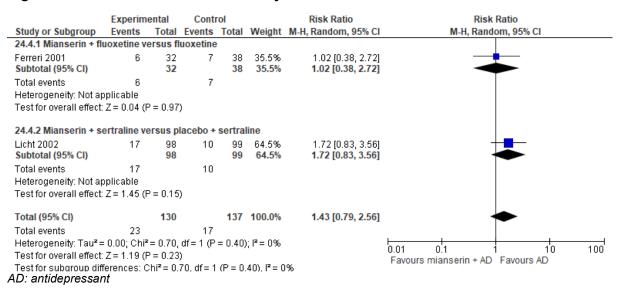
557

558 Figure 156: Response (ITT)



560

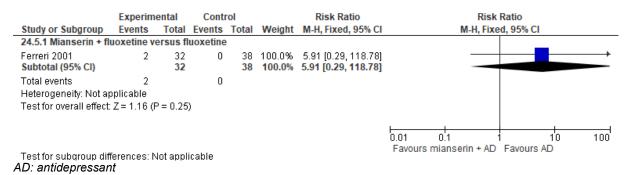
562 Figure 157: Discontinuation due to any reason



564

565

566 Figure 158: Discontinuation due to side effects



568

569

570

571 Comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

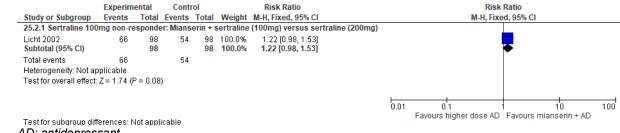
572 Figure 159: Remission (ITT)



573 574

74 AD: antidepressant

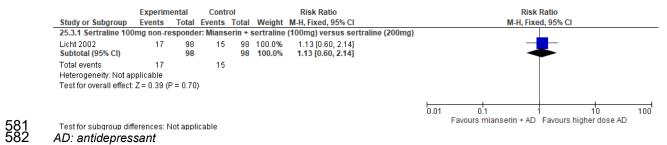
576 Figure 160: Response (ITT)



577 578 AD: antidepressant

579

580 Figure 161: Discontinuation due to any reason

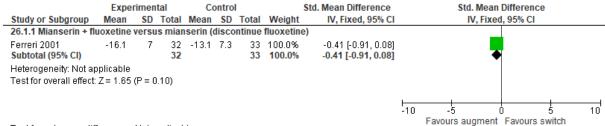


583

584

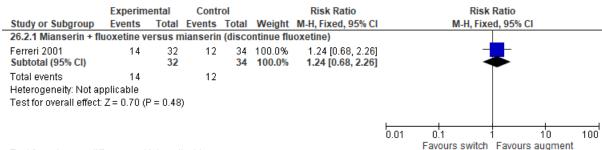
585 Comparison 26. Augmenting with mianserin versus switch to mianserin

586 Figure 162: Depression symptomatology change score

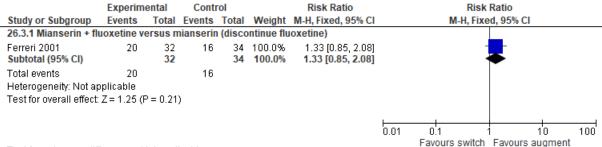


587 Test for subgroup differences: Not applicable

588 Figure 163: Remission (ITT)

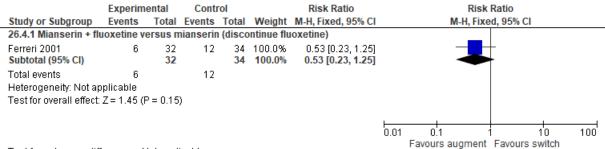


590 Figure 164: Response (ITT)



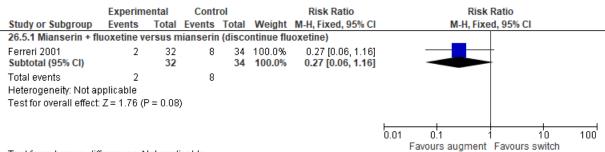
591 Test for subgroup differences: Not applicable

592 Figure 165: Discontinuation due to any reason



593 Test for subgroup differences: Not applicable

594 Figure 166: Discontinuation due to side effects

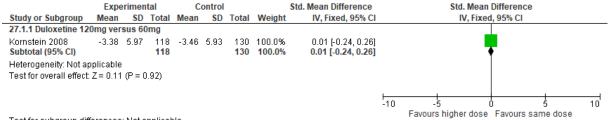


595 Test for subgroup differences: Not applicable

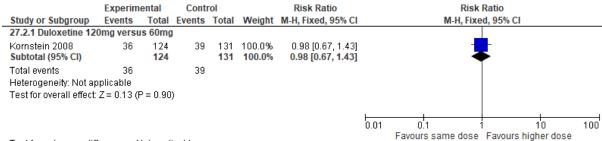
596

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

598 Figure 167: Depression symptomatology change score



600 Figure 168: Remission (ITT)



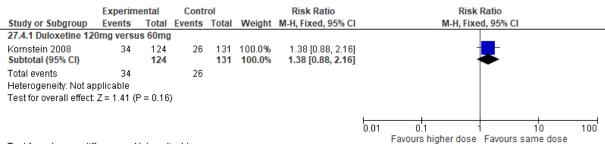
Test for subgroup differences: Not applicable

602 Figure 169: Response (ITT)

	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
27.3.1 Duloxetine 12	Omg versu	ıs 60mg	1							
Kornstein 2008 Subtotal (95% CI)	48	124 124	58	131 131	100.0% 100.0 %	0.87 [0.65, 1.17] 0.87 [0.65, 1.17]				
Total events Heterogeneity: Not a Test for overall effect		P = 0.37	58							
							0.01	0.1 Favours same dose	10 Favours higher dose	100

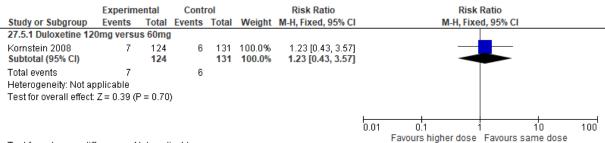
Test for subgroup differences: Not applicable

604 Figure 170: Discontinuation due to any reason



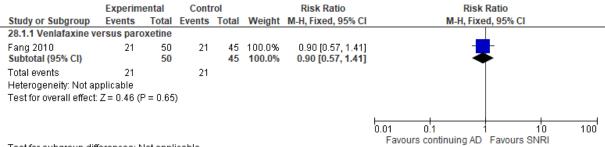
Test for subgroup differences: Not applicable

606 Figure 171: Discontinuation due to side effects



609 Comparison 28. Switching to SNRI versus continuing with antidepressant

610 Figure 172: Remission (ITT)



Test for subgroup differences: Not applicable 611 612

AD: antidepressant

613

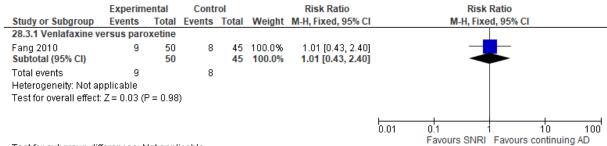
Figure 173: Response (ITT) 614

	Experim	ental	Cont	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI	
28.2.1 Venlafaxine v	ersus pard	etine								
Fang 2010 Subtotal (95% CI)	32	50 50	30	45 45	100.0% 100.0 %	0.96 [0.72, 1.29] 0.96 [0.72, 1.29]				
Total events Heterogeneity: Not a Test for overall effect		P = 0.78	30							
							0.01 Favo	0.1 1 urs continuing AD	10 Favours SNRI	100

615 616 Test for subgroup differences: Not applicable

AD: antidepressant

618 Figure 174: Discontinuation due to any reason

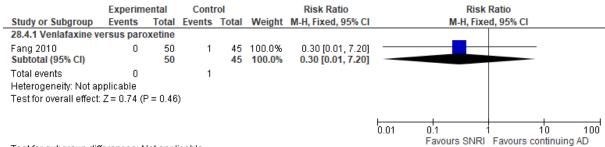


Test for subgroup differences: Not applicable

AD: antidepressant

621

622 Figure 175: Discontinuation due to side effects



623 624 Test for subgroup differences: Not applicable AD: antidepressant

625

626 Figure 176: Quality of life physical component score (PCS) change score

	Exp	erimen	tal	(Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
28.5.1 Venlafaxine v	ersus pa	aroxetir	ie						
Fang 2010 Subtotal (95% CI)	13.89	11.57	50 50	13.68	11.43		100.0% 100.0%	0.02 [-0.38, 0.42] 0.02 [-0.38, 0.42]	•
Heterogeneity: Not ap Test for overall effect			93)						
									-10 -5 0 5 10 Favours continuing AD Favours SNRI
Tact for cubarous dif	foroncoo	· Not or	nlicabl						ravours continuing AD Travours of the

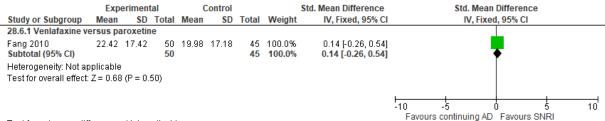
Test for subgroup differences: Not applicable

AD: antidepressant

629

627 628

630 Figure 177: Quality of life mental component score (MCS) change score

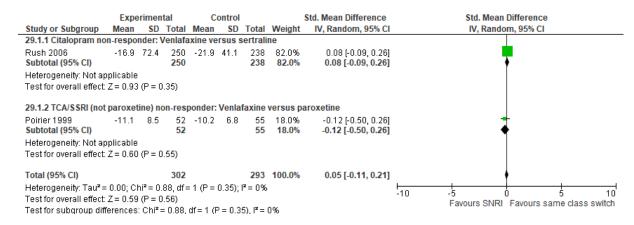


631 632 Test for subgroup differences: Not applicable

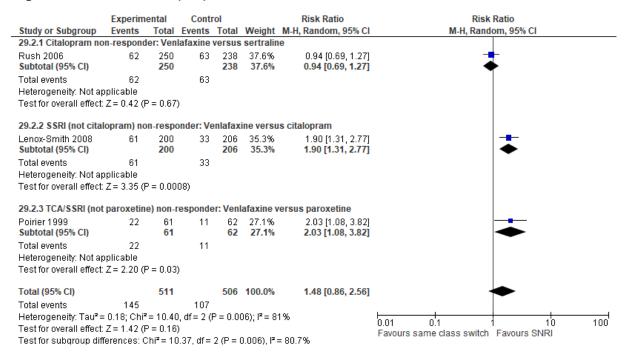
AD: antidepressant

635 Comparison 29. Switching to SNRI versus switching to another antidepressant from 636 same class

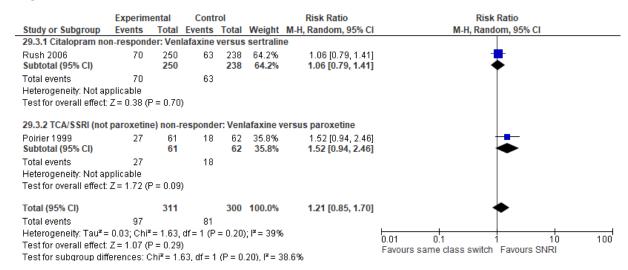
637 Figure 178: Depression symptomatology change score



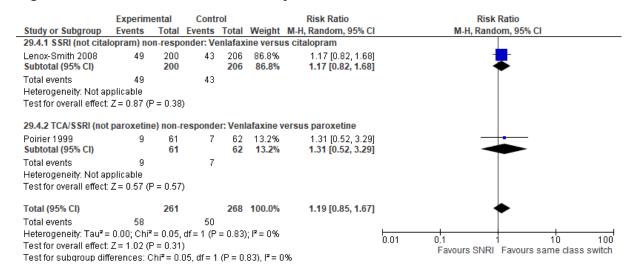
639 Figure 179: Remission (ITT)



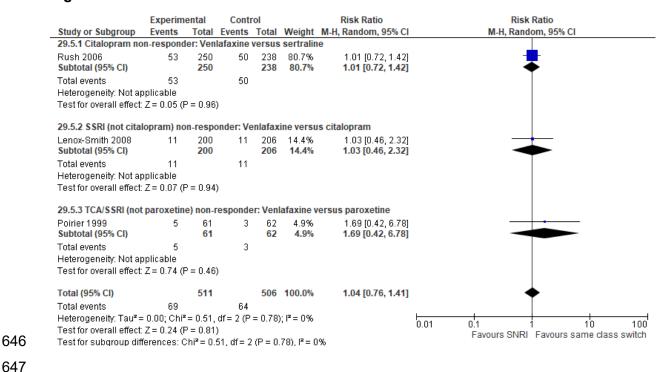
641 Figure 180: Response (ITT)



643 Figure 181: Discontinuation due to any reason

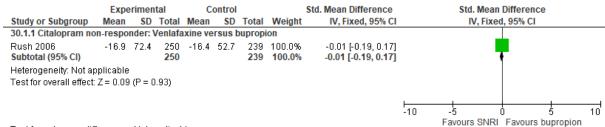


645 Figure 182: Discontinuation due to side effects



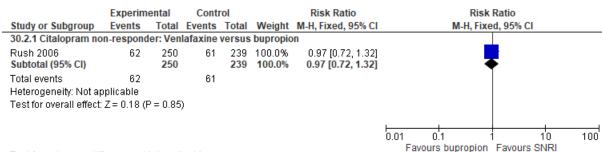
648 Comparison 30. Switching to SNRI versus switching to bupropion

649 Figure 183: Depression symptomatology change score

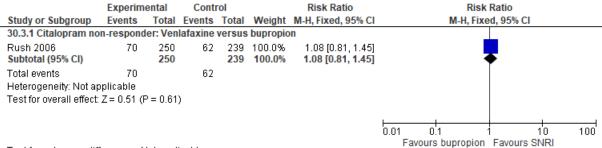


Test for subgroup differences: Not applicable

651 Figure 184: Remission (ITT)

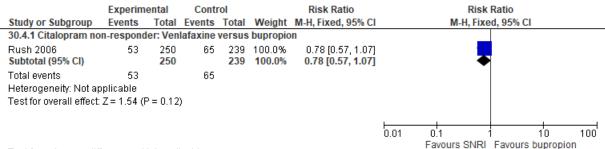


653 Figure 185: Response (ITT)



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)

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		
31.1.1 Paroxetine n	on-respond	ler: Ven	lafaxine	versus	mirtazap	ine				
Fang 2010 Subtotal (95% CI)	21	50 50	20	55 55	100.0% 100.0%	1.16 [0.72, 1.86] 1.16 [0.72, 1.86]				
Total events Heterogeneity: Not a Test for overall effec		P = 0.55	20							
							0.01 Far	0.1 1 1	I IO JRI	100

Test for subgroup differences: Not applicable

661 Figure 188: Response (ITT)

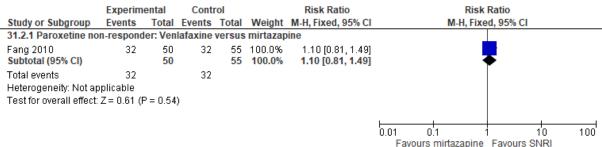
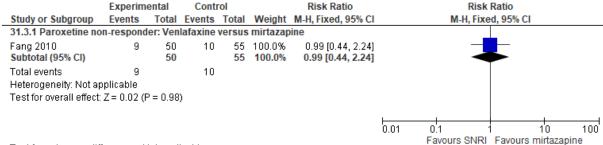


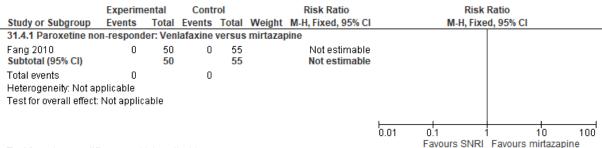
Figure 189: Discontinuation due to any reason



Test for subgroup differences: Not applicable

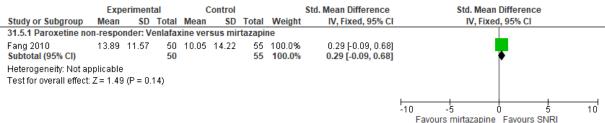
663

665 Figure 190: Discontinuation due to side effects



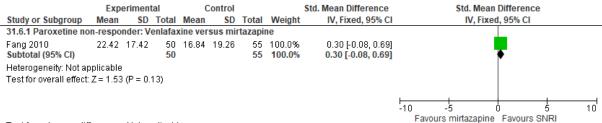
666 Test for subgroup differences: Not applicable

667 Figure 191: Quality of life physical component score (PCS) change score



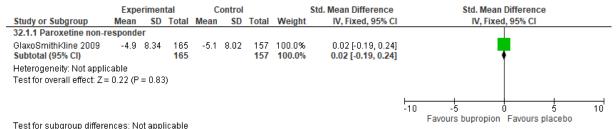
Test for subgroup differences: Not applicable

669 Figure 192: Quality of life mental component score (MCS) change score



671 Comparison 32. Switching to bupropion versus placebo

672 Figure 193: Depression symptomatology change score



673

674 Figure 194: Remission (ITT)

	Experime	ental	Conti	rol		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI	
32.2.1 Paroxetine non-r	esponder							_		
GlaxoSmithKline 2009 Subtotal (95% CI)	40	166 166	39	159 159	100.0% 100.0 %	0.98 [0.67, 1.44] 0.98 [0.67, 1.44]		1		
Total events Heterogeneity: Not appli Test for overall effect: Z=		0.93)	39							
Took for our borrous different							0.01 Favor	0.1 urs placebo switch	1 10 Favours AD switch	100

675 676 Test for subgroup differences: Not applicable AD: antidepressant

677

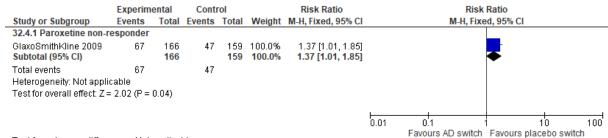
Figure 195: Response (ITT) 678

	Experime	Experimental		Control		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI		CI	
32.3.1 Paroxetine non-r	esponder										
GlaxoSmithKline 2009 Subtotal (95% CI)	63	166 166	58	159 159	100.0% 100.0 %	1.04 [0.78, 1.38] 1.04 [0.78, 1.38]					
Total events Heterogeneity: Not appli Test for overall effect: Z		0.78)	58								
Took for our barrens differen							0.01 Favo	0.1 urs placebo	switch Favour	10 s AD switch	100

Test for subgroup differences: Not applicable AD: antidepressant

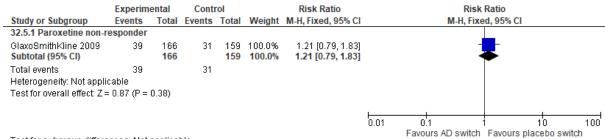
681

682 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

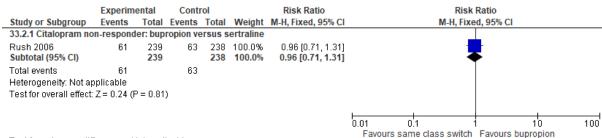
694

691 Comparison 33. Switching to bupropion versus switching to another antidepressant from 692 same class

693 Figure 198: Depression symptomatology change score

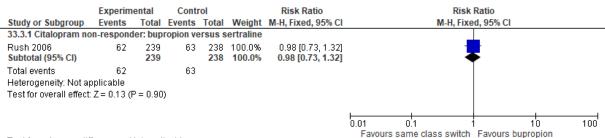
	Expe	erimen	ital	C	ontrol		Std. Mean Difference			Std. Mean Differe	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95%	CI	
33.1.1 Citalopram no	on-respo	nder: I	buprop	ion vers	us se	rtraline	,					
Rush 2006 Subtotal (95% CI)	-16.4	52.7	239 239	-21.9	41.1		100.0% 100.0 %	0.12 [-0.06, 0.30] 0.12 [-0.06, 0.30]		•		
Heterogeneity: Not ap Test for overall effect:			0.20)									
									-10	-5 0	 5	10
Test for subgroup dif	ferences	: Not a	pplicat	ole						Favours bupropion Favou	urs same class switc	ch

695 Figure 199: Remission (ITT)

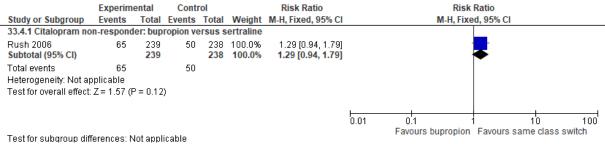


696 Test for subgroup differences: Not applicable

697 Figure 200: Response (ITT)



699 Figure 201: Discontinuation due to side effects



700

701

702 Comparison 34. Augmenting with bupropion versus placebo

703 Figure 202: Remission (ITT)

	Experim	ental	Conti	rol		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% (CI		
34.1.1 Augmenting 9	SSRI										
Gulrez 2012 Subtotal (95% CI)	18	30 30	7	30 30	100.0% 100.0%	2.57 [1.26, 5.24] 2.57 [1.26, 5.24]		4	- ►		
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	7 9)								
T-16	~						0.01	0.1 1 Favours placebo Favour	10 s bupropion	100	

704 Test for subgroup differences: Not applicable

705

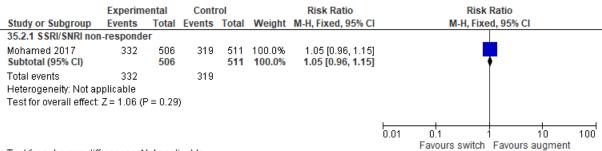
706 Comparison 35. Augmenting with bupropion versus switching to bupropion

707 Figure 203: Remission (ITT)

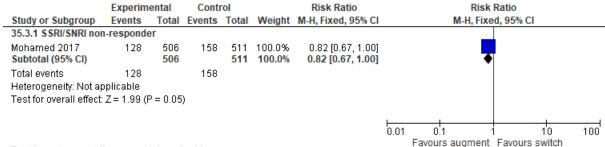
	Experimental		experimental Control			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
35.1.1 SSRI/SNRI no	n-responde	er						
Mohamed 2017 Subtotal (95% CI)	136	506 506	114	511 511	100.0% 100.0 %	1.20 [0.97, 1.50] 1.20 [0.97, 1.50]		•
Total events Heterogeneity: Not a Test for overall effect		P = 0.09	114					
							0.01	0.1 1 10 100 Favours switch Favours augment

708 Test for subgroup differences: Not applicable

709 Figure 204: Response (ITT)



711 Figure 205: Discontinuation due to any reason



712 Test for subgroup differences: Not applicable

713 Figure 206: Discontinuation due to side effects

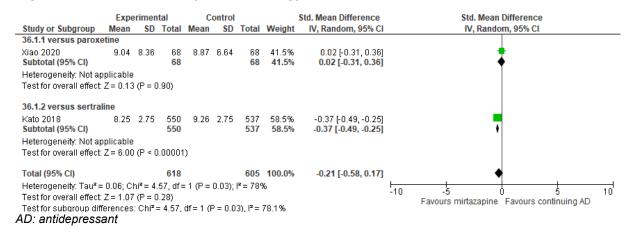
	Experimental		xperimental Control			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fi	M-H, Fixed, 95% CI		
35.4.1 SSRI/SNRI no	n-responde	er									
Mohamed 2017 Subtotal (95% CI)	37	506 506	51	511 511	100.0% 100.0 %	0.73 [0.49, 1.10] 0.73 [0.49, 1.10]		1			
Total events Heterogeneity: Not a Test for overall effect		P = 0.13	51								
							0.01	0.1 Favours augme	1 nt Favours	10 switch	100

714 Test for subgroup differences: Not applicable

715

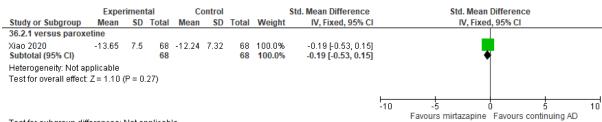
716 Comparison 36. Switching to mirtazapine versus continuing with antidepressant

717 Figure 207: Depression symptomatology endpoint



718 719 720

721 Figure 208: Depression symptomatology change score



Test for subgroup differences: Not applicable AD: antidepressant

724

725 Figure 209: Depression symptomatology at 4-month follow-up

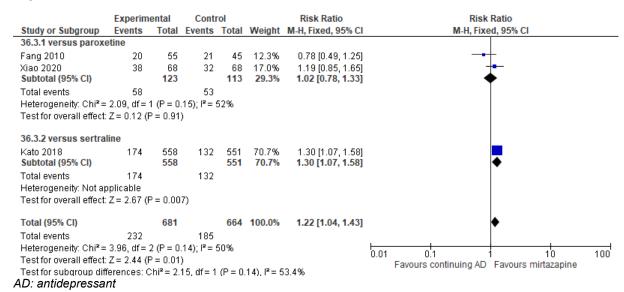
	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference		Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
36.7.1 versus sertra	aline											
Kato 2018 Subtotal (95% CI)	6.61	2.9	540 540	6.58	2.9	538 538	100.0% 100.0%	0.01 [-0.11, 0.13] 0.01 [-0.11, 0.13]		.		
Heterogeneity: Not a Test for overall effect	• •	(P = 0	1.87)									
									-10	-5 0 5 Favours mirtazapine Favours continuing AD	10	

726 727

Test for subgroup differences: Not applicable AD: antidepressant

728

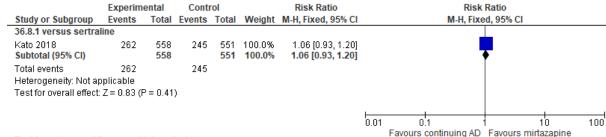
729 Figure 210: Remission (ITT)



730 731

732

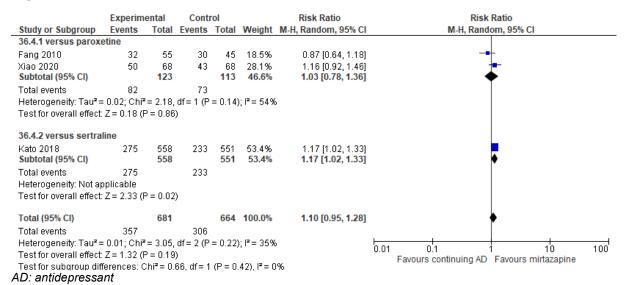
733 Figure 211: Remission (ITT) at 4-month follow-up



734 735 Test for subgroup differences: Not applicable

AD: antidepressant

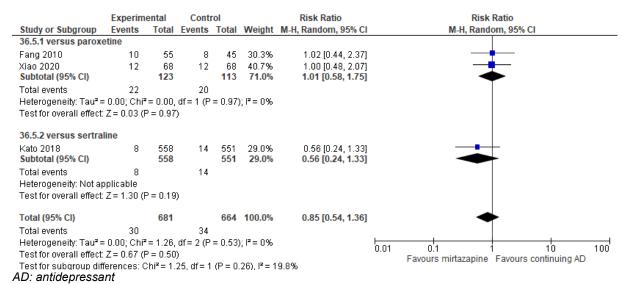
737 Figure 212: Response (ITT)



738

740

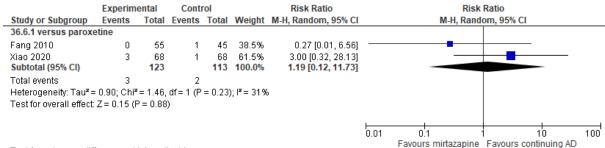
741 Figure 213: Discontinuation due to any reason



742 743

744

745 Figure 214: Discontinuation due to side effects

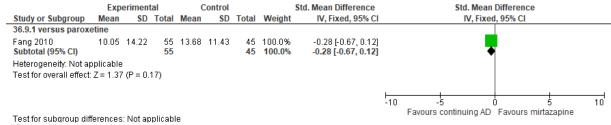


746 747

Test for subgroup differences: Not applicable

AD: antidepressant

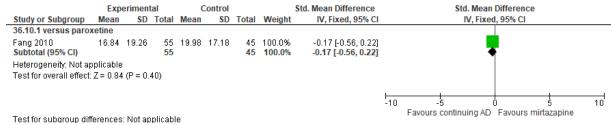
749 Figure 215: Quality of life physical component score (PCS) change score



750 Test for subgroup differences: Not applicable 751 *AD: antidepressant*

752

753 Figure 216: Quality of life mental component score (MCS) change score

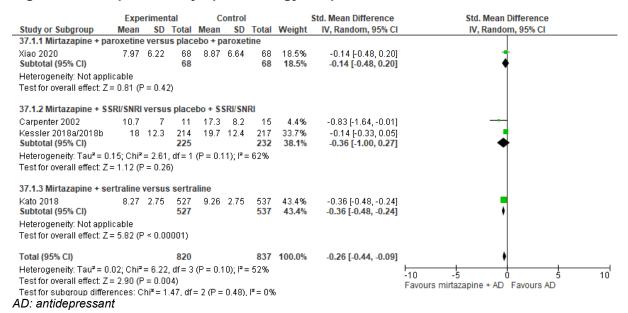


754 Test for subgroup differences: Not app 755 AD: antidepressant

756757

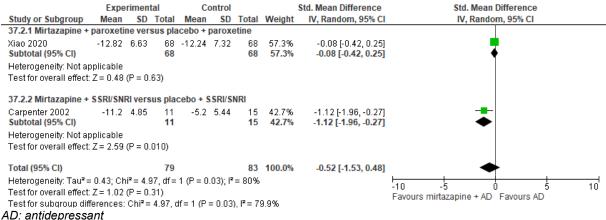
758 Comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/-759 placebo)

760 Figure 217: Depression symptomatology endpoint



761 762

764 Figure 218: Depression symptomatology change score



766 A

767

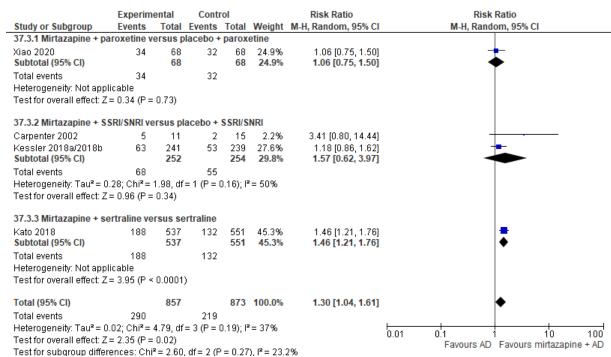
768 Figure 219: Depression symptomatology at 4-month follow-up

	Expe	rimen	tal	Co	Control Std. Mean Difference		Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV	Fixed, 95% CI		
37.7.1 Mirtazapine +	sertralin	e vers	sus sei	traline								
Kato 2018 Subtotal (95% CI)	6.37	2.88	520 520	6.58	2.9	538 538	100.0% 100.0%	-0.07 [-0.19, 0.05] - 0.07 [-0.19, 0.05]		-		
Heterogeneity: Not a Test for overall effect	•		1.24)									
									-10 -5	0_	5	10
									Favours mirtazapine	+ AD Favours	AD	

69 Test for subgroup differences: Not applicable 70 AD: antidepressant

771

772 Figure 220: Remission (ITT)

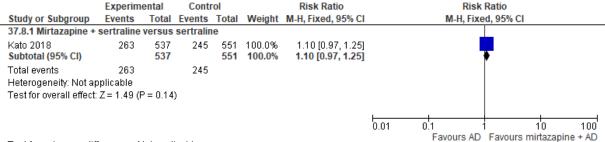


773

AD: antidepressant

775

776 Figure 221: Remission (ITT) at 4-month follow-up

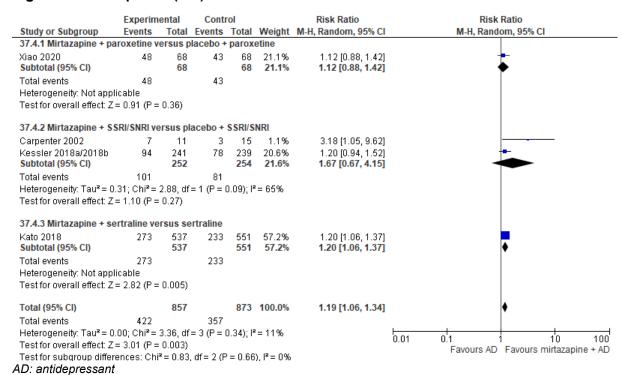


/// 778

779

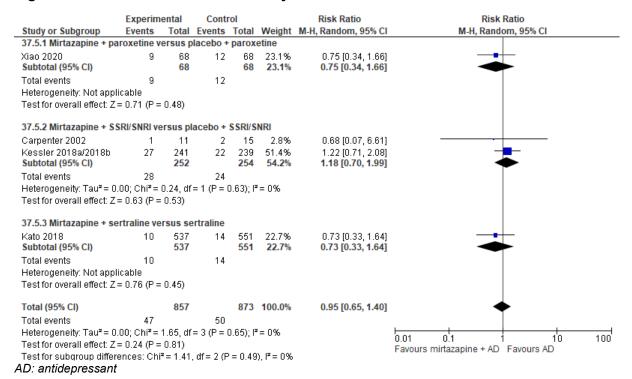
Test for subgroup differences: Not applicable AD: antidepressant

780 Figure 222: Response (ITT)



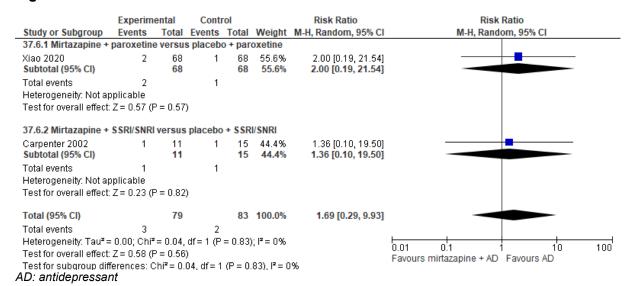
781 782

784 Figure 223: Discontinuation due to any reason



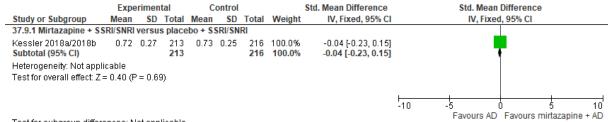
787

788 Figure 224: Discontinuation due to side effects



789 790

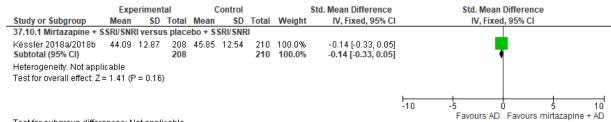
792 Figure 225: Quality of life endpoint



