Pharmacotherapy for Social Anxiety Disorder and Posttraumatic Stress Disorder: New Meta-Analytic Approaches to Synthesising the Evidence

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DOCTOR OF PHILOSOPHY

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Professor Dan J. Stein

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You made a way

When our backs were against the wall

And it looked as if it was over

You made a way

And we're standing here

Only because you made a way

You made a way

Travis Green

CONTENTS

DECLARATION

I, Taryn Amos (Williams), do hereby declare that this thesis is based on an introduction chapter (chapter 1) and conclusion chapter (chapter 7), three manuscripts of which have been published (chapter 2, 4, 5), and two manuscripts in peer review (3, 6). The three manuscripts have been formatted for the purposes of this thesis, with regards to referencing style and use of terms. The content of each manuscript remains unchanged, but the introduction and conclusion link each chapter to the next and the others. Chapter one, chapter 7 and the manuscripts included are listed below, with a description of my contribution to each.

Chapter 1.

Chapter one forms the introduction of my thesis and the backbone of my proposal. This chapter was compiled by me and provides an overview of the prevalence of SAD and PTSD, the nature of these comorbid disorders, treatment and methodology. Dr. Jonathan Ipser and Prof. Dan Stein guided this process and provided comments where relevant.

Chapter 2.

Williams T, Hattingh CJ, Kariuki CM, Tromp SA, van Balkom AJ, Ipser JC, Stein DJ. Pharmacotherapy for social anxiety disorder (SAD). Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD001206. DOI: 10.1002/14651858.CD001206.pub3.

I coordinated the update of this review. Dr. Jonathan Ipser and I compiled the updated version of the review, including rechecking all studies for eligibility and risk of bias, completing all GRADE tables (this was a new component), analysing the data, and updating the Abstract, Results, Discussion and Authors' conclusion sections of the review. Prof. Dan Stein, Catherine Kariuki, Dr. Sean Tromp, and Dr. Coenraad Hattingh reviewed the final draft and made comments where relevant. All revisions of this manuscript were managed by me.

Chapter 3.

Williams T, Phillips N, Stein DJ, Ipser JC. Pharmacotherapy for posttraumatic stress disorder (PTSD). Under review in Cochrane Database of Systematic Reviews.

The update of this review was coordinated by me. Dr. Jonathan Ipser and I assessed studies for eligibility and inclusion in the review. Nicole Phillips and I reassessed risk of bias following the new guidelines set out by the review group and extracted data for recent published studies. Thereafter I compiled GRADE tables and data analysis tables which were rechecked by Dr. Jonathan Ipser. The updating of the review Abstract, Results, Discussion and Authors' conclusion sections were all edited by me and Dr. Jonathan Ipser. Dr. Jonathan Ipser, Prof. Dan Stein and Dr. Nicole Phillips reviewed the final draft and made comments where relevant. All revisions of this manuscript will be managed by myself.

Chapter 4.

Williams T, Stein DJ, Ipser I. A systematic review of network meta-analyses for pharmacological treatment of common mental disorders. Evid Based Mental Health 2018; 21(1): 7-11.

In this systematic review I conducted the search and compiled the write up of the review. Dr. Jonathan Ipser and I assessed the included network meta-analysis for eligibility and extracted the relevant data. Prof. Dan Stein and Dr. Jonathan Ipser further provided guidance and additional commentary for the completion of the review. All revisions of this manuscript were managed by me.

Chapter 5.

Cipriani A, Amos T, Salanti G, Chaimani A, Nikolakopoulou A, Ipser J, Geddes J, Stein D. Comparative efficacy and acceptability of pharmacological treatments in the acute phase

treatment of posttraumatic stress disorder in adults: a network meta-analysis. Protocol, Version 3.1, Published October 2013.

Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ. Comparative efficacy and acceptability of pharmacological treatments for posttraumatic stress disorder in adults: a network meta-analysis. Psychological Medicine https://doi.org/10.1017/S003329171700349X

Chapter five forms the basis for my training (in Bristol) in the network meta-analysis method of understanding and analysis. Prof. Andrea Cipriani and I were the main leaders of this manuscript. We assessed articles for eligibility and inclusion in the study. I also hand searched for grey literature. Thereafter we assessed the quality of each study using the Cochrane Risk of Bias Tool. The analysis and interpretation were driven by Prof. Andrea Cipriani and conducted by Georgia Salanti and John Geddes. I compiled the tables for the description of study characteristics and risk of bias assessment. This was rechecked by Prof. Andrea Cipriani. In addition, all the authors provided input on the write up of the paper and review of the manuscript. The revision of this manuscript was managed by Prof. Andrea Cipriani with the help of all co-authors, including myself.

Chapter 6.

Taryn Amos, Jonathan Ipser, Andrea Cipriani, Debbie Caldwell, Dan Stein. Comparative efficacy and acceptability of pharmacological treatments in the treatment of social anxiety disorder in adults: a network meta-analysis. PROSPERO 2015: CRD42015017493 Available from

http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015017493

Comparative Efficacy and Acceptability of Pharmacological Treatments for Social Anxiety Disorder in Adults: A Systematic Review and Network Meta-Analysis. Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D, Ipser J. Under review in the Journal of Psychological Medicine.

I compiled and coordinated the manuscript. All data was extracted by me and Dr. Jonathan Ipser including risk of bias data. I conducted the analysis under the supervision of Michael McCaul, Guido Schwarzer and further training I received in Bristol. I also conducted GRADE for this manuscript which Michael McCaul rechecked. Prof. Andrea Cipriani, Prof. Dan Stein, Dr. Jonathan Ipser, Michael McCaul and Guido Schwarzer reviewed the manuscript and gave comments where relevant. I will manage the revisions of this manuscript.

Chapter 7.

Chapter seven provides a discussion of chapters' two to seven. I compiled the chapter with the guidance of my main supervisor and co supervisors.

I confirm that no part of this thesis has been submitted in the past, or is being, or is to be submitted for a degree in this or any other university. I hereby grant the University of Cape Town free license to reproduce this thesis in whole or part for the purposes of research or teaching.

This thesis is presented for examination in fulfilment of the requirements for the degree of Doctor of Philosophy in Psychiatry.

Signed,

Signed by candidate

Taryn Amos (Williams) February 2019

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

[1] Williams T, Hattingh CJ, Kariuki CM, Tromp SA, van Balkom AJ, Ipser JC, Stein DJ. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD001206.
DOI: 10.1002/14651858.CD001206.pub3.

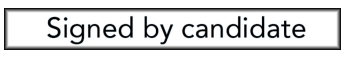
[2] Williams T, Stein DJ, Ipser JC. Pharmacotherapy for post-traumatic stress disorder (PTSD). Under review in Cochrane Database of Systematic Reviews.

[3] Williams T, Stein DJ, Ipser I. A systematic review of network meta-analyses for pharmacological treatment of common mental disorders. Evid Based Mental Health 2018; 21(1): 7-11.

[4] Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ. Comparative efficacy and acceptability of pharmacological treatments for posttraumatic stress disorder in adults: a network meta-analysis. Psychological Medicine https://doi.org/10.1017/S003329171700349X

[5] Williams T, McCaul M, Schwarzer G, Cipriani A, Stein D, Ipser J. Under review in the Journal of Psychological Medicine.

SIGNATURE: DATE: 25/02/2019



STUDENT NAME: Taryn Amos (Williams) STUDENT NUMBER: AMSTAR001

ABSTRACT

Background

Social anxiety disorder (SAD) and posttraumatic stress disorder (PTSD) are prevalent, disabling and highly comorbid disorders. SAD is the most prevalent of the anxiety disorders, and PTSD is the central disorder in the DSM-5 section on trauma- and stressor-related disorders. Given the growing need to consider the totality of evidence for pharmacological treatment for SAD, the publication of systematic reviews and of novel meta-analytic approaches have become of interest for the use of medication in their treatment and decision making. This dissertation has three objectives 1) To update Cochrane reviews of pharmacotherapy for SAD and PTSD, 2) To conduct a qualitative systematic review of network meta-analyses for pharmacological treatment of common mental disorders, 3) To conduct network meta-analyses for SAD and for PTSD and to compare findings to standard pairwise meta-analytic methods.

Methods

To obtain eligible trials to answer each aim, trials were identified through a systematic search of a variety of electronic databases: the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR-Studies and CCMDCTR-References), MEDLINE, EMBASE, PsycINFO, Google Scholar, Scopus, PubMed Central, the International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch), clinicaltrials.gov, the National PTSD Center Pilots database and the metaRegister module [mRCT] of the Controlled Trials database, specific to each aim.

RCTs of pharmacological treatments comparing active drug versus active drug or active drug versus placebo for SAD and PTSD were considered for inclusion in the respective chapters,

and in answering the aims, with the inclusion of add on trials in the SAD and PTSD NMA reviews. Adult participants (18-65 years) diagnosed with SAD and PTSD according to the Diagnostic Statistical Manual for Mental Disorders (DSM, all versions) were included in the individual reviews (i.e. for chapter two, three, five and six). In chapter three adolescents and adults with common mental disorders (depression, GAD, PD, OCD, PTSD, SAD and specific phobia) diagnosed according to the DSM or the International Classification of Diseases ((ICD-10) were included.

The primary and secondary outcomes across aims and reviews include clinical response rates (i.e. the Clinical Global Impressions Improvement scale (CGI-I) or similar) and acceptability (i.e. dropouts due to side effects); and the investigation of symptom severity for SAD with the Liebowitz Social Anxiety Scale (LSAS) and PTSD with the Clinician Administered PTSD Scale (CAPS). In addition, the proportion of dropouts due to any cause were also assessed.

The quality of each trial was assessed according to the Cochrane Risk of Bias Tool. GRADE was also used to grade the quality of evidence for the Cochrane reviews and NMAs and the International Society for Pharmacoeconomics and Outcomes Research checklist of good research practices for indirect treatment-comparison in assessing studies for aim two.

For aim one, the extracted data for the SAD and PTSD Cochrane reviews was exported into RevMan 5.3.5. Software, which was used to conduct a meta-analysis for SAD and PTSD separately. Pre-planned subgroup and sensitivity analyses were conducted for each review, as well as the generation of funnel plots to assess publication bias with the Eggers' regression test using the R statistical computing platform for the SAD review. In answering aim three, standard pairwise meta-analyses were performed using a random effects model and Frequentist

method in RStudio version 3.5 for the SAD NMA review, and Bayesian method using Markov chain Monte Carlo methods in WinBUGS version 1.4.3 for the PTSD NMA. The P-score, an analogue to the surface under the cumulative ranking curves (SUCRA), was used to rank the treatments on a continuous scale for all pairwise comparisons for the SAD NMA, and for the PTSD review, ranking probabilities using the surface under the cumulative ranking curve (SUCRA) and mean ranks were assessed.

Results

For aim one, the evidence for the standard pairwise Cochrane reviews of SAD and PTSD were most convincing for the treatment efficacy of SSRIs (number of studies (k) = 24, risk ratio (RR) 1.65; 95% confidence interval (CI) 1.48 to 1.85, N = 4984 and k = 8, RR 1.61; 95% CI 1.41 to 1.84, N = 1078, respectively), and was based on very low quality evidence. Evidence of a benefit for the SSRIs was also observed for the reduction of social anxiety symptoms on the LSAS (k = 14, mean difference (MD) −10.14 points, 95% CI −14.05 to −6.22, N = 1990) and posttraumatic symptoms on the CAPS (k = 14, MD −4.69 points, 95% CI −7.18 to −2.20, N = 2709). Other medications such as SSRIs, the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine, monoamine oxidase inhibitors (MAOIs), reversible monoamine oxidase inhibitors (RIMAs), benzodiazepines, the antipsychotic olanzapine, and the noradrenergic and specific serotonergic antidepressant (NaSSA) atomoxetine were also effective in reducing SAD symptoms, with evidence of a treatment response for anticonvulsants with gamma-amino butyric acid (GABA) analogues, the MAOIs, the RIMAs and the benzodiazepines. For the treatment of PTSD, the alpha-blocker prazosin and antipsychotics reduced symptom severity, and the alpha-blocker prazosin and the tricyclic antidepressant amitriptyline improved number of responders. Overall, SSRIs were less well tolerated than placebo in both reviews (SAD Review: k = 5131, RR 2.59; 95% CI 1.97 to 3.39, N = 5131; PTSD Review: (k = 15, RR 1.41;

95% CI 1.07 to 1.87, N = 2493), but there were low absolute rates of withdrawal compared to placebo (16% and 14%, respectively). There were no significant differences in dropouts due to any cause in both reviews for the SSRI intervention arms (SAD Review: k = 26, RR 1.01; 95% CI 0.90 to 1.14, N = 5208; ; PTSD Review: k = 21, RR 1.13; 95% CI 0.93 to 1.38, N = 3206).

Twenty NMAs (i.e. investigating depressive disorder, GAD, SAD, PTSD and OCD) were found in answering aim three, and antidepressants were found to be the most efficacious and tolerable agents for these disorders based on rankings (45% of NMAs) or statistical significance (55% of NMAs). The quality of the reporting of each NMA was high. Seventy percent of the NMAs included a network diagram and 75% of the included NMAs assessed consistency, made use of a random effects model, provided information on the model used to fit the data and adjusted for covariates. The review also revealed that few NMAs reported rankings of treatments.

The SAD and PTSD NMA provided similar findings to the Cochrane reviews, discussed in aim one. For aim three (the SAD NMA), the SSRI paroxetine was significantly more effective than placebo in reducing the number of responders (odds ratio (OR) 2.64; CI 1.97 to 3.54) and anxiety symptoms (mean difference (MD) -15.89; CI -29.94 to -1.84) yet performed worse in comparison to placebo for dropouts due to adverse events. Most of the medications (i.e.12 out of 19 comparisons) reported a decrease in dropout rates relative to placebo, but no statistically significant difference was found. There was also evidence that venlafaxine is efficacious in treating SAD symptoms. According to the rankings of individual treatments olanzapine performed better than the rest of the treatments in terms of treatment efficacy and buspirone for dropouts due to any cause. Bromazepam performed well in treating the number of responders due to adverse events. Similarly, for the PTSD NMA, paroxetine was also effective

in the treatment of PTSD symptoms (MD -15.89; CI -29.94 to -1.84). Evidence was also observed for phenelzine, desipramine and risperidone for the treatment of PTSD symptoms. Mirtazapine yielded a relatively high rank for efficacy, but the respective value for acceptability was not among the best treatments. Most evidence from both NMAs was associated with low to very low-quality evidence.

Conclusion

Different meta-analytic approaches are useful in presenting, synthesising, and reporting data. The evidence discussed here suggest that SSRIs are effective in the treatment and reduction of SAD and PTSD symptoms, even though the tolerability of SSRIs was lower than placebo for each disorder. It is noteworthy that similar estimates were found across the different approaches to synthesising data and across the different patient groups (i.e. SAD and PTSD). In addition, the NMAs found in this dissertation show high quality of reporting and that study limitations do not impact on the network estimate. The quality of reporting of individual RCTs included across the review however remain low, and so additional research is needed in this area.