793 Test for subgroup differences: Not applicable AD: antidepressant

795

796 Figure 226: Quality of life physical component score (PCS) endpoint



797 Test for subgroup differences: Not applicable AD: antidepressant

799

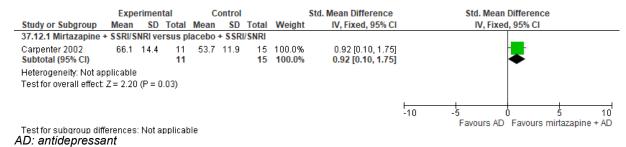
Figure 227: Quality of life mental component score (MCS) endpoint

	Exp	eriment	tal	(Control			Std. Mean Difference		Std. Mean Difference	e
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
37.11.1 Mirtazapine + 9	SSRI/SNF	RI versu	s place	ebo + S	SRI/SNF	RI					
Kessler 2018a/2018b Subtotal (95% CI)	39.94	12.27	208 208	36.33	12.53	210 210	100.0% 100.0%	0.29 [0.10, 0.48] 0.29 [0.10, 0.48]		 	
Heterogeneity: Not appl Test for overall effect: Z		P = 0.00	3)								
Test for subgroup differ	ences: N	lot appli	icable						-10	-5 0 Favours AD Favours	5 10 mirtazapine + AD

801 Test for subgroup differen AD: antidepressant

803

804 Figure 228: Global functioning endpoint



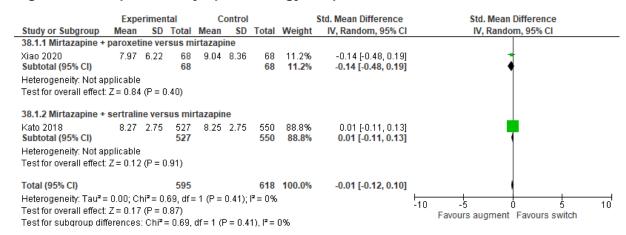
806 806

807

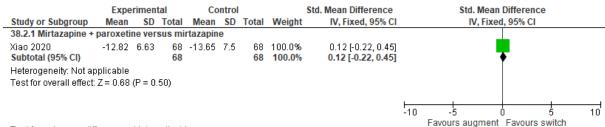
808

809 Comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

810 Figure 229: Depression symptomatology endpoint



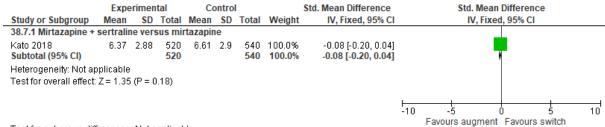
812 Figure 230: Depression symptomatology change score



813 Test for subgroup differences: Not applicable

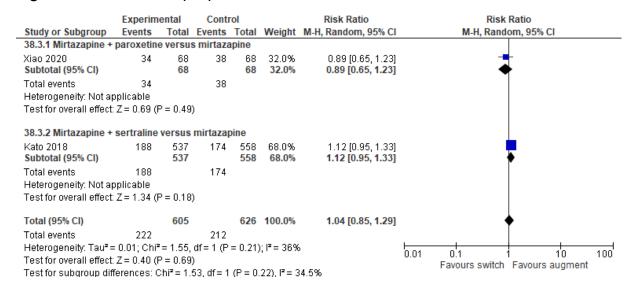
811

814 Figure 231: Depression symptomatology at 4-month follow-up

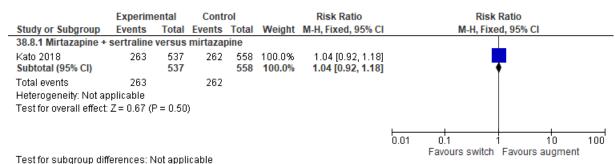


815 Test for subgroup differences: Not applicable

816 Figure 232: Remission (ITT)



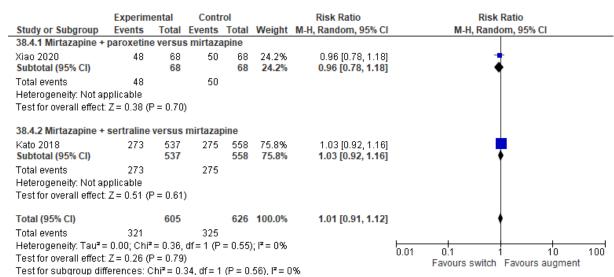
818 Figure 233: Remission (ITT) at 4-month follow-up



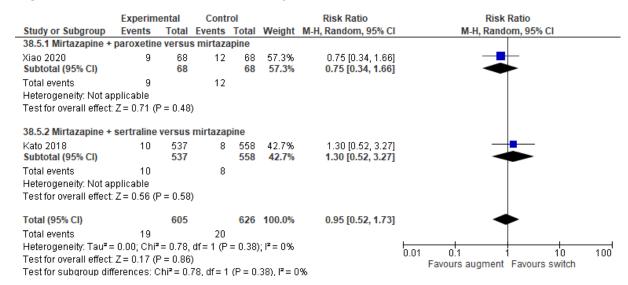
819

820 Figure 234: Response (ITT)

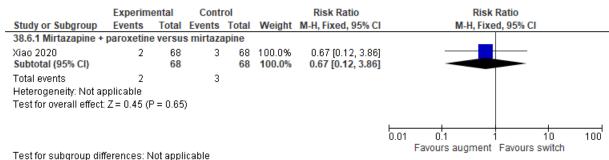
817



822 Figure 235: Discontinuation due to any reason



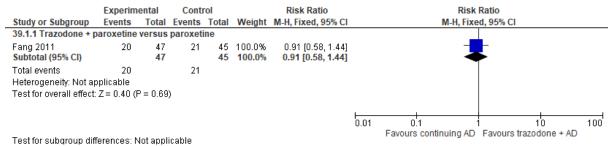
824 Figure 236: Discontinuation due to side effects



825

827 Comparison 39. Augmenting with trazodone versus continuing with antidepressant

828 Figure 237: Remission (ITT)

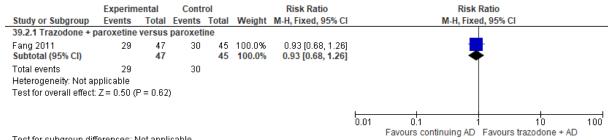


AD: antidepressant

831

823

832 Figure 238: Response (ITT)



833 Test for subgroup differences: Not applicable AD: antidepressant

835

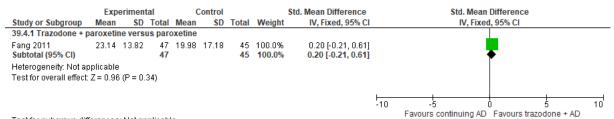
836 Figure 239: Quality of life physical component score (PCS) change score

	Exp	erimen	tal	(Control			Std. Mean Difference		Std. Mean	Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
39.3.1 Trazodone +	paroxetii	ne vers	us par	oxetine						_		
Fang 2011 Subtotal (95% CI)	10.71	11.58	47 47	13.68	11.43	45 45	100.0% 100.0 %	-0.26 [-0.67, 0.15] - 0.26 [-0.67, 0.15]				
Heterogeneity: Not a Test for overall effect			22)									
									-10	-5	5	10
Teet for subgroup di	fforoncos	· Not ar	nlicahl	lo.						Favours continuing AD	Favours trazodone + AD	

837 Test for subgroup differences: Not an AD: antidepressant

839

840 Figure 240: Quality of life mental component score (MCS) change score

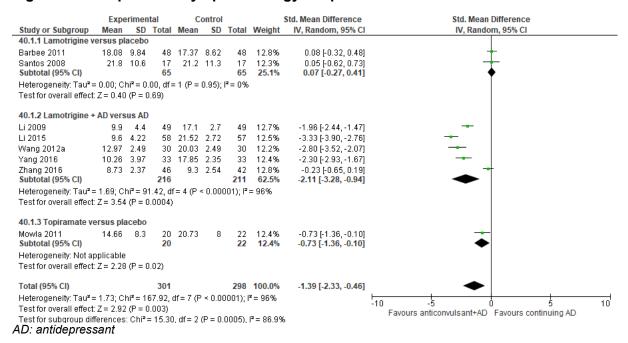


Test for subgroup differences: Not applicable AD: antidepressant

843

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

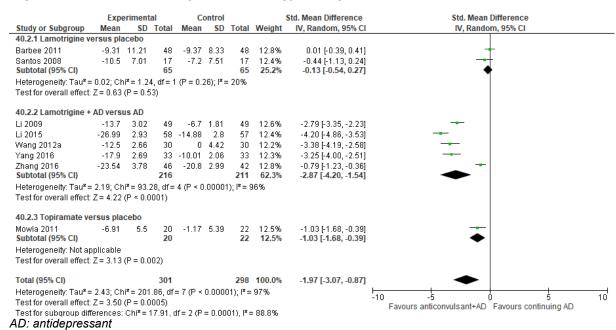
847 Figure 241: Depression symptomatology endpoint



848 849

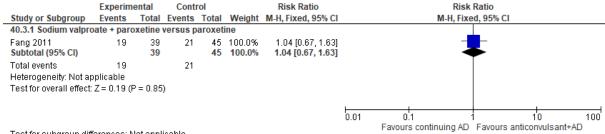
850

851 Figure 242: Depression symptomatology change score



352 353

855 Figure 243: Remission (ITT)

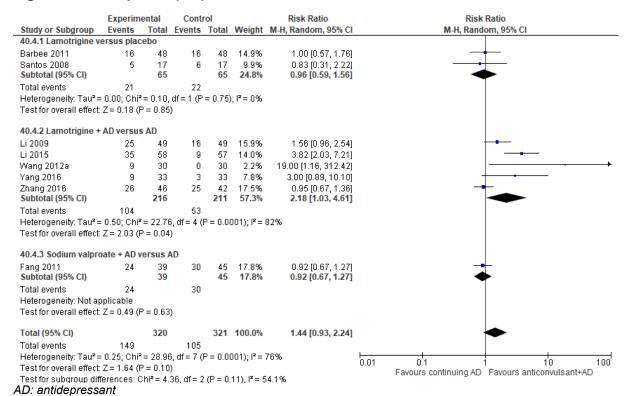


Test for subgroup differences: Not applicable AD: antidepressant

858

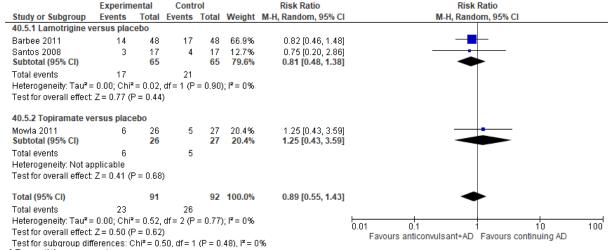
856

859 Figure 244: Response (ITT)



860 861

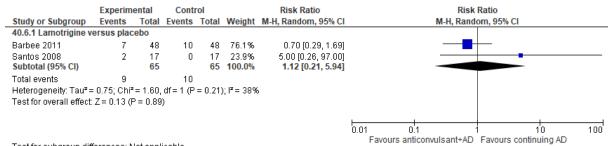
863 Figure 245: Discontinuation due to any reason



AD: antidepressant

866

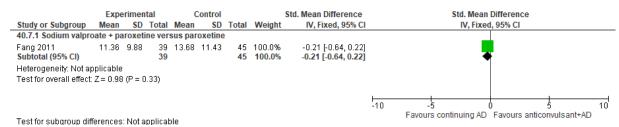
Figure 246: Discontinuation due to side effects 867



Test for subgroup differences: Not applicable AD: antidepressant

870

871 Figure 247: Quality of life physical component score (PCS) change score



AD: antidepressant

875 Figure 248: Quality of life mental component score (MCS) change score

	Exp	eriment	al	C	ontrol			Std. Mean Difference		Std. Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
40.8.1 Sodium valpro	oate + pa	aroxetin	e vers	us paro	xetine								
Fang 2011 Subtotal (95% CI)	23.04	14.05	39 39	19.98	17.18		100.0% 100.0 %	0.19 [-0.24, 0.62] 0.19 [-0.24, 0.62]			•		
Heterogeneity: Not ap Test for overall effect			38)										
									-10	-5	0	 5	10
										Favours continuing AD	Favours antic	onvulsant+AD	

Test for subgroup differences: Not applicable

876

877 AD: antidepressant

878

879

882

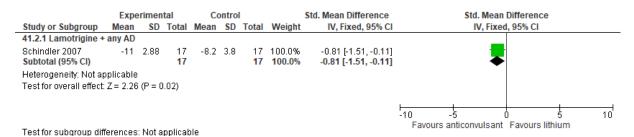
884

880 Comparison 41. Augmenting with anticonvulsant versus lithium

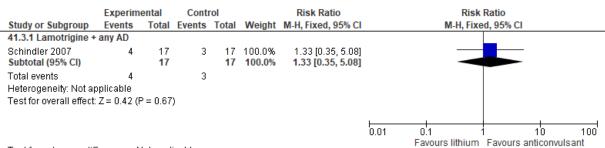
881 Figure 249: Depression symptomatology endpoint

	Expe	rimen	tal	Co	ontro	I		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
41.1.1 Lamotrigine +	any AD								
Schindler 2007 Subtotal (95% CI)	11.7	4.2	17 17	13.3	5.7	17 17	100.0% 100.0 %	-0.31 [-0.99, 0.36] -0.31 [-0.99, 0.36]	-
Heterogeneity: Not ap Test for overall effect			1.37)						
									-10 -5 0 5 10
Test for subgroup dif	ferences:	Not a	pplical	ole					Favours anticonvulsant Favours lithium

883 Figure 250: Depression symptomatology change score

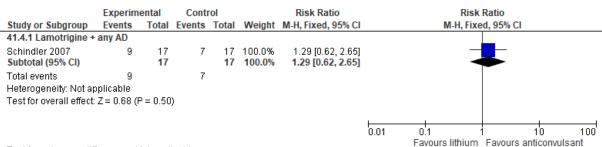


885 Figure 251: Remission (ITT)



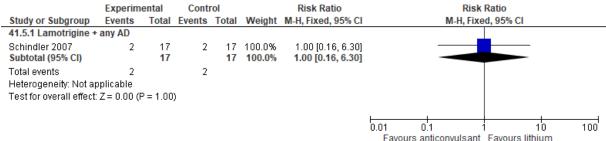
886 Test for subgroup differences: Not applicable

887 Figure 252: Response (ITT)



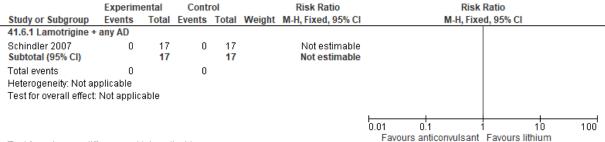
888 Test for subgroup differences: Not applicable

889 Figure 253: Discontinuation due to any reason



890 Test for subgroup differences: Not applicable

891 Figure 254: Discontinuation due to side effects

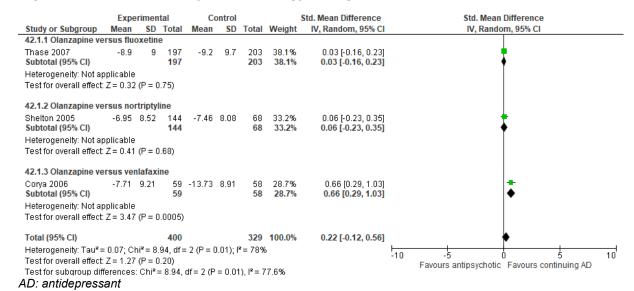


892 Test for subgroup differences: Not applicable

893

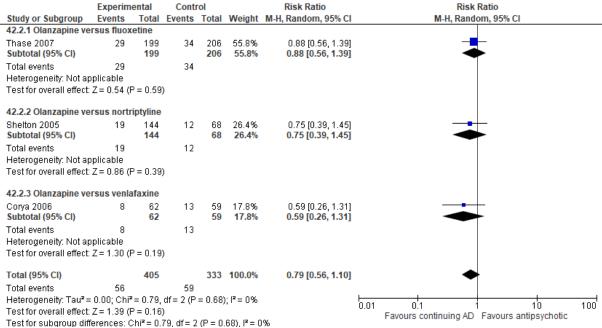
894 Comparison 42. Switching to antipsychotic versus continuing with antidepressant

895 Figure 255: Depression symptomatology change score



896 897

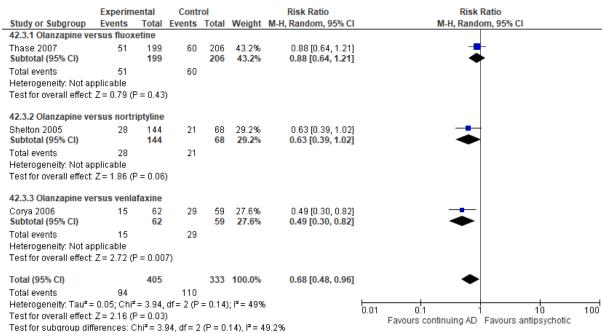
899 Figure 256: Remission (ITT)



901 AD: antidepressant

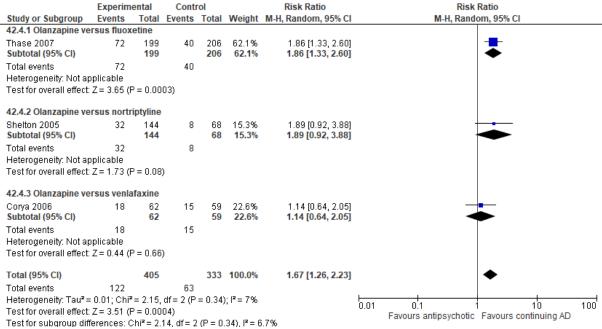
902

903 Figure 257: Response (ITT)



AD: antidepressant

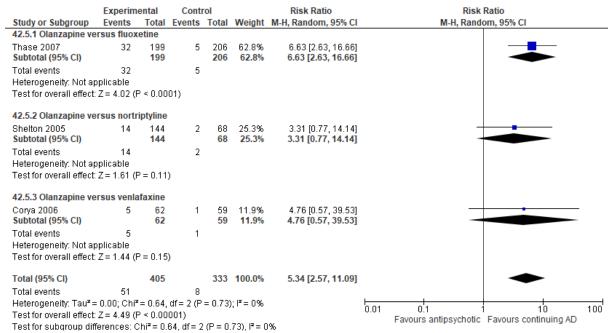
907 Figure 258: Discontinuation due to any reason



909 AD: antidepressant

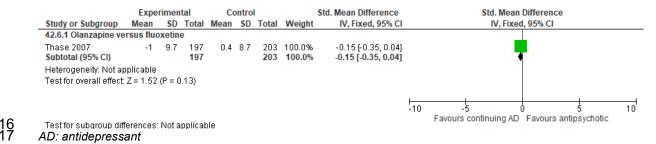
910

911 Figure 259: Discontinuation due to side effects

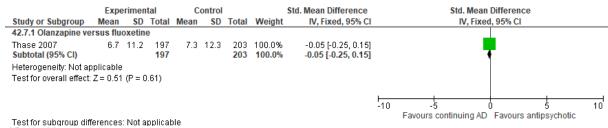


AD: antidepressant

915 Figure 260: Quality of life physical component score (PCS) change score



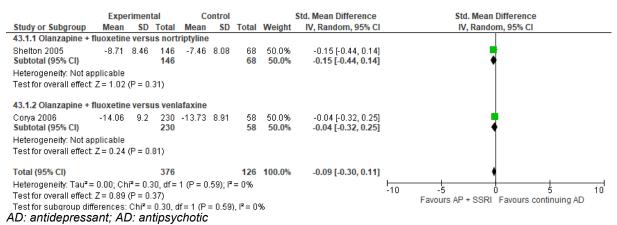
919 Figure 261: Quality of life mental component score (MCS) change score



920 Test for subgroup differences: Not applicable 921 *AD: antidepressant*

924 Comparison 43. Switching to combined antipsychotic + SSRI versus continuing with 925 antidepressant

926 Figure 262: Depression symptomatology change score

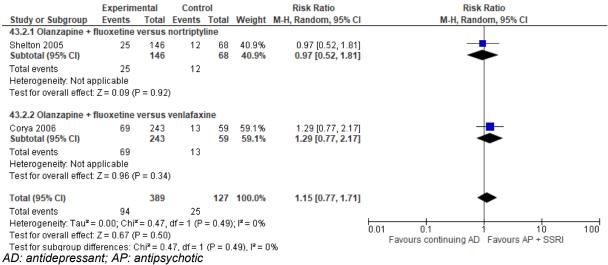


929

918

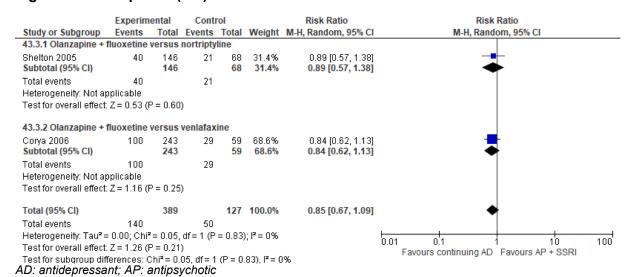
922

Figure 263: Remission (ITT)



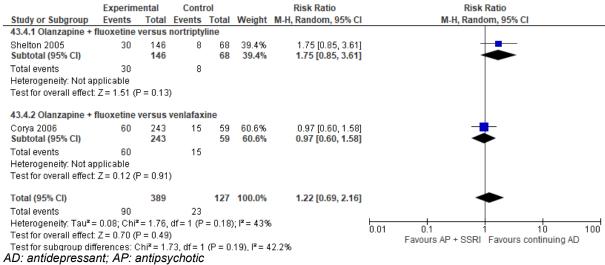
932

Figure 264: Response (ITT)



936

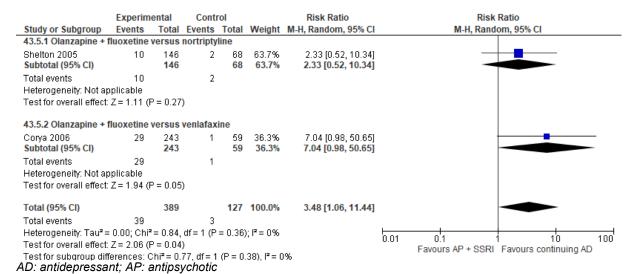
Figure 265: Discontinuation due to any reason



941

938

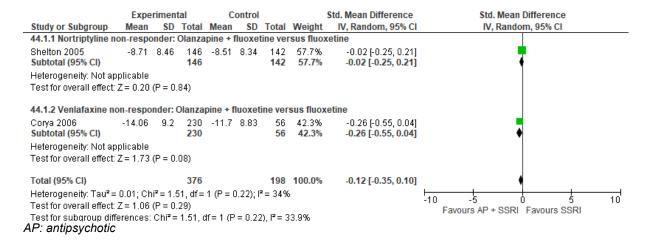
942 Figure 266: Discontinuation due to side effects



945

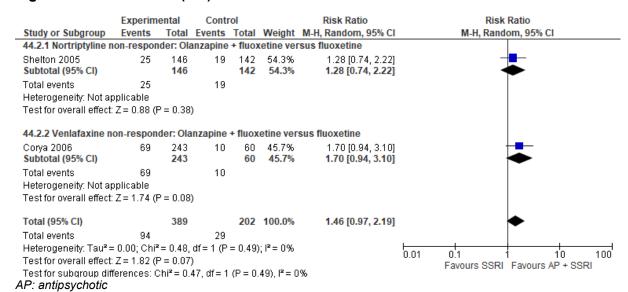
947 Comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

948 Figure 267: Depression symptomatology change score



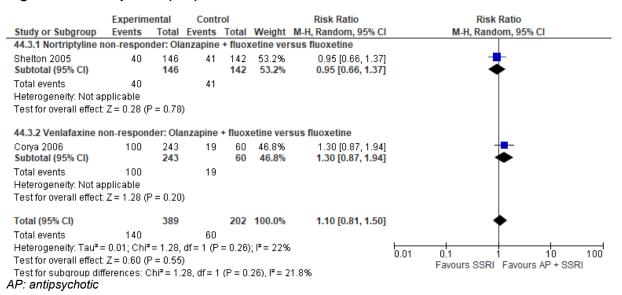
951

952 Figure 268: Remission (ITT)



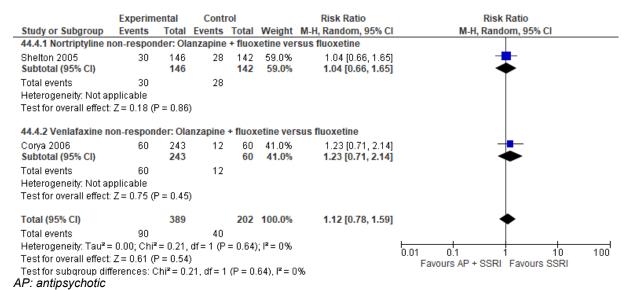
953 954

956 Figure 269: Response (ITT)

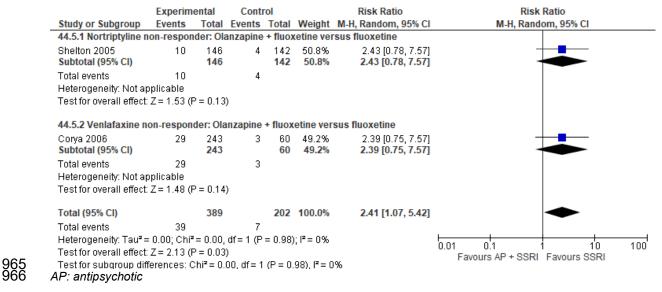


7

960 Figure 270: Discontinuation due to any reason



964 Figure 271: Discontinuation due to side effects

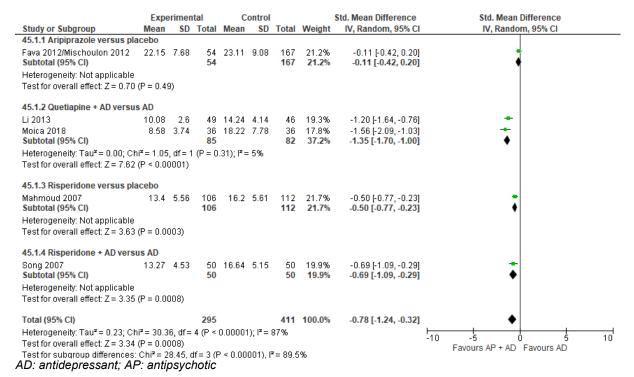


967

968

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

971 Figure 272: Depression symptomatology endpoint



972 973

Figure 273: Depression symptomatology change score 975

Study or Subgroup	Mean	rimenta SD	Total	Mean	ontrol SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
45.2.1 Aripiprazole versus place	ebo								
Berman 2009	-10.12	9.76	174	-6.39	9.62	169	5.7%	-0.38 [-0.60, -0.17]	•
Fava 2012/Mischoulon 2012	-8.54	7.21	54	-8.09	8.13	167	4.6%	-0.06 [-0.36, 0.25]	†
Kamijima 2013	-10.05	8.39	391	-7.4	8.38	195	6.2%	-0.32 [-0.49, -0.14]	
Kamijima 2018 Subtotal (95% CI)	-9.2	7.21	208 827	-7.2	7.12	203 734	6.0% 22.5 %	-0.28 [-0.47, -0.08] - 0.29 [-0.40, -0.19]	7
Heterogeneity: Tau² = 0.00; Chi²:	- 3 06 df	- 37P -		12 - 206		134	22.5/0	-0.23 [-0.40, -0.13]	'
Test for overall effect: Z = 5.42 (P			0.30),	1 - 230					
45.2.2 Brexpiprazole versus pla	cebo								
Hobart 2018a	-10.4	8.29	191	-8.1	8.53	202	5.9%	-0.27 [-0.47, -0.07]	*
Otsuka Pharmaceutical 2015	-8.2	8.41	184	-7.02	8.34	181	5.8%	-0.14 [-0.35, 0.06]]
Otsuka Pharmaceutical 2016 Thase 2015a	-7.19 -8.27	7.97 8.34	299 187	-6.09 -5.15	8.08 8.29	126 191	5.8% 5.9%	-0.14 [-0.35, 0.07]	_]
Thase 2015b	-7.82	7.58	451	-6.45	7.53	218	6.3%	-0.37 [-0.58, -0.17] -0.18 [-0.34, -0.02]	-
Subtotal (95% CI)	-1.02	1.50	1312	-0.43	1.55	918	29.7%	-0.22 [-0.30, -0.13]	•
Heterogeneity: Tau² = 0.00; Chi²: Test for overall effect: Z = 4.96 (P			0.42);	I² = 0%					
45.2.3 Brexpiprazole/quetiapine	versus	olacebo							
Hobart 2018b	-5.62	5.7	290	-4.6	5.73	205	6.1%	-0.18 [-0.36, 0.00]	-
Subtotal (95% CI)			290			205	6.1%	-0.18 [-0.36, 0.00]	•
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.95 (P	= 0.05)								
45.2.4 Cariprazine versus place	bo								
2	-13.998	9.11	544	-12.5	8.12	264	6.5%	-0.17 [-0.32, -0.02]	+
Earley 2018	-7.2	5.81	211	-6.5	5.92	219	6.0%	-0.12 [-0.31, 0.07]	†
Fava 2018 Subtotal (05% CI)	-8.63	9.54	149	-8	9	81	5.0% 47.6%	-0.07 [-0.34, 0.20]	7
Subtotal (95% CI)	- 0.40 24	- 27D -	904	12 _ OO		564	17.6%	-0.14 [-0.24, -0.03]	1
Heterogeneity: Tau² = 0.00; Chi²: Test for overall effect: Z = 2.53 (P		- 2 (P =	0.78);	i — U%o					
45.2.5 Olanzapine + AD versus A									
Thase 2007	-12.6	10.3	198	-9.2	9.7	203	5.9%	-0.34 [-0.54, -0.14]	Ĭ
Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 3.37 (P	= 0.0007	")	198			203	5.9%	-0.34 [-0.54, -0.14]	ľ
45.2.6 Pimavanserin versus pla	cebo								
Fava 2019	-11.9	7.65	45	-7.1	6.2	127	4.2%	-0.72 [-1.07, -0.37]	+
Subtotal (95% CI)			45			127	4.2%	-0.72 [-1.07, -0.37]	♦
Heterogeneity: Not applicable									
Test for overall effect: Z = 4.07 (P	< 0.0001)							
45.2.7 Quetiapine + AD versus A	ND.								
Li 2013	-15.88	2.96	49	-11.54	3.02	46	3.2%	-1.44 [-1.89, -0.99]	+
Moica 2018	-13.59	2.51	36	-6.39	5.4	36	2.6%	-1.69 [-2.23, -1.15]	-
Subtotal (95% CI)			85			82	5.7%	-1.54 [-1.89, -1.20]	•
Heterogeneity: Tau² = 0.00; Chi²: Test for overall effect: Z = 8.70 (P			0.49);	I ² = 0%					
45.2.8 Risperidone versus place	ebo								
Reeves 2008	-20.31	11.47	12	-13.2	11.48	11	1.3%	-0.60 [-1.44, 0.24]	
Subtotal (95% CI)			12	-		11	1.3%	-0.60 [-1.44, 0.24]	◆
Heterogeneity: Not applicable Test for overall effect: Z = 1.39 (P	= 0.16)								
45.2.9 Ziprasidone versus place	ebo								
Papakostas 2015	-6.4	6.4	71	-3.3	6.2	68	4.3%	-0.49 [-0.83, -0.15]	-
Subtotal (95% CI)	0.4	5.7	71	3.3	0.2	68	4.3%	-0.49 [-0.83, -0.15]	♦
Heterogeneity: Not applicable									-
Test for overall effect: Z = 2.84 (P	= 0.005)								
45.2.10 Ziprasidone + AD versus		0.00	40		0.00	0.0	2.00	0.001.000.00	
Dunner 2007 Subtotal (95% CI)	-7.07	8.96	40 40	-4.45	9.08	20 20	2.6% 2.6 %	-0.29 [-0.83, 0.25]	1
			40			20	2.070	-0.29 [-0.83, 0.25]	7
Heterogeneity: Not applicable Test for overall effect: Z = 1.04 (P	= 0.30)								
Total (95% CI)			3784			2932	100.0%	-0.33 [-0.44, -0.23]	
Heterogeneity: Tau² = 0.04; Chi²:	- 77.00 (4f = 19.0	⊃ < 0.0	0001); l ^a	= 75%				<u> </u>
									-10 -5 0 5
Test for overall effect: Z = 6.12 (P Test for subgroup differences: C	< 0.0000)1)							-10 -5 0 5 Favours AP + AD Favours AD