Keywords: common metal disorders, medication, network meta-analyses, NMAs, pharmacotherapy, posttraumatic stress disorder, PTSD, randomised controlled trials, randomized controlled trials, RCTs, SAD, social anxiety disorder, treatment.

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I would like to acknowledge and thank the following people: Dr. Jonathan Ipser, Professor Dan Stein and Professor Andrea Cipriani for their mentorship and guidance in the completion of my thesis. I am grateful for the knowledge and skills that they have taught me. Thank you, Professor Dan Stein, for giving me the opportunity to study (i.e. with a Departmental Scholarship) and supporting me in this regard, I am forever grateful. I came into a field that was unknown, however you always provided a way for me to learn and develop. Thank you, Dr. Jonathan Ipser, for availing yourself every Thursday of your week to guide and support me, but also to keep me on track, I have learnt so much from you. You have never given up on me. Although Professor Andrea Cipriani is miles away thank you for availing yourself on email and skype to review my work and guide me. You too have provided new ways of thinking and knowing which I will use throughout my career.

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I would like to thank my colleagues Dr. Nicole Phillips and Bulelwa Mtukushe for their continuous support and faith in my completion of my thesis. You have been there every step of the way throughout this process and I cannot thank you enough for your friendship.

To my family and friends, thank you for your tolerance, words of encouragement, motivation and continuous support, especially to my husband Andre Williams, and son Eli Williams. Love you all. Thank you also to Phillip Smith for your belief and support.

I would also like to thank Dr. Shazly Savahl for his support. You have inspired me to pursue my goals and strive to be better.

More importantly, I would like to thank God for seeing me through my studies and giving me the opportunity to grow within the field of psychiatry.

Taryn Amos (Williams)

Cape Town

February 2019

CHAPTER 1.

INTRODUCTION;

Social Anxiety Disorder and Posttraumatic Stress Disorder: Conceptualisation and Treatment.

In this chapter I provide a rationale for the dissertation. I review the nature and structure of SAD and PTSD, the prevalence and comorbidity of SAD and PTSD, and available treatment. Thereafter I provide information on meta-analytic approaches used to inform clinical decisions about the treatment of SAD and PTSD, and in particular standard pairwise meta-analyses and network meta-analyses.

The nature and structure of SAD and PTSD

Anxiety disorders were classified in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV-TR) into various categories, based on symptom presentation, including: acute stress disorder, agoraphobia, generalised anxiety disorder (GAD), panic disorders (PD), PTSD, OCD, SAD, and specific phobia. Patients diagnosed with SAD demonstrate persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. The person recognises that the fear is excessive or unreasonable and avoids or endures the situations with intense anxiety and distress; however, symptoms often lead to the disruption of daily functioning. In individuals under the age of 18 years, symptoms must occur for at least six months (Ipser, Kariuki & Stein, 2008; APA, 2004; APA, 2000). SAD is mediated by specific neurocircuitry, with serotonergic and dopaminergic systems particularly relevant (Frick, et al, 2015; Stein, 2002). Imaging studies emphasise the role of the amygdala and other

limbic structures, as well as neural networks involved in the dysfunction of SAD (Fouche, van Der Wee & Roelofs et al., 2013).

Brain imaging studies show that when individuals with SAD are exposed to emotional versus neutral stimuli the bilateral amygdala, anterior cingulate, and globus pallidus is activated. Increased activation also occurs in temporoparietal regions, including the posterior superior temporal sulcus (pSTS) and supramarginal gyrus (SMG)/temporo-parietal junction (TPJ). Functional imaging studies have found altered activity in the insula in SAD. When treated with pharmacotherapy, SAD patients have decreased insula activation at rest (Stein, 2015). Similarly, and with regards to the neurochemistry of SAD, multiple neurotransmitter and neuroendocrine systems have been investigated in SAD (Stein, 2015).

More recently, the fifth edition of the Diagnostic and Statistical Manual (DSM-5) has removed OCD, PTSD and acute stress disorder from the category of anxiety disorders, with the inclusion of panic attacks, separation anxiety disorder and selective mutism as manifestations of SAD (American Psychiatric Association, 2013). Changes with the DSM-V in criteria for agoraphobia, specific phobia, and SAD (social phobia) include deletion of the requirement that individuals over age 18 years recognise that their anxiety is excessive or unreasonable. This change is based on evidence that individuals with such disorders often overestimate the danger in "phobic" situations and that older individuals often misattribute "phobic" fears to aging. Instead, the anxiety must be out of proportion to the actual danger or threat in the situation, after taking cultural contextual factors into account. In addition, the six-month duration, which was limited to individuals under age 18 in DSM-IV, is now extended to all ages. This change is intended to minimise overdiagnosis of transient fears (American Psychiatric Association, 2013).

PTSD is recognised in the DSM-IV (APA, 1994) as a pathological response to severe traumas. To fulfil the DSM-IV criteria for PTSD, an individual must have been exposed to a traumatic event; have at least one re-experiencing, three avoidance, and two hyperarousal phenomena; have had the symptoms for at least one month; and the symptoms must cause clinically important distress or reduced day-to-day functioning. PTSD is labelled as acute for the first three months and chronic if it lasts beyond three months (Bisson, 2010).

PTSD is further characterised by different symptom clusters, including intrusive/re-experiencing, avoidant/numbing, and hyperarousal symptoms (according to DSM-IV criteria), and it is possible that each is mediated by different neurobiological mechanisms (Charney, Deutch & Krystal et al., 1993), which may be normalised by specific pharmacological interventions. There is growing evidence for rather specific dysregulations of neurotransmitter systems (including the serotonin, noradrenaline, and dopamine systems) and neuroendocrine systems (including the hypothalamus-pituitary-adrenal axis), as well as for structural and functional neuroanatomical abnormalities in PTSD (Bremner & Vermetten, 2004; Hull, 2002; Connor & Davidson, 1998; Canive, Lewine & Orrison et al., 1997; Yehuda & McFarlane, 1995; Charney, Deutch & Krystal, 1993).

The evidence suggests net upregulation of the noradrenergic system and its responsivity to stress in individuals with PTSD. The noradrenergic system is a central, modifiable link in a network of interconnected stress–response systems, which also includes the amygdala and its modulation by medial prefrontal cortex. Bidirectional signalling occurs between the noradrenaline and corticotropin-releasing factor (CRF) in coordinating these interconnected systems (Hendrickson & Raskind, 2016). The 2A subtype of serotonin receptors (5-HT2A receptor) are upregulated by a broad variety of stressors. Upregulation of 5-HT2A receptors

during stressful events forms associations that tune the brain to environmental cues that signal danger. In life-threatening situations these receptors may activate this system and contribute to the symptoms associated with PTSD (Murnane, 2019). As for the dopamine system, this system plays an important role in many neurological processes. Dysregulated dopamine is associated with various PTSD symptoms and influence the ability to deal with stress stimuli in subjects who have been exposed to traumatic events. The dopamine system is usually dysregulated in PTSD patients to counteract or worsen the crisis response to the stressful stimuli (Kelmendi & Adams et al., 2016). If worsened, this can impact on working memory and attention impairments over time (Vicario & Felmingham, 2018). In addition, dysregulation of the HPA axis is associated with stress-related pathologies like PTSD. PTSD increases sensitivity of glucocorticoid receptors (GRs) and moderates enhanced negative feedback which decreases cortisol levels. This endocrine dysregulation is mediated by lasting neurobiological alterations caused by extreme or repeated stress exposure, where trauma exposure is directly linked to the disease development (Dirven & Homberg et al., 2017). It is also noteworthy that given the wide action of effective drugs little is known however around the mechanisms of action (Steckler & Risbrough, 2012).

The fifth edition of the Diagnostic and Statistical Manual (DSM-5) has reclassified PTSD from an anxiety disorder to a 'trauma and stressor-related disorder'. This shift is reflected in the recognition of the etiology of PTSD over its phenomenological nature emphasised in the DSM-III and DSM-IV (Friedman, Resick & Bryant et al., 2011). To fulfil the diagnostic criteria for PTSD, an individual must have been exposed to a traumatic event; have at least one intrusion, one avoidance, two negative alterations in cognitions and mood, and two alterations in arousal and reactivity; have had the symptoms for more than one month; symptoms must cause distress or functional impairment; disturbances may not be due to medication, substance use, or other

illness; and the individual may experience high levels of depersonalisation or derealisation (American Psychiatric Association, 2013).

Prevalence of SAD and PTSD

Anxiety and related disorders are the most prevalent of all psychiatric disorders, and contribute a major portion of the global burden of disease (Kessler, Sonnega & Bromet et al., 1995; Kessler, McGonagle & Zhao et al., 1994), with studies reporting respective lifetime prevalence rates of 7.7%, 4.4% and 6.9% in developed countries (e.g. Belgium, France, Germany, Italy, the Netherlands, Spain, and the United States) compared to 2.6%, 1.6% and 5.5% in developing countries (e.g. Brazil, Colombia, India, Lebanon, Mexico, the Peoples' Republic of China, and Romania) (Kessler, Ormel & Petukhova et al., 2011). Numerous studies have investigated the prevalence of PTSD and SAD in individuals exposed to traumatic events. Recent evidence suggests an association between posttraumatic stress symptoms (PTSS) and SAD, in both adult veterans and adolescent samples (Gren-Landell, Aho & Carlsson et al., 2013; Carleton, Peluso & Collimore et al., 2011; Zayfert, DeViva & Hofmann, 2005). Common elements of both these disorders include a fear of negative evaluation, anxiety sensitivity, and depression (Carleton, Peluso & Collimore et al., 2011). Kashdan, Morina and Priebe (2009) further suggest that these associations are mediated by experimental avoidance and low quality of life. By examining the associations of PTSD, SAD and major depressive disorder (MDD) with distress and quality of life in 174 Albanian civilian survivors of the Kosovo War, being a refugee was associated with a higher likelihood of having SAD and MDD. There was also evidence to support that war survivors without SAD had low experimental avoidance and elevated levels of quality of life whereas people with either SAD or excessive reliance on experiential avoidance reported low quality of life.

There is evidence that social anxiety disorder (SAD) and post-traumatic stress disorder (PTSD) are associated with substantial reductions in quality of life, a high co-morbidity of psychiatric and medical disorders, marked functional impairment (Stein, 2008; Chakrabarti, 1993), and high economic costs (Schnurr, 2009; Erbes, 2007; Solomon & Davidson, 1997). The comorbidity of these disorders is consistent with evidence for the similarity of their underlying neurocircuitry (Charney, Deutch & Krystal et al., 1993, though see Etkin & Wager, 2007). Fortunately, there have been important advances in our understanding of the psychobiology of these conditions (Charney 2004; Furmark, Tillfors & Marteinsdottir et al., 2002) and numerous clinical trials of medication treatments have been undertaken in recent years (e.g. van der Kolk 2007; Brady et al., 2004).

Pharmacotherapy for SAD and PTSD

A range of medications have been studied in SAD and PTSD. Early reports noted the potential value of irreversible monoamine oxidase inhibitors (MAOIs) for the treatment of SAD. Subsequent work addressed the role of reversible inhibitors of monoamine oxidase A (RIMAs) (Versiani, Nardi & Mundim et al., 1992) and high potency benzodiazepines (Davidson, Ford & Smith et al., 1991). Monoamine oxidase inhibitors (MAOIs) increase biogenic amine neurotransmitter levels by inhibiting their degradation, facilitating presynaptic reuptake of these chemicals through specific transporter molecules, and inhibiting their deamination in mitochondria by the enzyme MAO. This inhibition may be either reversible or irreversible (Stahl, 2008). The efficacy of benzodiazepines in the treatment of many anxiety disorders strongly supports the role of gamma-aminobutyric acid (GABA) in these conditions. In low doses, benzodiazepines act as anxiolytic agents and may be especially useful in providing rapid control of anxiety symptoms (Stahl, 2008).

Other agents receiving attention in randomised controlled trials for the treatment of SAD include buspirone (van Vliet, den Boer & Westenberg, 1992), beta-blockers (Liebowitz, Schneier & Campeas et al., 1992), the new generation antipsychotics (Vaishnavi, Alamy & Zhang et al., 2007; Barnett, Kramer & Casat et al., 2002), the highly-selective noradrenaline reuptake inhibitor atomoxetine (Ravindran, Kim & Letamendi et al., 2009), certain anticonvulsants (Pande, 2004; Pande, Davidson & Jefferson et al., 1999), and the NK-1 receptor antagonist (Tauscher, Kielbasa & Iyengar et al., 2010). Norepinephrine and serotonin reuptake inhibitors (SNRIs) are potent inhibitors of the reuptake of both catecholamines but weak inhibitors of dopamine reuptake. A tetracyclic antidepressant, mirtazapine, has potent action on central adrenergic receptors, leading to a net increase in noradrenaline and serotonin, without the unwanted activation of cholinergic receptors. Nefazodone is an agent with both pre- and postsynaptic serotonin reuptake inhibition, but concerns about hepatotoxicity limit its use in clinical practice (Stahl, 2008; Van Ameringen, Mancini & Oakman et al., 2007; Muehlbacher, Nickel & Nickel et al., 2005). The anticonvulsants, gabapentin and pregabalin, reduce the release of norepinephrine, glutamate and substance P from the brain and spinal cord and may have a benefit in anxiety reduction. Similarly, blockade of neurokinin -1 receptors may have anxiolytic effects in SAD (Tauscher, 2010; Pande, 2004; Pande, 1999). Moreover, both pregabalin and gabapentin share a common site of action on the alpha 2 delta subunit of a voltage dependent calcium channel thought to modulate glutamate neurotransmission (Uchitel, 2010).

More recent studies have focused on the selective serotonin reuptake inhibitors (SSRIs) and support the perception of the SSRIs as first-line agents for the treatment of anxiety and affective disorders (Ipser, 2012; Stein, Ipser & Balkom, 2004). The inhibition of serotonin reuptake increases the bio-availability of this transmitter in synapses in the brain, and the corresponding

occupancy of serotonin receptors. Clinical efficacy for SSRIs for SAD has been observed at 70-80% receptor occupancy (Stahl, 2008). Other newer antidepressants (Van Ameringen, Mancini & Oakman et al., 2007; Muehlbacher, Nickel & Nickel et al., 2005; van der Linden, Stein & van Balkom, 2000) have also received attention.