976 977

979 Figure 274: Remission (ITT)

Study or Subgroup	Experime Events		Contr		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 Aripiprazole	Evolita	rotur	2101113	· Jul	rroignt	An managing 50% Cl	m-n random 55% of
Berman 2007	47	184	28	178	3.8%	1.62 [1.07, 2.47]	 • -
Berman 2009	64	177	32	172	4.5%	1.94 [1.34, 2.81]	-
ava 2012/Mischoulon 2012	4	56	16	169	0.9%	0.75 [0.26, 2.16]	
Kamijima 2013	123	391	40	195	5.3%	1.53 [1.12, 2.10]	-
Kamijima 2018	61	209	41	203	4.8%	1.45 [1.02, 2.04]	
.enze 2015 //arcus 2008	40 47	91 191	26 28	90 190	4.1% 3.8%	1.52 [1.02, 2.27] 1.67 [1.09, 2.55]	
Subtotal (95% CI)	47	1299	20	1197	27.1%	1.58 [1.36, 1.84]	•
otal events	386	1200	211		2	1100 [1100, 1101]	•
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 5.98 (i² = 3.51, df:			= 0%			
15.3.2 Brexpiprazole							
Bauer 2019	95	444	110	442	6.6%	0.86 [0.68, 1.09]	
Hobart 2018a	56	192	52	202	5.2%	1.13 [0.82, 1.56]	 -
Otsuka Pharmaceutical 2015	48	185	27	187	3.8%	1.80 [1.17, 2.75]	
Otsuka Pharmaceutical 2016	60	303	17	126	3.1%	1.47 [0.89, 2.41]	
hase 2015a	27	188	16	191	2.4%	1.71 [0.96, 3.08]	
Thase 2015b	64	456	25	221	3.7%	1.24 [0.80, 1.91]	+
Subtotal (95% CI)		1768		1369	24.6%	1.26 [0.98, 1.63]	•
otal events	350		247				
leterogeneity: Tau² = 0.06; Chi est for overall effect: Z = 1.79 (f= 5 (P	= 0.03);	F= 619	6		
I5.3.3 Brexpiprazole/quetiapin	ıe						
Hobart 2018b	15	297	9	205	1.4%	1.15 [0.51, 2.58]	
Subtotal (95% CI)		297	J	205	1.4%	1.15 [0.51, 2.58]	-
Total events	15		9			•	
Heterogeneity: Not applicable Fest for overall effect: Z = 0.34 ((P = 0.73)						
15.3.4 Cariprazine	•						
ourgam 2016	174	550	79	269	6.9%	1.08 [0.86, 1.35]	+
Earley 2018	65	269	49	258	5.0%	1.27 [0.92, 1.77]	 -
ava 2018	37	150	16	81	2.9%	1.25 [0.74, 2.10]	+
Subtotal (95% CI)		969		608	14.8%	1.15 [0.96, 1.36]	*
Fotal events	276		144				
Heterogeneity: Tau² = 0.00; Chi Fest for overall effect: Z = 1.55 (= 2 (P =	0.67); l²	= 0%			
I 5.3.5 Olanzapine Thase 2007	54	200	34	206	4.3%	1.64 [1.12, 2.40]	- <u>-</u> -
Subtotal (95% CI)		200	-	206	4.3%	1.64 [1.12, 2.40]	 ◆
Fotal events	54		34				
Heterogeneity: Not applicable Fest for overall effect: Z = 2.52 ((D = 0.01)						
	, = 0.01)						
45.3.6 Pimavanserin	4.0						
Fava 2019	12	52	17	155	2.0%	2.10 [1.08, 4.11]	
Subtotal (95% CI)	40	52	4.7	155	2.0%	2.10 [1.08, 4.11]	_
Fotal events Hotorogopoits: Not applicable	12		17				
Heterogeneity: Not applicable Fest for overall effect: Z = 2.18 ((P = 0.03)						
15.3.7 Quetiapine							
Bauer 2009	134	330	50	163	6.1%	1.32 [1.02, 1.73]	 -
El-Khalili 2010	137	298	47	148	6.1%	1.45 [1.11, 1.89]	-
i 2013	19	49	12	46	2.3%	1.49 [0.82, 2.71]	+
dcIntyre 2007	9	29	5	29	1.0%	1.80 [0.69, 4.72]	+
Subtotal (95% CI)		706		386	15.6%	1.40 [1.18, 1.68]	◆
Fotal events	299		114				
Heterogeneity: Tau² = 0.00; Chi Test for overall effect: Z = 3.78 (0.91); [²	= 0%			
· ·							
5.3.8 Risperidone							
ang 2011	12	45	21	45	2.5%	0.57 [0.32, 1.02]	
Keitner 2009	32	64	8	33	2.0%	2.06 [1.08, 3.95]	
Mahmoud 2007 Subtotal (95% CI)	26	141 250	12	133 211	2.1 % 6.6%	2.04 [1.08, 3.88] 1.33 [0.55, 3.17]	
Fotal events	70	230	41	211	0.076	1.55 [0.55, 5.17]	
Heterogeneity: Tau² = 0.49; Chi	i² = 11.76, d	f= 2 (P		; I² = 83	1%		
Fest for overall effect: Z = 0.63 (H = 0.53)						
15.3.9 Ziprasidone	_		,		0.00:	0.4470.00.40.511	
Dunner 2007	5	41	1	20	0.2%	2.44 [0.30, 19.51]	
Papakostas 2015 Subtotal (95% CI)	27	71	21	68 88	3.4%	1.23 [0.77, 1.96]	
Subtotal (95% CI) Fotal events	32	112	22	88	3.6%	1.27 [0.81, 2.00]	
Heterogeneity: Tau² = 0.00; Chi	i²= 0.41, df:	= 1 (P =		= 0%			
Fest for overall effect: Z = 1.04 (P = 0.30)						
otal (95% CI)		5653		4425	100.0%	1.37 [1.23, 1.52]	•
Fotal events Jotanaganoity: Tou s - 0.03: Chi	1494 2 - 4470 d	e_ 07 **	839	. 12 - 17	100		
Heterogeneity: Tau² = 0.03; Chi			~ = 0.02)	, r= 40	1%		0.01 0.1 1 10
Test for overall effect: Z = 5.94 (Test for subgroup differences:			(P = 0.2	2), I²= :	24.7%		Favours AD Favours AP + AD

981 AD: antidepressant; AP: antipsychotic

982 Figure 275: Response (ITT)

	Experime Events	Total I	Contr Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
15.4.1 Aripiprazole							
Berman 2007	61	184	42	178	4.0%	1.41 [1.01, 1.96]	•
Berman 2009	81	177	45	172	4.7%	1.75 [1.30, 2.36]	-
ava 2012/Mischoulon 2012	10	56	29	169	1.4%	1.04 [0.54, 2.00]	
Kamijima 2013 Kamijima 2018	159	391	55 53	195	5.6%	1.44 [1.12, 1.86]	<u> </u>
Kamijima 2018 Marcus 2008	78 60	209 191	52 32	203 190	4.8% 3.4%	1.46 [1.09, 1.95] 1.87 [1.28, 2.73]	
Subtotal (95% CI)	00	1208	32	1107	23.8%	1.52 [1.33, 1.74]	•
Fotal events	449		255			. , .	'
Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 6.20 (F	== 3.73, df=			= 0%			
15.4.2 Brexpiprazole	70	102	66	202	5 20¢	1 15 10 00 1 501	_
Hobart 2018a Otsuka Pharmaceutical 2015	72 55	192 185	66 36	202 187	5.3% 3.5%	1.15 [0.88, 1.50]	
Otsuka Pharmaceutical 2016	111	303	25	126	3.3%	1.54 [1.07, 2.23] 1.85 [1.26, 2.70]	-
Thase 2015a	44	188	28	191	2.8%	1.60 [1.04, 2.45]	
Thase 2015b	102	456	33	221	3.7%	1.50 [1.05, 2.14]	-
Subtotal (95% CI)		1324		927	18.6%	1.45 [1.22, 1.73]	◆
Fotal events	384		188				
Heterogeneity: Tau² = 0.01; Chi² est for overall effect: Z = 4.24 (f			0.30); l²	= 17%			
15.4.3 Brexpiprazole/quetiapin	e						
Hobart 2018b	28	297	14	205	1.5%	1.38 [0.75, 2.56]	+-
Subtotal (95% CI)		297		205	1.5%	1.38 [0.75, 2.56]	*
Fotal events	28		14				
Heterogeneity: Not applicable Test for overall effect: Z = 1.03 (F	P = 0.31)						
15.4.4 Cariprazine							
Durgam 2016	265	550	101	269	7.8%	1.28 [1.08, 1.53]	-
Earley 2018	75	269	71	258	5.1%	1.01 [0.77, 1.34]	+
ava 2018	51	150	21	81	2.8%	1.31 [0.85, 2.02]	 _
Subtotal (95% CI)		969		608	15.7%	1.21 [1.04, 1.40]	 ◆
otal events	391		193				
Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 2.44 (f		= 2 (P = I	J.34); l²	= 7%			
5.4.5 Olanzapine Thase 2007	80	200	60	206	5.2%	1.37 [1.05, 1.80]	_
Subtotal (95% CI)	00	200	00	206	5.2%	1.37 [1.05, 1.80]	•
Fotal events	80	200	60		01270	[,]	
Heterogeneity: Not applicable	00						
Fest for overall effect: Z = 2.28 (F	P = 0.02)						
15.4.6 Pimavanserin							
ava 2019	27	52	38	155	3.4%	2.12 [1.45, 3.10]	
Subtotal (95% CI)	21	52 52	30	155	3.4%	2.12 [1.45, 3.10]	•
Fotal events	27	-	38			2.12[.110,0110]	
Heterogeneity: Not applicable							
Fest for overall effect: Z = 3.87 (F	P = 0.0001)						
	P = 0.0001)						
15.4.7 Quetiapine			7.1	162	7 304	1 23 11 02 1 500	-
15.4.7 Quetiapine Bauer 2009	185	330	74 66	163 148	7.3% 6.9%	1.23 [1.02, 1.50] 1.20 [0.98. 1.48]	e-
15.4.7 Quetiapine Bauer 2009 EI-Khalili 2010	185 160		74 66 20	148	6.9%	1.20 [0.98, 1.48]	+
15.4.7 Quetiapine Bauer 2009 EI-Khalili 2010 Li 2013	185	330 298	66				-
15.4.7 Quetiapine Bauer 2009 EI-Khalili 2010 Li 2013 McIntyre 2007	185 160 24	330 298 49	66 20	148 46	6.9% 2.7%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74]	-
IS.4.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chiª	185 160 24 14 383 = 1.17, df=	330 298 49 29 706	66 20 8 168	148 46 29 386	6.9% 2.7% 1.2%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52]	•
15.4.7 Quetiapine Sauer 2009 SI-Khalilii 2010 J 2013 Glothyre 2007 Subtotal (95% CI) Total events Teterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (f	185 160 24 14 383 = 1.17, df=	330 298 49 29 706	66 20 8 168	148 46 29 386	6.9% 2.7% 1.2%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52]	•
15.4.7 Quetiapine 3auer 2009 3:I-Khalilii 2010 .i 2013 Acintyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² est for overall effect: Z = 3.03 (f	185 160 24 14 383 = 1.17, df= P = 0.002)	330 298 49 29 706 = 3 (P = 1	66 20 8 168 0.76); I²	148 46 29 386 = 0%	6.9% 2.7% 1.2% 18.1%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40]	•
15.4.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 Alchtyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (f	185 160 24 14 383 = 1.17, df= P = 0.002)	330 298 49 29 706 = 3 (P = 1	66 20 8 168 3.76); l²	148 46 29 386 = 0%	6.9% 2.7% 1.2% 18.1%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02]	- - -
15.4.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f	185 160 24 14 383 == 1.17, df= P = 0.002)	330 298 49 29 706 = 3 (P = 1	66 20 8 168 0.76); I ² 30 11	148 46 29 386 = 0%	6.9% 2.7% 1.2% 18.1% 3.4% 2.0%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72]	
15.4.7 Quetiapine Sauer 2009 SI-Khalili 2010 J 2013 Kolntyre 2007 Subtotal (95% CI) Total events Test for overall effect: Z = 3.03 (Files. 15.4.8 Risperidone Sang 2011 Settliner 2009 Mahmoud 2007	185 160 24 14 383 = 1.17, df= P = 0.002)	330 298 49 29 706 = 3 (P = 1	66 20 8 168 0.76); I ² 30 11 33	148 46 29 386 = 0% 45 33 133	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03]	•
15.4.7 Quetiapine Bauer 2009 El-Khalili 2010 i 2013 dcintyre 2007 subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² est for overall effect: Z = 3.03 (f 15.4.8 Risperidone Tang 2011 Geitner 2009 dahmoud 2007 Reeves 2008	185 160 24 14 383 2 = 1.17, df= P = 0.002) 21 34 49 6	330 298 49 29 706 = 3 (P = 1	66 20 8 168 0.76); I ² 30 11 33 4	148 46 29 386 = 0% 45 33 133 11	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61]	•
15.4.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 Alchtyre 2007 Soubtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (for the company of	185 160 24 14 383 = 1.17, df= P = 0.002)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60	66 20 8 168 0.76); I ² 30 11 33	148 46 29 386 = 0% 45 33 133 11 60	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83]	
15.4.7 Quetiapine 16.4.7 Quetiapine 16.4.7 Quetiapine 16.4.7 Quetiapine 16.4.7 Quetiapine 16.4.8 Quetiapine 16.4.8 Quetiapine 16.4.8 Risperidone 16.4.8 Risperidone 16.4.8 Quetiapine 16.4 Quetiapine 16.4.8 Quetiapine 16.4 Quetiapine 16	185 160 24 14 383 = 1.17, df= P = 0.002) 21 34 49 6 25	330 298 49 29 706 = 3 (P = 1	66 20 8 168 0.76); F 30 11 33 4 15	148 46 29 386 = 0% 45 33 133 11	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61]	
IS-4.7 Quetiapine Bauer 2009 El-Khalilli 2010 i 2013 Acintyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (f IS-4.8 Risperidone Tang 2011 Acinter 2009 Adahmoud 2007 Reeves 2008 Bong 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.12; Chi² Tetal events Heterogeneity: Tau² = 0.12; Chi²	185 160 24 14 383 = 1.17, df= P = 0.002) 21 34 49 6 25 135 = 11.56, df	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322	66 20 8 168 3.76); F 30 11 33 4 15	148 46 29 386 = 0% 45 33 133 11 60 282	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83]	
IS.4.7 Quetiapine Bauer 2009 BI-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f IS.4.8 Risperidone Fang 2011 Geitner 2009 Mahmoud 2007 Reeves 2008 Boong 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f	185 160 24 14 383 = 1.17, df= P = 0.002) 21 34 49 6 25 135 = 11.56, df	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322	66 20 8 168 3.76); F 30 11 33 4 15	148 46 29 386 = 0% 45 33 133 11 60 282	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83]	
15.4.7 Quetiapine 3auer 2009 31-Khalilli 2010 i. 2013 4cIntyre 2007 Subtotal (95% CI) Total events 4eterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (f 15.4.8 Risperidone Tang 2011 4cetiner 2009 4ahmoud 2007 Reeves 2008 Song 2007 Subtotal (95% CI) Total events 4eterogeneity: Tau² = 0.12; Chi² Test for overall effect: Z = 1.15 (f	185 160 24 14 383 = 1.17, df = P = 0.002) 21 34 49 6 25 135 = 11.56, df P = 0.25)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322 f = 4 (P =	66 20 8 168 0.76); F 30 11 33 4 15 93 : 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 *= 659	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
15.4.7 Quetiapine Bauer 2009 El-Khalilli 2010 i 2013 dcintyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Test for overall effect: Z = 3.03 (f 15.4.8 Risperidone Tang 2011 Getther 2009 Mahmoud 2007 Reeves 2008 Bong 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.12; Chi² Test for overall effect: Z = 1.15 (f 15.4.9 Ziprasidone Dunner 2007	185 160 24 14 383 3 = 1.17, df = P = 0.002) 21 34 49 6 25 135 2 = 11.56, df P = 0.25)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322 f = 4 (P =	66 20 8 168 0.76); F 30 11 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 = 659	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
15.4.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone Fang 2011 Mahmoud 2007 Reeves 2008 Bong 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f 15.4.9 Ziprasidone Dunner 2007 Papakostas 2015	185 160 24 14 383 = 1.17, df = P = 0.002) 21 34 49 6 25 135 = 11.56, df P = 0.25)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322 f = 4 (P =	66 20 8 168 0.76); F 30 11 33 4 15 93 : 0.02); I	148 46 29 386 = 0% 45 33 11 60 282 20 68	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
IS.4.7 Quetiapine Bauer 2009 BI-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f IS.4.8 Risperidone Fang 2011 Geither 2009 Mahmoud 2007 Reeves 2008 Bong 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f IS.4.9 Ziprasidone Dunner 2007 Papakostas 2015 Subtotal (95% CI)	185 160 24 14 383 3 = 1.17, df = P = 0.002) 21 34 49 6 25 135 2 = 11.56, df P = 0.25)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322 f = 4 (P =	66 20 8 168 0.76); F 30 11 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 = 659	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
15.4.7 Quetiapine	185 160 24 14 383 3=1.17, df= P=0.002) 21 34 49 6 25 135 7=11.56, df P=0.25) 10 25 35 7=0.21, df=	330 298 49 29 706 = 3 (P = 1 45 64 111 12 60 322 (= 4 (P = 1 112	66 20 8 168 2.76); F 30 111 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 113 11 60 282 20 68 88	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
15.4.7 Quetiapine Bauer 2009 21-Khalili 2010 .i 2013 //dintyre 2007 Subtotal (95% CI) Fotal events -leterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone -lang 2011 -leterogeneity: Tau² = 0.02; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone -lang 2017 -leterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f 15.4.9 Ziprasidone -lounner 2007 -leterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.05 (f 15.4.9 Ziprasidone -lounner 2007 -leterogeneity: Tau² = 0.00; Chi² Fotal events -leterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 2.19 (f	185 160 24 14 383 3=1.17, df= P=0.002) 21 34 49 6 25 135 7=11.56, df P=0.25) 10 25 35 7=0.21, df=	330 298 49 29 706 = 3 (P = 1 45 664 141 12 60 322 = 4 (P = 1 112 = 1 (P = 1	66 20 8 168 2.76); F 30 111 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 2 = 659 20 68 88 = 0%	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 2.0% 11.5% 6	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83] 2.44 [0.59, 10.10] 1.71 [0.97, 3.00] 1.79 [1.06, 3.03]	
15.4.7 Quetiapine 3auer 2009 3:I-Khalili 2010 .i 2013 4cintyre 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone Frang 2011 4ceither 2009 4shahmoud 2007 Reeves 2008 Song 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f 15.4.9 Ziprasidone Dunner 2007 Papakostas 2015 Subtotal (95% CI) Fotal events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 2.19 (f Fotal (95% CI)	185 160 24 14 383 383 3 = 1.17, df = P = 0.002) 21 34 49 6 25 315 3 = 11.56, dt P = 0.25) 10 25 35 3 = 0.21, df = P = 0.03)	330 298 49 29 706 = 3 (P = 1 45 64 111 12 60 322 (= 4 (P = 1 112	66 20 8 168 3.76); F 30 111 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 2 = 659 20 68 88 = 0%	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 3.5% 0.7% 11.5%	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83]	
15.4.7 Quetiapine Bauer 2009 21-Khalili 2010 .i 2013 //dintyre 2007 Subtotal (95% CI) Fotal events -leterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone -lang 2011 -leterogeneity: Tau² = 0.02; Chi² Fest for overall effect: Z = 3.03 (f 15.4.8 Risperidone -lang 2017 -leterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.15 (f 15.4.9 Ziprasidone -lounner 2007 -leterogeneity: Tau² = 0.12; Chi² Fest for overall effect: Z = 1.05 (f 15.4.9 Ziprasidone -lounner 2007 -leterogeneity: Tau² = 0.00; Chi² Fotal events -leterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 2.19 (f	185 160 24 14 383 3=1.17, df= P=0.002) 21 34 49 6 25 135 7=11.56, df P=0.25) 10 25 35 7=0.21, df= P=0.03)	330 298 49 29 706 = 3 (P = 1 45 64 141 12 60 322 41 71 71 112 = 1 (P = 1	66 20 8 168 30,76); F 30 11 33 4 15 93 0.02); I	148 46 29 386 = 0% 45 33 133 11 60 282 = 659 20 68 88 = 0% 3964	6.9% 2.7% 1.2% 18.1% 3.4% 2.0% 0.7% 2.0% 11.5% 6	1.20 [0.98, 1.48] 1.13 [0.73, 1.74] 1.75 [0.87, 3.52] 1.23 [1.08, 1.40] 0.70 [0.48, 1.02] 1.59 [0.93, 2.72] 1.40 [0.97, 2.03] 1.38 [0.52, 3.61] 1.67 [0.98, 2.83] 1.25 [0.85, 1.83] 2.44 [0.59, 10.10] 1.71 [0.97, 3.00] 1.79 [1.06, 3.03]	0.01 0.1 10 1

984 AD: antidepressant; AP: antipsychotic

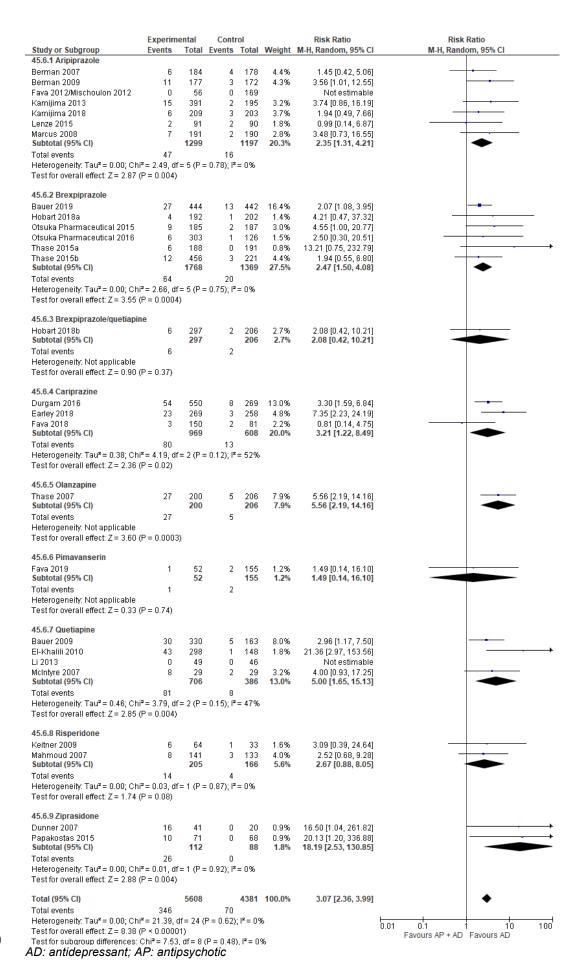
985 Figure 276: Discontinuation due to any reason

Study or Subgroup	Events	ntal Co Total Ever	ntrol ts Tot	al Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
15.5.1 Aripiprazole						
Berman 2007	22	184	16 17	8 3.0%	1.33 [0.72, 2.45]	+-
Berman 2009	30	177	23 17	2 4.4%	1.27 [0.77, 2.09]	 -
ava 2012/Mischoulon 2012	8		17 16	i9 1.9%	1.42 [0.65, 3.11]	
(amijima 2013	34	391	12 19	15 2.8%	1.41 [0.75, 2.67]	
(amijima 2018	15	209	20 20	13 2.7%	0.73 [0.38, 1.38]	
enze 2015.	4	91	7 9	0.8%	0.57 [0.17, 1.86]	
Marcus 2008	29		28 19		1.03 [0.64, 1.66]	
Subtotal (95% CI)		1299	119	7 20.4%	1.12 [0.89, 1.42]	•
"otal events Heterogeneity: Tau² = 0.00; Chi "est for overall effect: Z = 0.96 (I			23); I² = 09	6		
5.5.2 Brexpiprazole	, - 0.54)					
Sauer 2019	95	444	82 44	2 11 200	1 50 (1 1 4 0 0 4)	
Hobart 2018a	15	192	62 44 6 20		1.53 [1.14, 2.04] 2.63 [1.04, 6.64]	
Otsuka Pharmaceutical 2015	18		16 18			
Otsuka Pharmaceutical 2016	50		16 12		1.14 [0.60, 2.16]	
					1.30 [0.77, 2.19]	
hase 2015a	13		13 19		1.02 [0.48, 2.13]	
hase 2015b Subtotal (95% CI)	30	456 1768	13 22 13 6		1.12 [0.60, 2.10] 1.39 [1.13, 1.71]	_
	224			19 24.470	1.59 [1.15, 1.71]	\
"otal events Heterogeneity: Tau² = 0.00; Chi² "est for overall effect: Z = 3.11 (l			26); I² = 09	6		
5.5.3 Brexpiprazole/quetiapin	ie					
Hobart 2018b	40	297	20 20	16 4.3%	1.39 [0.84, 2.30]	+-
Subtotal (95% CI)		297	20		1.39 [0.84, 2.30]	★
Fotal events	40		20			
Heterogeneity: Not applicable Test for overall effect: Z = 1.27 (I						
45.5.4 Cariprazine						
Durgam 2016	57	550	35 26	9 6.7%	0.80 [0.54, 1.18]	-+
Earley 2018	56		36 25		1.49 [1.02, 2.19]	 -
ava 2018	17	150	9 8	1 2.0%	1.02 [0.48, 2.18]	
Subtotal (95% CI)		969	60	15.9%	1.08 [0.69, 1.67]	*
⁻ otal events Heterogeneity: Tau² = 0.09; Chi³			80); I² = 60	%		
est for overall effect: Z = 0.33 (I	P = 0.74)					
I 5.5.5 Olanzapine Thase 2007	52	200	40 20		1.34 [0.93, 1.93]	-
	32					
	32	200	20	6 7.8%	1.34 [0.93, 1.93]	▼
Subtotal (95% CI) Total events	52		20 40	16 7.8%	1.34 [0.93, 1.93]	
Subtotal (95% CI) Fotal events Heterogeneity: Not applicable	52			6 7.8%	1.34 [0.93, 1.93]	
Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 1.57 (I	52			16 7.8%	1.34 [0.93, 1.93]	
Subtotal (95% CI) Fotal events -deterogeneity. Not applicable Fest for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin	52 P = 0.12)		40			
Subtotal (95% CI) Total events Teterogeneity: Not applicable Test for overall effect: Z = 1.57 (I Test.5.6 Pimavanserin Test.2019	52	52	40 30 15	5 2.2%	0.79 [0.39, 1.62]	
Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.57 (I S.5.6 Pimavanserin Tava 2019 Subtotal (95% CI)	52 P = 0.12) 8	52 5 2	40 30 15 1 5	5 2.2%		*
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Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin Fava 2019 Subtotal (95% CI) Total events Heterogeneity: Not applicable	52 P = 0.12) 8 8	52 5 2	40 30 15 1 5	5 2.2%	0.79 [0.39, 1.62]	
Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin Tava 2019 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.63 (I	52 P = 0.12) 8 8	52 5 2	40 30 15 1 5	5 2.2%	0.79 [0.39, 1.62]	•
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Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin Sava 2019 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 0.63 (I 15.5.7 Quetiapine Bauer 2009 El-Khailii 2010 Li 2013 Acintyre 2007	52 P = 0.12) 8 8 P = 0.53) 51 79	52 52 52 330 298 49 29	40 30 15 15 30 18 16 23 14 0 4	35 2.2% 35 2.2% 33 4.3% 4.3% 4.6 6.99 3.0%	0.79 [0.39, 1.62] 0.79 [0.39, 1.62] 1.40 [0.85, 2.32] 1.71 [1.12, 2.60] Not estimable 0.85 [0.46, 1.57]	
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Subtotal (95% CI) Total events leterogeneity: Not applicable lest for overall effect: Z = 1.57 (I) 15.5.6 Pimavanserin Tava 2019 Subtotal (95% CI) Total events leterogeneity: Not applicable leterogeneity: Total 15.5.7 Quetiapine leterogeneity: Total 15.5.8 Quetiapine leterogeneity: Tau ² = 0.05; Chi ² 16 S.5.8 Risperidone leterogeneity: Tau ² = 0.05; Chi ² 16 S.5.8 Risperidone leterogeneity: Tau ² = 0.23; Chi ² 16 S.5.8 Risperidone leterogeneity: Tau ² = 0.23; Chi ² 16 S.5.9 Ziprasidone 16 S.5.9 Ziprasidone 17 Siprasidone 18 Siprasidone 1	52 P = 0.12) 8 8 P = 0.53) 51 79 0 11 141 = 3.47, df = P = 0.15) 12 35 1 = 48 48 421, df = P = 0.96) 21 22 43 = 0.56, df = 0.56, df = 0.56	52 52 52 330 298 49 29 706 2 (P = 0.18 64 141 12 217 2 (P = 0.12	40 40 15 15 15 16 17 17 18 18 18 18 18 18 18 18 18 18 18 18 18	65 2.2% 65 2.2% 63 4.3% 8 6.0% 60 13.3% 9 3.0% 61 13.3% 9 3.0% 10 1.7% 10 0.3% 11 0.3% 12 0.3% 13 4.6% 14 0.3% 15 0.6% 16 1.7% 17 6.6%	0.79 [0.39, 1.62] 0.79 [0.39, 1.62] 1.40 [0.85, 2.32] 1.71 [1.12, 2.60] Not estimable 0.85 [0.46, 1.57] 1.33 [0.90, 1.95] 0.88 [0.38, 2.03] 1.57 [0.97, 2.56] 0.23 [0.03, 1.75] 1.02 [0.48, 2.18] 2.05 [0.91, 4.63] 1.40 [0.80, 2.47]	
Subtotal (95% CI) Total events rest for overall effect: Z = 1.57 (I) St.5.6 Pimavanserin Sava 2019 Subtotal (95% CI) Total events rest for overall effect: Z = 0.63 (I) St.5.7 Quetiapine Sauer 2009 SH-Khalili 2010 Li 2013 SIGNIY e 2007 Subtotal (95% CI) Total events rest for overall effect: Z = 0.05; Chi Test for overall effect: Z = 1.45 (I) St.5.8 Risperidone Keitner 2009 Rahmoud 2007 Reeves 2008 Subtotal (95% CI) Total events rest for overall effect: Z = 0.05; Chi Test for overall effect: Z = 0.05 (I) St.5.9 Ziprasidone Dunner 2007 Papakostas 2015 Subtotal (95% CI) Total events rest for overall effect: Z = 0.00; Chi Test for overall effect: Z = 0.00; Chi Test for overall effect: Z = 0.00; Chi Test for overall effect: Z = 1.95 (I) Total events rest for overall effect: Z = 1.95 (I) Total events rest for overall effect: Z = 1.95 (I)	52 P = 0.12) 8 8 P = 0.53) 51 79 0 11 141 = 3.47, df = P = 0.15) 12 35 1 48 P = 0.96) 21 22 43 = 0.56, df = P = 0.05)	52 52 52 330 298 49 29 706 2 (P = 0.18 64 141 12 217 2 (P = 0.12	40 40 15 15 15 15 16 17 17 17 18 18 18 18 18 18 18 18 18 18 18 18 18	65 2.2% 65 2.2% 63 4.3% 8 6.0% 60 13.3% 9 3.0% 61 13.3% 9 3.0% 10 1.7% 10 0.3% 11 0.3% 12 0.3% 13 4.6% 14 0.3% 15 0.6% 16 1.7% 17 6.6%	0.79 [0.39, 1.62] 0.79 [0.39, 1.62] 1.40 [0.85, 2.32] 1.71 [1.12, 2.60] Not estimable 0.85 [0.46, 1.57] 1.33 [0.90, 1.95] 0.88 [0.38, 2.03] 1.57 [0.97, 2.56] 0.23 [0.03, 1.75] 1.02 [0.48, 2.18] 2.05 [0.91, 4.63] 1.40 [0.80, 2.47]	
Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin Fava 2019 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 0.63 (I 15.5.7 Quetiapine Bauer 2009 El-Khalili 2010 Li 2013 McIntyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.05; Chi² Fest for overall effect: Z = 1.45 (I 15.5.8 Risperidone Keitner 2009 Mahmoud 2007 Reeves 2008 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.23; Chi² Fest for overall effect: Z = 0.05 (I 15.5.9 Ziprasidone Ounner 2007 Papakostas 2015 Subtotal (95% CI)	52 P = 0.12) 8 8 P = 0.53) 51 79 0 11 141 = 3.47, df = P = 0.15) 12 35 1 48 P = 0.96) 21 22 43 = 0.56, df = P = 0.05)	52 52 52 330 298 49 29 706 2 (P = 0.18 64 141 12 217 2 (P = 0.12 41 71 112 1 (P = 0.46	40 40 15 15 15 15 16 17 17 17 18 18 18 18 18 18 18 18 18 18 18 18 18	15 2.2% 15 2.2% 13 4.3% 13 6.0% 16 13.3% 17 6.6% 10 1.7% 10 1.7% 10 1.7% 11 0.3% 12 0.3% 13 4.6% 14 0.3% 15 0.3% 16 0.3% 17 6.6%	0.79 [0.39, 1.62] 0.79 [0.39, 1.62] 1.40 [0.85, 2.32] 1.71 [1.12, 2.60] Not estimable 0.85 [0.46, 1.57] 1.33 [0.90, 1.95] 0.88 [0.38, 2.03] 1.57 [0.97, 2.56] 0.23 [0.03, 1.75] 1.02 [0.48, 2.18] 2.05 [0.91, 4.63] 1.40 [0.80, 2.47] 1.59 [1.00, 2.55]	
Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 1.57 (I 15.5.6 Pimavanserin Fava 2019 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: Z = 0.63 (I 15.5.7 Quetiapine Bauer 2009 El-Khalili 2010 I 2013 Michtyre 2007 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.05; Chi² Fest for overall effect: Z = 1.45 (I 15.5.8 Risperidone Keitner 2009 Mahmoud 2007 Reeves 2008 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.23; Chi² Fest for overall effect: Z = 0.05 (I 15.5.9 Ziprasidone Dunner 2007 Papakostas 2015 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 1.95 (I 15.5.9 Ziprasidone Dunner 2007 Papakostas 2015 Subtotal (95% CI) Total events Heterogeneity: Tau² = 0.00; Chi² Fest for overall effect: Z = 1.95 (I Total (95% CI)	52 P = 0.12) 8 8 P = 0.53) 51 79 0 11 141 = 3.47, df = P = 0.15) 12 35 1 48 = 4.21, df = P = 0.96) 21 22 43 = 0.56, df = P = 0.05) 825	52 52 52 330 298 49 29 706 2 (P = 0.18 64 141 12 217 2 (P = 0.12 41 71 112 1 (P = 0.46	40 40 40 40 40 40 40 40 40 40 40 40 40 4	33 4.3% 83 6.0% 69 3.0% 61 13.3% 80 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7% 81 1.7%	0.79 [0.39, 1.62] 0.79 [0.39, 1.62] 1.40 [0.85, 2.32] 1.71 [1.12, 2.60] Not estimable 0.85 [0.46, 1.57] 1.33 [0.90, 1.95] 0.88 [0.38, 2.03] 1.57 [0.97, 2.56] 0.23 [0.03, 1.75] 1.02 [0.48, 2.18] 2.05 [0.91, 4.63] 1.40 [0.80, 2.47] 1.59 [1.00, 2.55]	0.01 0.1 10 1

987 <Insert Note here>
988 AD: antidepressant; AP: antipsychotic

989

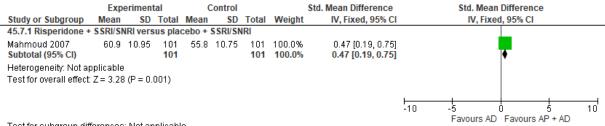
Figure 277: Discontinuation due to side effects



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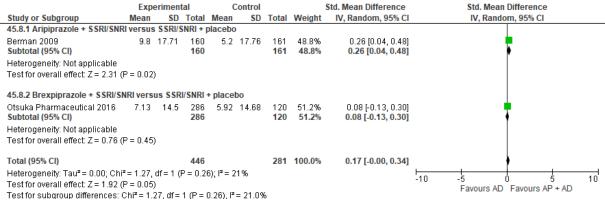
Figure 278: Quality of life endpoint



994 Test for subgroup differences: Not applicable 995 AD: antidepressant; AP: antipsychotic

996

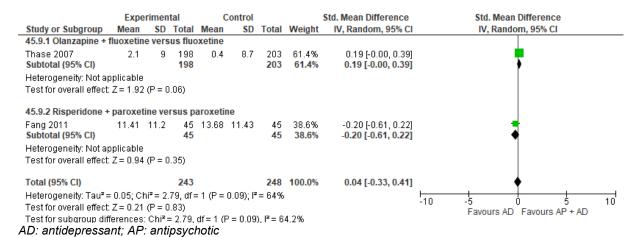
997 Figure 279: Quality of life change score



AD: antidepressant; AP: antipsychotic

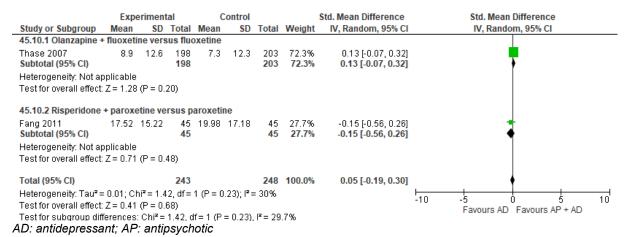
1000

1001 Figure 280: Quality of life physical component score (PCS) change score

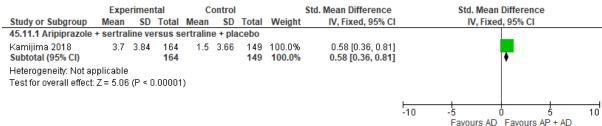


1002

1005 Figure 281: Quality of life mental component score (MCS) change score

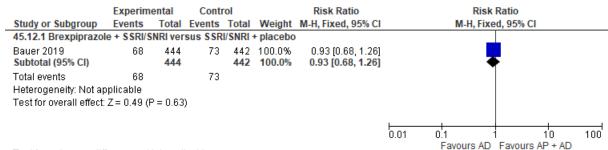


1009 Figure 282: Global functioning change score



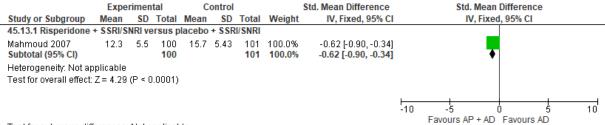
 Test for subgroup differences: Not applicable AD: antidepressant; AP: antipsychotic

Figure 283: Functional remission (≤6 total score on SDS and all SDS domain scores ≤2)



 Test for subgroup differences: Not applicable AD: antidepressant; AP: antipsychotic

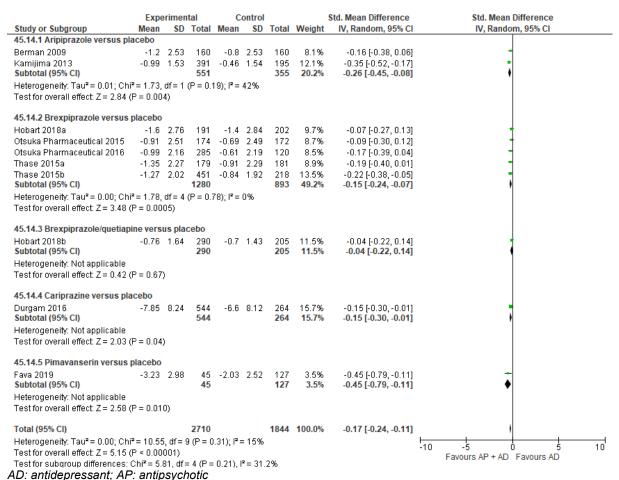
1018 Figure 284: Functional impairment endpoint



019 Test for subgroup differences: Not applicable AD: antidepressant; AP: antipsychotic

1021

1022 Figure 285: Functional impairment change score

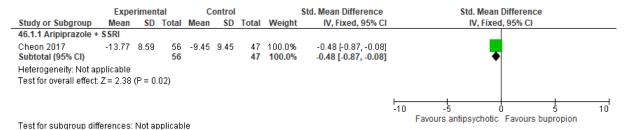


1023 1024

1025

1027 Comparison 46. Augmenting with antipsychotic versus bupropion

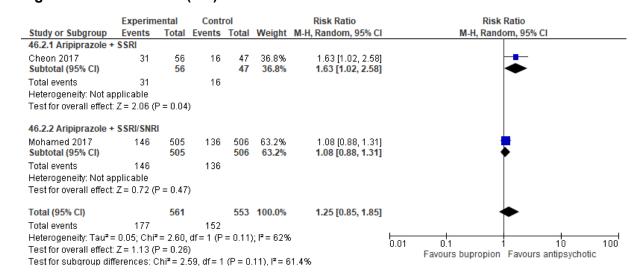
1028 Figure 286: Depression symptomatology change score



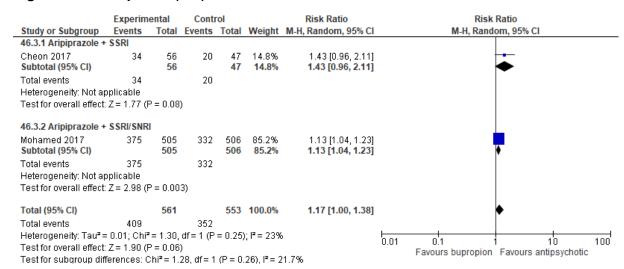
1030 Figure 287: Remission (ITT)

1029

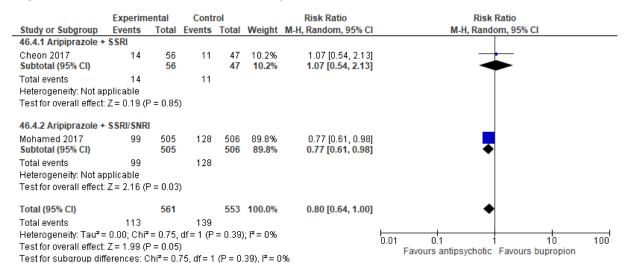
1031



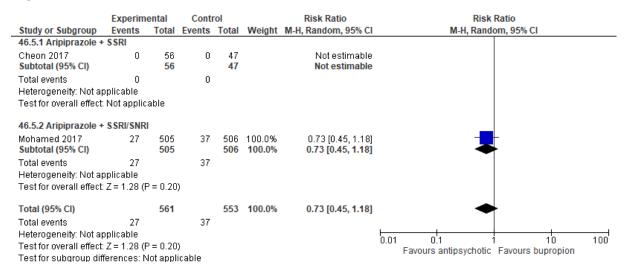
1032 Figure 288: Response (ITT)



1034 Figure 289: Discontinuation due to any reason



1036 Figure 290: Discontinuation due to side effects

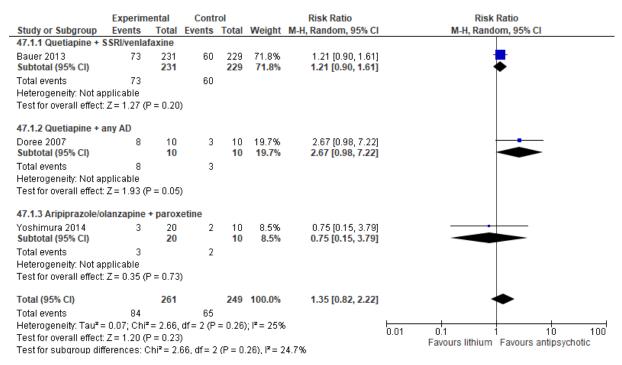


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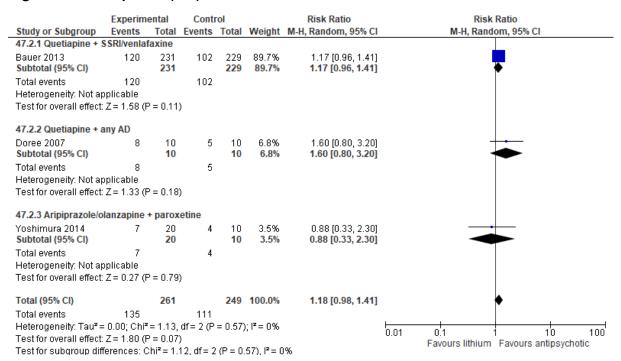
1039 Comparison 47. Augmenting with antipsychotic versus lithium

1040 Figure 291: Remission (ITT)

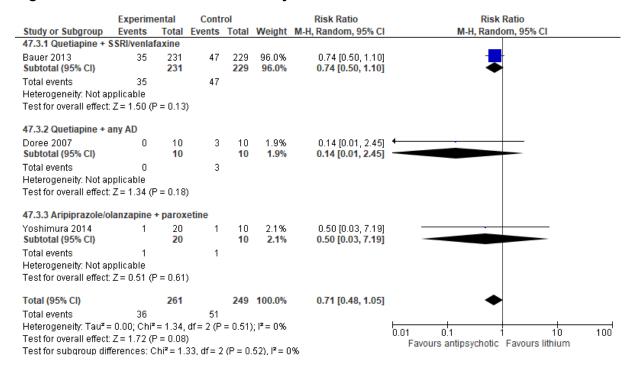


1042 Figure 292: Response (ITT)

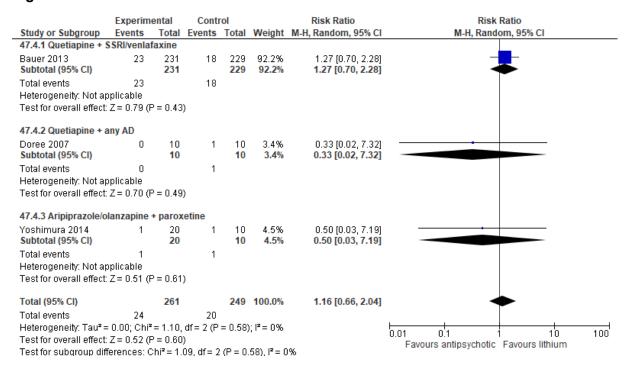
1041



1044 Figure 293: Discontinuation due to any reason



1046 Figure 294: Discontinuation due to side effects

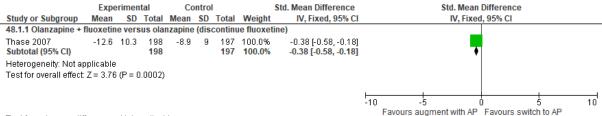


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1045

1049 Comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

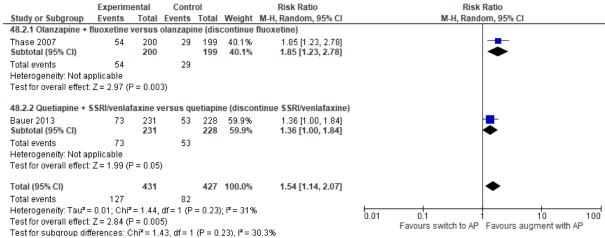
1050 Figure 295: Depression symptomatology change score



1051 Test for subgroup differences: Not applicable AP: antipsychotic

1053

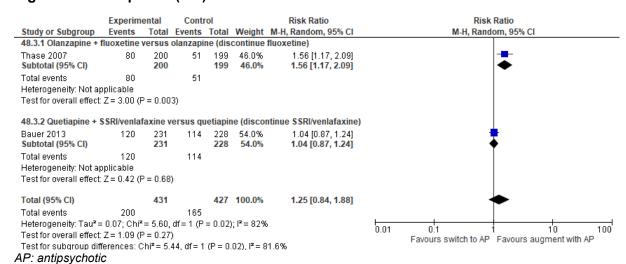
1054 Figure 296: Remission (ITT)



1055 Test for subgroup differ 1056 AP: antipsychotic

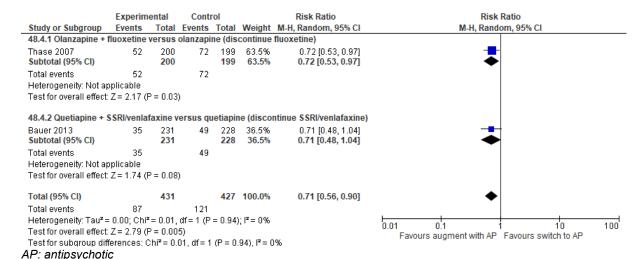
1057

1058 Figure 297: Response (ITT)



1059 1060

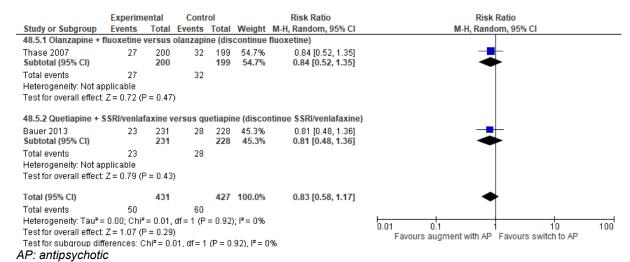
1062 Figure 298: Discontinuation due to any reason



1063 1064

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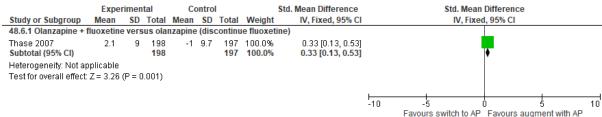
1066 Figure 299: Discontinuation due to side effects



1067 1068

1069

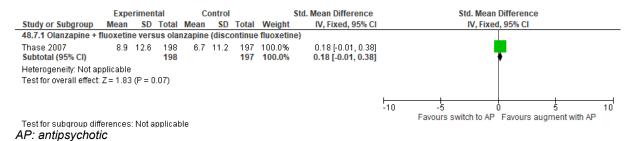
1070 Figure 300: Quality of life physical component score (PCS) change score



1071 1072 Test for subgroup differences: Not applicable

AP: antipsychotic

1074 Figure 301: Quality of life mental component score (MCS) change score



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1078

1079 Comparison 49. Augmenting with antipsychotic versus switch to bupropion

1080 Figure 302: Remission (ITT)

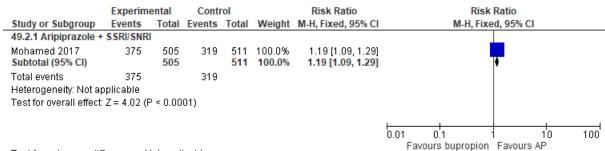
	Experim	ental	Conti	rol		Risk Ratio		Ri	isk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, F	ixed, 95% CI		
49.1.1 Aripiprazole +	SSRI/SNR	I									
Mohamed 2017 Subtotal (95% CI)	146	505 505	114	511 511	100.0% 100.0 %	1.30 [1.05, 1.60] 1.30 [1.05, 1.60]			•		
Total events Heterogeneity: Not ap Test for overall effect:		P = 0.02	114								
T-16 10							0.01 Fav	0.1 /ours bupropi	on Favours A	10 P	100

1081 1082 Test for subgroup differences: Not applicable

AP: antipsychotic

1083

1084 Figure 303: Response (ITT)

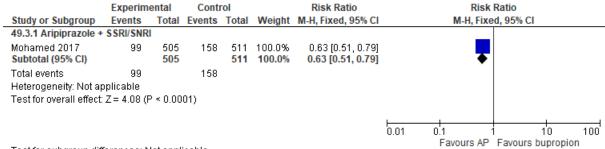


1085

Test for subgroup differences: Not applicable

AP: antipsychotic

1088 Figure 304: Discontinuation due to any reason



1089 Test for subgroup differences: Not applicable 1090 AP: antipsychotic

1091

1092 Figure 305: Discontinuation due to side effects

	Experim	ental	Conti	rol		Risk Ratio		Risl	(Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95% CI		
49.4.1 Aripiprazole +	SSRI/SNR	I									
Mohamed 2017 Subtotal (95% CI)	27	505 505	51	511 511	100.0% 100.0 %	0.54 [0.34, 0.84] 0.54 [0.34, 0.84]					
Total events Heterogeneity: Not a Test for overall effect		P = 0.00	51 17)								
T16							0.01	0.1 Favours AF	Favours b	10 upropio	100

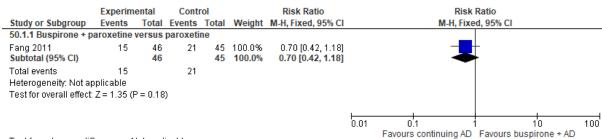
1093 Test for subgroup differences: Not applicable 1094 AP: antipsychotic

1095

1096

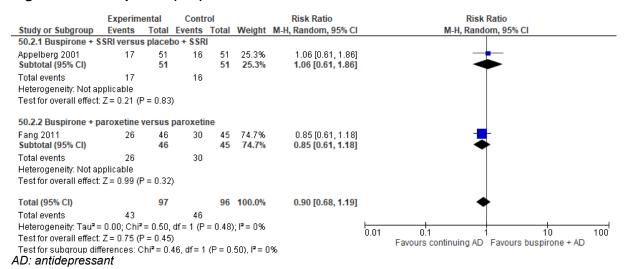
1097 Comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/-1098 placebo)

1099 Figure 306: Remission (ITT)



1100 Test for subgroup differences: Not applicable 1101 AD: antidepressant

1103 Figure 307: Response (ITT)



1104 1105

1106

1107 Figure 308: Quality of life physical component score (PCS) change score

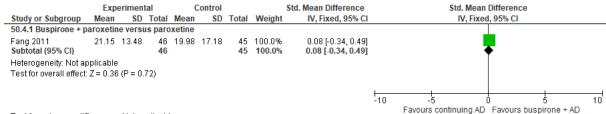
	Exp	eriment	tal	(Control			Std. Mean Difference		Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
50.3.1 Buspirone + p	paroxetin	ie versi	ıs pard	xetine							
Fang 2011	12.94	11.42	46	13.68	11.43	45	100.0%	-0.06 [-0.48, 0.35]			
Subtotal (95% CI)			46			45	100.0%	-0.06 [-0.48, 0.35]		▼	
Heterogeneity: Not a	pplicable										
Test for overall effect	: Z = 0.31	(P = 0.1)	76)								
									-10	5 0 5	10
									-10	Favours continuing AD Favours buspirone + AD	10

1108 1109 Test for subgroup differences: Not applicable

AD: antidepressant

1110

1111 Figure 309: Quality of life mental component score (MCS) change score



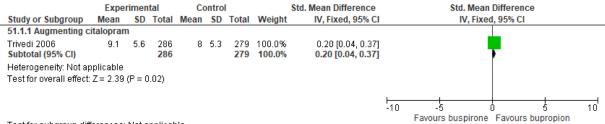
1112

Test for subgroup differences: Not applicable AD: antidepressant

1114

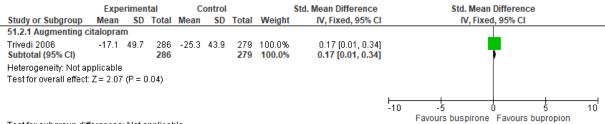
1116 Comparison 51. Augmenting with buspirone versus bupropion

1117 Figure 310: Depression symptomatology endpoint



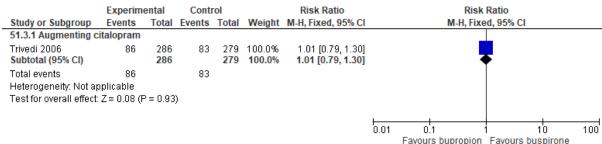
1118 Test for subgroup differences: Not applicable

1119 Figure 311: Depression symptomatology change score



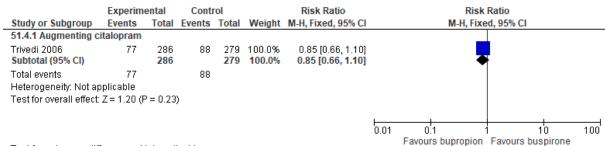
1120 Test for subgroup differences: Not applicable

1121 Figure 312: Remission (ITT)



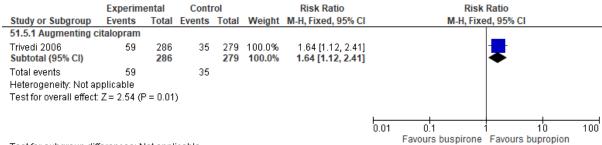
1122 Test for subgroup differences: Not applicable

1123 Figure 313: Response (ITT)



1124 Test for subgroup differences: Not applicable

1125 Figure 314: Discontinuation due to side effects



1126 Test for subgroup differences: Not applicable

1127

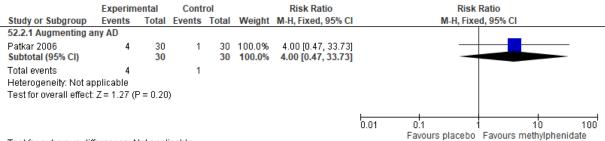
1128 Comparison 52. Augmenting with methylphenidate versus placebo

1129 Figure 315: Depression symptomatology change score

	Expe	Experimental			ontrol			Std. Mean Difference	St	td. Mean Differer	ice	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% C	1	
52.1.1 Augmenting a	ny AD											
Ravindran 2008a Subtotal (95% CI)	-10.38	8.13	72 72	-10.83	8.12	72 72	100.0% 100.0%	0.06 [-0.27, 0.38] 0.06 [-0.27, 0.38]		•		
Heterogeneity: Not ap Test for overall effect			.74)									
									-10 -5 Favours methylph	0 henidate Favour	5 rs placebo	10

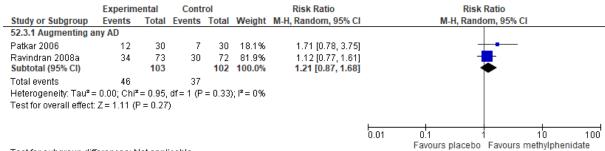
1130 Test for subgroup differences: Not applicable

1131 Figure 316: Remission (ITT)



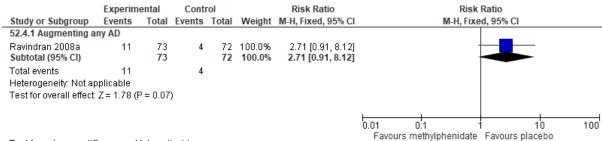
1132 Test for subgroup differences: Not applicable

1133 Figure 317: Response (ITT)



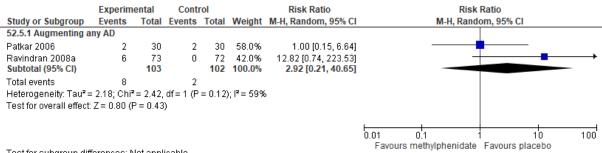
1134 Test for subgroup differences: Not applicable

1135 Figure 318: Discontinuation due to any reason



1136 Test for subgroup differences: Not applicable

1137 Figure 319: Discontinuation due to side effects

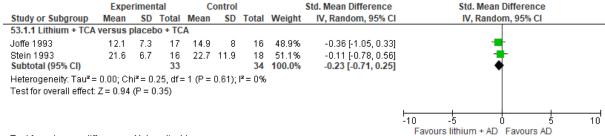


1138 Test for subgroup differences: Not applicable

1139

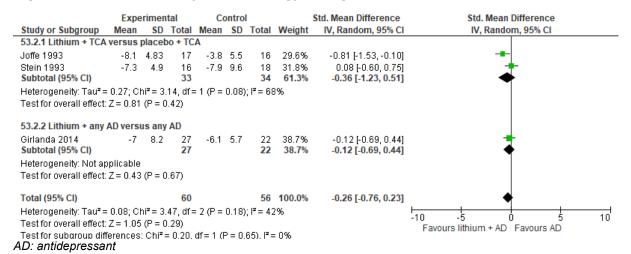
1140 Comparison 53. Augmenting with lithium versus continuing with antidepressant (+/-1141 placebo)

1142 Figure 320: Depression symptomatology endpoint



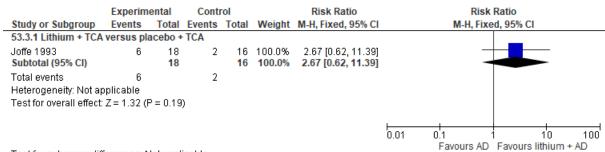
Test for subgroup differences: Not applicable AD: antidepressant

1146 Figure 321: Depression symptomatology change score



1149

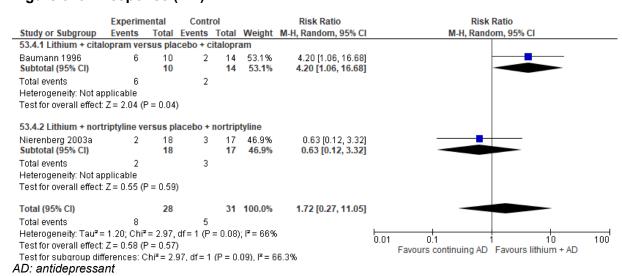
1150 Figure 322: Remission (ITT)



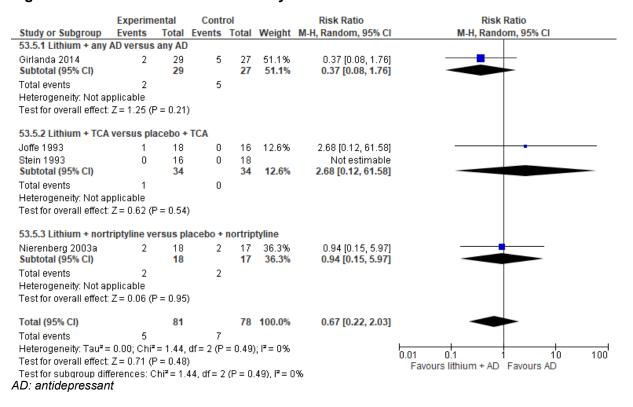
1151 1152 Test for subgroup differences: Not applicable AD: antidepressant

1153

1154 Figure 323: Response (ITT)



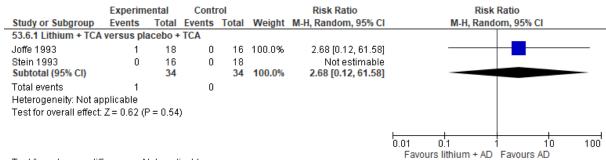
1158 Figure 324: Discontinuation due to any reason



1159 1160

1161

1162 Figure 325: Discontinuation due to side effects



1163 1164

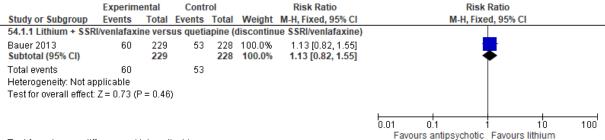
Test for subgroup differences: Not applicable

AD: antidepressant

1165

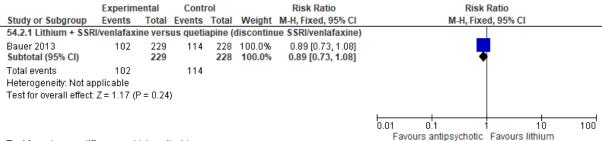
1167 Comparison 54. Augmenting with lithium versus switch to antipsychotic

1168 Figure 326: Remission (ITT)



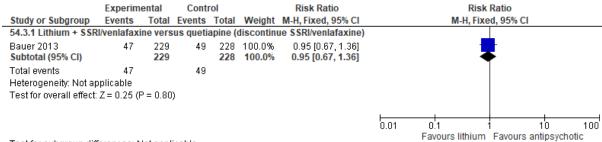
1169 Test for subgroup differences: Not applicable

1170 Figure 327: Response (ITT)



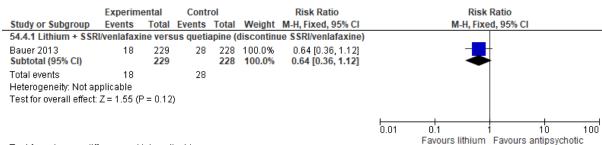
1171 Test for subgroup differences: Not applicable

1172 Figure 328: Discontinuation due to any reason



1173 Test for subgroup differences: Not applicable

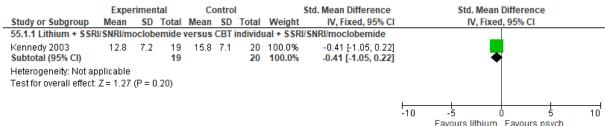
1174 Figure 329: Discontinuation due to side effects



1175 Test for subgroup differences: Not applicable

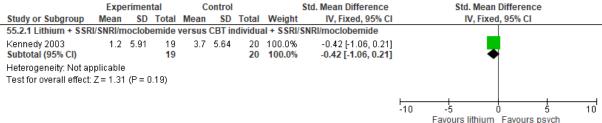
1177 Comparison 55. Augmenting with lithium versus augmenting with a psychological 1178 intervention

1179 Figure 330: Depression symptomatology endpoint



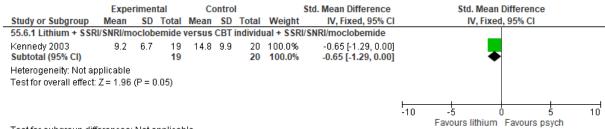
1180 Test for subgroup differences: Not applicable

1181 Figure 331: Depression symptomatology change score



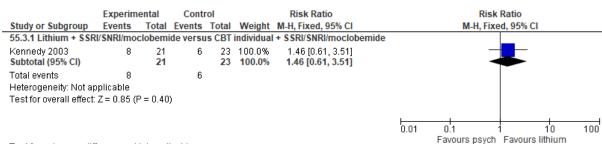
1182 Test for subgroup differences; Not applicable

1183 Figure 332: Depression symptomatology at 1-month follow-up



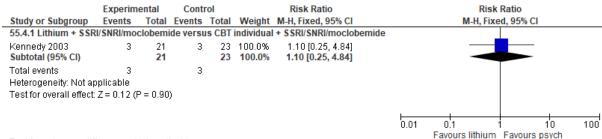
1184 Test for subgroup differences: Not applicable

1185 Figure 333: Remission (ITT)



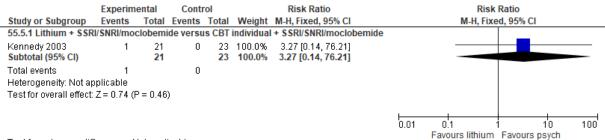
1186 Test for subgroup differences: Not applicable

1187 Figure 334: Discontinuation due to any reason



1188 Test for subgroup differences: Not applicable

1189 Figure 335: Discontinuation due to side effects

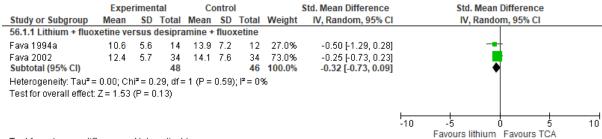


1190 Test for subgroup differences: Not applicable

1191

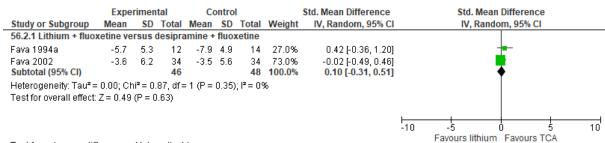
1192 Comparison 56. Augmenting with lithium versus augmenting with TCA

1193 Figure 336: Depression symptomatology endpoint



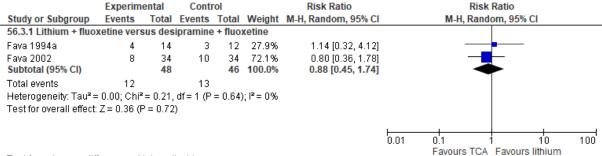
1194 Test for subgroup differences: Not applicable

1195 Figure 337: Depression symptomatology change score



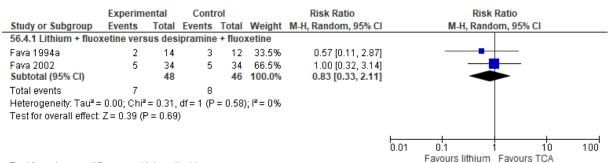
1196 Test for subgroup differences: Not applicable

1197 Figure 338: Remission (ITT)



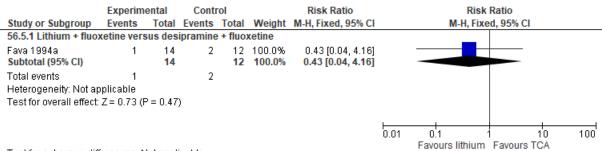
1198 Test for subgroup differences: Not applicable

1199 Figure 339: Discontinuation due to any reason



1200 Test for subgroup differences: Not applicable

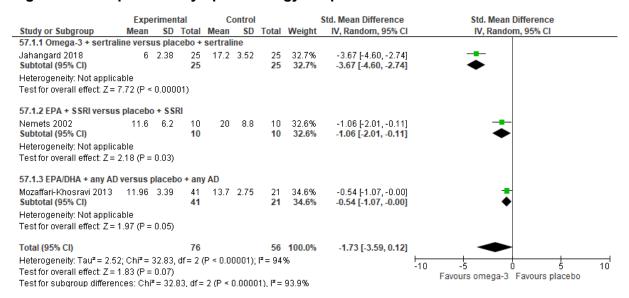
1201 Figure 340: Discontinuation due to side effects



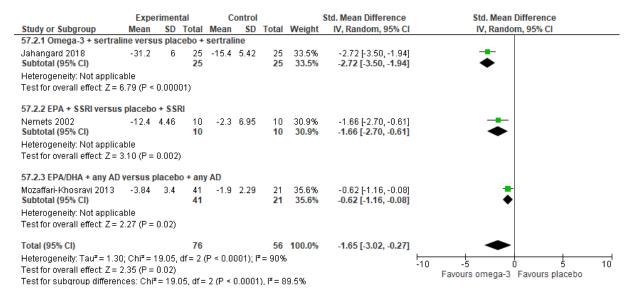
1202 Test for subgroup differences: Not applicable

1204 Comparison 57. Augmenting with omega-3 fatty acids versus placebo

1205 Figure 341: Depression symptomatology endpoint



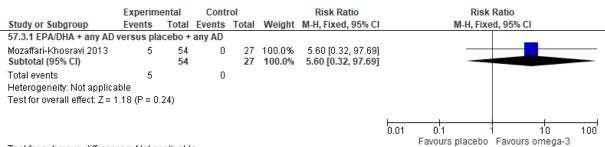
1207 Figure 342: Depression symptomatology change score