Early reports of the pharmacotherapy of PTSD focused on the tricyclic antidepressants (TCAs) and the irreversible monoamine oxidase inhibitors (MAOIs) (Davidson, 1989; Frank, Kosten & Giller et al., 1988; Shestatzky, Greenberg & Lerer, 1988; Kosten, Frank & Dan et al., 1991) in the treatment of PTSD. A randomised control trial revealed that male veterans treated with phenelzine and imipramine for five to eight weeks improved significantly, however this improvement was greater for those treated with phenelzine (Kosten, Frank & Dan et al., 1991). Many of the recent RCTs have focused on selective serotonin reuptake inhibitors (SSRIs) (Ipser, 2012; Friedman, Marmar & Baker et al., 2007; Tucker, Trautman & Wyatt et al., 2007; Brady, Sonne & Anton et al., 2004; Tucker, Potter-Kimball & Wyatt et al., 2003), with a few trials conducted for the serotonin antagonists and reuptake inhibitors (SARIs) as well (Hidalgo, 1999; Hertzberg, Feldman & Beckham et al., 1998). Administration of citalopram, sertraline, or placebo for ten weeks in outpatients who experienced an exposure to trauma (e.g. sexual abuse, rape, physical abuse, assault, witness violent death, tornado, combat, motor vehicle accident, terrorist bomb, nuclear bomb exposure, and life threatening events) resulted in significant reductions in systolic and diastolic blood pressures and improvement in avoidance/numbing symptoms (Tucker, Potter-Kimball & Wyatt et al., 2003). Similarly, paroxetine-treated patients have demonstrated significantly greater improvement on primary outcome measures compared to placebo treated patients resulting in statistically significant improvement on all three PTSD symptom clusters (re-experiencing, avoidance/numbing, and hyperarousal), social and occupational impairment, and comorbid depression (Marshall, 2011).

Other agents that have been assessed for the treatment of PTSD include antidepressants (Davis, Ambrose & English et al., 2001; Connor, Davidson & Weisler et al., 1999; Baker, 1995), beta-blockers (Famularo, Kinscherff & Fenton, 1988; Kolb, Burris & Griffiths, 1984), buspirone (Duffy & Malloy, 1994; Fichtner, Arora & O'Connor et al., 1994), clonidine (Harmon & Riggs, 1996; Kinzie & Leung, 1989; Kolb, Burris & Griffiths, 1984) and guanfacine (Horrigan, 1996), cyproheptadine (Gupta, Popli & Bathurst et al., 1998; Brophy, 1991), d-cycloserine (Heresco-Levy, Kremer & Javitt et al., 2002), inositol (Kaplan, Amir & Swartz et al., 1996), mood-stabilizers (Hertzberg, Butterfield & Feldman et al., 1999; Szymanski & Olympia, 1991; van der Kolk, 1987); typical (Dillard, Bendfeldt & Jernigan, 1993; Bleich, Siegel & Garb et al., 1986) and atypical neuroleptics (Hamner, Faldowski & Ulmer et al., 2003; Butterfield, Becker & Connor et al., 2001); and opioids (Glover, 1993).

New meta-analytic approaches

The Cochrane Collaboration is an international collaboration aimed at rigorously synthesising the available data using standardised methods of meta-analysis (Higgins, 2011). Although the Cochrane Collaboration prescribes rigorous methodological guidelines, there is some question regarding the extent to which these reviews impact clinical practice. Cochrane reviews are restricted to head-to-head comparisons of interventions (including placebo) that have been directly compared in clinical trials, while clinicians may be more interested in the relative efficacy and side effect profile of different agents in treating a disorder.

A different methodological framework that allows one to compare not only outcomes for interventions that have been contrasted within the same trial (e.g. a standard or pair-wise meta-analysis of paroxetine versus a control intervention), but also the relative efficacy of all the interventions of interest (Mill, Ioannidis & Thorlund et al., 2012) would therefore be useful.

One such approach that has become increasingly popular is known as multiple treatments meta-analysis (MTM). MTM allows one to use both direct evidence (head to head) and indirect evidence (via a third common comparator) from all treatment arms included in a network of randomised controlled trials (RCTs). By making greater use of the available evidence-base, MTM's facilitates determination of predictors of response to pharmacotherapy in these disorders, using methods such as meta-regression. Currently research on the use of MTM for establishing the relative efficacy of medication agents in psychiatry has been limited to papers on major depression and acute mania, which my co-supervisor has authored (Cipriani, Furukawa & Salanti et al., 2009; Cipriani, Barbui & Salanti et al., 2011). Thus, this doctoral research is novel insofar as it extends such methods to SAD and PTSD. This dissertation compares the relative merits of the different approaches employed in synthesising data from clinical trials. In this way, insight into the extent to which these approaches can inform clinical decision-making based on the totality of evidence for pharmacological treatment for SAD, as well as the contributions they may make towards informing future medical research and public policy can be established.

RESEARCH AIMS AND OBJECTIVES

This dissertation explores the utility of a standard pairwise approach and the multiple treatment meta-analytic approach in comparing the efficacy of all medications tested within pharmacotherapy RCTs for SAD and PTSD separately, and to compare the efficacy of agents across these frequently comorbid disorders. More specifically, the following objectives were employed:

1. To update the Cochrane reviews of pharmacotherapy for SAD and PTSD,
2. To conduct a qualitative systematic review on network meta-analyses for pharmacological treatment of common mental disorders, and
3. To conduct a network meta-analysis for SAD and PTSD and compare findings across methods.

In the next chapter I utilise the Cochrane standard pairwise approach in synthesising data for SAD.

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CHAPTER 2.

Pharmacotherapy for social anxiety disorder (SAD).

Chapter two includes a comprehensive search, literature review and methodology specifically looking at SAD and the medication for its treatment. Cochrane risk of bias and GRADE was used to assess the quality of each trial by medication class. Data for clinical response, symptom severity and acceptability (i.e. dropouts due to side effects or dropouts due to any cause) was analysed using a standard pairwise approach, and both subgroup and sensitivity analyses were conducted to consider confounding variables that may have impacted on the overall heterogeneity and effect estimates of outcomes. Funnel plots were also generated to assess publication bias. Maintenance trials were also analysed however for the discussion of the thesis I only report data for acute outcomes. Secondary outcomes for depression, disability and relapse were measured although I do not report this in the discussion of the dissertation, keeping in mind the NMAs and to be consistent in my reporting. Because Cochrane methods are one of the robust methods in synthesising information from trials in order to make clinical decisions, it is important to start here before utilising the new network meta-analytic approach which it an extension of such an approach. This then applies to chapter three as well.

BACKGROUND

In the previous chapter I introduced the concept of SAD and PTSD. Here I will discuss in detail information relating to SAD, the existing trials, and the need for additional trials.

Description of the condition

Although the symptoms of social anxiety disorder (SAD) have long been recognised (Marks 1966), the disorder only appeared within the official psychiatric nomenclature in 1980 (DSM-

III 1980). Diagnostic criteria for SAD in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) encouraged research on its epidemiology, psychobiology, and treatment. Subsequent epidemiological research determined that the disorder is highly prevalent in a wide range of settings, that it is characterised by significant chronicity and comorbidity, and that it is associated with marked functional impairment, including academic, occupational, marital, and social dysfunction (Stein 2008). Such data allay skepticism about whether SAD is really a medical disorder and support the importance of pharmacotherapy for its treatment.

SAD usually begins in childhood or adolescence, with studies reporting lifetime prevalence rates of between 3% and 16% (Kessler 1994; Kessler 2005). Some European studies describe a one-year prevalence of 2% to 5% (Wancata 2009). Typically, individuals with SAD experience severe, intense fear of drawing attention to themselves in unfamiliar social situations or negative evaluation in situations that are potentially embarrassing or humiliating. This in turn results in avoiding the phobic situation or tolerating it with extreme distress. The affected individual recognises this fear as unreasonable, excessive, and more than mere shyness. These symptoms may take the form of a situationally predisposed panic attack and always impair functioning on several levels (DSM-IV 2004).

There is a growing body of work demonstrating that SAD is mediated by specific neurocircuitry, with serotonergic and dopaminergic systems particularly relevant (Stein 2002d), providing a rationale for the use of pharmacotherapy. The glutamatergic and noradrenergic systems, as well as substance P, may also be implicated in the neurological basis of SAD, suggesting a role for agents such as gabapentin, pregabalin, and neurokinin-1 receptor antagonists (Pande 1999; Pande 2004, Tauscher 2010). This is confirmed by various brain and

functional imaging studies for the treatment of SAD in comparison to controls. Brain imaging studies show that when individuals with SAD are exposed to emotional versus neutral stimuli the bilateral amygdala, anterior cingulate, and globus pallidus is activated. Increased activation also occurs in temporoparietal regions, including the posterior superior temporal sulcus (pSTS) and supramarginal gyrus (SMG)/temporo-parietal junction (TPJ). Functional imaging studies have found altered activity in the insula in SAD. When treated with pharmacotherapy, SAD patients have decreased insula activation at rest (Stein, 2015). Similarly, and with regards to the neurochemistry of SAD, multiple neurotransmitter and neuroendocrine systems have been investigated in SAD (Stein, 2015). It is also noteworthy that given the wide action of effective drugs little is known however around the mechanisms of action (Steckler & Risbrough, 2012).

The effectiveness of cognitive-behavioural therapy (CBT) in managing SAD has also received increasing empirical support (Dorrepaal 2014; Fedoroff 2001; Gould 1997), and current expert consensus is that both pharmacotherapy and psychotherapy have a role in the management of this disorder (Ballenger 1998; Bandelow 2002; Bandelow 2012; Bandelow 2015). Interestingly, both CBT and pharmacotherapy can normalise functional neuroanatomical abnormalities in SAD (Furmark 2002). Nevertheless, this review focuses exclusively on pharmacotherapy interventions.

Description of the intervention

Research has evaluated a range of medications for SAD. Early reports noted the potential value of irreversible monoamine oxidase inhibitors (MAOIs) (Fahlen 1995; Van Vliet 1992), beta blockers (Gorman 1987; Turner 1994), reversible inhibitors of monoamine oxidase A (RIMAs) (Tyrer 1973; Versiani 1992), and high potency benzodiazepines (Davidson 1991). More recent studies have focused on the selective serotonin reuptake inhibitors (SSRIs) (Van der Linden

2000), plus other newer agents such as GW876008 (NCT00397722). Randomised controlled trials (RCTs) have also assessed buspirone (Davidson 1993), the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine (Muehlbacher 2005), the new generation antipsychotic olanzapine (Barnett 2002), the highly selective noradrenaline reuptake inhibitor (NARI) atomoxetine (Ravindran 2009), the serotonin antagonist and reuptake inhibitor (SARI) nefazodone (Van Ameringen 2007), the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (Rickels 2004), and certain anticonvulsants/gamma-amino butyric acids (GABAs) (Pande 1999; Pande 2004).

How the intervention might work

Although the pathophysiology of SAD is incompletely understood, various mono-aminergic systems, such as the serotonergic, dopaminergic, and noradrenergic systems, play a role in mediating SAD symptoms. Strongly serotonergic drugs such as SSRIs have specific activity in the inhibition of serotonin reuptake, with minimal direct effects on norepinephrine and dopamine reuptake. This inhibition of reuptake increases the bio-available concentration of serotonin, which then binds to and activates various receptors. Clinical efficacy is observed with 70% to 80% occupancy of serotonin transporters (Stahl 2008). SNRIs are potent inhibitors of the reuptake of catecholamines but weak inhibitors of dopamine reuptake (Rickels 2004; Stahl 2008). The putative effects of the selective NARI atomoxetine on the noradrenergic neurotransmitter system in adults and children with attention deficit/hyperactivity disorder (ADHD), reported by Chamberlain 2007 and Michelson 2001, suggest potential use for anxiety and mood disorders (Ravindran 2009). There is evidence to suggest that some serotonin-dopamine antagonists (SDAs) such as quetiapine and olanzapine may possess anxiolytic properties, and they may potentially have a role in treatment-resistant SAD (Barnett 2002;

Vaishnavi 2007). Nefazodone is an agent with both pre- and postsynaptic serotonin reuptake inhibition, but concerns about hepatotoxicity limit its use in clinical practice (Van Ameringen 2007).

MAOIs increase biogenic amine neurotransmitter levels by inhibiting their degradation, facilitating presynaptic reuptake of these chemicals through specific transporter molecules and inhibiting their de-amination in mitochondria by the enzyme MAO. This inhibition may be either reversible or irreversible (Stahl 2008). RIMAs are generally safer and better tolerated than MAOIs and have shown efficacy in treating SAD (Versiani 1992). The drug functions by selectively binding to a specific isoenzyme of monoamine oxidase (Davidson 2006).

Beta-adrenoreceptor antagonists block catecholamines released in the stress response, thus potentially reducing the physiological symptoms associated with SAD. This may then enable the individual to function with fewer objective signs of anxiety (Liebowitz 1992; Stahl 2008; Turner 1994). The NaSSA mirtazapine has potent action on central adrenergic receptors, leading to a net increase in noradrenaline and serotonin, without the unwanted activation of cholinergic receptors (Muehlbacher 2005).

The efficacy of benzodiazepines in the treatment of many anxiety disorders is consistent with the hypothesised role of GABA in these conditions. In low doses, benzodiazepines act as anxiolytic agents and may be especially useful in providing rapid control of anxiety symptoms (Gorman 2003; Pecknold 1997; Stahl 2008). Repeated buspirone treatment may desensitise inhibitory 5-HT1A receptors and this, together with its modest postsynaptic 5-HT1A receptor agonist actions, could lead to an overall increase in 5-HT neurotransmission as well (Cowen 1997).

The anticonvulsant pregabalin reduces the release of norepinephrine, glutamate, and substance P from the brain and spinal cord and may have a benefit in anxiety reduction (Pande 2004). Gabapentin may be similarly effective for these conditions (Stephen 2013).

Newer medications such as the GW876008 have corticotropin-releasing factors (CRFs) that target behavioural, autonomic, and neurochemical responses linked to a variety of anxiety and stress-related disorders (Hubbard 2011). GW876008 also plays a role in the activation of the hypothalamus in patients with anxiety (Hubbard 2011).

Why it is important to do this review

A systematic review of pharmacotherapy studies is useful in tackling several questions for the field. First, is pharmacotherapy in fact an effective form of treatment in SAD? Given skepticism about SAD diagnosis and the importance of psychological models and psychotherapy studies for the disorder, the role of pharmacotherapy remains moot for some. For those who accept the role of pharmacotherapy, questions remain about the appropriate dose and duration of treatments. Although in the late 1990s expert consensus suggested continuing pharmacotherapy for at least a year, there was arguably relatively little data to support this conclusion at the time (Ballenger 1998).

Second, are medication classes more effective in treating symptoms, more tolerable to the patient in terms of adverse events, or both? The use of antidepressants (e.g. SSRIs) for SAD has raised the question of how these agents compare with older medications (e.g. MAOIs). Current expert consensus has suggested that in view of their efficacy and tolerability, SSRIs should be considered as first-line medications for the treatment of SAD, while beta-blockers have a role in the management of performance anxiety (Ballenger 1998; Bandelow 2002;

Bandelow 2012; Bandelow 2015); it is important to determine whether such recommendations are still supported by evidence from RCTs.

Third, can a systematic review of RCTs provide information about the most important variables affecting pharmacotherapy response? Methodological factors such as the number of participating centers or the duration of the trial may affect treatment outcomes (Stein 2002c). Some authors have also suggested that clinical factors such as the nature of the SAD sub-type present (e.g. generalised versus non-generalised), and the severity of baseline symptoms, may play a role (Stein 2002c). The body of evidence from RCTs may provide more conclusive information about the predictors of pharmacotherapy response in this disorder.