1209 Figure 343: Remission (ITT)

1206

1208

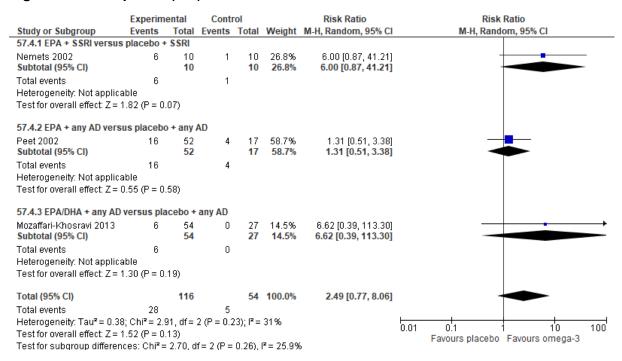


1210 Test for subgroup differences: Not applicable

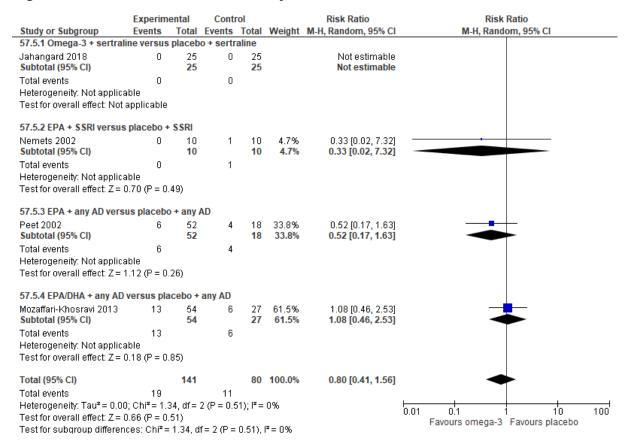
1211 Figure 344: Response (ITT)

1212

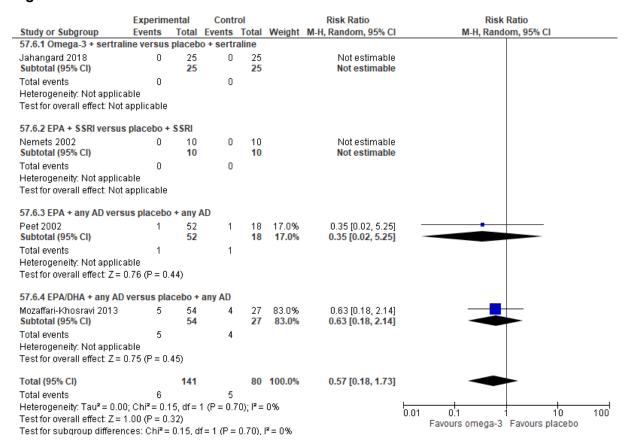
1214



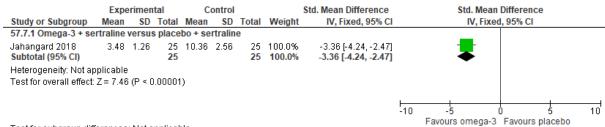
1213 Figure 345: Discontinuation due to any reason



1215 Figure 346: Discontinuation due to side effects



1217 Figure 347: Sleeping difficulties endpoint



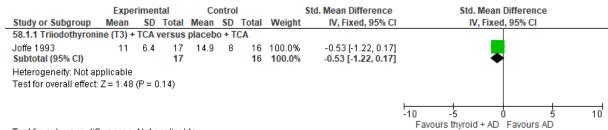
1218 Test for subgroup differences: Not applicable

1219

1216

1220 Comparison 58. Augmenting with thyroid hormone versus continuing with 1221 antidepressant (+/- placebo)

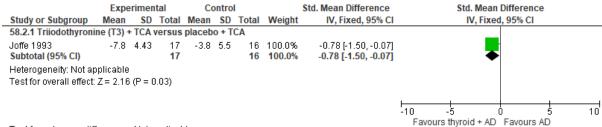
1222 Figure 348: Depression symptomatology endpoint



1223 1224 Test for subgroup differences: Not applicable

AD: antidepressant

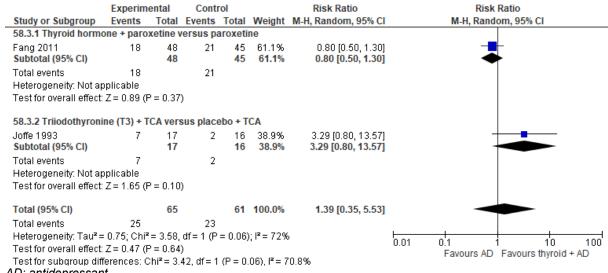
1226 Figure 349: Depression symptoms change score



1227 Test for subgroup differences: Not applicable AD: antidepressant

1229

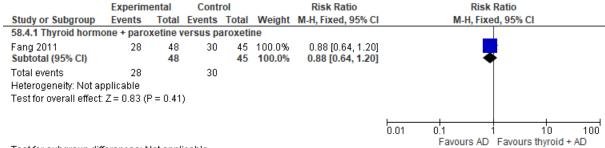
1230 Figure 350: Remission (ITT)



1232 AD: antidepressant

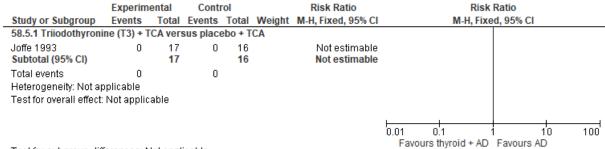
1233

1234 Figure 351: Response (ITT)



Test for subgroup differences: Not applicable AD: antidepressant

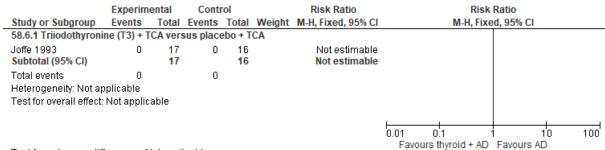
1238 Figure 352: Discontinuation due to any reason



| 239 | Test for subgroup differences: Not applicable | 240 | AD: antidepressant

1241

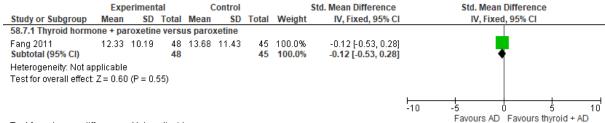
1242 Figure 353: Discontinuation due to side effects



1243 Test for subgroup differences: Not applicable 1244 AD: antidepressant

1245

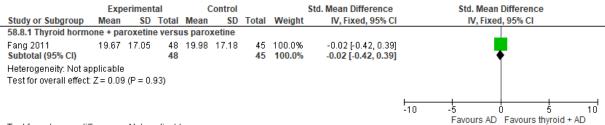
1246 Figure 354: Quality of life physical component score (PCS) change score



1247 Test for subgroup differences: Not applicable 1248 AD: antidepressant

1249

1250 Figure 355: Quality of life mental component score (MCS) change score



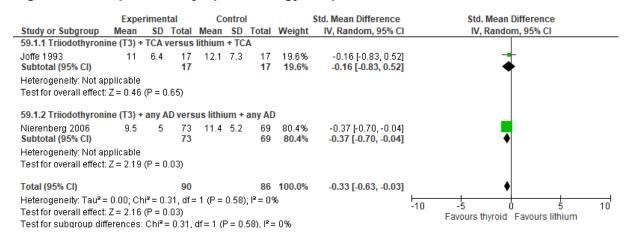
1251

Test for subgroup differences: Not applicable

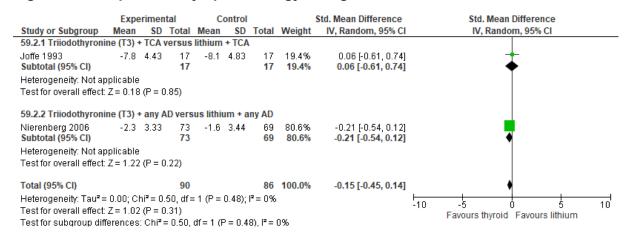
AD: antidepressant

1254 Comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

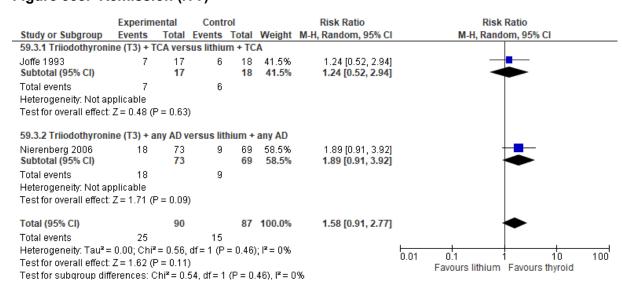
1255 Figure 356: Depression symptomatology endpoint



1257 Figure 357: Depression symptomatology change score

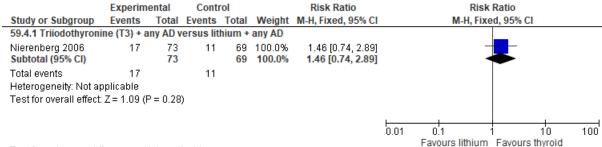


1259 Figure 358: Remission (ITT)



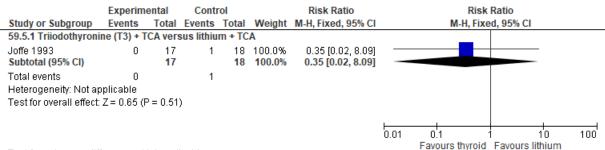
1256

1261 Figure 359: Response (ITT)



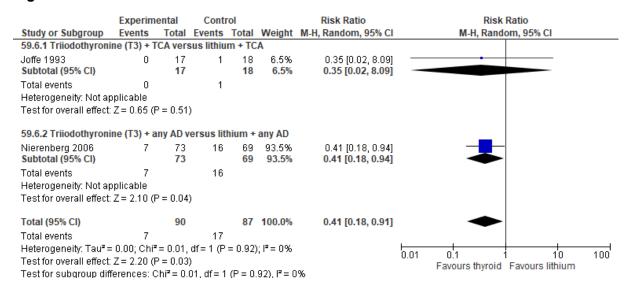
1262 Test for subgroup differences: Not applicable

1263 Figure 360: Discontinuation due to any reason



1264 Test for subgroup differences: Not applicable

1265 Figure 361: Discontinuation due to side effects



12661267

1268 Comparison 60. Switching to ECT versus switching to paroxetine

1269 Figure 362: Depression symptomatology endpoint

	Experimental						9	Std. Mean Difference	Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixe	d, 95% C	1	
Folkerts 1997	12.5	3.9	21	23	10.4	18	100.0%	-1.35 [-2.06, -0.65]					
Total (95% CI)			21			18	100.0%	-1.35 [-2.06, -0.65]		•			
Heterogeneity: Not a Test for overall effect		(P = 0	0.0002)						-10	-5 Favours ECT	0 Favou	5 rs AD	10

1271

AD: antidepressant

1272

1273 Figure 363: Depression symptomatology change score

	Expe	erimen	tal	C	ontrol			Std. Mean Difference		Std.	Mean	Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV	, Fixed	, 95% CI		
Folkerts 1997	-18.6	3.25	21	-9.6	7.29	18	100.0%	-1.61 [-2.34, -0.87]						
Total (95% CI)			21			18	100.0%	-1.61 [-2.34, -0.87]			•			
Heterogeneity: Not ap Test for overall effect).0001)						-10	-5 Favours	FCT) Favours Al	5	10

1274 1275

AD: antidepressant

1276

1277 Figure 364: Response (ITT)

	Experim	ental	Cont	rol		Risk Ratio	R	isk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	М-Н, Г	Fixed, 95% CI	
Folkerts 1997	15	21	5	19	100.0%	2.71 [1.22, 6.04]			
Total (95% CI)		21		19	100.0%	2.71 [1.22, 6.04]		•	
Total events	15		5						
Heterogeneity: Not as	oplicable						0.01 0.1	1 10	100
Test for overall effect:	Z = 2.45 (F	P = 0.01)					AD Favours ECT	100

1278 1279

AD: antidepressant

1280

1281 Figure 365: Discontinuation due to any reason

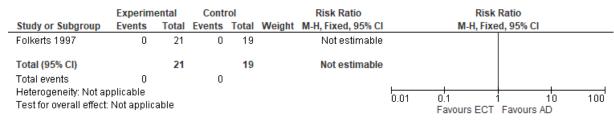
	Experim	ental	Conti	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Folkerts 1997	0	21	1	19	100.0%	0.30 [0.01, 7.02]		
Total (95% CI)		21		19	100.0%	0.30 [0.01, 7.02]		
Total events	0		1					
Heterogeneity: Not ap Test for overall effect:	•	o = 0.46)				0.01	100

1282 1283

AD: antidepressant

1284

1285 Figure 366: Discontinuation due to side effects



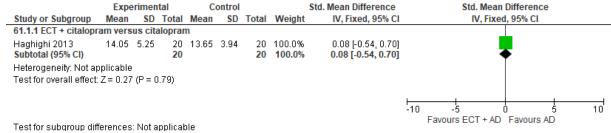
1286 1287

AD: antidepressant

1288

1290 Comparison 61. Augmenting with ECT versus continuing with antidepressant

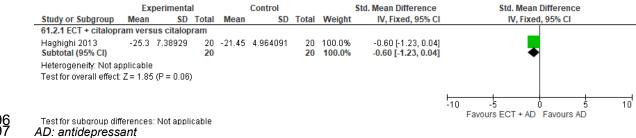
1291 Figure 367: Depression symptomatology endpoint



1292 Test for subgroup differences: Not a 1293 AD: antidepressant

1294

1295 Figure 368: Depression symptomatology change score



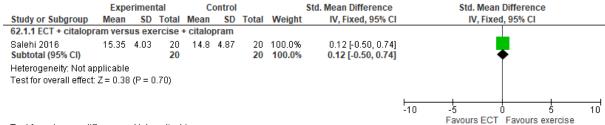
1291 AD: an

1298 1299

1304

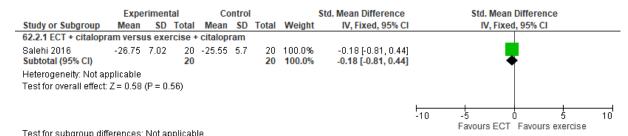
1300 Comparison 62. Augmenting with ECT versus augmenting with exercise

1301 Figure 369: Depression symptomatology endpoint

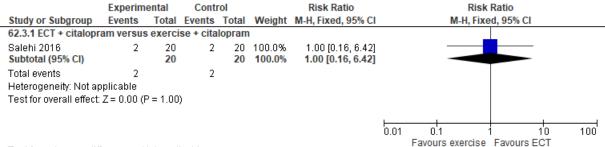


1302 Test for subgroup differences: Not applicable

1303 Figure 370: Depression symptomatology change score



1305 Figure 371: Remission (ITT)

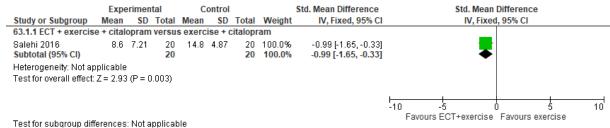


1306 Test for subgroup differences: Not applicable

1307

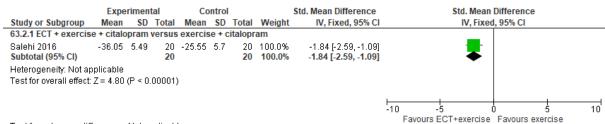
1308 Comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

1309 Figure 372: Depression symptomatology endpoint



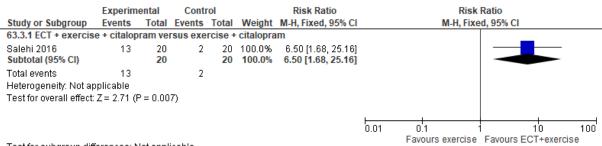
1310 Test for subgroup differences: Not applicable

1311 Figure 373: Depression symptomatology change score



1312 Test for subgroup differences: Not applicable

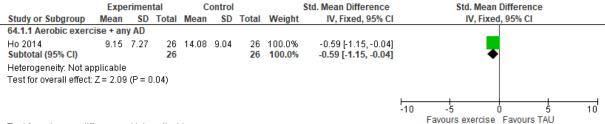
1313 Figure 374: Remission (ITT)



1314 Test for subgroup differences: Not applicable

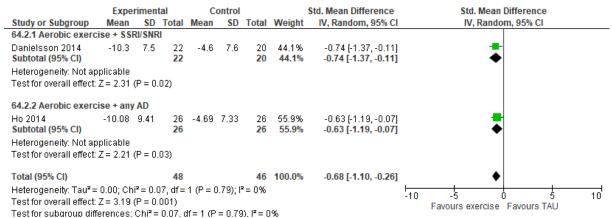
1316 Comparison 64. Augmenting with exercise versus TAU

1317 Figure 375: Depression symptomatology endpoint



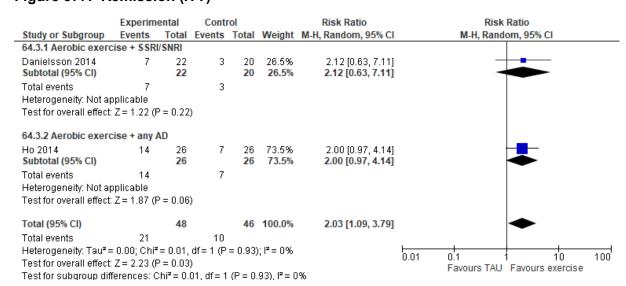
1318 Test for subgroup differences: Not applicable

1319 Figure 376: Depression symptomatology change score

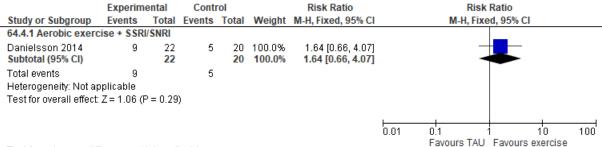


Test for subaroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79)

1321 Figure 377: Remission (ITT)

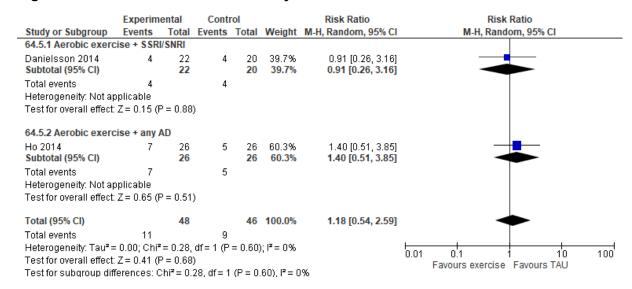


1323 Figure 378: Response (ITT)



1324 Test for subgroup differences: Not applicable

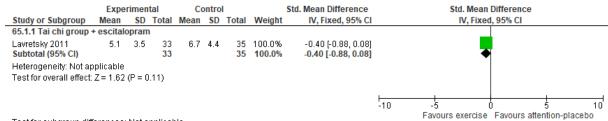
1325 Figure 379: Discontinuation due to any reason



1326 1327

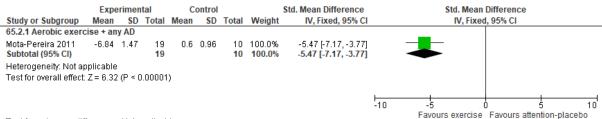
1328 Comparison 65. Augmenting with exercise versus attention-placebo

1329 Figure 380: Depression symptomatology endpoint



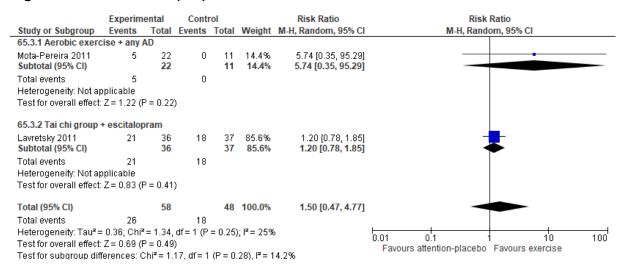
1330 Test for subgroup differences: Not applicable

1331 Figure 381: Depression symptomatology change score



1332 Test for subgroup differences: Not applicable

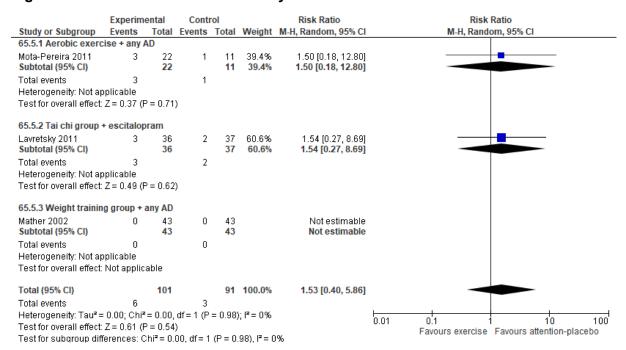
1333 Figure 382: Remission (ITT)



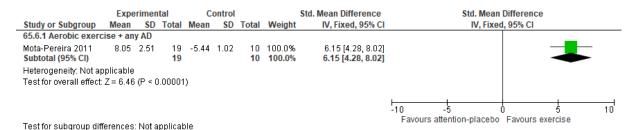
1335 Figure 383: Response (ITT)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
65.4.1 Aerobic exerci	ise + any i	AD					
Mota-Pereira 2011 Subtotal (95% CI)	4	22 22	0	11 11	3.2% 3.2%	4.70 [0.28, 80.14] 4.70 [0.28, 80.14]	
Total events Heterogeneity: Not ap	4 plicable		0				
Test for overall effect:	Z = 1.07 (F	P = 0.29)				
65.4.2 Weight training	g group +	any AD					
Mather 2002 Subtotal (95% CI)	23	43 43	14	43 43	96.8% 96.8%	1.64 [0.98, 2.74] 1.64 [0.98, 2.74]	
Total events Heterogeneity: Not ap	23 plicable		14				
Test for overall effect:	•	P = 0.06))				
Total (95% CI)		65		54	100.0%	1.70 [1.03, 2.81]	•
Total events	27		14				
Heterogeneity: Tau² = Test for overall effect:	Z = 2.06 (F	P = 0.04)		; I² = 0% 48), I² = 0		0.01 0.1 1 10 10 Favours attention-placebo Favours exercise

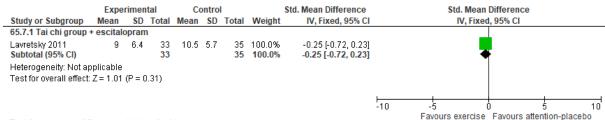
1337 Figure 384: Discontinuation due to any reason



1339 Figure 385: Global functioning change score



1341 Figure 386: Sleeping difficulties endpoint



1342 Test for subgroup differences: Not applicable

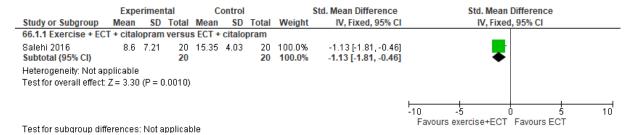
1343

1338

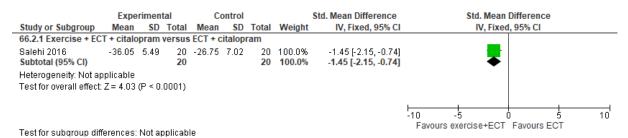
1340

1345 Comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

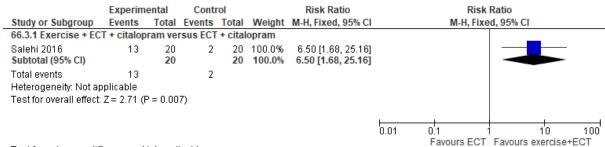
1346 Figure 387: Depression symptomatology endpoint



1348 Figure 388: Depression symptomatology change score



1350 Figure 389: Remission (ITT)



1351 Test for subgroup differences: Not applicable

1352

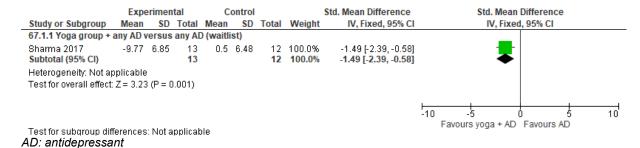
1347

1349

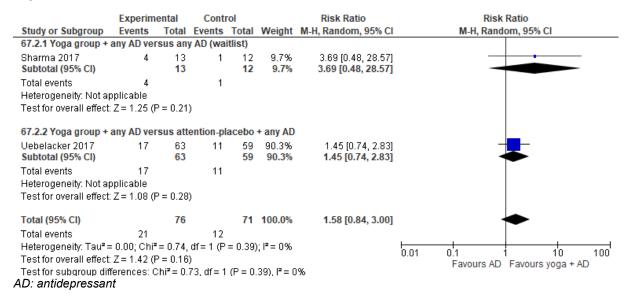
1353

1354 Comparison 67. Augmenting with yoga versus continuing with antidepressant (+/1355 waitlist or attention-placebo)

1356 Figure 390: Depression symptomatology change score



1360 Figure 391: Remission (ITT)



1363

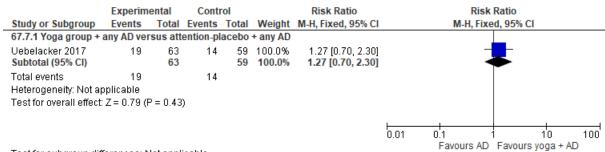
1364 Figure 392: Remission (ITT) at 3-month follow-up

	Experime	ental	Conti	rol		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% C	I
67.5.1 Yoga group + a	any AD ver	sus att	ention-pl	acebo	+ any AD				
Uebelacker 2017 Subtotal (95% CI)	19	63 63	11	59 59	100.0% 100.0%	1.62 [0.84, 3.11] 1.62 [0.84, 3.11]			
Total events	19		11						
Heterogeneity: Not ap Test for overall effect:	•	P = 0.15)						
							0.01	0.1 1 Favours AD Favours	10 100

Test for subgroup differences: Not applicable AD: antidepressant

1367

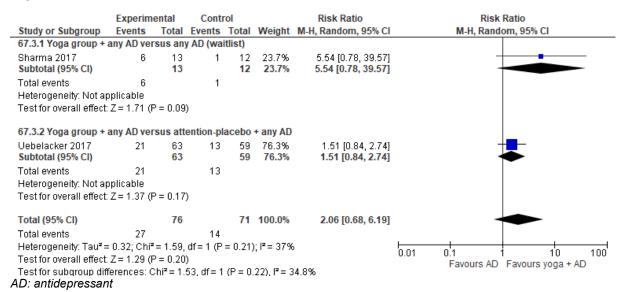
1368 Figure 393: Remission (ITT) at 6-month follow-up



Test for subgroup differences: Not applicable

AD: antidepressant

1372 Figure 394: Response (ITT)



1375

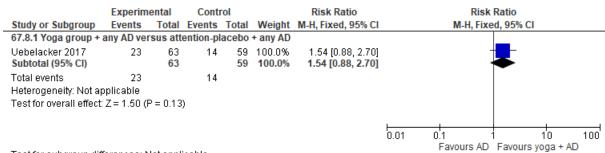
1376 Figure 395: Response (ITT) at 3-month follow-up

	Experim	ental	Conti	rol		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% CI		
67.6.1 Yoga group +	any AD ver	sus att	ention-pl	acebo	+ any AD						
Uebelacker 2017 Subtotal (95% CI)	22	63 63	13	59 59	100.0% 100.0 %	1.58 [0.88, 2.85] 1.58 [0.88, 2.85]					
Total events Heterogeneity: Not a Test for overall effect		P = 0.12	13								
T16	~						0.01	0.1 Favours AD	Favours)	10 yoga + A	100 D

1377 1378 Test for subgroup differences: Not applicable AD: antidepressant

1379

1380 Figure 396: Response (ITT) at 6-month follow-up

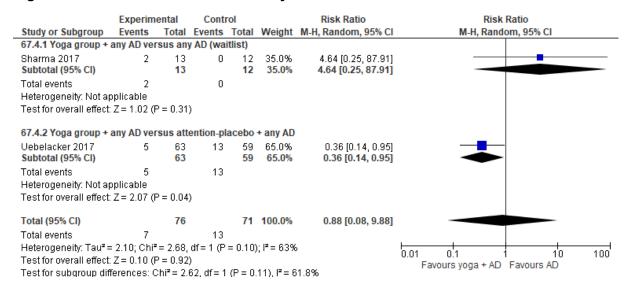


1381

Test for subgroup differences: Not applicable

AD: antidepressant

1384 Figure 397: Discontinuation due to any reason



1385 1386 1387

AD: antidepressant

1 Appendix F – GRADE tables

- 2 GRADE tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial,
- 3 pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate
- 4 response to at least one previous intervention for the current episode?
- 5 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			
No of studies	Docido	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)		Quality	Importance
Depression symptomato by lower values)	logy endpoi	nt (follov	v-up 8-26 weeks	; measured v	vith: Beck De	pression Invent	ory (BDI/BDI-II) o	r Hamilton Rating S	Scale for	Depression	(HAMD); Bet	ter indicated
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		no serious indirectness	serious ³	none	666	558	-	SMD 0.74 lower (1.03 to 0.45 lower)	VERY LOW	CRITICAL
Depression symptomato from baseline to endpoir		•	•	veeks; measu	red with: Bed	k Depression In	ventory (BDI/BD	I-II) or Hamilton Rat	ting Scale	for Depres	sion (HAMD)	change
10 (Chan 2012, Chiesa 2015, Dozois 2009, Dunn 1979, Embling 2002, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a)		serious ¹	,	no serious indirectness	no serious imprecision	none	265	259	<u>-</u>	SMD 1.36 lower (1.87 to 0.86 lower)	VERY LOW	CRITICAL

2 (Chiesa 2015, Nakagawa 2017)	randomised trials		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)												alues)
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 weel	ks; asses	ssed with: Num	ber of people	scoring =<7/	10 on Hamilton F	Rating Scale for I	Depression (HAM-D	0) or <10 o	on Beck Dep	ression Inve	entory (BDI-
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-mo	nth follow-u	p (follow	-up mean 3 mo	nths; assesse	d with: Numb	per of people sco	oring =<7 on Ham	ilton Rating Scale	for Depre	ssion (HAM	-D))	
1 (Nakagawa 2017)	randomised trials		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 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

(Nakagawa 2017)	randomised trials		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-m	onth follow-ι	ıp (follov	v-up mean 40 n	nonths; asses	sed with: Nu	mber of people s	coring <10 on B	eck Depression In	ventory (B	DI-II))		
(Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	38/234 (16.2%)	20/235 (8.5%)	(1.15 to	77 more per 1000 (from 13 more to 186 more)	LOW	CRITICAL
Response (ITT) (follow- Depression Inventory (E		s; asses	sed with: Resp	onse: Numbe	r of people st	nowing at least 5	0% improvemen	t on Hamilton Rati	ng Scale f	or Depression	on (HAM-D)/I	Beck
6 (Eisendrath 2016, Nakagawa 2017, Nakao 2018, Watkins 2011a, Viles 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-mol	nth follow-up	(follow-	up mean 3 mor	nths; assessed	d with: Numb	er of people sho	wing at least 50%	% improvement on	Hamilton	Rating Scale	e for Depres	sion (HAM-
(Nakagawa 2017)	randomised trials		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-more Rating Scale for Depres			up mean 6 mor	nths; assessed	d with: Numb	er of people sho	wing at least 50%	% improvement on	Beck Dep	ression Inve	entory (BDI-I	l)/Hamilton
! (Nakagawa 2017, Wiles 013/2016)	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-mo	onth follow-u	p (follow	-up mean 12 m	onths; assess	sed with: Nur	nber of people sl	nowing at least 5	60% improvement	on Hamilto	on Rating Sc	ale for Depr	ession
(Nakagawa 2017)	randomised trials		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

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 a	any reason (follow-up	8-26 weeks; a	ssessed with:	Number of p	articipants who	dropped out for	any reason (includi	ing adver	se 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)			no serious inconsistency	no serious indirectness	serious ³	none	111/807 (13.8%)	103/687 (15%)		7 fewer per 1000 (from 39 fewer to 31 more)	MODERATE	CRITICAL
Discontinuation due to s	side effects (follow-u	p mean 12 wee	ks; assessed	with: Number	of participants	who dropped ou	t due to adverse ev	ents)			
1 (Kocsis 2009/ Klein 2011)	randomised trials		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 m	ean 12 w	eeks; measure	d with: Europ	ean Quality o	f Life Questionn	aire-5 Dimension	s (EQ-5D); Better i	ndicated	by higher va	lues)	
1 (Nakao 2018)	randomised trials		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 c indicated by higher valu		core (PC	S) endpoint (fo	llow-up 12-26	weeks; meas	sured with: 12-ite	m/36-item Short	-Form Survey (SF-	12/SF-36):	Physical co	omponent sc	ore; Better
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 coi indicated by higher valu		ore (MCS	endpoint (foll	ow-up 12-26 v	veeks; measu	red with: 12-iten	n/36-item Short-F	Form Survey (SF-12	2/SF-36): I	Mental comp	onent score	; Better
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 c indicated by higher valu		core (PC	S) at 3-month f	follow-up (follo	ow-up mean 3	months; measu	red with: 36-iten	n Short-Form Surve	ey (SF-36)	: Physical c	omponent s	core; Better
1 (Nakagawa 2017)	randomised trials		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 cor		ore (MCS) at 3-month fo	llow-up (follo	w-up mean 3 เ	months; measure	ed with: 36-item	Short-Form Survey	(SF-36):	J ,	oonent scor	e; Better
1 (Nakagawa 2015)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	none	40	40	-	SMD 0.15 lower (0.58 lower to 0.29 higher)	MODERATE	IMPORTAN
Quality of life physical coscore; Better indicated b	•	•	S) at 6-month f	ollow-up (follo	ow-up mean 6	months; measu	red with: 12-iten	n/36-item Short-For	m Surve	y (SF-12/SF-3	66): Physical	l componen
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	IMPORTAN
Quality of life mental cor score; Better indicated b) at 6-month fo	llow-up (follo	w-up mean 6 ı	months; measure	ed with: 12-item/	36-item Short-Form	Survey	(SF-12/SF-36): Mental co	mponent
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	IMPORTAN
Quality of life physical co Better indicated by highe		core (PC	S) at 12-month	follow-up (fol	llow-up mean	12 months; mea	sured with: 36-it	em Short-Form Sur	vey (SF-	-36): Physical	component	score;
1 (Nakagawa 2015)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	SMD 0.05 higher (0.39 lower to 0.49 higher)	HIGH	IMPORTAN
Quality of life mental cor indicated by higher value		ore (MCS) at 12-month f	ollow-up (follo	ow-up mean 1	2 months; meas	ured with: 36-ite	m Short-Form Surv	ey (SF-3	6): Mental co	mponent sc	ore; Better
1 (Nakagawa 2015)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	none	40	40	-	SMD 0.2 lower (0.64 lower to 0.24 higher)	MODERATE	IMPORTAN
Quality of life physical co Better indicated by highe		core (PC	S) at 40-month	follow-up (fol	llow-up mean	40 months; mea	sured with: 12-it	em Short-Form Sur	vey (SF-	12): Physical	component	t score;
1 (Wiles 2013/2016)	randomised trials	serious ¹		no serious indirectness	no serious imprecision	none	132	110	-	SMD 0.22 higher (0.03 lower to 0.47 higher)	MODERATE	IMPORTAN
Quality of life mental cor indicated by higher value		ore (MCS) at 40-month f	ollow-up (follo	ow-up mean 4	0 months; meas	ured with: 12-ite	m Short-Form Surv	ey (SF-1	2): Mental co	mponent sc	ore; Better
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	IMPORTAN

										to 0.6 higher)		
Functional impairment e Scale (SAS); Better indic				asured with:	Longitudinal	Interval Follow-u	ıp Evaluation Ra	nge of Impaired Fu	nctioning	Tool (LIFE-I	RIFT)/Socia	l Adjustment
2 (Kocsis 2009/ Klein 2011, Paykel 1999/ Scott 2000)		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 a	t 11-month f	ollow-up	(follow-up mea	an 11 months	; measured w	rith: Social Adjus	stment Scale (SA	S); Better indicated	d by lowe	r values)		
1 (Paykel 1999/ Scott 2000)		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

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Table 71: Clinical evidence profile for comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

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Quality as:	sessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cognitive and		Relative (95% CI)	Absolute	Quality	Importance
Depressio	n symptomat	tology end	dpoint (follow-up	mean 12 week	ks; measured	with: Hamilton Ra	ating Scale for Depres	sion (HAM-D); B	etter indica	ted by lower va	lues)	
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 HAM-D))	(ITT) (follow	-up mean	12 weeks; asses	ssed with: Nun	nber of people	scoring <=7 on h	Hamilton Rating Scale	for Depression	(HAM-D) AN	ND responding (≥50% improv	rement on
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

Risk of bias is high or unclear across multiple domains
 Substantial heterogeneity
 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

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Table 72: Clinical evidence profile for comparison 3. Augmenting with counselling versus continuing with antidepressant

Quality ass	sessment						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	n symptomat	ology end	point (follow-up	mean 12 weeks	; measured w	ith: Hamilton Rat	ing Scale for De	pression (HAM-D);	Better indic	ated by lower va	lues)	
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency		no serious imprecision	none	168	76	-	SMD 0.06 higher (0.21 lower to 0.33 higher)	HIGH	CRITICAL
Remission HAM-D))	(ITT) (follow-	up mean	12 weeks; assess	sed with: Numb	per of people s	coring <=7 on Ha	milton Rating S	cale for Depression	(HAM-D) A	ND responding (≥50% improv	ement on
1 (Kocsis 2009/ Klein 2011)		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
Discontinu	ation due to	any reaso	n (follow-up mea	n 12 weeks; as	sessed with: N	Number of partici	pants who dropp	oed out for any reas	son (includi	ng adverse even	ts))	

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

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
Discontinu	ation due to	side effec	ts (follow-up me	an 12 weeks; as	ssessed with:	Number of partici	pants who dropp	ed out due to adve	erse 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
	impairment y lower valu		(follow-up mean	12 weeks; mea	sured with: Lo	ngitudinal Interva	l Follow-up Eval	uation Range of Im	paired Fun	ctioning Tool (LIF	E-RIFT); Be	etter
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

Table 73: Clinical evidence profile for comparison 4. Augmenting with IPT versus continuing with antidepressant

Quality assessmen	t						No of patients	1	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 sympto	matology en	dpoint (fol	low-up 5-19 wee	ks; measured v	with: Hamilto	n Rating Scale fo	or Depression ((HAM-D); Better inc	licated by le	ower values)		
2 (Schramm 2007, Souza 2016)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	79	79	-	SMD 0.36 lower (0.68 to 0.05 lower)	LOW	CRITICAL
Depression sympto by lower values)	matology ch	ange score	e (follow-up 5-19	weeks; measu	red with: Ha	milton Rating Sca	ale for Depress	sion (HAM-D) chang	ge from bas	seline to endpoin	; Bette	rindicated
3 (Murray 2010, Schramm 2007, Souza 2016)	randomised trials	no serious risk of bias		no serious indirectness	serious ²	none	106	106	-	SMD 0.73 lower (1.38 to 0.08 lower)	LOW	CRITICAL
Depression sympto	matology at	1-3 month	follow-up (follow	v-up 1-3 month	s; measured	with: Hamilton F	Rating Scale fo	r Depression (HAM	-D); Better	indicated by lowe	er value	s)
2 (Schramm 2007, Souza 2016)	randomised trials		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 sympto	matology at	12-month f	follow-up (follow	-up mean 12 m	onths; meas	ured with: Hamil	ton Rating Sca	ale for Depression (HAM-D); Be	etter indicated by	lower	/alues)

¹ 95% CI crosses thresholds for both clinically important harm and no effect

^{3 2 95%} CI crosses thresholds for no effect and both clinically important benefit and harm

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) (fo	llow-up 5-19	weeks; as	sessed with: Nu	mber of people	scoring <=	7 on Hamilton Rat	ing Scale for De	epression (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) (fo	llow-up 5-19 v	weeks; as	sessed with: Nur	mber of people	showing at	least 50% improve	ement on Hamil	ton Rating Scale fo	or Depress	ion (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 du	e to any reas	on (follow	v-up 5-19 weeks;	assessed with	Number of	participants who	dropped out fo	r 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 (fo	llow-up me	ean 5 weeks; me	asured with: G	lobal Assess	sment of Function	(GAF); Better i	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 fo	ollow-up (1	follow-up mean 3	3 months; meas	sured with: (Global Assessmer	nt of Function (GAF); Better indica	ted by hig	her 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; me	easured with	: Global Assessm	ent of Function	n (GAF); Better indi	cated by h	igher 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

Table 74: Clinical evidence profile for comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

					I_	
(Quality assessment Quality assessment	No of patients	Effect	Quality	Importance	

³ Substantial heterogeneity

⁴ 95% CI crosses thresholds for both clinically important harm and no effect

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	symptomato	ology end	lpoint (follow-up	mean 26 weel	ks; measured	with: Hamilton R	ating Scale for Depres	sion (HAM-D); Bet	ter indicate	ed by lower valu	ues)	
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.56 lower (1.07 to 0.04 lower)	MODERATE	CRITICAL
	symptomato y lower value		inge score (follo	w-up mean 26	weeks; meas	ured with: Hamilt	ton Rating Scale for De	pression (HAM-D)	change fro	om baseline to	endpoint; Be	tter
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	symptomato	ology at 3	-month follow-u	p (follow-up m	ean 3 months	; measured with	: Hamilton Rating Scale	e for Depression (F	HAM-D); Be	etter indicated b	oy lower valu	es)
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	symptomato	ology at 6	-month follow-u	ıp (follow-up m	ean 6 months	; measured with	: Hamilton Rating Scale	e for Depression (H	HAM-D); Be	etter indicated b	y lower valu	es)
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.56 lower (1.08 to 0.05 lower)	MODERATE	CRITICAL
Depression	symptomato	ology at 1	2-month follow-	up (follow-up i	mean 12 mont	hs; measured wi	th: Hamilton Rating Sc	ale for Depression	(HAM-D);	Better indicate	d by lower va	alues)
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; asses	ssed with: Nun	nber of people	scoring <=7 on	Hamilton Rating Scale	for Depression (H	AM-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-m	onth follo	ow-up (follow-up	mean 12 mon	ths; assessed	with: Number of	f people scoring <=7 or	Hamilton Rating	Scale for D	epression (HA	M-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 ((HAM-D))	ITT) at 12-mo	onth follo	w-up (follow-up	mean 12 mont	hs; assessed	with: Number of	people showing at leas	t 50% improveme	nt on Hami	ilton Rating Sca	le for Depre	ession
1 (Town 2017/2020)		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
Discontinua	ation due to a	any reaso	n (follow-up me	an 26 weeks; a	assessed with	: Number of part	icipants who dropped o	out for any reason)				
1 (Town 2017/2020)		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

Table 75: Clinical evidence profile for comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidenressant

	with ai	itiaepi	Josuit									
Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	term nsvcnodvnamic	_	Relative (95% CI)	Absolute		•
Depressio	n symptoma	tology er	ndpoint (follow-u	ıp mean 78 wee	ks; measure	d with: Hamilton	Rating Scale for Depress	ion (HAM-D); Bette	r indicated	by lower values)		
1 (Fonagy 2015)	randomised trials		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
Depressio	n symptoma	tology at	6-month follow-	-up (follow-up r	nean 6 montl	hs; measured wit	h: Hamilton Rating Scale	for Depression (HA	AM-D); Bette	er indicated by lo	wer valu	es)
1 (Fonagy 2015)	randomised trials		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	n symptoma	tology at	12-month follov	v-up (follow-up	mean 12 mo	nths; measured	with: Hamilton Rating Sca	le for Depression (HAM-D); Be	tter indicated by	lower va	alues)
1 (Fonagy 2015)	randomised trials		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

 ^{95%} CI crosses thresholds for both clinically important benefit and no effect
 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Depressio	n symptoma	tology at	24-month follow	v-up (follow-up	mean 2 year	rs; measured with	n: Hamilton Rating Scale f	or Depression (HAI	M-D); Better	indicated by low	er value	es)
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	n (ITT) (follow	v-up mea	n 78 weeks; ass	essed with: Nu	mber of peo	ple scoring <=8 o	n Hamilton Rating Scale f	or Depression (HAI	M-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	n (ITT) at 24-r	nonth fo	llow-up (follow-u	ıp mean 2 years	s; assessed	with: Number of p	people scoring <=8 on Har	milton Rating Scale	for Depres	sion (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
Discontin	uation due to	any reas	son (follow-up m	ean 78 weeks;	assessed w	ith: Number of pa	rticipants who dropped o	ut 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

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Table 76: Clinical evidence profile for comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/attention-placebo)

0.110	meron pie	,										
Quality assessme	ent						No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	with colf holp	ith self-help attention-placebo)		Absolute	<u> </u>	portuno
Depression symp lower values)	tomatology	endpoint (follow-up 1.4-6	weeks; measu	red with: Ham	ilton Rating Sca	le for Depression	on (HAM-D) or Beck D	epression	Inventory (BI	OI-II); Better i	ndicated b
3 (Baert 2010_study 2, Dai 2019,	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	80	77	-	SMD 0.29 lower (0.61	MODERATE	CRITICAL

Statistically significant group difference at baseline
 95% CI crosses thresholds for both clinically important benefit and no effect
 Study partially funded by the International Psychoanalytic Association
 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Schlogelhofer 2014)		risk of bias								lower to 0.03 higher)		
Depression symp baseline to endpo				•	easured with:	Hamilton Rating	Scale for Depr	ression (HAM-D) or Be	ck Depres	ssion Inventor	y (BDI-II) cha	nge from
3 (Baert 2010_study 2, Dai 2019, Schlogelhofer 2014)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	80	77	-	SMD 0.39 lower (0.71 to 0.08 lower)	MODERATE	CRITICAL
Depression symp	tomatology	at 1-month	n follow-up (follo	ow-up mean 1	months; mea	sured with: Hami	Iton Rating Sca	ale for Depression (HA	M-D); Bet	ter indicated b	y lower valu	es)
1 (Dai 2019)	randomised trials		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 d	lue to any re	ason (follo	ow-up 1.4-6 wee	ks; assessed v	with: Number	of participants w	ho dropped ou	t for any reason)				
2 (Dai 2019, Schlogelhofer 2014)	randomised trials		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

Table 77: Clinical evidence profile for comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only 5

Quality as	sessment		·		, J	Š	No of patients	J	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Augmenting with self-help and switching to SSRI	Switching to SSRI-only	Relative (95% CI)	Absolute		
Depression	n symptoma	tology end	point (follow-up n	nean 9 weeks; ı	measured with:	Patient Health Q	uestionnaire (PHQ-9);	Better indicat	ted 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 values)	on symptoma	tology char	nge score (follow	-up mean 9 wee	eks; measured	with: Patient Hea	Ith Questionnaire (PH	Q-9) change fr	om baseline	to endpoint; Bette	r indicat	ed by lower
1 (Mantani 2017)	i 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	mission (ITT) (follow-up mean 9 weeks; assessed with: Number of people scoring <=4 on Patient Health Questionnaire (PHQ-9))											

 ^{95%} CI crosses thresholds for both clinically important benefit and no effect
 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

1 (Mantan 2017)	i 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; assesse	d with: Number	of people show	wing at least 50%	improvement on Patie	nt Health Que	stionnaire (PHQ-9))		
1 (Mantan 2017)	i 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
Discontin	uation due to	any reasoi	n (follow-up mea	n 9 weeks; asse	essed with: Nur	nber of participar	nts who dropped out fo	r any reason)				
1 (Mantan 2017)	i randomised trials		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

Table 78: Clinical evidence profile for comparison 9. Augmenting with art therapy versus attention-placebo

Quality a	ssessment			_	-		No of patients		Effect		Quality	Importance
No of studies	I Jacian	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with art therapy		Relative (95% CI)	Absolute		
Depressi	on symptoma	itology en	ndpoint (follow-up	mean 6 weeks;	measured with	: Beck Depressio	n Inventory (BDI-II); Better indi	cated by lov	ver values)		
1 (Nan 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	52	48	-	SMD 0.56 lower (0.96 to 0.16 lower)	LOW	CRITICAL
Depressi values)	on symptoma	itology ch	nange score (follo	w-up mean 6 we	eeks; measured	with: Beck Depre	ession Inventory (E	BDI-II) change	e from basel	line to endpoint; Bet	ter indicated	by lower
1 (Nan 2017)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	52	48	-	SMD 1.22 lower (1.64 to 0.79 lower)	MODERATE	CRITICAL
Discontir	nuation due to	any reas	son (follow-up me	an 6 weeks; ass	essed with: Nu	mber of participa	nts who dropped o	out for any re	ason)			
1 (Nan 2017)	trials		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

Study partially funded by pharmaceutical companies
 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

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Table 79: Clinical evidence profile for comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Quality as	ssessment						No of patients		Effect		Over like v	
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	Quality	Importance
Depression	on symptoma	atology en	dpoint (follow-u	p 13-26 weeks;	measured w	vith: Beck Depres	ssion Inventory (BDI-II); B	etter indicated by lo	wer values	s)		
1 (Ostacoli 2018)	randomised trials		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
Remissio	n (ITT) (follo	w-up 13-26	weeks; assess	ed with: Numbe	er of people	scoring <13 on B	eck Depression Inventory	(BDI-II))				
1 (Ostacoli 2018)	randomised trials		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
Remissio	n (ITT) at 6-m	onth follo	w-up (follow-up	mean 6 month	s; assessed	with: Number of	people scoring <13 on Be	eck Depression Inve	entory (BDI	-II))		
1 (Ostacoli 2018)	randomised trials		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
Discontin	uation due to	o any reaso	on (follow-up 13	-26 weeks; ass	essed with:	Number of partic	ipants who dropped out f	or any reason)				
1 (Ostacoli 2018)	randomised trials		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 fu	nctioning at	endpoint (f	follow-up 13-26	weeks; measur	ed with: Glo	bal Assessment	of Function (GAF); Better	indicated by highe	r values)			
1 (Ostacoli 2018)	randomised trials		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 fu	nctioning at	6-month fo	llow-up (follow-	up mean 6 moi	nths; measu	red with: Global	Assessment of Function (GAF); Better indica	ted by high	ner values)		

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for both clinically important benefit and no effect
 95% CI crosses thresholds for no effect and both clinically important benefit and harm

1	randomised	serious ¹	no serious	no serious	serious ²	reporting bias ³	31	35	-	SMD 0.24	VERY	IMPORTANT
(Ostacoli	trials		inconsistency	indirectness						higher (0.24	LOW	
2018)										lower to 0.73		
										higher)		

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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	S	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 symptom	natology end	point (follo	ow-up mean 6 w	eeks; measure	d with: Hamilt	ton Rating Scale	for Depressio	n (HAM-D); Bet	ter indicate	ed by lower valu	ies)	
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 symptom (MADRS) change from						ton Rating Scale	for Depression	on (HAM-D) or N	lontgomer	y Asberg Depre	ssion Rating	j Scale
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) (follo		eks; asse	ssed with: Numb	per of people s	coring <=7/<=	8 on Hamilton Ra	ating Scale for	Depression (H	AM-D) or <	=10 on Montgo	mery Asberg	Depression
5 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer 2001)	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) (follo Depression Rating Se									for Depres	ssion (HAM-D)/I	Montgomery	Asberg
6 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer	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

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

1990, Schweizer 2001)										fewer to 180 more)		
Discontinuation due	to any reaso	n (follow-	up 5-6 weeks; as	sessed with: N	lumber of part	icipants who dro	pped out for a	ıny reason (incl	uding adv	erse events))		
5 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer 2001)	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 effec	ts (follow-	up 5-6 weeks; as	sessed with:	Number of par	ticipants who dro	opped out due	to adverse eve	nts)			
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 physica higher values)	al componen	it score (P	CS) endpoint (fo	llow-up mean	6 weeks; mea	sured with: 36-ite	m Short-Form	Survey (SF-36)	: Physical	component sc	ore; Better i	ndicated by
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	IMPORTAN
Quality of life mental higher values)	component	score (MC	S) endpoint (fol	ow-up mean 6	weeks; meas	ured with: 36-iten	n Short-Form	Survey (SF-36):	Mental co	mponent score	; Better indi	cated by
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	IMPORTAN'

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

Table 81: Clinical evidence profile for comparison 12. Increasing the dose of SSRI versus switching to SNRI

Quality a	ssessment			·	-	No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Increasing the dose of SSRI		Relative (95% CI)	Absolute			
Depressi	Depression symptomatology endpoint (follow-up mean 8 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS); Better indicated by lower values)												

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

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
	ion symptoma I by lower val		nge score (follow	-up mean 8 weel	ks; measured w	ith: Quick Invento	ry of Depressive	Symptomat	ology (QIDS)	change from baseline	e to end	point; Bette
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	on (ITT) (follo	w-up mean 8	3 weeks; assesse	d with: Number	of people scori	ng <=10 on Montg	omery Asberg De	epression Ra	ating Scale (M	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)		CRITICAL
Respons	e (ITT) (follov	v-up mean 8	weeks; assessed	d with: Number	of people showi	ng at least 50% in	provement on M	ontgomery A	Asberg Depre	ession Rating Scale (M	//ADRS))
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
Disconti	nuation due to	o any reasoi	n (follow-up mear	n 8 weeks; asses	sed with: Num	ber of participants	who dropped ou	it for any rea	son (includir	ng adverse events))		
1 (Bose 2012)	randomised trials		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)		CRITICAL
Disconti	nuation due to	o side effect	s (follow-up mea	n 8 weeks; asse	ssed with: Num	ber of participants	who dropped o	ut due to adv	verse events)			
1 (Bose 2012)	randomised trials		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 o	of life endpoin	t (follow-up	mean 8 weeks; n	neasured with: 0	Quality of Life E	njoyment and Sati	sfaction Questio	nnaire-short	form (Q-LES	-Q-SF); Better indicat	ed by h	gher 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	IMPORTAN

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

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	

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

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			Augmenting with TCA	Relative (95% CI)	Absolute		
Depression s	symptomatol	ogy endpoii	nt (follow-up mea	n 4 weeks; meas	sured with: I	Hamilton Rating S	cale for Depress	sion (HAM-D); B	etter indicat	ed by lower values)		
2 (Fava 1994a, Fava 2002)		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 sindicated by			score (follow-up	mean 4 weeks;	measured w	ith: Hamilton Rati	ng Scale for De	oression (HAM-	D) change fr	om baseline to endpo	oint; Bet	ter
2 (Fava 1994a, Fava 2002)		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 (I	TT) (follow-u	p mean 4 w	eeks; assessed w	ith: Number of p	people scori	ng <=7 on Hamilto	on 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
Discontinuat	tion due to ar	ny reason (f	ollow-up mean 4	weeks; assesse	d with: Num	ber of participants	who dropped o	out for any reaso	on (including	g adverse events))		
2 (Fava 1994a, Fava 2002)	randomised trials		no serious inconsistency		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
Discontinuat	tion due to si	de effects (f	follow-up mean 4	weeks; assesse	d with: Num	ber of participant	s who dropped	out due to adve	rse events)			
`	randomised trials	risk of bias	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)	LOW	CRITICAL

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

7 Table 83: Clinical evidence profile for comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Quality a	ssessment					No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Increasing the dose of SSRI	Augmenting with antipsychotic	Relative (95% CI)	Absolute		
Depressi	on symptoma	atology end	dpoint (follow-up				Depression (HAM-D); Better inc	dicated by lower val	lues)	

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

1 (Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.1 higher (0.41 lower to 0.6 higher)	MODERATE	CRITICAL
	on symptoma by lower val		inge score (follo	w-up mean 13 v	veeks; meas	ured with: Hamilto	on Rating Scale	for Depression (H	AM-D) chang	ge from baseline to	endpoint; B	etter
1 (Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.07 higher (0.43 lower to 0.58 higher)	MODERATE	CRITICAL
Remissio	n (ITT) (follo	w-up mean	13 weeks; asse	ssed with: Num	ber of people	e scoring <=7 on I	Hamilton Rating	Scale for Depress	ion (HAM-D))		
1 (Rocca 2002b)	randomised trials		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	e (ITT) (follov	v-up mean '	13 weeks; asses	sed with: Numb	er of people	showing at least	50% improveme	ent on Hamilton Ra	ting Scale f	or Depression (HAI	M-D))	
1 (Rocca 2002b)	randomised trials		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
Discontin	uation due to	o any reaso	n (follow-up me	ean 13 weeks; as	sessed with	: Number of parti	cipants who dro	pped out for any r	eason (inclu	iding adverse even	ts))	
1 (Rocca 2002b)	randomised trials		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
Discontin	uation due to	o side effec	ts (follow-up me	ean 13 weeks; a	ssessed with	n: Number of parti	icipants who dro	opped out due to a	dverse even	its)		
1 (Rocca 2002b)	randomised trials		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
Function	al remission	(follow-up r	mean 13 weeks;	assessed with:	Number of p	people scoring =>	71 on Global As	sessment of Func	tion (GAF))			
1 (Rocca 2002b)	randomised trials		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	IMPORTAN
Global fu	nctioning en	dpoint (follo	ow-up mean 13	weeks; measure	ed with: Glob	oal Assessment of	Function (GAF)); Better indicated	by higher va	alues)		
•	randomised trials	risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.67 lower (1.19 to 0.15 lower)		IMPORTAN'

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

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	

 ^{95%} CI crosses thresholds for both clinically important harm and no effect
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

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	symptomatol	ogy endpoir	nt (follow-up mea	n 4 weeks; mea	sured with: I	Hamilton Rating S	cale for Depres	sion (HAM-D); B	etter indicate	ed by lower values)		
2 (Fava 1994a, Fava 2002)		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 sindicated by			score (follow-up	mean 4 weeks;	measured w	ith: Hamilton Rat	ng Scale for De	pression (HAM-l	O) change fro	om baseline to endpo	oint; Bet	ter
2 (Fava 1994a, Fava 2002)		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 (I	TT) (follow-u	p mean 4 w	eeks; assessed w	vith: Number of	people scori	ng <=7 on Hamilto	on 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
Discontinua	tion due to a	ny reason (fo	ollow-up mean 4	weeks; assesse	d with: Num	ber of participant	s who dropped o	out for any reaso	on (including	adverse events))		
2 (Fava 1994a, Fava 2002)	randomised trials		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
Discontinua	tion due to si	de effects (f	follow-up mean 4	weeks; assesse	ed with: Num	ber of participant	s who dropped	out due to adver	se events)			
1 (Fava 1994a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	reporting bias4	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

¹ CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

Table 85: Clinical evidence profile for comparison 16. Switching to SSRI versus continuing with antidepressant

Quality asse	ssment						No of patier	nts	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		_		Relative (95% CI)	Absolute		
Depression sindicated by			score (follow-up	8-12 weeks; m	easured with: I	Montgomery Asb	erg Depressi	on Rating Scale (MA	DRS) chang	ge from baseline to	endpoin	t; Better

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

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-u	p 8-12 week	ks; assessed witl	n: Number of pe	ople scoring <	=8 on Montgomer	ry Asberg De	pression Rating Sca	le (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-uլ	8-12 week	s; assessed with	: Number of peo	ople showing a	nt least 50% impro	vement on M	lontgomery Asberg	Depression	Rating Scale (MAD	RS))	
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
Discontinua	ation due to a	ny reason (f	follow-up 8-12 we	eks; assessed	with: Number of	of participants wh	o dropped ou	ut for any reason (in	cluding adv	erse 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
Discontinua	ation due to si	de effects (follow-up 8-12 w	eeks; assessed	with: Number	of participants wh	no dropped o	ut due to adverse ev	vents)			
2 (Corya 2006, Shelton 2005)	randomised trials	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

Table 86: Clinical evidence profile for comparison 17. Switching to a different SSRI versus continuing same SSRI

Quality ass	essment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to a different SSRI		Relative (95% CI)	Absolute		
Remission	(ITT) (follow-u	ıp mean 6	weeks; assessed	d with: Number	of people scori	ing <=10 on Mont	gomery Asberg	Depression Rat	ing Scale (M	ADRS))		

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

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 (I	ITT) (follow-u	ıp mean 6	weeks; assesse	d with: Number	of people show	ving at least 50% in	nprovement on M	Montgomery A	sberg Depres	sion Rating Scale (M	ADRS))	
` ,	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
Discontinus	41 4 4-											
Discontinua	ation due to a	iny reasoi	n (follow-up meai	ı 6 weeks; asse	ssed with: Num	ber of participants	who dropped o	ut for any reas	son (including	g adverse events))		
1 (Nakajima	1	serious ¹	n (follow-up mear no serious inconsistency	n 6 weeks; assessing serious indirectness	ssed with: Num	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
1 (Nakajima 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³		2/20 (10%)	5/21 (23.8%)	RR 0.42 (0.09 to 1.92)	138 fewer per 1000 (from 217 fewer to		CRITICAL

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

Table 87: Clinical evidence profile for comparison 18. Switching to SSRI versus antipsychotic

Quality assess		·				No of patient		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to SSRI		Relative (95% CI)	Absolute		
Depression sy indicated by lo		gy change so	core (follow-up 8-	l2 weeks; measi	ured with: M	ontgomery Asber	g Depression	Rating Scale ((MADRS) cha	nge from baseline to	endpoin	t; Better
2 (Corya 2006, Shelton 2005)			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 (IT	Γ) (follow-up	8-12 weeks;	assessed with: N	umber of people	scoring <=8	3 on Montgomery	Asberg Depre	ession Rating	Scale (MADR	S))		
2 (Corya 2006, Shelton 2005)			no serious inconsistency		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)		CRITICAL
Response (ITT) (follow-up 8	3-12 weeks; a	assessed with: No	ımber of people	showing at	least 50% improve	ement on Mor	ntgomery Asbe	erg Depression	on Rating Scale (MAD	RS))	
2 (Corya 2006, Shelton 2005)			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	n due to any	reason (follo	ow-up 8-12 weeks	; assessed with	: Number of	participants who	dropped out t	for any reason	(including a	dverse events))		

Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug in switch arm
 Study partially funded by pharmaceutical company
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

2 (Corya 2006, Shelton 2005)			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	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)			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

Table 88: Clinical evidence profile for comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychoticonly

Quality as	sessment						No of patients		Effect		Quality	Important
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		
	n symptomato by lower value		ge score (follow-	up 8-12 weeks;	measured w	rith: Montgomery	Asberg Depression	Rating Scale (MAD	RS) change	from baseline to	endpoin	t; Better
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 we	eks; assessed w	ith: Number of	people scori	ng <=8 on Montg	omery Asberg Depre	ssion 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-u	ıp 8-12 wee	eks; assessed wi	th: Number of լ	people show	ing at least 50% i	mprovement on Mon	tgomery Asberg De	epression R	ating Scale (MAD	RS))	
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

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses thresholds for both clinically important benefit and no effect

Funding from pharmaceutical companies
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

2 (Corya 2006, Shelton 2005)	randomised trials		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
Discontinua	ation due to s	side effects	(follow-up 8-12	weeks; assesse	ed with: Num	ber of participant	s who dropped out d	lue to adverse even	ts)			
2 (Corya 2006, Shelton 2005)	randomised trials		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)		CRITICAL

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

7 Table 89: Clinical evidence profile for comparison 20. Augmenting with SSRI versus augmenting with lithium

Quality ass	sessment					- -	No of patients	-	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision		Augmenting with SSRI		Relative (95% CI)	Absolute		
	n symptomato by lower value		nge score (follow-	up mean 10 wee	ks; measure	d with: Hamilton I	Rating Scale for	Depression (HAN	I-D) change f	rom baseline to endpo	oint; Be	tter
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 1	10 weeks; assesse	ed with: Number	of people so	coring <=7 on Han	nilton Rating Sca	ale for Depression	n (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

⁸ CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

11 Table 90: Clinical evidence profile for comparison 21. Switching to TCA versus SSRI

Quality assessment	No of patients	Effect	Quality	Importance	

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

^{9 &}lt;sup>1</sup> Risk of bias is high or unclear across multiple domains

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

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7 Table 91: Clinical evidence profile for comparison 22. Switching to TCA versus augmenting with mirtazapine

Quality ass	sessment			·		-	No of patien	ts	Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		_	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		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)			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	Remission (ITT) (follow-up mean 10 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												

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

1 (Navarro 2019a)	randomised trials	,	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
Discontinu	ation due to	any reaso	on (follow-up mea	n 10 weeks; ass	essed with: Nu	mber of participan	ts who dropp	oed out for any rea	son (includii	ng 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%)	,	54 more per 1000 (from 18 fewer to 405 more)		CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

Table 92: Clinical evidence profile for comparison 23. Switching to mianserin versus continuing with antidepressant

Quality as	ssessment						No of patients	.	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to mianserin		Relative (95% CI)	Absolute		
	on symptoma by lower valu		ange score (follo	w-up mean 6 we	eeks; measur	ed with: Hamiltor	Rating Scale	for Depression (HAM	-D) change fro	om baseline to endp	oint; Bett	ter
1 (Ferreri 2001)	randomised trials		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
Remissio	n (ITT) (follov	v-up meai	n 6 weeks; assess	sed with: Numbe	er of people s	scoring <=8 on Ha	milton Rating	Scale for Depression	(HAM-D))			
1 (Ferreri 2001)	randomised trials	,	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; assess	ed with: Numbe	r of people s	howing at least 5	0% improveme	ent on Hamilton Ratin	g Scale for De	epression (HAM-D))		
1 (Ferreri 2001)	randomised trials	, ,	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
Discontin	uation due to	any reas	on (follow-up me	an 6 weeks; ass	essed with:	Number of partici	pants who dro	pped out for any reas	son (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
Discontin	uation due to	side effe	cts (follow-up me	ean 6 weeks; as	sessed with:	Number of partic	ipants who dro	pped out due to adv	erse events)			
•	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 rapid tapering of failed drug in switch arm ² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 93: Clinical evidence profile for comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

			- p		=						. ,	,
Quality ass	essment						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		,
	symptomato y lower value		ge score (follow-	up mean 6 wee	ks; measure	d with: Hamilton	Rating Scale for	Depression (HAM-D)	change from	baseline to endpo	oint; Bett	er
1 (Ferreri 2001)	randomised trials		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 wee	ks; assessed wit	h: Number of p	eople scorin	g <=7/<=8 on Hai	milton Rating Sc	ale for Depression (HA	AM-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-ι	ıp 5-6 week	s; assessed witl	n: Number of pe	eople showin	ig at least 50% in	nprovement on H	lamilton Rating Scale	for Depressi	on (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
Discontinua	ation due to a	any reason	(follow-up 5-6 w	eeks; assessed	l with: Numb	er of participants	who dropped o	ut for any reason (incl	uding advers	se events))		
`	randomised trials		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
Discontinua	ation due to s	side effects	(follow-up mear	n 6 weeks; asse	ssed with: N	umber of particip	pants who dropp	ed out due to adverse	events)			
1 (Ferreri 2001)	randomised trials		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 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

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and harm

- 1 ³ Funding from pharmaceutical company
- 2 ⁴ Substantial heterogeneity
- 3 5 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

4 Table 94: Clinical evidence profile for comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

Quality a	ssessment						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		
Remissio	emission (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
Respons	e (ITT) (follow	v-up mean (5 weeks; assesse	d with: Number	of people si	nowing at least 50	0% improvement	on Hamilton Rating	Scale for Dep	pression (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
Disconti	nuation due t	o any reaso	n (follow-up mea	n 5 weeks; ass	essed with: N	Number of partici	pants who dropp	ed out for any reaso	n (including	adverse events))		
1 (Licht 2002)		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

⁵ CI: confidence interval; ITT: intention to treat; RR: relative risk

9 10

11 Table 95: Clinical evidence profile for comparison 26. Augmenting with mianserin versus switch to mianserin

Quality a	ssessment					<u>-</u>	No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with mianserin		Relative (95% CI)	Absolute		
	on symptoma by lower valu		ge score (follow-ι	ıp mean 6 weeks	; measured	with: Hamilton Ra	ting Scale for Dep	oression (HAN	I-D) change f	from baseline to endp	oint; Bett	ter

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

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
Remissio	n (ITT) (follov	v-up mean 6	weeks; assessed	l with: Number o	f people sco	ring <=8 on Hamil	ton Rating Scale fo	or Depression	n (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 v	weeks; assessed	with: Number of	people show	wing at least 50%	improvement on H	amilton Ratir	g Scale for I	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
Discontin	uation due to	any reason	(follow-up mean	6 weeks; assess	ed with: Nur	mber of participan	ts who dropped ou	ut for any rea	son (includir	ng adverse events))		
1 (Ferreri 2001)	randomised trials		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
Discontin	uation due to	side effects	(follow-up mean	6 weeks; asses	sed with: Nu	mber of participar	nts who dropped o	ut due to adv	erse 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