Indeed, a series of reviews of the pharmacotherapy of SAD has been published (Blanco 2002; Blanco 2013; Curtiss 2017; De Menezes 2011). These reviews have been useful in summarising the existing research, pointing to methodological flaws, and outlining areas for future research. Several systematic reviews also exist (Blanco 2003; Davis 2014; Fedoroff 2001; Gould 1997; Van der Linden 2000), and these have provided useful lessons for both clinicians and researchers. Further reviews in this area, from Cochrane or elsewhere, need to adhere to guidelines for the systematic identification of trials, investigation of sources of heterogeneity, measurement of methodological quality, and estimation of the effects of intervention (Moher 1999; Mulrow 1997).

Therefore, in this systematic review I update RCTs of the pharmacotherapy of SAD, following Cochrane guidelines and software (Higgins 2011; RevMan 2014).

OBJECTIVES

To assess the effects of pharmacotherapy for social anxiety disorder in adults and identify which factors (methodological or clinical) predict response to treatment.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs, irrespective of publication status, methodological differences, or language were considered for inclusion in the review. Trials were only included comparing multiple forms of medication if one of the comparison groups was a placebo group. Because publication is not necessarily related to study quality and indeed may imply certain biases (Dickersin 1992; Easterbrook 1991; Scherer 1994), unpublished reports, abstracts, and brief and preliminary reports were also considered. Cluster-randomised controlled trials, cross-over trials and multiple treatment trials were also included in the analysis.

Types of participants

Participant characteristics

Adult participants diagnosed with SAD irrespective of diagnostic criteria and measure, duration and severity of SAD symptoms, age, and sex were included in the review. Descriptors were however tabulated in order to address the question of their possible impact on the effects of medication. Studies investigating performance anxiety were excluded.

Comorbidities

No restrictions were placed on comorbid psychopathological disorders secondary to SAD.

Setting

No restrictions were placed on setting.

Subsets of participants

Trials that only included a subset of participants that met the review inclusion criteria in the analysis were excluded. None of the trials provided such information, so randomisation was preserved.

Types of interventions

Any medication administered to treat SAD versus an active or non-active placebo was considered. Trials with multiple treatment arms if the comparator was a placebo, as well as placebo-controlled trials studying multimodal treatments (cognitive behavioural therapy), if an active drug was a comparator, were also included.

Experimental interventions

Specific pharmacological interventions were grouped according to medication class. Anticonvulsants/GABAs, the anticonvulsant levetiracetam, NARIs, NaSSAs, and SARIs were added post hoc. The medication classes are listed below:

- 5HT1A partial agonists (e.g. buspirone).
- Anticonvulsants/gamma-amino butyric acids (GABAs, e.g. gabapentin and pregabalin).
- The anticonvulsant levetiracetam.
- Antipsychotics (e.g. olanzapine).
- Benzodiazepines (e.g. clonazepam and bromazepam).
- Beta-blockers (e.g. atenolol).

- Mono-amine oxidase inhibitors (MAOIs, e.g. brofaromine and moclobemide).
- Noradrenaline reuptake inhibitors (NARIs, e.g. atomoxetine).
- Noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g. mirtazapine).
- Reversible inhibitors of monoamine oxidase A (RIMAs, e.g. phenelzine).
- Serotonin antagonist and reuptake inhibitors (SARIs, e.g. nefazodone).
- Serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine).
- Selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, fluvoxamine, sertraline, fluoxetine and citalopram).
- Other medications (e.g. GW876008, GR205171 and LY686017).

Comparator interventions

- Placebo (active or non-active).

No restrictions were placed on timing, dose, duration, or co-interventions.

Types of outcome measures

Primary outcomes

1. **Treatment efficacy:** Clinical Global Impressions Improvement Scale (CGI-I) or similar: treatment efficacy was determined from the number of participants with SAD who responded to treatment, as assessed by the Clinical Global Impressions Improvement Scale (CGI-I) or a closely related measure or definition (Guy 1976). The CGI ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). Responders were defined as having a change item score of 1 (’very much’) improved and 2 (’much’) improved. Given the CGI-I’s wide use and its reliability as a robust measure of the clinical value of treatment in SAD, the CGI-I served as a primary outcome measure for comparisons of short-term trials in this review. Short term trials

were defined as 6 – 14 weeks of treatment, depending on data provided by studies included in the analyses.

2. **Treatment tolerability:** the total proportion of participants who withdrew from the RCTs due to treatment-emergent side effects in the analysis as a surrogate measure of treatment tolerability were included, in the absence of other more direct indicators.

Secondary outcomes

1. **Reduction in SAD symptoms:** symptom severity was assessed and, where available, symptom cluster response, using the Liebowitz Social Anxiety Scale (LSAS), a validated, commonly used, and psychometrically sound instrument (Liebowitz 1987). The LSAS is a 24-item scale that provides separate scores for fear and avoidance in social and performance situations, with higher scores representing increased social anxiety. The LSAS contains three total scores: a total fear score (0 to 72), a total avoidance score (0 to 72), and a total overall score (0 to 144). Suggested interpretations are that total scores of 55 to 65 indicate moderate social phobia; 65 to 80, marked social phobia; 80 to 95, severe social phobia; and greater than 95, very severe social phobia.
2. **Dropout rates:** All-cause dropout rates were compared for short-term trials in order to provide some indication of treatment effectiveness.

Timing of outcome assessment

For studies that assessed outcomes at multiple time points (e.g. Baldwin 1999; Blomhoff 2001; Feltner 2011), data was synthesised from the last assessment within a 16-week, post baseline period to estimate the acute effects of medication.

Search methods for identification of studies

Cochrane Specialised Register (CCMDCTR)

The Cochrane Common Mental Disorders Group maintained a comprehensive, specialised register of randomised controlled trials (to June 2016). The register contains over 39,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with >50% of reference records tagged to c12,500 individually PICO coded study records. Reports of trials for inclusion in the register were collated from (weekly) generic searches of Medline (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials were also sourced from international trial registries, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. The following search strategies (used to identify RCTs) were used:

CCMDCTR core MEDLINE search

Core Ovid MEDLINE search used to inform the Cochrane Common Mental Disorders Specialised Register (CCMD-CTR). A weekly search alert based on Condition + RCT filter only.

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or

affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or

hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.

Similar weekly search alerts were also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

A quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted c/o the Cochrane Register of Studies Online (CRSO).

CCMD searches to 2015

#1 (social* NEAR2 (anxious or anxiety or phobi*)) or "phobic avoidance" or "social avoidance" or "interpersonal anxiety"

#2 "social* inhib*" or "social* stress*" or heterosocial* or "taijin kyofusho"

#3 (#1 or #2)

CCMD update search 2017

In August 2017 the CCMD Group's information specialist ran an update search to identify new studies published or registered since the date of the last search. Records were de-duplicated, screened and x new studies placed in awaiting classification. These will be incorporated in the next version of this review.

As the CCMD Group's specialised register was out of date at this point, the information specialist ran searches on the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (c/o Cochrane Register of Studies Online (CRSO))

Search All Fields [condition only]: (“social anxiety” or “social phobia”) AND 31/01/2015 to 31/08/2017:DL

2. CCMDCTR (studies and references)

(“social anxiety” or “social phobia”) 18/08/2015 to 14/06/2016

3. OVID Cross-search

Databases: PsycINFO <1806 to July Week 4 2017>, Embase <1974 to 2017 Week 31>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to 2-Aug-2017>

Search Strategy:

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1 (social* adj2 (phobi* or anxi*)).ab,kf,id,hw.

2 trial.ti.

3 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf,kw,id.

4 (RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,kf,kw,id.

5 placebo.hw,ti,ab,kf,kw,id.

6 (control* adj2 (trial or group?)).ab.

7 Randomized Controlled Trial.sh,pt.

8 Double Blind Procedure/

9 Double Blind Method/

10 Controlled Clinical Trial and placebo.af.

11 (clinical trial or empirical study).md.

12 ((single or double or triple) adj2 (blind* or mask* or dummy)).ti,ab,kf,kw,id.

13 or/2-12

14 placebo.af.

15 drug therapy.fs.

16 exp Central Nervous System Agents/

17 drug literature index.ec.

18 drug activity/ or drug effect/ or drug efficacy/

19 "Clinical Psychopharmacology ".cc.

20 drug therapy/

21 exp drugs/

22 or/15-21

23 (2015* or 2016* or 2017*).yr.

24 (2015* or 2016* or 2017*).dd.

25 (2015* or 2016* or 2017*).dc,ed. and (medline* or pubmed* or in-data-review or in-process or publisher).st.

26 (2015* or 2016* or 2017*).an. and PsycINFO database record.ab.

27 or/23-26

28 (1 and 13 and 14 and 27)

29 (1 and 13 and 22 and 27)

30 (28 or 29)

31 remove duplicates from 30

4. International Trial Registers

ClinicalTrials.gov

Advanced Search: Interventional Studies | social phobia OR social anxiety | Studies received from 01/01/2015 to 02/08/2017

WHO ICTRP

Advanced Search: All Studies social phobia OR social anxiety | Studies received from 01/01/2015 to 02/08/2017

5. PubMed (not MEDLINE) 2-Aug-2017

#1 Search ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))

#2 Search (social anxiety[Title] OR social phobia[Title])

#3 Search RCT OR random* OR placebo

#4 Search (#1 AND #2 AND #3) Sort by: Publication Date Filters: Publication date from 2015/01/01 to 2017/12/31

Electronic searches

The CCMD Group's information specialist searched the CCMDCTR (studies and references) registers on condition alone, due to concerns regarding multiple searches, change of authorship, and broad scope of this review. The latest version of the review incorporates results of searches to 17 August 2015. The information specialist ran a pre-publication search (2 August 2017) and two additional studies were placed in Awaiting Classification. These will be incorporated in the next version of the review, as appropriate.

I also conducted earlier searches on PubMed, PsycINFO and clinicaltrials.gov (1966 to 2011), using terms 'social phobia OR social anxiety disorder' and 'medication OR pharmacotherapy OR treatment'. I undertook an initial broad search to find RCTs and open-label trials, as well as journal and chapter reviews of the pharmacotherapy of SAD. The ICTRP was also searched (apps.who.int/trialsearch) using the terms 'social phobia' or 'social anxiety' as search queries for this database (August 2012). I repeated this search on 4 November 2015 and 15 March 2017. A 2016 Google Scholar search also yielded an additional included study by Nordahl 2016. This search was repeated on 15 March 2017.

Searching other resources

Reference lists

Bibliographies of all identified trials for additional studies were searched.

Personal communication

Published and unpublished trials were obtained from key researchers, who were identified by the frequency with which they were cited in the bibliographies of RCTs and open-label studies.

Data collection and analysis

Except for the Egger test of funnel plot asymmetry, and generation of the contour enhanced funnel plots (created using the metafor package of the R statistical computing platform (Viechtbauer 2010), Review Manager 5 (RevMan 5) was used to perform all analyses reported in this review (RevMan 2014).

Selection of studies

My main supervisor and I independently assessed the title and abstract of RCTs identified from the search, and subsequently scanned full-text articles agreed upon as potentially eligible. I then independently collated the data listed under Data extraction and management that satisfied the inclusion criteria specified in the criteria for considering studies for this review section.

Studies for which additional information to determine eligibility were listed in the Studies awaiting classification table, pending the availability of this information. Any disagreements in the trial assessment and data collation procedures were addressed with my co-supervisor (DS).

Data extraction and management

The following information from each trial was extracted and managed:

1. Description of the trials, including the year of publication, diagnostic instrument used (e.g. the Structured Clinical Interview for DSM-IV (SCID)), use of placebo run-in, use of a minimal severity criterion, number of participating centers, presence of support from the pharmaceutical industry, and methodological quality.
2. Characteristics of participants, including the diagnostic criteria met (e.g. DSM-IV), subtype of SAD (e.g. generalized SAD), duration of symptoms, presence of comorbid depression, mean age, age range, and sex distribution.
3. Characteristics of the intervention, including its duration, the class of medication used, and the doses employed.
4. Outcome measures employed (primary and secondary), and summary continuous (means and standard deviations) and dichotomous (number of responders) data. Information on dropouts per group as well as the number that dropped out due to treatment emergent side effects were also extracted.

Assessment of risk of bias in included studies

Risk of bias was assessed for each included study using the Cochrane 'Risk of bias' tool (Higgins 2011). The following six domains were considered:

1. Random sequence generation: did investigators use a random number table or a computerised random number generator?
2. Allocation concealment: was the medication sequentially numbered, sealed, and placed in opaque envelopes?

3. Blinding of participants, personnel, and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated treatment or assessment adequately prevented during the study?
4. Incomplete outcome data for each main outcome or class of outcomes: were missing or excluded outcome data adequately addressed?
5. Selective outcome reporting: were the reports of the study free of suggestion of selective outcome reporting? A judgement such as this could only be made based on the availability of the protocol.
6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

My main supervisor and I extracted relevant information from each study report, where provided. A judgement was made on the risk of bias for each domain within and across studies, based on the following three categories: 'low' risk of bias, 'unclear' risk of bias, and 'high' risk of bias. Any disagreements were addressed with my co-supervisor (DS). Where necessary, I contacted the authors of the studies that required further information. All risk of bias data is presented graphically and described in the text below.

Measures of treatment effect

Categorical data

Risk ratio (RR) of response to treatment was calculated for the dichotomous outcomes of interest.

Continuous data

In cases in which studies used a range of scales for each outcome, the treatment outcome was calculated using the standardised mean difference (SMD). The SMD standardises the differences between the means of the treatment and control groups in terms of the variability observed across all participants in the trial.

Unit of analysis issues

Cluster-randomised trials

In cluster-randomised trials, groups of individuals are randomised to different interventions rather than individuals themselves. Analysing treatment response in cluster-randomised trials without taking these groupings into account is potentially problematic, as participants within any one cluster often tend to respond in a similar manner, and thus analyses cannot assume that participants' data are independent of the rest of the cluster. Cluster-randomised trials also face additional risk of bias issues including recruitment bias, baseline imbalance, loss of clusters, and non-comparability with trials randomising individuals (Higgins 2011). No cluster randomised trials were eligible for inclusion in this review. To prevent unit of analysis errors in future updates of this review, I plan to divide the effective sample size of each comparison group in trials that do not adjust for clustering by the design effect metric (Higgins 2011). For these analyses the intraclass correlation coefficient (ICC) that is incorporated within the design effect will be set equivalent to the median ICC from published cluster-randomised pharmacotherapy RCTs for anxiety disorders.

Cross-over trials

Cross-over trials were only included in the calculation of summary statistics when it was possible to extract medication and placebo/comparator data from the first treatment period or

when the inclusion of these data from both treatment periods was justified by a washout period of enough duration that minimised the risk of carry-over effects. In the latter case, data from both periods were included only when it was possible to determine the correlation between participants' responses to the interventions in the different phases (Elbourne 2002). A washout period of at least two weeks was necessary in the case of trials assessing the efficacy of agents with extended half-lives, such as the SSRI fluoxetine (Gury 1999).

Multiple treatment groups

Several trials included in this review compared more than two intervention groups or multiple doses of the same medication against placebo. Including data from the same placebo group for these studies repeatedly in the same comparison would result in a unit of analysis error (Higgins 2011). To prevent these errors for trials comparing multiple dosages of the same agent to placebo, the mean and standard deviation of the outcome of interest across dosage groups were averaged. Outcome data was included from multiple treatment arms in the same comparison if the agents tested were from different medication classes. The subtotals of the outcome were switched off if the placebo group appeared twice in the analysis to accommodate for the second medication. In the case of trials testing multiple agents from the same classes, and in calculating the total effect across all medication classes, data was restricted to the agent that was least represented in the database.

Dealing with missing data

All analyses of dichotomous data were intention-to-treat (ITT). Data from trials providing information on the original group size (prior to dropouts) were included in the analyses of treatment efficacy. Preference was given within studies to the inclusion of summary statistics for continuous outcome measures derived from mixed-effects models, followed by last

observation carried forward (LOCF) and observed cases (OC) summary statistics (in that order). This is in line with evidence that mixed-effects methods are more robust to bias than LOCF analyses (Verbeke 2000).

Assessment of heterogeneity

Heterogeneity was assessed by means of the Chi^2 test for heterogeneity to assess whether observed differences in results were compatible with chance alone. A low P value (or a large Chi^2 test relative to its degree of freedom (df)) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). If the Chi^2 test had a P value of less than 0.10, this was interpreted as evidence of heterogeneity, given the low power of the Chi^2 test when the number of trials is small (Deeks 2011). The Deeks' stratified test of heterogeneity (Deeks 200) was also used, as implemented in RevMan 5, to assess differences by means of the Qb metric in treatment response between subgroups, by subtracting the sum of the Chi^2 statistic for the subgroups from the total Chi^2 statistic for those subgroups.

In addition, the I^2 statistic was used and reported by RevMan 5 to quantify the inconsistency of the trial results within each analysis (Higgins 2003). Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. Thus, a rough guide for interpretation was used:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Funnel plots provide a graphic illustration of the effect estimates of an intervention from individual studies against some measure of the precision of that estimate. I visually inspected publication bias from the funnel plot for treatment efficacy, with the consideration of confounding selection bias, poor methodological quality, true heterogeneity, artefact, and chance. The Eggers' regression test was also used as a more objective quantitative measure of funnel plot asymmetry using the Dersimonian and Laird estimator of heterogeneity (Egger 1997). Given that both tests are dependent on having 10 trials per outcome, this could only be calculated for the SSRIs. Irwig 1998 and others have voiced concerns that the statistical phenomenon increasing the likelihood of falsely detecting publication bias when applying the Egger test to odds ratio effect estimates may extend to risk ratio effect estimates (Sterne 2011).

Accordingly, contour enhanced funnel plots were generated, which explicitly illustrate the relationship between missing studies and the statistical significance of study findings at various statistical thresholds (e.g. alpha = 0.1, 0.05, and 0.01) (Peters 2008). The position of missing studies in these plots using the trim and fill method were estimated.

Data synthesis

Binary and continuous treatment effects were obtained from a random-effects model. Random-effects analytic models include both within-study sampling error and between-study variation in determining the precision of the confidence interval around the overall effect size, whereas fixed-effect modelling approaches take only within-study variation into account. In recognition of the possibility of differential effects for different types of medication, such as the SSRIs and the MAOIs, all the comparisons were stratified by medication class. The outcomes of these

comparisons were expressed in terms of an average effect and 95% confidence interval (CI) for each subgroup.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were conducted to assess the degree to which methodological differences between trials might have systematically influenced differences observed in the primary treatment outcomes (Thompson 1994):

- Multi-center versus single-center trials. The latter are more likely to be associated with lower sample size but will tend to have less variability in clinician ratings.
- Trials including only participants diagnosed with the generalized form of SAD versus those including both the generalized and specific subtypes of SAD. Specialists recognise generalized SAD as often representing a more severe form of the disorder.

In addition, the following was assessed:

- Whether or not trials were industry funded. In general, published trials sponsored by pharmaceutical companies appear more likely to report positive findings than trials that are not supported by profit companies (Als-Nielsen 2003; Baker 2003).
- Whether or not the sample included patients diagnosed with major depression. Such an analysis might assist in determining the extent to which the efficacy of a medication agent in treating SAD is independent of its ability to reduce symptoms of depression, an important consideration given the classification of many of these medications as anti-depressants.

Sensitivity analysis

Sensitivity analyses determine the robustness of the review authors' conclusion to methodological assumptions made in conducting the meta-analysis. I planned to compare the effect of assessing interventions in terms of clinical treatment response (those that responded to treatment) versus nonresponse (those that did not respond to treatment) considering evidence that treatment response may result in less consistent outcome statistics than non-response (Deeks 2002). However, reports on this potential difference in outcome consistency have arisen only when the control group event rate was above 50%, far higher than the baseline proportion of response observed across trials in this review (30%). Accordingly, I did not conduct this analysis.

In addition, a 'worst case/best case' analysis was performed to determine whether the coding of participants who were lost to follow-up influenced the findings of treatment efficacy (Deeks 2011). In this analysis, I recorded all the missing data for the treatment group as responders in the worst-case scenario, whereas in the best case, I coded all missing data for the control group as non-responders. If the conclusions regarding treatment efficacy did not differ between these two comparisons, I assumed that missing data in trial reports did not have a significant influence on this outcome.

Summary of findings tables

'Summary of findings' tables were compiled to summarise the best evidence for all relevant outcomes (i.e. experimental versus comparator interventions), reporting the following six elements according to a fixed format (Higgins 2011):

- A list of all important outcomes, both desirable and undesirable.

- A measure of the typical burden of these outcomes (e.g. illustrative risk, or illustrative mean, on control intervention).
- Absolute and relative magnitude of effect (if both are appropriate).
- Numbers of participants and studies addressing these outcomes.
- A grade of the overall quality of the body of evidence for each outcome.
- Space for comments.

I based downgrading of the evidence rating for outcomes on five factors, and classified reasons for downgrading the evidence as 'serious' (downgrading the quality rating by one level) or 'very serious' (downgrading the quality grade by two levels) according to the following:

- Limitations in the design and implementation of the trial.
- Indirectness of evidence.
- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

I then classified the quality of evidence for each outcome according to the following categories:

- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.

Main comparisons

The following outcomes were planned, and I grouped specific pharmacological interventions according to medication class:

- 5HT1A partial agonists versus placebo.
- Anticonvulsants/GABAs versus placebo.
- The anticonvulsant levetiracetam versus placebo.
- Antipsychotics versus placebo.
- Benzodiazepines versus placebo.
- Beta-blockers versus placebo.
- MAOIs versus placebo.
- NARIs versus placebo.
- NaSSAs versus placebo.
- Other medication versus placebo.
- RIMAs versus placebo.
- SARIs versus placebo.
- SNRIs versus placebo.
- SSRIs versus placebo.

RESULTS

NOTE: Due to the limited word count, tables for some data analyses, and for the characteristics of studies (included, excluded, awaiting publication and ongoing) can be found in the original publication of this review. Appendices can also be found in the publication of this review.

Description of studies

Results of the search

A total of 2611 study reports were found through the search process (CCMDCTR 2162; ICTRP 449). Each title and abstract were scanned (if provided) for eligibility. Three hundred and two studies initially seemed relevant, but after further inspection I excluded 166 of these, leaving 136 studies that potentially met the inclusion criteria (I found the additional study by Nordahl 2016 from a search conducted in 2016). After independent review of the full-text studies, 70 studies failed to meet inclusion criteria, leaving 66 RCTs eligible for inclusion in the review (see Characteristics of included studies and Figure 1). Of the 66 trials, 63 RCTs were included in the meta-analysis. Eleven studies are awaiting classification, and five studies are ongoing (see Studies awaiting classification and Ongoing studies in the published review).

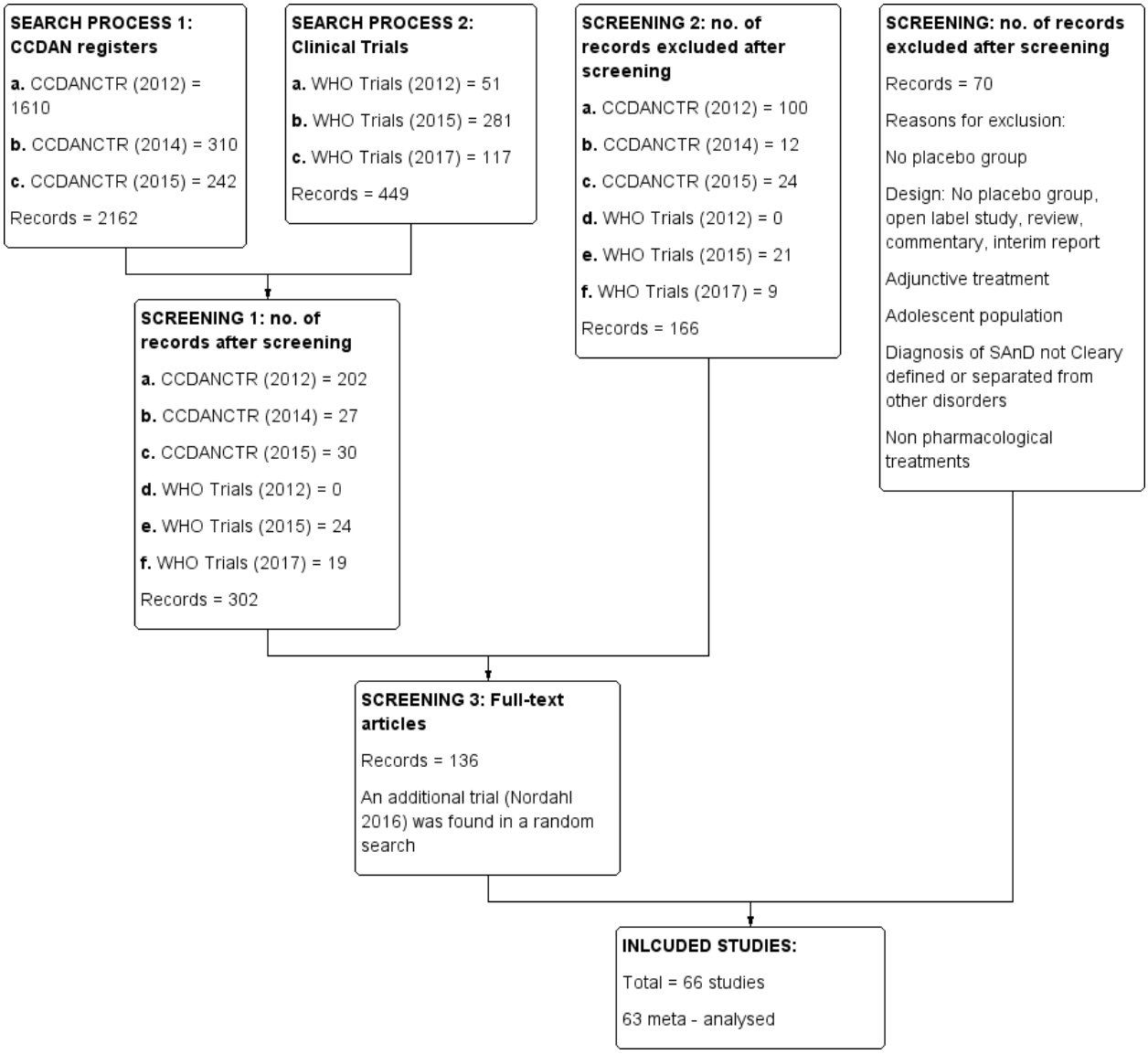


Figure 1. Study flow diagram.

The updated search performed by CCMD's information specialist retrieved 754 records (de-duplicated), and after screening the abstracts, an additional two studies were identified and added to studies awaiting classification. These studies will be incorporated into the next version of the review as appropriate.

Included studies

Design

The review includes 66 RCTs treating participants for SAD from one to 24 weeks. Of these, 56 of the trials were short term (14 weeks or less), while seven trials included a maintenance component, and four trials a relapse component (14 to 24 weeks or less). This update includes 29 new studies. All trials included a placebo comparison group, with eight studies having two medication arms (i.e. two trials assessing paroxetine and venlafaxine, and one trial each assessing citalopram and NK1 antagonist GR205171, paroxetine and escitalopram, phenelzine and atenolol, paroxetine and neurokinin-1 (NK-1) antagonist LY686017, phenelzine and moclobemide, and GW876008 and paroxetine) (Allgulander 2004; Furmark 2005; Lader 2004; Liebowitz 1992; Liebowitz 2005b; NCT00397722; Tauscher 2010; Versiani 1992). Katzelnick 1995 employed a crossover design in testing the efficacy of sertraline. All trials were published in English, and pharmaceutical companies contributed funding for 41 included trials.

Participants

The 66 eligible trials included 11,597 participants aged 18 to 70, most of whom were outpatients. The average sample size was 176 and ranged from 12 in Barnett 2002 and Katzelnick 1995 to 839 in Lader 2004. Sixty trials included both men and women, while Muehlbacher 2005 included only women and Moghadam 2015 only men. Adult participants were diagnosed with SAD according to DSM criteria (DSM-IV-TR, DSM-IV, DSM-IIIR), assessed by means of a variety of instruments, including the Structured Clinical Interview for DSM (SCID/SCID-I) (e.g. Moghadam 2015; NCT00470483), the Mini International Neuropsychiatric Interview (MINI) (e.g. Furmark 2005; Lepola 2004;NCT00403962; Stein 2002b; Zhang 2005), the Initial Evaluation Form, and the Anxiety Disorders Interview Schedule-Revised (ADIS-R) (e.g. Turner 1994).

Twenty-one studies included individuals with major depressive disorder (MDD), while MDD was an exclusion criterion for 41. Four studies did not specify, so I was unable to determine whether individuals with MDD could take part (Moghadam 2015; NCT00470483; Nordahl 2016; Tauscher 2010). Other comorbidities related to functional disability and avoidant personality were also reported, where provided.

Setting

Most eligible RCTs took place in the USA (number of studies (k) = 58), while others were in Europe (k = 10), Japan (k = 2), South Africa (k = 6), and Iran (k = 1). Of the trials included in the analysis, 24 studies were single-center trials, and 42 studies took place in multiple centers. Participants were recruited via telephone, newspaper, radio, or clinical referral. Recruitment settings included university-based hospitals and centers, medical centers, and research and private clinics.