6 Table 96: Clinical evidence profile for comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

Quality asso	essment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			Continuing SNRI at the same dose		Absolute		
	symptomato lower value		nge score (follow	-up mean 8 wee	ks; measured	with: Hamilton Ra	ting Scale for D	epression (HAM-D	change fro	m baseline to endpo	oint; Bett	er
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	8 weeks; assesse	d with: Number	of people sco	ring <=7 on Hamil	ton Rating Scale	for Depression (F	IAM-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

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

Study funded by pharmaceutical company
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Response (ITT) (follow-u	p mean 8	weeks; assesse	d with: Number	of people show	ving at least 50% i	mprovement on	Hamilton Rating S	cale for De	pression (HAM-D))			
1 (Kornstein 2008)		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)		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	
Discontinua	ation due to s	ide effect	ts (follow-up mea	n 8 weeks; asse	essed with: Nur	nber of participan	ts who dropped	out due to adverse	e 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

Table 97: Clinical evidence profile for comparison 28. Switching to SNRI versus continuing with antidepressant

Quality a	ssessment						No of patien	ts	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		
Remissio	on (ITT) (follo	w-up mea	n 8 weeks; asses	sed with: Numb	er of people sc	oring <=7 on Ham	ilton 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
Respons	e (ITT) (follov	v-up mear	n 8 weeks; assess	sed with: Numbe	er of people sh	owing at least 50%	improveme	nt on Hamilton Ratin	g Scale for D	epression (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
Discontir	nuation due t	o any reas	son (follow-up me	ean 8 weeks; ass	sessed with: No	umber of participa	nts who dro	oped out for any reas	son (includin	g adverse events))		
1 (Fang 2010)	10) trials inconsistency indirectness						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
Discontir	nuation due t	o side effe	ects (follow-up m	ean 8 weeks; as	sessed with: N	umber of participa	ants who dro	pped out due to adve	erse events)			

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

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 o		I compon	ent score (PCS)	change score (fo	ollow-up mean	8 weeks; measure	d with: 36-ite	m Short-Form Surve	y (SF-36): Ph	ysical component se	core; Be	tter indicated
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 o		compone	nt score (MCS) cl	hange score (fol	low-up mean 8	weeks; measured	with: 36-item	Short-Form Survey	(SF-36): Mer	ntal component score	e; Better	indicated by
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

6 Table 98: Clinical evidence profile for comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Quality assess	sment						No of patier	nts	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		
	•	•	score (follow-upoint; Better indi	•		: Hamilton Rating	Scale for D	Depression (HAM-D) or	Quick Inve	ntory of Depress	sive Symptor	natology
2 (Poirier ra 1999, Rush tr 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 (IT Symptomatolo		4-14 week	s; assessed with	h: Number of p	eople scoring	<=4/<10 on Hami	Iton Rating	Scale for Depression (I	HAM-D) or	<=5 on Quick Inv	entory of De	pressive
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
			•			at least 50% imp Depressive Symp		n Hamilton Rating Scal ((QIDS))	e for Depre	ession (HAM-D)	AND much/ve	ery much

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

2 (Poirier 1999, Rush 2006)	randomised trials		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
Discontinuati	on due to any	y reason (f	ollow-up 4-12 we	eeks; assessed	with: Number	of participants w	ho dropped	l out for any reason (in	cluding ad	verse events))		
2 (Lenox-Smitl 2008, Poirier 1999)	n randomised trials		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
Discontinuati	on due to sid	le effects (f	ollow-up 4-14 w	eeks; assessed	d with: Numbe	r of participants v	vho droppe	d out due to adverse ev	rents)			
3 (Lenox-Smitl 2008, Poirier 1999, Rush 2006)	n randomised trials		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

Table 99: Clinical evidence profile for comparison 30. Switching to SNRI versus switching to bupropion

Quality a	ssessment		·	·			No of patient	s	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Switching to bupropion	Relative (95% CI)	Absolute		
			•	v-up mean 14 we	eks; measured	with: Quick Invent	tory of Depre	ssive Symptom	atology (QIDS	s) change from baselin	e to end	point;
1 (Rush 2006)	,							239	-	SMD 0.01 lower (0.19 lower to 0.17 higher)	LOW	CRITICAL
Remissio	n (ITT) (follov	v-up mear	n 14 weeks; asses	sed with: Numbe	er of people sco	ring <=5 on Quick	Inventory of	Depressive Syn	nptomatology	(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%)		8 fewer per 1000 (from 71 fewer to 82 more)	VERY LOW	CRITICAL
Respons	e (ITT) (follow	-up mean	14 weeks; assess	sed with: Numbe	r of people show	wing at least 50% i	mprovement	on Quick Inven	tory of Depre	ssive Symptomatology	y (QIDS))	

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

Funding from pharmaceutical companies
 95% CI crosses thresholds for both clinically important harm and no effect
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

1 (Rush 2006)	randomised trials	,	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
Discontin	nuation due to	side effe	cts (follow-up me	an 14 weeks; as:	sessed with: Nu	mber of participant	ts who dropp	ed out due to a	dverse events	s)		
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

5 **Table 100:** Clinical evidence profile for comparison 31. Switching to SNRI versus switching to mirtazapine

Quality a	ssessment		·			J	No of patien	its	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		
Remissio	n (ITT) (follo	w-up mea	n 8 weeks; asses	sed with: Numb	er of people sc	oring <=7 on Ham	ilton Rating	Scale for Depres	sion (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
Respons	e (ITT) (follov	v-up mear	n 8 weeks; assess	sed with: Numbe	er of people sho	owing at least 50%	6 improveme	nt on Hamilton R	ating Scale f	or 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
Discontir	nuation due to	o any reas	son (follow-up me	ean 8 weeks; ass	sessed with: Nเ	ımber of participa	nts who dro	pped out for any	reason (inclu	iding adverse events	s))	
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
Discontir	nuation due to	o side effe	ects (follow-up m	ean 8 weeks; as	sessed with: N	umber of participa	ants who dro	pped out due to	adverse ever	nts)		
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 o		l compon	ent score (PCS) o	hange score (fo	llow-up mean 8	3 weeks; measure	d with: 36-ite	m Short-Form S	urvey (SF-36)	: Physical compone	nt score; Be	tter indicated
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

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

Quality o		compone	nt score (MCS) ch	nange score (fol	low-up mean 8 v	weeks; measured	with: 36-item	Short-Form Sur	vey (SF-36):	Mental component s	score; Better	indicated by
1 (Fang 2010)	randomised trials		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

Table 101: Clinical evidence profile for comparison 32. Switching to bupropion versus placebo 6

Quality assessmer	nt			·			No of patients	·	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to bupropion	Placebo	Relative (95% CI)	Absolute		
Depression symptomicated by lower		ange sco	re (follow-up mea	ın 12 weeks; me	asured with: Ha	amilton Rating Sca	ale for Depressi	ion (HAN	I-D) change f	from baseline to endp	ooint; Be	tter
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) (fo	llow-up mea	n 12 week	s; assessed with	: Number of peo	ple scoring <=7	on Hamilton Rati	ng Scale for De	pression	n (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) (fo	llow-up mean	12 week	s; assessed with:	Number of peop	ple showing at	east 50% improve	ement on Hamil	ton Ratir	ng Scale for I	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)		CRITICAL
Discontinuation du	ie to any reas	on (follov	w-up mean 12 wee	eks; assessed w	rith: Number of	participants who	dropped out for	any rea	son (includir	ng 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 du	e to side effe	ects (follo	w-up mean 12 we	eks; assessed v	vith: Number of	participants who	dropped out du	ie to adv	erse 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)		CRITICAL

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 102: Clinical evidence profile for comparison 33. Switching to bupropion versus switching to another antidepressant from same class

Quality a	ssessment						No of patients	s	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		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 endpetter indicated by lower values)										point;		
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	on (ITT) (follo	w-up mea	an 14 weeks; ass	essed with: Nu	mber of people	scoring <=5 on 0	Quick Inventor	y of Depressive Symptom	atology (QI	DS))		
1 (Rush 2006)		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
Respons	e (ITT) (follov	w-up mea	ın 14 weeks; asse	essed with: Nun	nber of people	showing at least	50% improven	nent on Quick Inventory o	f Depressiv	e Symptomatology	(QIDS))	
1 (Rush 2006)		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
Disconti	nuation due t	o side eff	fects (follow-up n	nean 14 weeks;	assessed with	: Number of parti	cipants who d	ropped out due to advers	e 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

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CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Rapid tapering of previous treatment

Study run and funded by pharmaceutical company
 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

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

1 Table 103: Clinical evidence profile for comparison 34. Augmenting with bupropion versus placebo

Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(1111)					
Remissio	n (ITT) (follow	/-up mean	4 weeks; assess	ed with: Number	of people scor	ing <=7 on Hamilt	on Rating Scale fo	r Depres	sion (HAM-D))		
1 (Gulrez 2012)	Gulrez randomised serious no serious no serious none inconsistency indirectness 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

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Table 104: Clinical evidence profile for comparison 35. Augmenting with bupropion versus switching to bupropion

Quality asse	essment			·			No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with bupropion		Relative (95% CI)	Absolute		
Remission (ITT) (follow-u	ıp mean 12	weeks; assesse	d with: Number	of people scor	ring <=5 on Quick	Inventory of Dep	oressive Symp	tomatology	(QIDS))		
1 (Mohamed 2017)	randomised trials		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 (I	TT) (follow-u	p mean 12	weeks; assessed	with: Number	of people shov	ving at least 50%	improvement on	Quick Invento	ry of Depres	ssive Symptomato	logy (QIDS))	
1 (Mohamed 2017)	randomised trials		no serious inconsistency		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
Discontinua	tion due to a	ny reason ((follow-up mean	12 weeks; asses	ssed with: Nun	nber of participan	ts who dropped	out for any rea	son (includ	ing adverse events	s))	
1 (Mohamed 2017)	randomised trials		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)		CRITICAL
Discontinua	tion due to s	ide effects	(follow-up mean	12 weeks; asse	ssed with: Nur	nber of participar	nts who dropped	out due to adv	erse events	s)		
1 (Mohamed 2017)	randomised trials		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

⁶ CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ Risk of bias is high or unclear across multiple domains

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

2 Table 105: Clinical evidence profile for comparison 36. Switching to mirtazapine versus continuing with antidepressant

Quality assessment								No of patients		Effect		Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to mirtazapine	Continuing with antidepressant	Relative (95% CI)	Absolute		
	symptomatol lower values		int (follow-up m	ean 6 weeks; n	neasured with:	Patient Health Q	uestionnaire (F	PHQ-9) or Hamilton	Rating Sca	ale for Depression	n (HAM-D); E	Setter
2 (Kato 2018, (iao 2020)	, randomised trials	no serious risk of bias		no serious indirectness	serious ²	none	618	605	-	SMD 0.21 lower (0.58 lower to 0.17 higher)	LOW	CRITICAL
	symptomatol lower values		e score (follow-	up mean 6 wee	ks; measured	with: Hamilton Ra	ating Scale for	Depression (HAM-	D) change f	rom baseline to e	endpoint; Be	tter
l (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	symptomatol	ogy at 4-m	onth follow-up (follow-up mear	n 4 months; m	easured with: Pat	ient Health Qu	estionnaire (PHQ-9); Better in	dicated by lower	values)	
(Kato 2018)	randomised trials		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 (I	ITT) (follow-u	p 6-8 week	s; assessed wit	h: Number of p	eople scoring	<=7 on Hamilton	Rating Scale for	or Depression (HAI	M-D) or <=4	on Patient Healtl	n Questionna	aire (PHQ-9
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias		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 (I	TT) at 4-mon	th follow-u	p (follow-up me	an 4 months; a	ssessed with:	Number of peopl	e scoring <=4	on Patient Health C	uestionnai	re (PHQ-9))		
I (Kato 2018)) randomised trials		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 (l' Questionnai		o 6-8 weeks	s; assessed with	: Number of pe	eople showing	at least 50% imp	rovement on H	lamilton Rating Sca	ale for Depr	ession (HAM-D) (or Patient He	alth
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials		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

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)		CRITICAL
Discontinua	tion due to si	ide effects	(follow-up 6-8 w	eeks; assessed	l with: Number	r of participants v	vho dropped o	ut due to adverse e	vents)			
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)		CRITICAL
Quality of lif by higher va		omponent s	score (PCS) cha	nge score (follo	w-up mean 8 v	weeks; measured	with: 36-item S	Short-Form Survey	(SF-36): Pł	nysical componer	nt score; Bet	ter indicated
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 lif higher value		nponent sc	ore (MCS) chan	ge score (follow	/-up mean 8 w	eeks; measured v	with: 36-item SI	hort-Form Survey (S	SF-36): Mei	ntal component s	core; Better	indicated by
1 (Fang 2010)	trials	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

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Clinical evidence profile for comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/-**Table 106:** placebo)

Quality assessmen	nt						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	with	antidonroccant (+/-	Relative (95% CI)	Absolute	,	,
Depression sympto Depression Invento					d with: Hamil	ton Rating Scale	for Depression	n (HAM-D) or Patien	t Health Q	uestionnaire (PHQ-9) or Be	ck

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

4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)		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 sympto lower values)	omatology cl	nange sco	ore (follow-up 4-	-6 weeks; mea	sured with: Ha	amilton Rating So	cale for Depres	sion (HAM-D) chang	ge from ba	seline to endp	oint; Better	indicated by
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 sympto	omatology at	4-month	follow-up (follo	w-up mean 4 r	months; meas	ured with: Patier	t Health Quest	ionnaire (PHQ-9); B	etter indic	ated 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) (fo or <10 on Beck De				Number of peo	ple scoring <=	-7 on Hamilton R	ating Scale for	Depression (HAM-D)) or <=4 o	n Patient Heal	th Question	naire (PHQ-9)
4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)		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 follo	ow-up (fo	llow-up mean 4	months; asses	ssed with: Nu	mber of people s	coring <=4 on l	Patient Health Ques	tionnaire	(PHQ-9))		
1 (Kato 2018)	randomised											
. (1330 20 10)	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
	trials	serious risk of bias weeks; as	inconsistency ssessed with: N	indirectness umber of peop			(49%)		(0.97 to 1.25)	1000 (from 13 fewer to 111 more)		
Response (ITT) (fo	trials llow-up 4-12 Q-9) or Beck randomised	serious risk of bias weeks; as Depressi	inconsistency ssessed with: N on Inventory (B	indirectness umber of peop			(49%)	(44.5%)	(0.97 to 1.25) for Depres	1000 (from 13 fewer to 111 more)		
Response (ITT) (fo Questionnaire (PHo 4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	trials Ilow-up 4-12 Q-9) or Beck randomised trials	serious risk of bias weeks; as Depressi serious ¹	ssessed with: Non Inventory (B	umber of peop DI-II)) no serious indirectness	ole showing at serious ⁴	t least 50% impro	(49%) Evement on Har 422/857 (49.2%)	(44.5%) milton Rating Scale 357/873	(0.97 to 1.25) for Depres RR 1.19 (1.06 to 1.34)	1000 (from 13 fewer to 111 more) ssion (HAM-D) 78 more per 1000 (from 25 more to 139 more)	or Patient H	lealth
Response (ITT) (fo Questionnaire (PHo 4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	llow-up 4-12 Q-9) or Beck randomised trials	serious risk of bias weeks; as Depressi serious son (follo	ssessed with: Non Inventory (B	umber of peop DI-II)) no serious indirectness	ole showing at serious ⁴	t least 50% impro none f participants wh	(49%) Evement on Har 422/857 (49.2%)	(44.5%) milton Rating Scale 357/873 (40.9%)	(0.97 to 1.25) for Depres RR 1.19 (1.06 to 1.34) uding adv RR 0.95	1000 (from 13 fewer to 111 more) ssion (HAM-D) 78 more per 1000 (from 25 more to 139 more)	or Patient H	CRITICAL
Response (ITT) (fo Questionnaire (PHe 4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020) Discontinuation du 4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)	Illow-up 4-12 Q-9) or Beck randomised trials te to any reas randomised trials	serious risk of bias weeks; as Depressi serious serious serious serious	inconsistency ssessed with: Non Inventory (B no serious inconsistency w-up 4-12 week no serious inconsistency	umber of peop DI-II)) no serious indirectness s; assessed w no serious indirectness	serious ⁴ ith: Number o very serious ⁶	none f participants wh	(49%) Evement on Har 422/857 (49.2%) O dropped out 47/857 (5.5%)	(44.5%) milton Rating Scale 357/873 (40.9%) for any reason (incl 50/873	(0.97 to 1.25) for Depres RR 1.19 (1.06 to 1.34) uding adv RR 0.95 (0.65 to 1.4)	1000 (from 13 fewer to 111 more) Ssion (HAM-D) 78 more per 1000 (from 25 more to 139 more) erse events)) 3 fewer per 1000 (from 20 fewer to 23	or Patient H	CRITICAL

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 phys higher values)	sical compon	ent score	(PCS) endpoin	t (follow-up me	ean 12 weeks	; measured with:	12-item Short-F	Form Survey (SF-12): Physica	component so	ore; Better	indicated by
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 men higher values)	tal componei	nt score (MCS) endpoint	(follow-up mea	an 12 weeks;	measured with: 1	2-item Short-Fo	orm Survey (SF-12):	Mental co	mponent score	e; Better inc	dicated by
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 (fo	llow-up n	nean 4 weeks; n	neasured with:	Global Asse	ssment of Function	on (GAF); Bette	er indicated by high	er 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

Table 107: Clinical evidence profile for comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

Quality ass	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	With	3	Relative (95% CI)	Absolute		
-	n symptomat y lower value		oint (follow-up m	ean 6 weeks; m	neasured with:	Patient Health Qu	uestionnaire (PH	Q-9) or Hamilton	n Rating Sca	ale for Depression	(HAM-D); Be	tter

Risk of bias is high or unclear across multiple domains
 Substantial heterogeneity
 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

2 (Kato 2018, Xiao 2020)		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
	n symptomate y lower value		ge score (follow-	up mean 6 wee	ks; measured	with: Hamilton Ra	ting Scale for Dep	oression (HAM-	·D) change f	from baseline to er	ndpoint; Bett	er
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	symptomate	ology at 4-n	nonth follow-up	(follow-up mear	n 4 months; me	easured with: Pati	ent Health Questi	onnaire (PHQ-9	e); Better in	dicated by lower v	alues)	
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 (HAM-D))	(ITT) (follow-	up mean 6	weeks; assesse	d with: Number	of people sco	ring <=4 on Patien	t Health Question	nnaire (PHQ-9)	or <=7 on H	amilton Rating Sca	ale for Depre	ession
2 (Kato 2018, Xiao 2020)	randomised trials		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-mo	nth follow-	up (follow-up me	an 4 months; a	ssessed with:	Number of people	scoring <=4 on I	Patient Health (Questionnai	re (PHQ-9))		
1 (Kato 2018)	randomised trials		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 Depression		up mean 6 v	weeks; assessed	with: Number	of people shov	ving at least 50% i	mprovement on I	Patient Health (Questionnai	re (PHQ-9) or Ham	ilton Rating	Scale for
2 (Kato 2018, Xiao 2020)	randomised trials		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
Discontinu	ation due to	any reason	(follow-up mean	6 weeks; asse	ssed with: Nun	nber of participant	ts who dropped o	out for any reas	on (includir	ng adverse events))	
2 (Kato 2018, Xiao 2020)	randomised trials		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
Discontinu	ation due to	side effects	(follow-up mear	n 6 weeks; asse	essed with: Nur	mber of participan	ts who dropped	out due to adve	rse events)			
1 (Xiao 2020)	randomised trials		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

Risk of bias is high across multiple domains
 Study partially funded by pharmaceutical company
 95% CI crosses threshold for both clinically important benefit and no effect
 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 a	ssessment						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		
Remissio	on (ITT) (follo	w-up mea	ın 8 weeks; asses	ssed with: Numb	per of people	scoring <=7 on I	Hamilton Rating S	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
Respons	e (ITT) (follov	v-up mea	n 8 weeks; asses	sed with: Numb	er of people	showing at least	50% improvemen	nt on Hamilton Rating	Scale for D	epression (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
_	of life physica r values)	l compon	ent score (PCS)	change score (f	ollow-up mea	an 8 weeks; meas	sured with: 36-iter	m Short-Form Survey	/ (SF-36): Ph	ysical component s	core; Be	tter indicated
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	IMPORTAN ⁻
Quality o		compone	nt score (MCS) cl	hange score (fol	llow-up mear	n 8 weeks; measu	red with: 36-item	Short-Form Survey	(SF-36): Mer	ntal component scor	e; Better	indicated by
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	IMPORTAN ⁻

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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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)			

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

3 (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 symptom MADRS) change fro						lamilton Rating S	Scale for Depression	on (HAM-D) or Mon	tgomery As	sberg Depressi	on Ratir	ng Scale
3 (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) (fol	low-up mear	8 weeks	s; assessed wit	h: Number of p	eople scoring	<=7 on Hamilton	n Rating Scale for	Depression (HAM-	O))			
(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) (folloppression Rating S			ssessed with: N	lumber of peop	ole showing at	least 50% impro	vement on Hamilt	on Rating Scale for	Depressio	n (HAM-D) or N	lontgon	nery Asber
3 (Barbee 2011, Fang 2011, Li 2009, Li 2015, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised		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)		CRITICAL
Discontinuation due	to any reas	on (follo	w-up 8-10 week	s; assessed w	ith: Number o	f participants wh	o dropped out for	any reason (includ	ing adverse	e events))		
8 (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 effe	cts (follo	w-up 8-10 weel	ks; assessed w	vith: Number o	f participants wh	no dropped out du	e to adverse events	5)			
(Barbee 2011, antos 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

1 (Fang 2011)	randomised trials		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 menta higher values)	al componen	t score (MCS) change so	core (follow-up	mean 8 week	s; measured witl	h: 36-item Short-F	orm Survey (SF-36):	Mental co	mponent score	; Better	indicated by
1 (Fang 2011)	randomised trials		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

Table 110: Clinical evidence profile for comparison 41. Augmenting with anticonvulsant versus lithium

Quality asse	essment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with anticonvulsant	Lithium	Relative (95% CI)	Absolute		
Depression	symptomato	logy endpoi	nt (follow-up mea	n 8 weeks; mea	sured with: Har	milton Rating Sca	le for Depression (HA	AM-D); B	etter indicat	ed by lower values)		
`	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
•	symptomato / lower value		score (follow-up	mean 8 weeks;	measured with	: Hamilton Rating	Scale for Depressio	n (HAM-	D) change fr	om baseline to endp	oint; Bett	er
•	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-ι	ip mean 8 w	eeks; assessed v	vith: Number of	people scoring	<=7 on Hamilton	Rating Scale for Dep	ression	(HAM-D))			
•	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 (I	TT) (follow-u	p mean 8 we	eeks; assessed w	ith: Number of p	eople showing	at least 50% imp	rovement on Hamilto	n Rating	Scale for D	epression (HAM-D))		

¹ Risk of bias is high or unclear across multiple domains

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

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
Discontinua	ation due to a	ny reason (f	follow-up mean 8	weeks; assesse	d with: Numbe	r of participants w	ho dropped out for a	any reaso	on (including	g 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)		CRITICAL
Discontinua	ation due to s	ide effects (follow-up mean 8	weeks; assess	ed with: Numbe	er of participants v	vho dropped out due	to adve	rse 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

Table 111: Clinical evidence profile for comparison 42. Switching to antipsychotic versus continuing with antidepressant 5

Quality asses	sment						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 sy indicated by I	•	•	e score (follow-	up 8-12 weeks;	measured wit	h: Montgomery A	Asberg Depression	on Rating Scale (M	ADRS) cha	nge from baseli	ne to endpoi	nt; Better
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 (IT	T) (follow-u	p 8-12 wee	ks; assessed wi	th: Number of	people scoring	g <=8/<=10 on Me	ontgomery Asbe	rg Depression Rati	ng Scale (N	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 (IT	T) (follow-up	8-12 week	s; assessed wit	h: Number of p	eople showin	g at least 50% im	provement on M	lontgomery Asberç	g Depressio	on 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
Discontinuati	on due to ar	ny reason (follow-up 8-12 w	veeks; assesse	d with: Number	er of participants	who dropped ou	ut for any reason (i	ncluding a	dverse events))		

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for both clinically important benefit and no effect
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

3 (Corya 2006, Shelton 2005, Thase 2007)			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
Discontinuati	on due to si	de effects (follow-up 8-12	weeks; assesse	ed with: Numb	er of participants	who dropped o	ut due to adverse e	vents)			
3 (Corya 2006, Shelton 2005, Thase 2007)			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 by higher value	•	mponent s	core (PCS) cha	nge score (follo	ow-up mean 8	weeks; measured	d with: 36-item S	hort-Form Survey (SF-36): Ph	ysical compone	nt score; Be	tter indicated
`	randomised trials		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 higher values		ponent sco	ore (MCS) chan	ge score (follow	v-up mean 8 w	veeks; measured	with: 36-item Sh	ort-Form Survey (S	F-36): Men	tal component s	core; Better	indicated by
,	randomised trials		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

Table 112: Clinical evidence profile for comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

	untidopi											
Quality ass	y assessment Besign Risk of bias Inconsistency Indirectness Imprecision Other consider						No of patients		Effect			
No of studies	Design		Inconsistency	Indirectness	Improcision	Other considerations			Relative (95% CI)	Absolute	Quality	Importance
	symptomato y lower value		ge score (follow	-up 8-12 weeks	; measured wi	th: Montgomery	Asberg Depression F	Rating Scale (MADR	RS) change	from baseline to	endpoin	t; Better
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹		no serious indirectness	no serious imprecision	reporting bias ²	376	126	-	SMD 0.09 lower (0.3 lower to 0.11 higher)	LOW	CRITICAL

² Substantial heterogeneity

³ 95% CI crosses thresholds for both clinically important harm and no effect ⁴ Funding from pharmaceutical companies

Remission	(ITT) (follow-	up 8-12 we	eks; assessed v	vith: Number o	f people scorir	ng <=8 on Montgo	mery Asberg Depres	sion Rating Scale (MADRS))			
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias²	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 wee	eks; assessed w	vith: Number of	people showi	ng at least 50% in	nprovement on Mont	gomery Asberg De	oression Ra	ting Scale (MAD	RS))	
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias²	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
Discontinu	ation due to	any reason	(follow-up 8-12	weeks; assess	ed with: Numb	er of participants	who dropped out fo	r any reason (inclu	ding advers	se events))		
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias²	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
Discontinu	ation due to	side effects	s (follow-up 8-12	weeks; assess	sed with: Numl	ber of participants	s who dropped out d	ue to adverse even	ts)			
2 (Corya 2006, Shelton 2005)	randomised trials		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

Table 113: Clinical evidence profile for comparison 44. Switching to combined antipsychotic + SSRI versus switch to SSRI-only

Quality asse			P			3	No of patients		Effect			,
No of studies	of Design Risk of Inconsistency Indirectness Imprecision Other Switching to Switch to Relative Absolute								Quality	Importance		
•	symptomatol lower values		score (follow-up	8-12 weeks; m	easured with:	Montgomery Asb	erg Depression Rating	Scale (MA	DRS) chang	e from baseline to	endpoin	t; Better
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency		no serious imprecision	reporting bias ²	376	198	-	SMD 0.12 lower (0.35 lower to 0.1 higher)	LOW	CRITICAL
Remission (I	TT) (follow-u	p 8-12 week	s; assessed with	: Number of pe	ople scoring <	=8 on Montgome	ry Asberg Depression	Rating Sca	le (MADRS))			

¹ Risk of bias is high or unclear across multiple domains

Funding from pharmaceutical companies
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 95% CI crosses thresholds for both clinically important harm and no effect 4

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 (I	TT) (follow-u _l	9 8-12 week	s; assessed with	: Number of pe	ople showing a	it least 50% impro	vement on Montgome	ry Asberg I	Depression	Rating Scale (MAD	RS))	
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
Discontinua	tion due to a	ny reason (f	follow-up 8-12 we	eeks; assessed	with: Number o	of participants wh	o dropped out for any	reason (inc	cluding adve	erse 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
Discontinua	tion due to si	de effects (follow-up 8-12 w	eeks; assessed	with: Number	of participants wh	o dropped out due to	adverse ev	rents)			
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

Clinical evidence profile for comparison 45. Augmenting with antipsychotic versus antidepressant-only or **Table 114:** antidepressant + placebo

antidepressa	ant · pia	CCDC										
Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	onneiderations	with	Antidepressant- only or antidepressant + placebo	Relative (95% CI)	Absolute	Quality	Importance
Depression symptomatology of Better indicated by lower valu		llow-up 4	I-8 weeks; mea	sured with: N	lontgomery A	Asberg Depress	ion Rating Sca	le (MADRS) or Har	nilton Ra	ting Scale	for Depressi	on (HAM-D);
5 (Fava 2012/ Mischoulon 2012, Li 2013, Mahmoud 2007, Moica 2018, Song 2007)		l serious¹	,	no serious indirectness	serious ³	none	295	411	-	SMD 0.78 lower (1.24 to	VERY LOW	CRITICAL

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

										0.32 lower)		
Depression symptomatology (HAM-D) change from baseling					ith: Montgom	ery Asberg Dep	ression Rating	Scale (MADRS) o	r Hamilto	n Rating S	cale for Dep	ression
20 (Berman 2009, Dunner 2007 Durgam 2016, Earley 2018, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2018, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Li 2013, Moica 2018, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Thase 2015b)	trials	serious ¹	serious ⁴	no serious indirectness		reporting bias⁵	3784	2932	-	SMD 0.33 lower (0.44 to 0.23 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 4-2 Depression (HAM-D))	4 weeks; as	sessed	with: Number o	f people scor	ring <=10 on l	Montgomery Asl	berg Depressio	on Rating Scale (M	IADRS) o	r <=7 on Ha	milton Ratin	g Scale for
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 indirectness	serious ³	reporting bias ⁵	1494/5653 (26.4%)	839/4425 (19%)	RR 1.37 (1.23 to 1.52)		VERY LOW	CRITICAL
Response (ITT) (follow-up 4-8 Rating Scale for Depression (I		essed wi	th: Number of	people showi	ng at least 50	0% improvement	on Montgome	ry Asberg Depres	sion Rati	ng Scale (N	MADRS) or H	amilton
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,	trials	serious ¹		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 rea	ason (follow	/-up 4-24	weeks; assess	sed with: Nun	nber of partic	ipants who drop	pped out for any	y reason (includir	g advers	e 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 inconsistency	no serious indirectness	serious ⁶	reporting bias ⁵	825/5620 (14.7%)	525/4392 (12%)		31 more per 1000 (from 16 more to 48 more)		CRITICAL
Discontinuation due to side ef	fects (follow	v-up 4-24	4 weeks; asses	sed with: Nur	mber of partic	cipants who dro	pped 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	serious risk of bias	no serious inconsistency	no serious indirectness	imprecision	reporting bias ⁵	346/5608 (6.2%)	70/4381 (1.6%)	RR 3.07 (2.36 to 3.99)	per 1000 (from 22 more to 48 more)		
Quality of life endpoint (follow	-up mean 6	weeks;	measured with	Quality of Li	fe Enjoymen	t and Satisfactio	n Questionnair	e-short form (Q-L	ES-Q-SF	; Better inc	licated by hi	gher 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	VERY LOW	IMPORTAN'

2 (Berman 2009, Otsuka Pharmaceutical 2016)	randomised trials		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 compo by higher values)	nent score	(PCS) ch	ange score (fo	llow-up mean	8 weeks; me	asured with: 36	item Short-For	m Survey (SF-36)	: Physica	l compone	nt score; Bet	ter indicated
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 compon higher values)	ent score (N	ICS) cha	nge score (follo	ow-up mean 8	3 weeks; mea	sured with: 36-i	tem Short-Form	Survey (SF-36):	Mental co	mponent s	score; Better	indicated by
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)		IMPORTANT
Global functioning change sc higher values)	ore (follow-u	ıp mean	6 weeks; meas	sured with: So	ocial Adaptati	on Self-evaluati	on Scale (SASS	6) change from ba	seline to	endpoint;	Better indica	ted by
1 (Kamijima 2018)	randomised trials		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; a	ssessed with:	Number of pe	eople scoring	<=6 total score	on Sheehan Di	sability Scale (SD	S) and al	I SDS dom	ain 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)		VERY LOW	IMPORTANT
Functional impairment endpo	int (follow-u	p mean (6 weeks; meas	ured with: Sh	eehan Disabi	lity Scale (SDS)	Better indicate	d by lower values	s)			
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	e score (follo	ow-up 5-	8 weeks; meas	ured with: Sh	eehan Disab	ility Scale (SDS)	change from b	aseline to endpoi	nt; Better	indicated	by lower val	ues)
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

8 9

6

Clinical evidence profile for comparison 46. Augmenting with antipsychotic versus bupropion 10 **Table 115:**

Quality assess	ment						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 syr indicated by lo		y change s	core (follow-up n	nean 6 weeks; n	neasured wi	th: Montgomery	Asberg Depression	Rating Sca	le (MADRS)	change from base	line to endp	oint; Better
1 (Cheon 2017)	randomised trials		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 Depressive Syr			assessed with:	Number of peop	ole scoring <	=10 on Montgom	ery Asberg Depres	sion Rating	Scale (MAI	DRS) or <=5 on Qui	ick Inventory	of
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) Inventory of De				lumber of peop	le showing a	at least 50% impre	ovement on Montgo	omery Asbe	erg Depress	ion Rating Scale (M	MADRS) or Q	uick
2 (Cheon 2017, Mohamed 2017)	randomised trials		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	n due to any	reason (foll	low-up 6-12 week	s; assessed wi	th: Number	of participants wh	o dropped out for	any reason	(including	adverse events))		
2 (Cheon 2017, Mohamed 2017)	randomised trials		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)		CRITICAL

2 (Cheon 2017,	, randomised	no serious	no serious	no serious	serious ²	none	27/561	37/553	RR 0.73	18 fewer per 1000	MODERATE CRITICAL
Mohamed	trials	risk of bias	inconsistency	indirectness			(4.8%)	(6.7%)	(0.45 to	(from 37 fewer to	
2017)									1.18)	12 more)	

- 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
- 4 ³ Funding from pharmaceutical companies
- ⁴ Substantial heterogeneity