Interventions

Approximately half of the included RCTs tested the efficacy of selective serotonin reuptake inhibitors (SSRIs; k = 34), including 19 studies of paroxetine, of which two studies had a third arm investigating venlafaxine, one study had a third arm investigating escitalopram, one had a third arm investigating LY686017 and another a third arm investigating GW876008 (Allgulander 1999; Allgulander 2004; Baldwin 1999; Book 2008; Lader 2004; Lepola 2004; Liebowitz 2002; Liebowitz 2005b; NCT00273039; NCT00318669; NCT00403962; NCT00397722; NCT00470483; Nordahl 2016; Randall 2001; Stein 1996; Stein 1998; Stein 2003; Tauscher 2010). In addition, the SSRI RCTs included five trials of fluvoxamine (Asakura 2007; Davidson 2004a; Stein 1999; Van Vliet 1994; Westenberg 2004), six trials of sertraline (Blomhoff 2001; Katzelnick 1995; Liebowitz 2003; Moghadam2015; Van Ameringen 2001a;

Walker 2000), two trials of fluoxetine (Davidson 2004b; Kobak 2002), and single RCTs of citalopram (Furmark 2005, with a third arm investigating NK1 antagonist GR205171) and escitalopram (Kasper 2005). The lowest and highest dosage for paroxetine ranged from 7.5 mg/d (NCT00403962) to 60 mg/d (Book 2008; NCT00397722; Nordahl 2016); for sertraline from 50 mg/d (Blomhoff 2001; Katzelnick 1995) to 200mg/d (Katzelnick 1995; Liebowitz 2003; Van Ameringen 2001a; Walker 2000); for fluoxetine from 20 mg/d to 60 mg/d (Davidson 2004b); for fluvoxamine from 50mg/d (Asakura 2007; Stein 1999; van Vliet 1997) to 300 mg/d (Asakura 2007; Davidson 2004a; Stein 1999; Stein 2003; Westenberg 2004); for citalopram from 20 mg/d to 40 mg/d (Furmark 2005); and for escitalopram from 10 mg/d to 20 mg/d (Kasper 2005).

Eight trials studied reversible inhibitors of monoamine oxidase A (RIMAs), including three RCTs of brofaromine (Fahlen 1995; Lott 1997; Van Vliet 1992), plus five of moclobemide (Katschnig 1997; Noyes 1997; Oosterbaan 2001; Schneier 1998; Stein 2002a). For brofaromine, the daily dosage ranged from 50 mg/d to 150 mg/d in both Lott 1997 and Van Vliet 1992, and for moclobemide, it ranged from 75 mg/d in Noyes 1997 to 750 mg/d in Stein 2002a.

Four trials evaluated the mono-amine oxidase inhibitor (MAOI) phenelzine, one of which had a third arm investigating atenolol and another investigating moclobemide (Blanco 2010; Heimberg 1998; Liebowitz 1992; Versiani 1992). Dosage for phenelzine ranged from 15 mg/d in Blanco 2010 and Heimberg 1998 to 100 mg/d in Liebowitz 1992.

There were four trials of the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine (Liebowitz 2005a; Liebowitz 2005b; Stein 2005; Rickels 2004). Dosage ranged from 75 mg/d to 225 mg/d in all these trials.

Three trials focused on anticonvulsants comprising gamma-amino butyric acid (GABA) analogues (including two studies of pregabalin, Feltner 2011 and Pande 2004, and one of gabapentin, Pande 1999). Two trials investigated levetiracetam, another anticonvulsant (Stein 2010; Zhang 2005).

Three trials studied benzodiazepines, including two studies of clonazepam in doses ranging from 0.25 mg/d in both Connor 1998 and Davidson 1993 to 2.5 mg/d in Connor 1998, and one of bromazepam (Versiani 1997), administered in doses of 3 mg/d to 9 mg/d.

There were two trials on antipsychotics, including one study of olanzapine, with dosage ranging from 5mg/d to 20mg/d (Barnett 2002), and another study on quetiapine, with dosage of 25 mg/d to 300 mg/d (Vaishnavi 2007). Two trials evaluated the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, in doses ranging from 30 mg/d in Muehlbacher 2005 and Schutters 2010 to 45 mg/d in Schutters 2010.

Turner 1994 assessed the beta-blocker atenolol, administered in doses of 25 mg/d to 100 mg/d; Ravindran 2009 assessed the noradrenaline reuptake inhibitor (NARI) atomoxetine, administered in doses of 20 mg/d to 100 mg/d; Van Ameringen 2007 looked at the serotonin antagonist and reuptake inhibitor (SARI) nefazodone, with dosage of 100 mg/d to 600 mg/d; NCT00397722 studied GW876008, at doses of 25 mg/d to 50 mg/d; Tauscher 2010 studied LY686017 at 50 mg/d; Furmark 2005 investigated the NK1 antagonist GR205171, at 4 mL to

100 mL; and Van Vliet 1997 the 5HT1A partial agonist buspirone, at doses of 15 mg/d to 30 mg/d.

Psychiatrists, pharmacists, mental health professionals, and multidisciplinary teams of investigators administered the interventions.

Outcomes

Twenty-three trials assessed the primary efficacy outcome – number of participants with SAD who responded to treatment – using the Clinical Global Impression - Global Improvement (CGII) Scale, whilst 27 other trials assessed this outcome as a secondary measure using the same scale. Forty-two trials used the Liebowitz Social Anxiety Scale (LSAS) to assess the reduction of SAD symptoms, while eight used the Clinical Global Impression – Severity scale (CGI-S). Post-treatment follow-up assessments ranged from two weeks in Tauscher 2010 to 15 months in Oosterbaan 2001. See Characteristics of included studies for more details, which can be found in the original publication.

Excluded studies

Seventy studies were excluded from the review (see Characteristics of excluded studies, Williams 2017). The most common reason considered was the absence of a placebo comparator (Allsopp 1984; ACTRN12608000363381; Atmaca 2002; Blank 2006; Bystritsky 2005; Clark 2003; Dunlop 2007; Falloon 1981; Gelernter 1991; EUCTR2004-001894-24-DE; Guastella 2009; Hofmann 2006; Krishman 1976; Liappas 2003; Liebowitz 1999; Oosterbaan 1997; Otto 2000; Pecknold 1982; Rickels 2004; Seedat 2003; Simon 2010; Tubaki 2012; ACTRN12609000091202). Studies with participants under the age of 18 and those with combined populations and certain comorbidities were also excluded (Dempsey 2009; Grosser

2012; Ionescu 2013). The study by Dempsey 2009, Gale 2007, and Mangano 2003 was excluded because these trials were secondary analyses of previous studies. Open-label studies that did not employ a randomised double-blind placebo-control study design were also excluded (Angelini 1989). Twelve early trials with anxiety disorders did not report data separately for patients with SAD, so I could not include them (Angelini 1989; Coupland 2000; NCT00248612; Greenhill 1999; Heun 2013; Malcolm 1992; Mountjoy 1977; Pine 2001; Schuurmans 2004; Solyom 1973; Solyom 1981; Tyrer 1973). One study focused on neuroendocrine and behavioural responses of SAD (Shlik 2002). Four studies on brain functioning, with specific reference to the modulation of amygdala-frontal reactivity and connectivity, were ineligible for inclusion (Dodhia 2014; Gorka 2015; NCT00332046; Phan 2015). Several trials assessed the effect of medication on individuals with performance anxiety who were not diagnosed with SAD (Brantigan 1982; Clark-Elford 2015; Fang 2014; Gates 1985; Gorka 2015; Hartley 1983; James 1977; James 1984; James 1983; Liebowitz 2014; Liden 1974; NCT00308724; NCT00343707; Neftel 1982; Siitonen 1976; Wardle 2012). One excluded study only measured treatment-emergent side effects (Rynn 2008). Finally, studies that combined pharmacotherapy and psychotherapy (Donahue 2009; Feifel 2011; Haug 2003; Mortberg 2007; NCT00308724; Prasko 2004; Ravindran 2014; Silverstone 1973; Wardle 2012), as well as studies using herbal treatments (NCT00118833) were excluded.

Studies awaiting classification

Thirteen trials are awaiting classification (Asakura 2016; Careri 2015; De la Barquera 2008; Frick 2015; Krylov 1996; NCT00114127; NCT00208741; NCT00215254; NCT00246441; NCT00294346; NCT00485888; NCT00612859; NCT01316302). NCT00294346 conducted a study on the effectiveness of an investigational drug AV608 in subjects with social anxiety disorder (SAD), using the Liebowitz Social Anxiety Scale (LSAS) to assess reductions of

anxiety symptoms. De la Barquera 2008 assessed clonazepam compared to placebo in patients with social phobia, and Frick 2015 citalopram, GR205171, or placebo. Frick 2015 involved 18 SAD patients and used the Liebowitz Social Anxiety Scale (LSAS) to assess symptom severity and positron emission tomography (PET) imaging to assess brain function. Krylov 1996 assessed alprazolam, buspirone, or placebo in 66 patients with social phobia. NCT00485888 investigated the effects of cipralex on the reduction of social phobia, as measured by the LSAS and various other secondary scales, in 71 outpatients aged 18 to 75 years and diagnosed with social phobia.

NCT01316302 studied desvenlafaxine (Pristiq) compared to matching placebo over 12 weeks. Sixty-three patients enrolled, and the primary outcome of symptom severity was measured with the LSAS. Similarly, NCT00208741 investigated Gabitril compared to placebo over 24 weeks with 50 patients using the LSAS and CGI-C scales as primary outcome measures; NCT00246441 compared paroxetine to placebo over 16 weeks with 42 patients; and NCT00114127 compared duloxetine to placebo for 18 weeks with 28 patients whose symptoms were assessed with the LSAS. The additional trial by NCT00612859 assessed the efficacy and safety of levetiracetam versus placebo for the treatment of generalized SAD measured by the LSAS. See Characteristics of studies awaiting classification (Williams 2017) and Figure 1 for more details. Two studies from the update search performed by CCMD's information specialist were identified (Asakura 2016; Careri 2015). These studies will be incorporated into the next version of the review as appropriate.

Ongoing studies

Five studies are ongoing (NCT00182533; NCT01712321; NCT02083926; NCT02294305; NCT02432703). NCT02083926 will compare ketamine compared placebo (saline) using the

Beck Anxiety Inventory (BAI), the CGI scale, and the LSAS to determine levels of anxiety severity in SAD patients, whereas NCT02432703 will compare JNJ-42165279 to placebo for 12 weeks on the LSAS. NCT00182533 will assess the efficacy of sertraline, and NCT01712321 and NCT02294305 will compare vortioxetine to placebo for treating generalized social anxiety disorder in outpatients. The most common secondary outcome measures include the assessment of depression (NCT00182533; NCT01712321; NCT02294305), anxiety (NCT01712321; NCT02294305), functional disability, and quality of life (NCT00182533). See Characteristics of ongoing studies (Williams 2017) and Figure 1 for more details.

Risk of bias in included studies

The review assessed risk of bias using the Cochrane 'Risk of bias' tool for allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. Twelve of the included studies were classified as being at high risk for at least one type of bias (see Figure 2 and Figure 3).

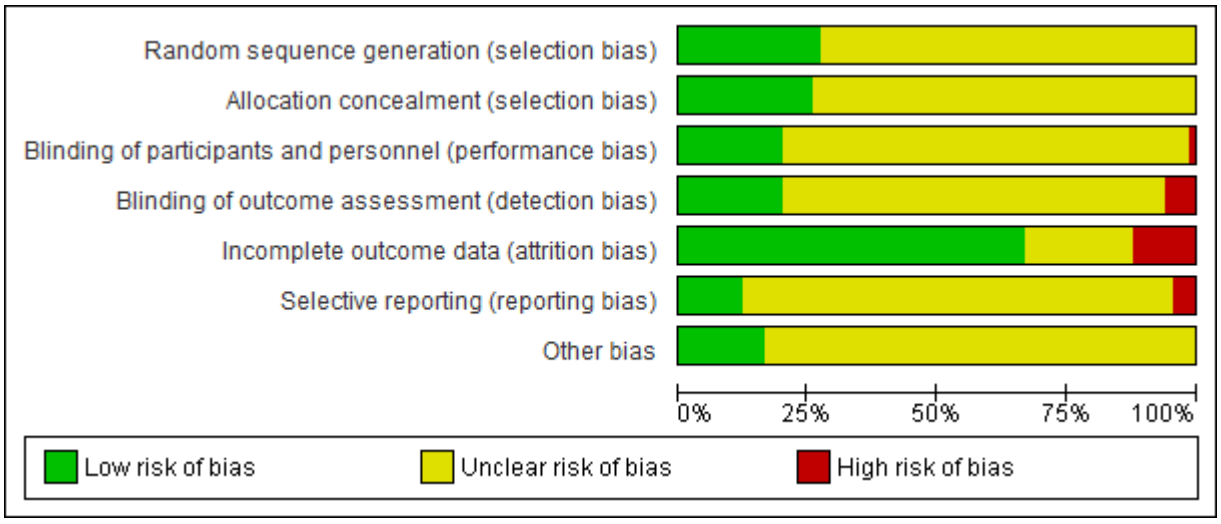


Figure 2. Risk of bias graph: review author judgements about each risk of bias item presented as percentages across all included studies.

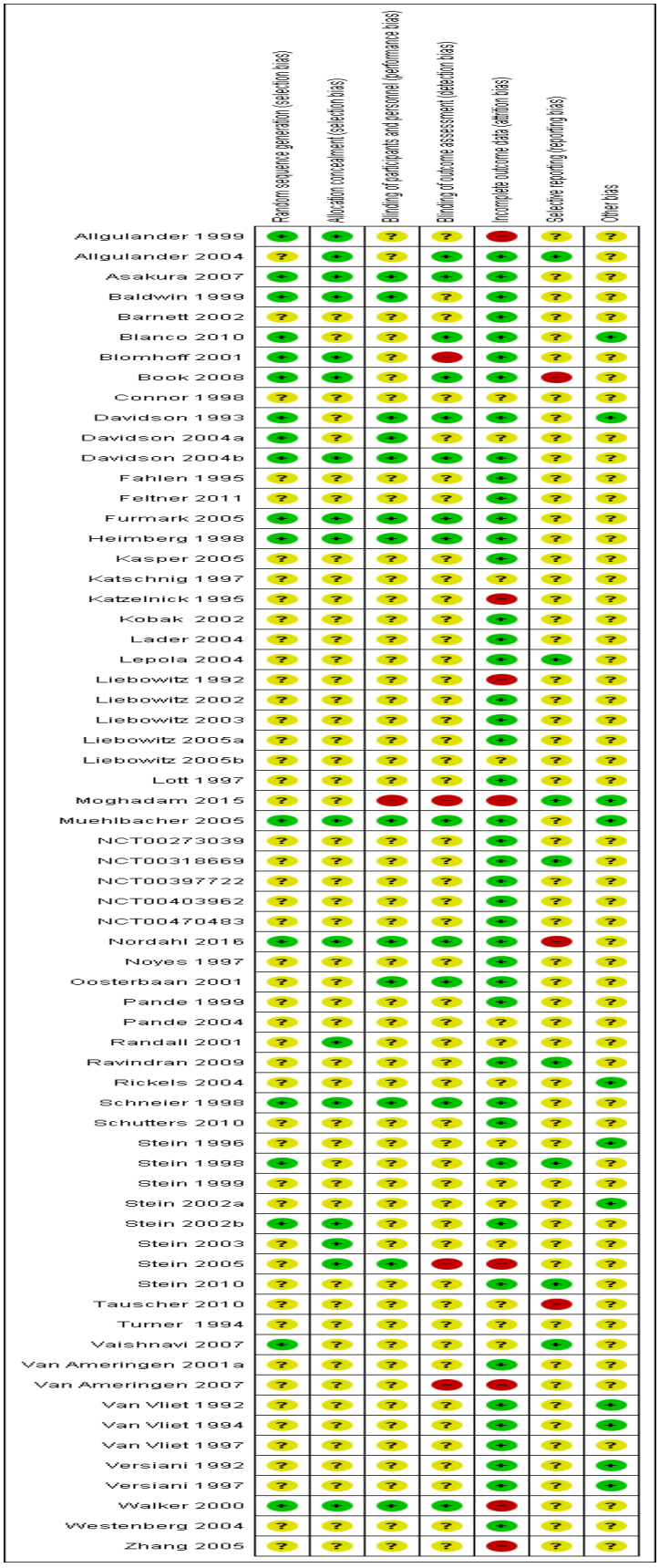


Figure 3. Risk of bias summary: review author judgements about each risk of bias item for each included study.

Allocation

Randomisation

Seventeen of the included studies described the sequence generation as randomised. Allgulander 1999, Blanco 2010, Heimberg 1998, Muehlbacher 2005, and Walker 2000 used tabulated random numbers to randomly assign participants to two groups. In other studies, group assignment was via a computer-generated urn program (Book 2008; Vaishnavi 2007), block program or randomisation (Baldwin 1999; Davidson 2004b; Furmark 2005; Nordahl 2016; Stein 1998), or a computer-generated randomisation list (Blomhoff 2001; Davidson 1993; Stein 2002b). Asakura 2007 used a randomisation scheme by double-dummy method, whereas Davidson 2004a and Schneier 1998 determined randomisation through the sponsor of the central source (e.g. pharmacy) or through a data manager with no patient contact. The review classified all these studies as being at low risk for selection bias, while the risk of bias was designated as unclear in the remaining studies.

Allocation concealment

Only 17 of the 66 trials included in the review were classified as being at low risk for allocation concealment from their description of the method of allocation. A pharmacist or sponsor who prepared and supplied the study medication maintained allocation concealment in nine trials (Allgulander 1999; Allgulander 2004; Asakura 2007; Baldwin 1999; Blomhoff 2001; Book 2008; Nordahl 2016; Randall 2001; Walker 2000). Other studies maintained concealment with the use of sealed envelopes (Blomhoff 2001; Furmark 2005; Schneier 1998), double-blind packaging (Asakura 2007; Davidson 2004b; Stein 2002b; Stein 2003; Walker 2000), label coding for each participant or numbered boxes (Davidson 2004b; Muehlbacher 2005; Schneier 1998; Stein 2005; Stein 2003), and cohorts of patients randomly intermixed (Heimberg 1998).

Blinding

Blinding of participants and personnel

Thirteen studies included in the review were classified as being at low risk of performance bias, as participants and personnel were explicitly described as blinded in the study report (Asakura 2007; Baldwin 1999; Davidson 1993; Davidson 2004a; Davidson 2004b; Furmark 2005; Heimberg 1998; Muehlbacher 2005; Nordahl 2016; Oosterbaan 2001; Schneier 1998; Stein 2005; Walker 2000). In Oosterbaan 2001 and Schneier 1998, participants and therapists or independent evaluators guessed post-test whether medication or placebo had been administered. Correct classifications did not differ from chance. One trial was classified as being at high risk because it provided no information on blinding participants or personnel, nor did investigators describe the study as double-blind (Moghadam 2015). The risk of bias for the remaining trials were classified as unclear, despite investigators describing them in the study reports as double-blinded, as they did not specify the actual parties blinded.

Blinding of outcome assessors

Thirteen of the studies included in the review were classified as being at low risk of detection bias, as the study reports explicitly described outcome assessors as blinded in the study report (Allgulander 2004; Asakura 2007; Blanco 2010; Book 2008; Davidson 1993; Davidson 2004b; Furmark 2005; Heimberg 1998; Muehlbacher 2005; Nordahl 2016; Oosterbaan 2001; Schneier 1998; Walker 2000). The trials by Blomhoff 2001, Stein 2005, and Van Ameringen 2007 were classified as being at high risk, as these studies reported that outcome assessors were not blinded to treatment, and Moghadam 2015 because authors provided no information to determine if outcome assessors were blinded, nor if the study was double blind. The remaining studies were classified as being at unclear risk.

Incomplete outcome data

Fourteen studies failed to provide sufficient information to determine whether the medication and placebo groups were comparable with respect to dropout proportions, or in terms of the demographic and clinical characteristics of those who withdrew (Connor 1998; Davidson 2004a; Katschnig 1997; Liebowitz 2005b; Pande 2004; Randall 2001; Rickels 2004; Stein 1996; Stein 1999; Stein 2002a; Stein 2003; Tauscher 2010; Turner 1994; Vaishnavi 2007). The risk of attrition bias was rated as unclear for these trials. Substantial differences in the proportion of study dropouts were observed between the medication and placebo groups in Allgulander 1999, Katzelnick 1995, Liebowitz 1992, Moghadam 2015; Stein 2005, Van Ameringen 2007, and in the maintenance treatment design that Walker 2000 and Zhang 2005 employed, justifying a rating of high risk. The remaining 44 studies were rated as being at low risk for this domain, based on comparable dropout rates in each comparison group and no difference in the demographic characteristics. Overall, the total dropout rate was 25% across all medications compared to placebo (with the exclusion of one trial of paroxetine, to give preference to the experimental drug that is least represented in the data set). The review assessed intention-to-treat data for all outcomes in 11 studies and used LOCF (k = 46), observed cases (k = 9) and mixed-effect models (k = 3) to account for missing data in the rest of the trials. Thirteen studies did not specify how they addressed the issue of missing data.

Selective reporting

It was unclear whether selective reporting took place in 55 trials because the study protocols were not available for the study. Eight studies were classified as being at low risk for selective reporting because authors reported on all outcomes as specified in their respective trial protocols (Allgulander 2004; Lepola 2004; Moghadam 2015; NCT00318669; Ravindran 2009; Stein 1998; Stein 2010; Vaishnavi 2007). In Book 2008, Nordahl 2016, and Tauscher 2010,

the pre-specified secondary outcomes in the protocol did not appear in the study report, meriting a classification of high risk.

Other potential sources of bias

Eleven studies were classified as being at low risk for other potential sources of bias (Blanco 2010; Davidson 1993; Moghadam 2015; Muehlbacher 2005; Rickels 2004; Stein 1996; Stein 2002a; Van Vliet 1992; Van Vliet 1994; Versiani 1992; Versiani 1997). The risk of other bias for the remaining studies were rated as unclear due to industry involvement, whether through funding or provision of study medication.

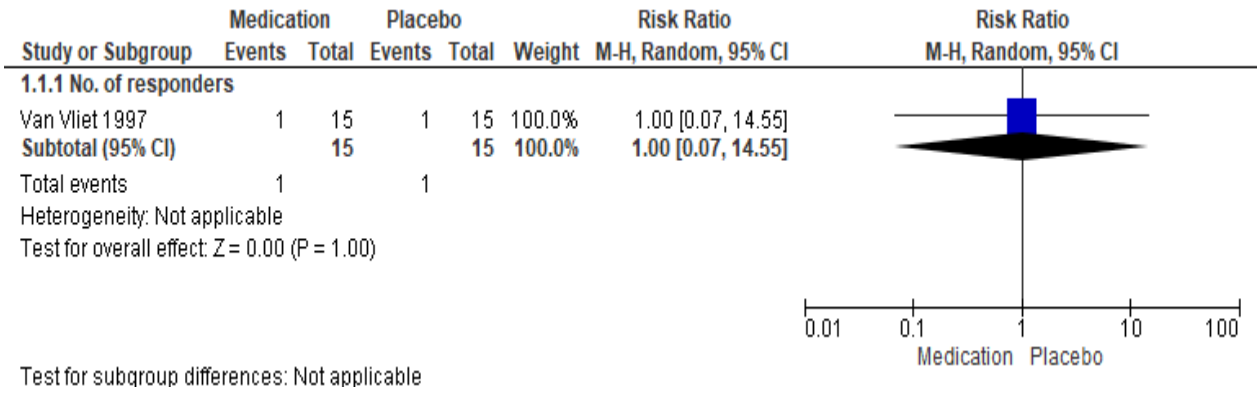
Effects of interventions

See: Summary of findings tables for the main comparisons.

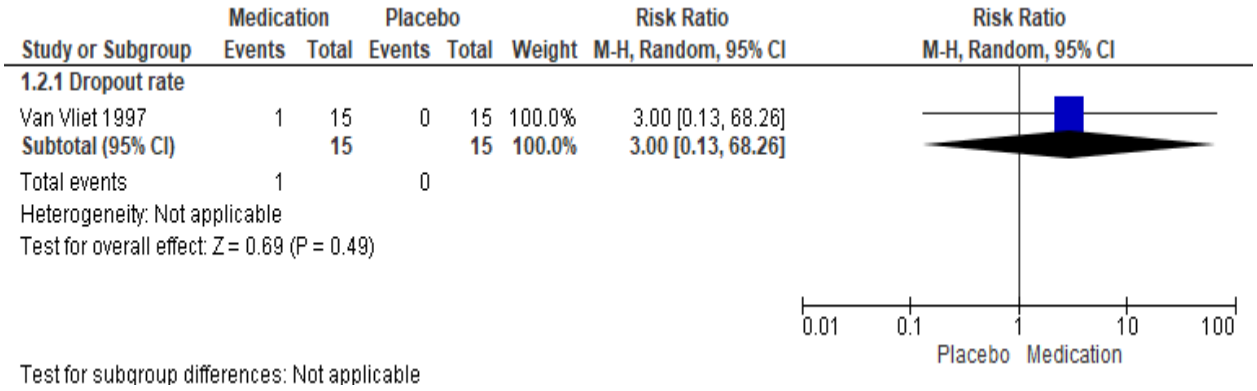
Comparison 1: 5HT1A partial agonists versus placebo

Primary outcome measures

There was no evidence of an effect of buspirone on treatment efficacy in participants with SAD compared to placebo (k = 1, risk ratio (RR) 1.00, 95% confidence interval (CI) 0.07 to 14.55, N = 30; see Analysis 1.1; Van Vliet 1997). In addition, the quality of the evidence for this outcome is very low. Dropout rates due to adverse events were low in the medication arm of one RCT of buspirone (1/30, 3%) (see Analysis 1.2); again, however, this conclusion is based on very low-quality evidence.



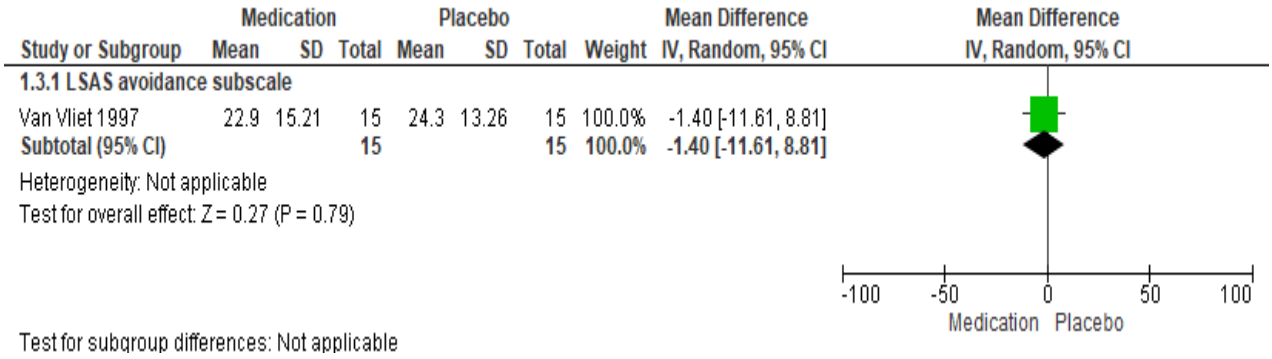
Analysis 1.1. 5HT1A partial agonists versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.



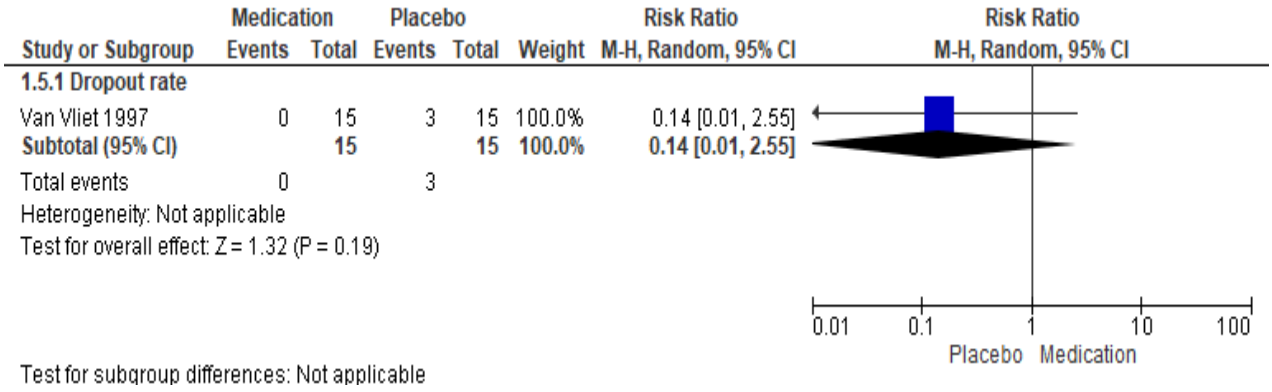
Analysis 1.2. **5HT1A partial agonists versus placebo.** Adverse events (acute phase): Dropout rate.

Secondary outcomes measures

Buspirone was not superior to placebo on the avoidance subscale of the LSAS for the reduction of anxiety symptoms (k = 1, mean difference (MD) −1.40 points, 95% CI −11.61 to 8.81; N = 30; Analysis 1.3; Van Vliet 1997). The evidence that was available for this outcome was of very low quality. More participants withdrew from the placebo group (3/15; 20%) compared to the buspirone group (0/15; 0%). Nevertheless, the total proportion of dropouts (20%) is relatively low and is confirmed by the lack of evidence of a difference between the two groups (k = 1, RR 0.14; 95%CI 0.01 to 2.55, N= 30; see Analysis 1.5).



Analysis 1.3. 5HT1A partial agonists versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms; LSAS avoidance subscale.