6 Table 116: Clinical evidence profile for comparison 47. Augmenting with antipsychotic versus lithium

Quality assessme	nt						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) (for Depression (H	•	veeks; asse	ssed with: Numb	er of people sc	oring <=8/<=	10 on Montgomer				DRS) or <=7 on Ham	nilton Ra	ting Scale
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) (for Rating Scale for D			ssed with: Number	er of people sho	wing at leas	t 50% improveme	nt on Montgomery	Asberg	Depression	Rating Scale (MADR	RS) or Ha	milton
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	135/261 (51.7%)	111/249 (44.6%)		80 more per 1000 (from 9 fewer to 183 more)	LOW	CRITICAL
Discontinuation d	ue to any reas	on (follow-	up 4-8 weeks; ass	sessed with: Nu	mber of part	icipants who dro	oped out for any rea	ason (in	cluding adve	erse events))		
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials		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 d	ue to side effe	ects (follow-	up 4-8 weeks; as	sessed with: No	umber of par	ticipants who dro	pped out due to ad	verse ev	rents)			
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials		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

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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

1 Table 117: Clinical evidence profile for comparison 48. Augmenting with antipsychotic versus switch to antipsychotic

Quality asse	essment						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		
	symptomato lower value		e score (follow-	up mean 8 weel	ks; measured v	with: Montgomery	Asberg Depression	on Rating Scale (MADRS) ch	ange from baselin	e to end	point; Better
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 week	s; assessed wit	h: Number of p	eople scoring	<=10 on Montgom	ery Asberg Depre	ssion Rating Sca	le (MADRS))		
2 (Bauer 2013, Thase 2007)	randomised trials		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)		CRITICAL
Response (I	ITT) (follow-u	ıp 6-8 week	s; assessed with	n: Number of pe	ople showing	at least 50% impr	ovement on Montg	jomery Asberg D	epression	Rating Scale (MAD	RS))	
2 (Bauer 2013, Thase 2007)		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
Discontinua	ition due to a	any reason ((follow-up 6-8 w	eeks; assessed	with: Number	of participants wi	no dropped out for	r any reason (inc	luding adve	erse events))		
2 (Bauer 2013, Thase 2007)	randomised trials		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
Discontinua	ition due to s	side effects	(follow-up 6-8 w	eeks; assessed	with: Number	of participants w	ho dropped out du	ue to adverse eve	ents)			
2 (Bauer 2013, Thase 2007)	randomised trials		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 li		omponent s	score (PCS) cha	nge score (follo	w-up mean 8 v	veeks; measured	with: 36-item Shor	t-Form Survey (SF-36): Phys	sical component s	core; Be	tter indicated
1 (Thase 2007)	randomised trials		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	IMPORTAN
Quality of lith		mponent sc	ore (MCS) chan	ge score (follow	v-up mean 8 we	eeks; measured w	ith: 36-item Short-	Form Survey (SI	F-36): Menta	al component scor	e; Bettei	r indicated b
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	IMPORTAN [*]

² CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

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Clinical evidence profile for comparison 49. Augmenting with antipsychotic versus switch to bupropion **Table 118:**

Quality as	sessment						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	n (ITT) (follow	v-up mean	12 weeks; assess	sed with: Numb	er of people so	coring <=5 on Qui	ck Inventory of De	pressive Sym	ptomatology	y (QIDS))		
1 (Mohamed 2017)	randomised trials		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 1	2 weeks; assess	ed with: Numbe	er of people sh	owing at least 50	% improvement on	Quick Invent	ory of Depre	essive Symptomato	logy (QIDS))	
1 (Mohamed 2017)	randomised trials		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
Discontinu	uation due to	any reaso	n (follow-up mea	n 12 weeks; as	sessed with: N	umber of particip	ants who dropped	out for any re	ason (includ	ding adverse event	s))	
1 (Mohamed 2017)	randomised trials		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
Discontinu	uation due to	side effect	s (follow-up mea	an 12 weeks; as	sessed with: N	lumber of particip	ants who dropped	out due to ac	lverse event	s)		
1 (Mohamed 2017)	randomised trials		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

Table 119: Clinical evidence profile for comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/placebo)

•	Quality assessment	No of patients	Effect	Quality	Importance

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for both clinically important benefit and no effect

³ Funding from pharmaceutical companies

⁴ Considerable heterogeneity

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

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	with huspirone	Continuing with antidepressant (+/-placebo)	Relative (95% CI)	Absolute		
Remission (IT	T) (follow-up	mean 8	weeks; assesse	d with: Numbe	r of people sc	oring <=7 on Han	nilton Rating Sc	cale for Depression (H	IAM-D))			
1 (Fang 2011)	randomised trials			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
			ks; assessed wit Scale for Depress		people rated a	s much or very m	uch improved o	on Clinical Global Imp	oressions	scale (CGI-I) or s	howing at le	ast 50%
111 3	randomised trials			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 by higher valu	• •	nponent	score (PCS) cha	inge score (fol	low-up mean 8	B weeks; measure	ed with: 36-item	Short-Form Survey (SF-36): Ph	ysical compone	nt score; Be	tter indicate
1 (Fang 2011)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.06 lower (0.48 lower to 0.35 higher)	MODERATE	IMPORTAN
Quality of life higher values		ponent s	core (MCS) char	ge score (follo	w-up mean 8	weeks; measured	d with: 36-item S	Short-Form Survey (S	F-36): Men	ital component s	core; Better	indicated b
1 (Fang 2011)	trials			no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.08 higher (0.34 lower to 0.49 higher)	MODERATE	IMPORTAN

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

Clinical evidence profile for comparison 51. Augmenting with buspirone versus bupropion **Table 120:**

Iable	ie 120. Chinical evidence prome for companson 31. Augmenting with buspirone versus bupropion												
Quality a	ssessment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with buspirone		Relative (95% CI)	Absolute			
Depressi	on symptoma	tology endp	point (follow-up m	iean 6 weeks; m	easured with:	Quick Inventory o	f Depressive Sym	ptomatolog	y (QIDS); Be	etter indicated by lov	wer values)		
1 (Trivedi 2006)	randomised trials	serious ¹	no serious inconsistency		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)												

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for both clinically important harm and no effect

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)		CRITICAL
Remissio	n (ITT) (follov	v-up mean 6	weeks; assesse	d with: Number	of people scori	ng <=7 on Hamilto	on Rating Scale fo	r Depressi	on (HAM-D))			
1 (Trivedi 2006)		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	e (ITT) (follow	v-up mean 6	weeks; assessed	l with: Number o	of people show	ing at least 50% in	nprovement on Q	uick Invent	ory of Depre	ssive Symptomatolo	gy (QIDS))	
1 (Trivedi 2006)		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
Discontin	uation due to	side effect	s (follow-up mear	n 6 weeks; asse	ssed with: Num	ber of participants	s who dropped ou	ut due to ac	lverse events	s)		
1 (Trivedi 2006)	randomised trials		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

Table 121: Clinical evidence profile for comparison 52. Augmenting with methylphenidate versus placebo

Quality assessr	nent			·			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 synindicated by lov		y change so	core (follow-up m	iean 5 weeks; n	neasured with:	Montgomery Ash	erg Depression Ratin	g Scale ((MADRS) ch	ange from baseline	to endp	oint; Better
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 n	nean 4 weel	ks; assessed witl	h: Number of pe	eople showing	at least 50% impi	ovement on Hamilton	Rating S	Scale for Dep	pression (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) Depression Rat			ssessed with: Nu	mber of people	showing at lea	ast 50% improver	nent on Hamilton Rati	ng Scale	for Depress	ion (HAM-D) or Mo	ntgomer	y Asberg
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

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 95% CI crosses thresholds for both clinically important harm and no effect

Discontinuation	n due to any i	reason (follo	ow-up mean 5 we	eeks; assessed	with: Number	of participants wh	no dropped out for any	y reason	(including a	dverse events))					
1 (Ravindran 2008a)	DO8a) trials inconsistency indirectness (15.1%) (5.6%) (0.91 to (from 5 fewer to LOW 8.12) 396 more)														
Discontinuation	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)		no serious risk of bias		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

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Table 122: Clinical evidence profile for comparison 53. Augmenting with lithium versus continuing with antidepressant (+/nlacahal

piac	eno)											
Quality assessmen	ıt						No of patients		Effect		Quality	Importanc
No of studies	I Jacian	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with lithium	Continuing with antidepressant (+/-placebo)	Relative (95% CI)	Absolute	quanty	portaine
Depression sympto Better indicated by			illow-up 2-3 wee	ks; measured	with: Hamilto	on Rating Scale f	or Depression	(HAM-D) or Montgom	ery Asberg	Depression Rat	ing Scal	e (MADRS)
2 (Joffe 1993, Stein 1993)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	33	34	-	SMD 0.23 lower (0.71 lower to 0.25 higher)	LOW	CRITICAL
								ssion (HAM-D) or Mo ated by lower values)		sberg Depression	n Rating	g Scale
3 (Girlanda 2014, Joffe 1993, Stein 1993)	randomised trials		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) (fo on HAM-D))	llow-up mea	n 3 weeks	; assessed with	Number of pe	ople scoring	<=7 on Hamiltor	Rating Scale f	for Depression (HAM	-D) AND res	sponding (at leas	st 50% in	nprovemen
1 (Joffe 1993)			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

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

										fewer to 1000 more)		
Response (ITT) (fo	llow-up 1-6 v	veeks; ass	essed with: Nun	nber of people	showing at I	east 50% improv	ement on Hami	Iton Rating Scale for	Depression	n (HAM-D))		
2 (Baumann 1996, Nierenberg 2003a)		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 du	ie to any rea	son (follow	/-up 2-52 weeks	; assessed with	n: Number o	f participants who	o dropped out f	or any reason (includ	ing advers	e events))		
4 (Girlanda 2014, Joffe 1993, Nierenberg 2003a, Stein 1993)	randomised trials		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 du	ue to side eff	ects (follow	v-up 2-3 weeks;	assessed with	: Number of	participants who	dropped out d	ue to adverse events)				
2 (Joffe 1993, Stein 1993)	randomised trials		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

Table 123: Clinical evidence profile for comparison 54. Augmenting with lithium versus switch to antipsychotic

Quality as	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other considerations	Augmenting with lithium		Relative (95% CI)	Absolute		
Remissio	n (ITT) (follow	v-up mear	n 6 weeks; assess	ed with: Numbe	r of people s	coring <=10 on M	ontgomery Asbe	rg Depression Ra	ting Scale (N	IADRS))		
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)		CRITICAL
Response	e (ITT) (follow	-up mean	6 weeks; assesse	ed with: Number	of people sh	nowing at least 50	% improvement	on Montgomery A	sberg Depre	ssion Rating Scale (M	IADRS))	
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)		CRITICAL
Discontin	uation due to	any reas	on (follow-up mea	an 6 weeks; asso	essed with: N	lumber of particip	ticipants who dropped out for any reason (including adverse events)			g adverse events))		

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

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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
Discontin	nuation due to	side effe	cts (follow-up me	an 6 weeks; ass	sessed with:	Number of particip	ants who droppe	ed out due to adve	erse 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)		CRITICAL

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

Table 124: Clinical evidence profile for comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

	intervei	ILIOII										
Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with lithium	Augmenting with a psychological intervention	Relative (95% CI)	Absolute	,	,
Depressio	n symptomat	tology end	point (follow-up	mean 8 weeks;	measured w	ith: Hamilton Ra	ting Scale for D	epression (HAM-D); B	etter indica	ted by lower value	es)	
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	SMD 0.41 lower (1.05 lower to 0.22 higher)	MODERATE	CRITICAL
-	n symptomat by lower valu		nge score (follow	v-up mean 8 we	eks; measui	ed with: Hamilto	n Rating Scale	for Depression (HAM-	D) change f	rom baseline to e	ndpoint; Bett	er
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	SMD 0.42 lower (1.06 lower to 0.21 higher)	MODERATE	CRITICAL
Depressio	n symptomat	tology at 1-	-month follow-uլ	(follow-up me	an 1 months	; measured with:	Hamilton Ratin	g Scale for Depressio	n (HAM-D);	Better indicated b	y lower valu	es)
1 (Kennedy 2003)	randomised trials		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	8 weeks; assess	ed with: Numbe	er of people :	scoring <=7 on H	amilton Rating	Scale for Depression	(HAM-D))			

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

1 (Kennedy 2003)	randomised trials		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
Discontinu	uation due to	any reason	n (follow-up mea	an 8 weeks; ass	essed with:	Number of partic	ipants who drop	oped out for any reaso	n (includin	g adverse events))		
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	3/21 (14.3%)	3/23 (13%)		13 more per 1000 (from 98 fewer to 501 more)	LOW	CRITICAL
Discontinu	uation due to	side effect	ts (follow-up me	an 8 weeks; as:	sessed with:	Number of partic	ipants who dro	pped out due to adver	se events)			
1 (Kennedy 2003)	randomised trials		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

Clinical evidence profile for comparison 56. Augmenting with lithium versus augmenting with TCA **Table 125:** 4

Quality asse	ssment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with lithium	Augmenting with TCA	Relative (95% CI)	Absolute		
Depression :	symptomatol	ogy endpoir	nt (follow-up mea	n 4 weeks; mea	sured with: H	Hamilton Rating S	cale for Depress	sion (HAM-D); Be	etter indicate	ed 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 sindicated by	-		score (follow-up	mean 4 weeks;	measured w	ith: Hamilton Rati	ng Scale for Dep	oression (HAM-I	O) change fro	om baseline to endp	oint; Bet	ter
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 (I	TT) (follow-u	p mean 4 w	eeks; assessed w	ith: Number of	people scori	ng <=7 on Hamilto	on Rating Scale f	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
Discontinuat	tion due to ar	ny reason (fo	ollow-up mean 4	weeks; assesse	d with: Numl	ber of participants	who dropped o	ut for any reaso	n (including	adverse events))		
2 (Fava 1994a, Fava 2002)	randomised trials		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

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

Discontinu	ation due to s	ide effects (follow-up mean 4	weeks; assess	ed with: Nun	nber of participant	s who dropped o	ut due to adver	se events)		
1 (Fava 1994a)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ⁵	1/14 (7.1%)	2/12 (16.7%)		95 fewer per 1000 (from 160 fewer to 527 more)	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

Clinical evidence profile for comparison 57. Augmenting with omega-3 fatty acids versus placebo **Table 126:** 8

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 symptoma	tology endpo	int (follow	-up 4-12 weeks;	measured with	: Hamilton Rat	ing Scale for Dep	ression (HAM-D);	Better in	dicated 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 symptomathy lower values)	tology chang	je score (fo	llow-up 4-12 wed	eks; measured	with: Hamilton	n Rating Scale fo	r Depression (HAN	I-D) char	ige from ba	seline to endpoi	nt; Bette	r indicated
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; as	sessed with: Nu	mber of people	scoring <=7 c	n Hamilton Ratin	g Scale for Depres	ssion (HA	AM-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) (followers 50% improvement of		•			wing at least 5	0% improvement	on Montgomery A	sberg D	epression F	Rating Scale (MA	DRS) or	at least 30%
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; asse	essed with: Nu	mber of partici	pants who dropp	ed out for any rea	son (incl	uding adve	rse events))		

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

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; ass	essed with: Nu	mber of partic	ipants who dropp	oed out due to adv	erse evei	nts)			
4 (Jahangard 2018, Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials		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 er	ndpoint (follo	w-up mean	12 weeks; meas	sured with: Inse	omnia Severity	Index (ISI); Bette	er indicated by low	ver values	s)			
1 (Jahangard 2018)	randomised trials		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

Clinical evidence profile for comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant **Table 127:** (+/- placebo)

Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Lincian	Risk of bias	Inconsistency	Indirectness		Other considerations	Augmenting with thyroid hormone	Continuing with antidepressant (+/-placebo)	Relative (95% CI)	Absolute		
Depression	n symptoms	endpoint (follow-up mean	2 weeks; meas	sured with: Ha	milton Rating Sc	ale for Depression	on (HAM-D); Better in	dicated by	lower values)		
1 (Joffe 1993)			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 lower value		change so	core (follow-up n	nean 2 weeks;	measured witl	h: Hamilton Ratir	ng Scale for Depr	ession (HAM-D) char	ige from ba	seline to endpo	int; Better ind	dicated by
1 (Joffe 1993)			no serious inconsistency	no serious indirectness	serious ¹	none	17	16	-	SMD 0.78 lower (1.5 to 0.07 lower)	MODERATE	CRITICAL
Remission	n (ITT) (follow	/-up 2-8 we	eks; assessed v	with: Number o	f people scori	ng <=7 on Hamil	ton Rating Scale	for Depression (HAM	I-D))			

Risk of bias is high or unclear across multiple domains
 Considerable heterogeneity
 95% CI crosses thresholds for both clinically important benefit and no effect
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

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; assess	sed with: Numb	er of people s	howing at least 5	60% improvement	on Hamilton Rating	Scale for D	epression (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
Discontinu	uation due to	any reaso	on (follow-up me	ean 2 weeks; as	ssessed with:	Number of partic	ipants who dropp	ed out for any reaso	n (includin	g adverse events	s))	
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
Discontinu	uation due to	side effec	cts (follow-up m	ean 2 weeks; a	ssessed with:	Number of partic	ipants who drop	ped out due to adver	se 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 by higher		compone	nt score (PCS) o	change score (f	ollow-up mear	n 8 weeks; measu	red with: 36-item	Short-Form Survey	(SF-36): Ph	ysical componer	nt score; Be	tter indicated
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 higher val		omponent	score (MCS) ch	ange score (fo	llow-up mean	8 weeks; measur	ed with: 36-item	Short-Form Survey (SF-36): M er	ntal component s	core; Better	indicated by
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

Table 128: Clinical evidence profile for comparison 59. Augmenting with thyroid hormone versus augmenting with lithium

Qual	lity assessr	nent						No of patients		Effect		Quality	Importance	
No o	of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with thyroid hormone	Augmenting with lithium	Relative (95% CI)	Absolute			

 ^{95%} CI crosses thresholds for both clinically important benefit and no effect
 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

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
			core (follow-up int; Better indica			lamilton Rating S	cale for Depressio	n (HAM-D) or Q	uick Invent	ory of Depressive	Sympto	matology
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 Symptomatolo		?-14 weeks;	assessed with:	Number of peo	pple scoring <=	7 on Hamilton Ra	ting Scale for Dep	ression (HAM-D)) or <=5 on	Quick Inventory o	f Depre	ssive
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 m	ean 14 we	eks; assessed w	ith: Number of	people showir	ng at least 50% im	provement on Qu	ck 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
Discontinuatio	n due to any	reason (fol	low-up mean 2 v	veeks; assesse	d with: Numbe	r of participants v	vho dropped out f	or any reason (i	ncluding ac	dverse events))		
1 (Joffe 1993)	randomised trials		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
Discontinuatio	n due to side	effects (fol	llow-up 2-14 wee	eks; assessed v	vith: Number o	of participants who	o dropped out due	to adverse eve	nts)			
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

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

Table 129: Clinical evidence profile for comparison 60. Switching to ECT versus switching to paroxetine

Quality as	sessment						No of patier	ıts	Effect		Quality	Importance
No of studies									Relative (95% CI)	Absolute		

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

Depressio	n symptomat	ology endpo	oint (follow-up 2-4	weeks; measure	ed with: Hamilto	on Rating Scale fo	or Depression	(HAM-D); Bett	er indicated b	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 lower value		ology chang	je score (follow-u	p 2-4 weeks; me	asured with: Ha	amilton Rating Sc	ale for Depres	sion (HAM-D)	change from	baseline to endpoint;	Better in	ndicated by
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 week	s; assessed with:	Number of peop	ole showing at	least 50% improve	ement on Ham	ilton Rating So	cale for Depre	ession (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
Discontinu	ation due to	any reason ((follow-up 2-4 we	eks; assessed w	ith: Number of	participants who	dropped out f	or any reason	(including ad	verse events))		
1 (Folkerts 1997)	randomised trials		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
Discontinu	ation due to	side effects	(follow-up 2-4 we	eks; assessed w	vith: Number of	participants who	dropped out	due to adverse	events)			
1997)	randomised trials	risk of bias	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

Table 130: Clinical evidence profile for comparison 61. Augmenting with ECT versus continuing with antidepressant

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Quality ass	essment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Impracicion		Augmenting with ECT	Continuing with antidepressant	Relative (95% CI)	Absolute	·	·
Depression	symptomato	logy endp	ooint (follow-up m	ean 4 weeks; me	easured with	: Hamilton Rating	Scale for Depre	ssion (HAM-D); Bette	r indicate	ed by lower values)		
1 (Haghighi 2013)	randomised trials	serious ¹		no serious indirectness	very serious ²	none	20	20	-	SMD 0.08 higher (0.54 lower to 0.7 higher)	VERY LOW	CRITICAL
	symptomato y lower value		nge score (follow-	up mean 4 week	s; measured	with: Hamilton Ra	ating Scale for D	epression (HAM-D) c	hange fro	om baseline to endp	oint; Bett	ter
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)		CRITICAL

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

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

Table 131: Clinical evidence profile for comparison 62. Augmenting with ECT versus augmenting with exercise

Quality as	ssessment					- -	No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with ECT		Relative (95% CI)	Absolute		
Depressi	on symptoma	tology end	point (follow-up n	nean 4 weeks; n	neasured wit	h: Hamilton Ratin	g Scale for Dep	ression (HAM-D);	Better indic	cated by lower value	es)	
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
	on symptoma by lower val		nge score (follow	-up mean 4 wee	ks; measure	d with: Hamilton I	Rating Scale for	Depression (HAI	И-D) change	from baseline to e	ndpoint; Bett	er
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
Remissio	n (ITT) (follov	w-up mean 4	4 weeks; assesse	d with: Number	of people so	oring <=7 on Han	nilton Rating Sc	ale for Depressio	n (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

10 Table 132: Clinical evidence profile for comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision		Augmenting with ECT + exercise		Relative (95% CI)	Absolute		
Depressi	on symptom	atology en	dpoint (follow-up	mean 4 weeks	; measured wit	h: Hamilton Ratir	ng Scale for Depre	ssion (HAM-D);	Better indica	ated by lower value	es)	

³ 95% CI crosses thresholds for both clinically important benefit and no effect

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

1 (Salehi 2016)			no serious inconsistency	no serious indirectness	serious ¹	none	20	20	-	SMD 0.99 lower (1.65 to 0.33 lower)	MODERATE	CRITICAL
-	on symptom I by lower va		ange score (follo	w-up mean 4 w	eeks; measure	d with: Hamilton l	Rating Scale for D	epression (HAM	-D) change	from baseline to er	ndpoint; Bett	er
1 (Salehi 2016)			no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	SMD 1.84 lower (2.59 to 1.09 lower)	HIGH	CRITICAL
Remissio	on (ITT) (follo	w-up mean	4 weeks; assess	sed with: Numb	er of people so	coring <=7 on Han	nilton Rating Scal	e for Depression	(HAM-D))			
1 (Salehi 2016)				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 195% 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 assessm		Risk of				Other	No of patients		Effect Relative		Quality	Importance
No of studies	Design	bias	Inconsistency	Indirectness	Imprecision	considerations	with exercise	TAU	(95% CI)	Absolute		
Depression sym	ptomatology	endpoint (f	ollow-up mean 3	weeks; measure	ed with: Mon	tgomery Asberg	Depression Ratin	g Scale	(MADRS); B	etter indicated by lo	wer 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 symindicated by low		change sco	ore (follow-up 3-1	0 weeks; meası	red with: Mo	ontgomery Asberg	p Depression Rati	ing Scal	e (MADRS) o	change from baselin	e to endpoin	t; Better
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; a	ssessed with: Nu	mber of people	scoring <=1	0 on Montgomery	Asberg Depress	ion Rati	ng Scale (M	ADRS))		
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 me	ean 10 week	s; assessed with	: Number of pec	ple showing	at least 50% imp	rovement on Mor	ntgomer	y Asberg De	pression Rating Sca	ile (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

Discontinuatio	n due to any r	eason (follo	w-up 3-10 weeks	; assessed with	: Number of	participants who d	dropped out for a	ny reaso	n (including	adverse events))		
2 (Danielsson 2014, Ho 2014)			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

Table 134: Clinical evidence profile for comparison 65. Augmenting with exercise versus attention-placebo

Quality assessme	nt						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Attention- placebo	Relative (95% CI)	Absolute		
Depression symp	tomatology e	endpoint (fo	ollow-up mean 1	0 weeks; meas	ured with: Har	nilton Rating Sca	le for Depression	n (HAM-D);	Better indi	cated by lower va	lues)	
1 (Lavretsky 2011)	randomised trials			no serious indirectness	serious ¹	none	33	35	-	SMD 0.4 lower (0.88 lower to 0.08 higher)	MODERATE	CRITICAL
Depression symptindicated by lower		change sco	re (follow-up me	an 12 weeks; r	neasured with	: Hamilton Rating	Scale for Depr	ession (HAN	I-D) change	e from baseline to	endpoint; E	Setter
1 (Mota-Pereira 2011)	randomised trials		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) (f	ollow-up 10-	12 weeks; a	assessed with: N	lumber of peop	ole scoring <=	7 or <7 on Hamilt	on Rating Scale	for Depress	ion (HAM-I	O))		
2 (Lavretsky 2011, Mota-Pereira 2011)	randomised trials			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) (fo	ollow-up 10-1	l2 weeks; a	ssessed with: N	umber of peop	le showing at	least 30% or 50%	improvement o	n Hamilton	Rating Sca	le for Depression	(HAM-D))	
2 (Mather 2002, Mota-Pereira 2011)	randomised trials		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 d	ue to any rea	ason (follov	v-up 10-12 week	s; assessed wi	th: Number of	participants who	dropped out fo	r any reasor	(including	adverse events)))	
3 (Lavretsky 2011, Mather 2002, Mota-Pereira 2011)	randomised trials		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)		CRITICAL

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

1 (Mota-Pereira 2011)	randomised trials			no serious indirectness	no serious imprecision	reporting bias ³	19	10	-	SMD 6.15 higher (4.28 to 8.02 higher)	LOW	IMPORTANT
Sleeping difficult	ies endpoint	(follow-up	mean 10 weeks;	measured with	: Pittsburgh S	leep Quality Index	k (PSQI); Better	indicated by	lower valu	ues)		
1 (Lavretsky 2011)				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

Table 135: Clinical evidence profile for comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with exercise + ECT		Relative (95% CI)	Absolute		
Depressi	on symptoma	atology end	dpoint (follow-up	mean 4 weeks;	measured wit	h: Hamilton Ratin	g Scale for Depres	sion (HAM-D);	Better indic	ated by lower value	es)	
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	20	20	-	SMD 1.13 lower (1.81 to 0.46 lower)	MODERATE	CRITICAL
-	on symptoma I by lower val		ange score (follo	w-up mean 4 we	eeks; measure	d with: Hamilton F	Rating Scale for De	epression (HAN	I-D) change	from baseline to er	ndpoint; Bett	er
1 (Salehi 2016)		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)		CRITICAL
Remissio	on (ITT) (follo	w-up mean	4 weeks; assess	sed with: Numb	er of people sc	oring <=7 on Ham	nilton Rating Scale	for Depression	n (HAM-D))			
1 (Salehi 2016)		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

Table 136: Clinical evidence profile for comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

Quality assessment No of pat	atients Effect Q	Quality	Importance	
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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

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

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 sylindicated by lo		gy change	score (follow-up	mean 8 weeks	s; measured w	vith: Hamilton Ra	ting Scale for	Depression (HAM-D) cha	nge from b	aseline to endpo	int; Bet	ter
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 Symptomatolo	, ,	8-10 weeks	s; assessed with	n: Number of p	eople scoring	<=7 on Hamilton	Rating Scale f	or Depression (HAM-D)	or <=5 on C	uick Inventory o	f Depre	ssive
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	n 3 months; as	sessed with: N	lumber of people	scoring <=5 c	on Quick Inventory of De	pressive Sy	mptomatology (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 mear	n 6 months; as	sessed with: N	lumber of people	scoring <=5 c	on Quick Inventory of De	pressive S	mptomatology (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 Depressive Sy			; assessed with	: Number of pe	ople showing	at least 50% imp	rovement on I	Hamilton Rating Scale fo	r Depressio	on (HAM-D) or Qu	uick Inv	entory of
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 Symptomatolo		follow-up ((follow-up mean	3 months; ass	essed with: N	umber of people	showing at lea	ast 50% improvement on	Quick Inve	entory of Depress	sive	
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) Symptomatolo		follow-up ((follow-up mean	6 months; ass	essed with: N	umber of people	showing at lea	ast 50% improvement on	Quick Inve	entory of Depress	sive	
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)	
Discontinuatio	n due to any	reason (fo	llow-up 8-10 we	eks; assessed	with: Number	of participants w	ho dropped ou	ıt for any reason (includ	ing advers	e 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)	•	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

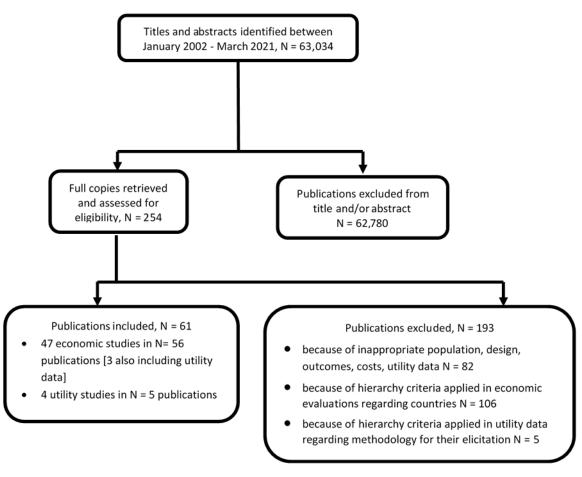
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 ¹ Risk of bias is high or unclear across multiple domains
 2 95% CI crosses thresholds for both clinically important benefit and no effect
 3 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 4 Substantial heterogeneity

Appendix G – Economic evidence study selection

- 2 Economic evidence study selection for review question: What are the relative
- 3 benefits and harms of further-line psychological, psychosocial,
- 4 pharmacological and physical interventions (alone or in combination), for
- 5 adults with depression showing an inadequate response to at least one
- 6 previous intervention for the current episode?
- 7 A global health economics search was undertaken for all areas covered in the guideline.
- 8 Figure 398 shows the flow diagram of the selection process for economic evaluations of
- 9 interventions and strategies for adults with depression and studies reporting depression-
- 10 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



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1 Appendix H – Economic evidence tables

- 2 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
- 4 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

	cpressants				
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 week 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 Scott 2003 UK Cost effectiveness analysis	Intervention and comparator 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	Study population, design and data sources 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.	Costs and outcomes (descriptions and values) 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)	Results 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	Comments Perspective: NHS/PSS Currency: GBP£ Cost year: 1999 Time horizon: 17 months Discounting: 6% Applicability: partially applicable Quality: minor limitations
	during the 48-week follow-up) (CT & AD) Antidepressants and clinical management alone (AD)	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		method of missing data imputation	
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 Applicabile 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)		

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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

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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 costeffective 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

1 Table 141: Economic evidence table for continuation of current treatment (citalopram) versus switching to another antidepressant 2 (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 costeffectiveness 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

1 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 costeffective 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

1 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% 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

	order ouritoring to	papi opion			
Study country type	Intervention and and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Yoon 20° US Cost- effectiver and cost- utility analysis	Aripiprazole adjunct to an antidepressant	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

	mone, corone amana	ressaint 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; Ethium & TCA maintenance in ECT 8. SNRI, SSRI, ECT; 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 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 applicabl Quality: potentiall 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 At WTP \$100,000/QALY probability that at least 1 ECT strategy is costeffective: 74-78%; probability of costeffectiveness 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

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1 Appendix I – Economic evidence profiles

- 2 Economic evidence profiles for review question: What are the relative benefits and harms of further-line psychological,
- 3 psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing
- 4 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

1 5. UK study; NHS & PSS perspective; QALYs estimated based on EQ-5D ratings (UK tariff)

2 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	Increment al costs ¹	Incremental effects	ICER ¹	Uncertainty ¹
Kessler 2018a/2018 b 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).

7 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)

^{8 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 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)

- 1 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;
- 15 funded by industry

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16 5. Swedish study; societal perspective but analysis based on healthcare costs presented separately; QALYs based on EQ

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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	Incremen tal costs ¹	Increment al 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).

Economic evidence profile for aripiprazole adjunct to antidepressants versus bupropion adjunct to antidepressants **Table 156:** 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 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)

¹¹ 2. Time horizon 12 weeks; analysis conducted alongside RCT (N=1522; complete data for n=1131); national unit costs used; statistical analyses (including bootstrapping) 12 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 13

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

1 Table 157: Economic evidence profile for brexpiprazole versus quetiapine (150 and 300mg/day) versus olanzapine/fluoxetine 2 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:	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).

8 Table 158: Economic evidence profile for ECT versus TCAs, SSRIs, SNRIs, and lithium augmentation

Study and country	Limitations	Applicability	Other comments	Incremen tal costs ¹	Increment al 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

^{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

Study and country	Limitations	Applicability	Other comments	Incremen tal costs ¹	Increment al 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

1 Appendix J - Economic analysis

- 2 Economic analysis for review question: What are the relative benefits and harms
- 3 of further-line psychological, psychosocial, pharmacological and physical
- 4 interventions (alone or in combination), for adults with depression showing an
- 5 inadequate response to at least one previous intervention for the current
- 6 episode?
- 7 No economic analysis was conducted for this review question.

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1 Appendix K - Excluded studies

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

7 Clinical studies

- 8 Please refer to the excluded studies in supplement D Clinical evidence tables for Evidence
- 9 Review D Further-line treatment.

10 Economic studies

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

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1 Appendix L - Research recommendations

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

7 Research question

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

12 Why this is important

- 13 Not all people with depression respond well to first-line treatments and approximately one-
- 14 third do not fully recover with first line treatment and may remain symptomatic even after a
- 15 second-line treatment. Finding improved models of treatment for people who do not respond
- 16 to first-line treatment is critical. We do not know what treatment options best follow
- 17 inadequate response to a first-line psychological intervention, including adding
- 18 antidepressant medication or switching to another psychological intervention or how to make
- 19 this choice.

20 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 Relevance to NICE guidance	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? 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

1 NA: not applicable

2 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.

ECT: electroconvulsive therapy

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