Analysis 1.5. 5HT1A partial agonists versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 1: 5HT1A partial agonists versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: 5HT1A partial agonists **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With 5HT1A partial agonists**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.00** (0.07 to 14.55)	30 (1 study)	⨁⊖⊖⊖ **Very low**[a,b]	There was no evidence of an effect on the number of participants in the 5HT1A partial agonist group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 1.00).
	67 per 1000	**67 per 1000** (5 to 970)				
	Moderate					
	67 per 1000	**67 per 1000** (5 to 975)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 3.00** (0.13 to 68.26)	30 (1 study)	⨁⊖⊖⊖ **Very low**[a,b]	Dropout rates due to adverse events were low in the
	0 per 1000	**0 per 1000** (0 to 0)				

	Moderate					5HT1A partial agonist group (1/30, 3%). No participants withdrew from the placebo group.
	0 per 1000	**0 per 1000** (0 to 0)				
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 24.3	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **1.4 points lower** (11.61 lower to 8.81 higher)		30 (1 study)	⨁⊖⊖⊖ **Very low**[a,c]	The mean LSAS avoidance anxiety score for the 5HT1A partial agonist intervention group was 22.9 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 1. Comparison 1: 5HT1A partial agonists versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (small sample size, few events and wide confidence interval).

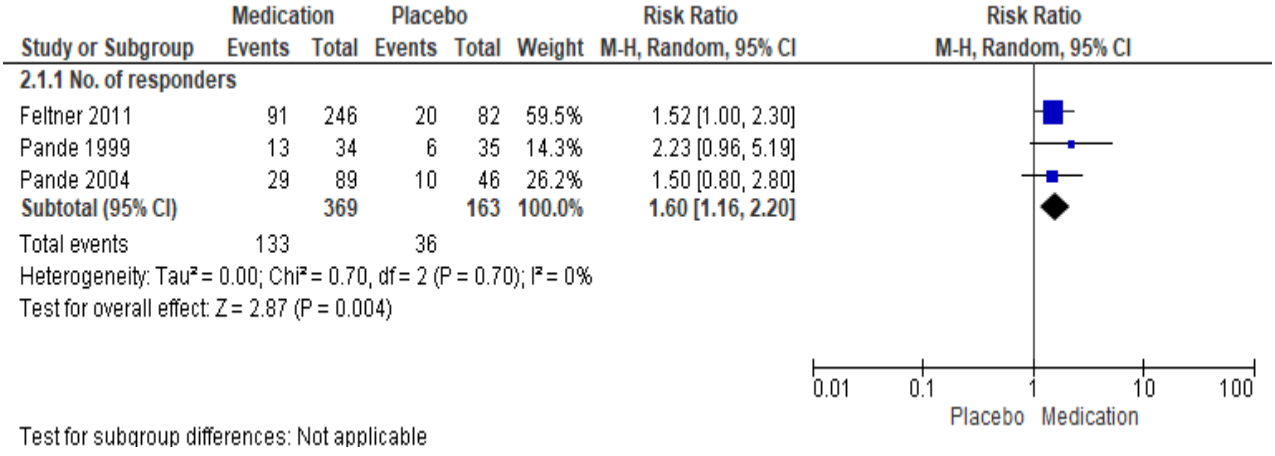
[c]Downgraded two levels due to very serious imprecision (small sample size and wide confidence interval).

[d]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

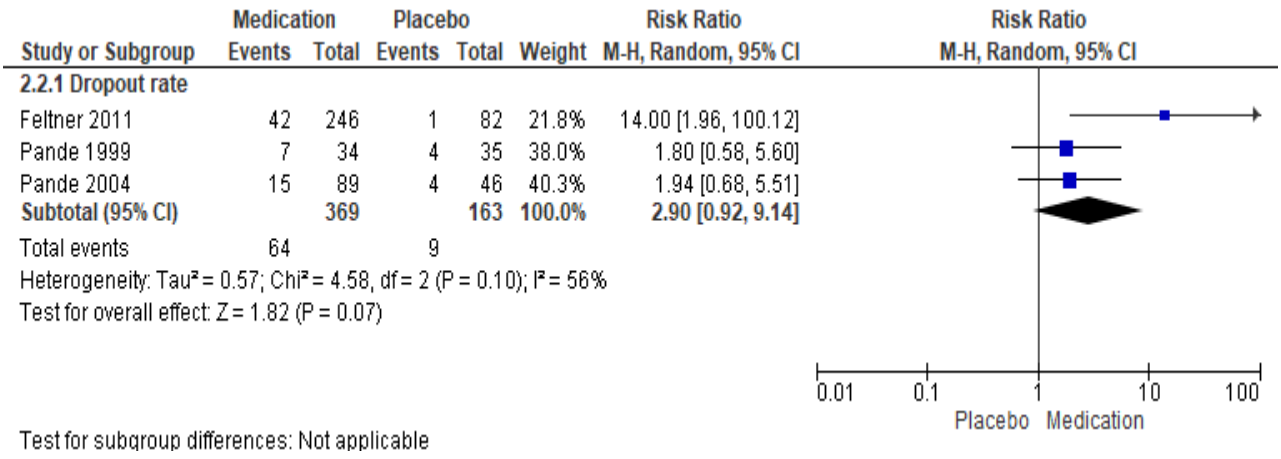
Comparison 2: anticonvulsants/GABAs versus placebo

Primary outcome measures

There was evidence of benefit for gabapentin and pregabalin compared to placebo on the number of participants with SAD who responded to treatment (k = 3, RR 1.60; 95% CI 1.16 to 2.20, N = 532; see Analysis 2.1; Feltner 2011; Pande 2004; Pande 1999), with moderate-quality evidence. The proportion of dropouts due to adverse events was approximately three times as high in participants receiving gabapentin or pregabalin (64/369, 17%) relative to placebo (9/163, 6%) (k = 3, RR 2.90; 95%CI 0.92 to 9.14; see Analysis 2.2). The higher dropout rate associated with medication was particularly apparent in the Feltner 2011 trial of pregabalin, with the proportion of discontinuations due to adverse events ranging between 14% and 20.5% for the three dosages tested (300 mg/d, 450 mg/d, 600 mg/d), versus 1.2% in the placebo group (RR 14.00; 95% CI 1.96 to 100.12). The GABA anticonvulsants were significantly more efficacious than the anticonvulsant levetiracetam (Chi^2 = 4.25, df = 1, P = 0.04; I^2 = 76.5%).



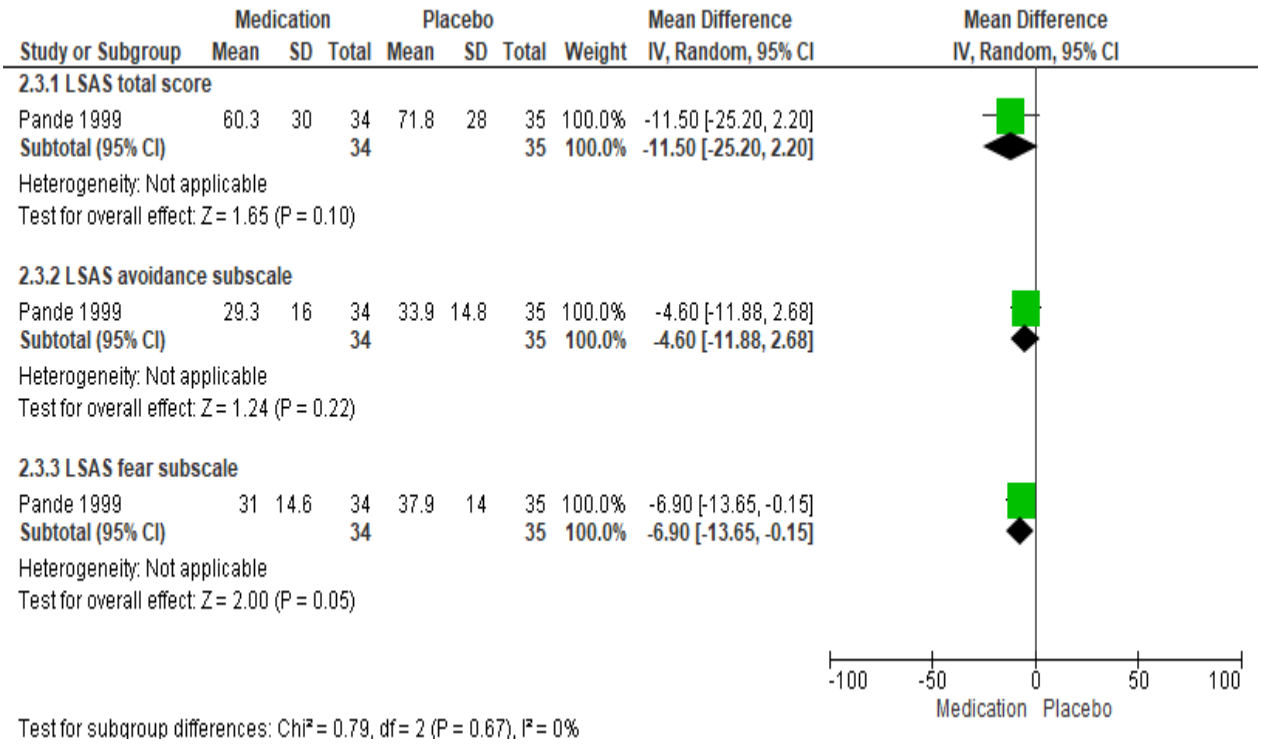
Analysis 2.1. anticonvulsants/GABAs versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.



Analysis 2.2. anticonvulsants/GABAs versus placebo. Adverse events (acute phase): Dropout rate.

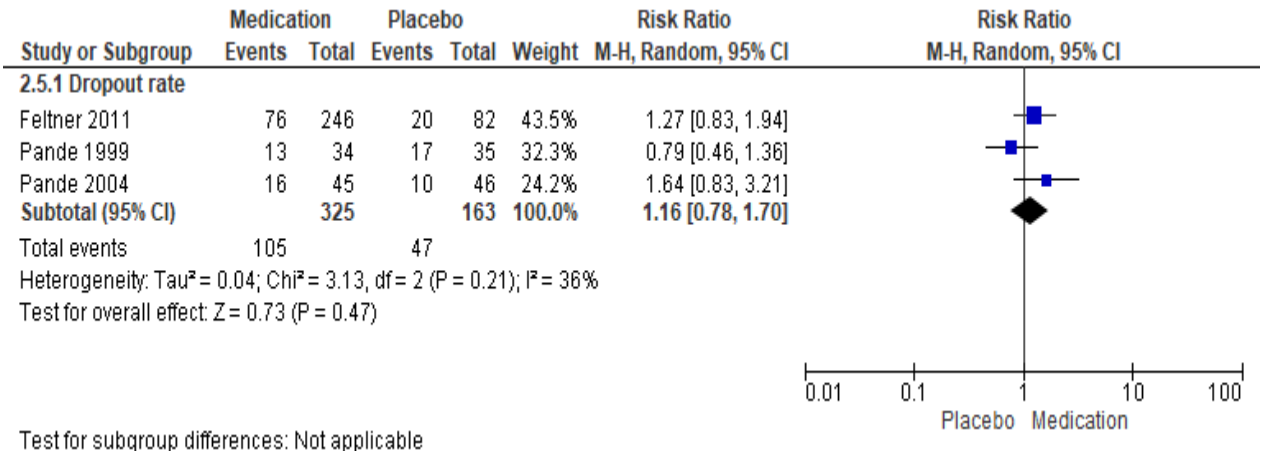
Secondary outcomes measures

There was no evidence that gabapentin reduced total SAD symptom severity scores on the LSAS (k = 1, MD −11.50 points, 95% CI −25.20 to 2.20, N = 69; see Analysis 2.3; Pande 1999). In addition, there was no evidence of a difference on either the avoidance (MD −4.60 points, 95% CI −11.88 to 2.68, see Analysis 2.3) or fear subscale of the LSAS (MD −6.90 points, 95% CI −13.65 to −0.15, see Analysis 2.3).



Analysis 2.3. anticonvulsants/GABAs versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Three studies with 488 participants reported similar proportions of dropouts due to any cause in the medication and placebo groups (RR 1.16; 95% CI 0.78 to 1.70; see Analysis 2.5; Feltner 2011; Pande 2004; Pande 1999).



Analysis 2.5. anticonvulsants/GABAs versus placebo. All-cause dropouts (acute phase):

Dropout rate.

<table>
<tr><td colspan="6">Comparison 2: anticonvulsants/GABAs versus placebo for social anxiety disorder (SAD)</td></tr>
<tr><td colspan="6">Patient or population: adults with SAD
Settings: outpatient settings
Intervention: anticonvulsants/GABAs
Comparison: placebo</td></tr>
<tr><td rowspan="3">Outcomes</td><td colspan="2">Illustrative comparative risks* (95% CI)</td><td rowspan="3">Relative effect (95% CI)</td><td rowspan="3">No. of participants (studies)</td><td rowspan="3">Quality of the evidence (GRADE)</td><td rowspan="3">Comments</td></tr>
<tr><td>Assumed risk</td><td>Corresponding risk</td></tr>
<tr><td>With placebo</td><td>With anticonvulsants/GABAs</td></tr>
<tr><td rowspan="4">Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)</td><td colspan="2">Study population</td><td rowspan="4">RR 1.60
(1.16 to 2.20)</td><td rowspan="4">532
(3 studies)</td><td rowspan="4">⊕⊕⊕⊖
Moderate[a]</td><td rowspan="4">There was evidence of benefit on the number of participants with SAD who responded to treatment (P = 0.004). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the anticonvulsant/GABA groups compared to the placebo groups who responded, 'Very</td></tr>
<tr><td>221 per 1000</td><td>353 per 1000
(256 to 486)</td></tr>
<tr><td colspan="2">Moderate</td></tr>
<tr><td>217 per 1000</td><td>347 per 1000
(252 to 477)</td></tr>
</table>

						Much Improved' or 'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 2.90** (0.92 to 9.14)	532 (3 studies)	⨁⊖⊖⊖ **Very low**[a,b,c]	Dropout rates due to adverse events were high in the anticonvulsant/GABA groups (64/369, 17%) relative to placebo (9/163, 6%).
	55 per 1000	**160 per 1000** (51 to 505)				
	Moderate					
	87 per 1000	**252 per 1000** (80 to 795)				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score for the control group was 71.8	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **11.50 lower** (25.20 lower to 2.20 higher)		69 (1 study)	⨁⨁⊖⊖ **Low**[a,d]	The mean LSAS total anxiety score for the anticonvulsant/GABA intervention group was 60.3 which suggests 'moderate' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 33.9	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **4.60 points lower** (11.88 lower to 2.68 higher)		69 (1 study)	⨁⨁⊖⊖ **Low**[a,d]	The mean LSAS avoidance anxiety score for the anticonvulsant/GABA intervention group was 29.3 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-	The mean anxiety score	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention		69 (1 study)	⨁⨁⊖⊖ **Low**[a,d]	The mean LSAS fear anxiety score for the anticonvulsant/GABA intervention group

rated: LSAS fear subscale	for the control group was 37.9	groups was **6.90 points lower** (13.65 lower to 0.15 lower)				was 31.0 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 2. Comparison 2: anticonvulsants/GABAs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to moderate heterogeneity (I^2 of 56%).

[c]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

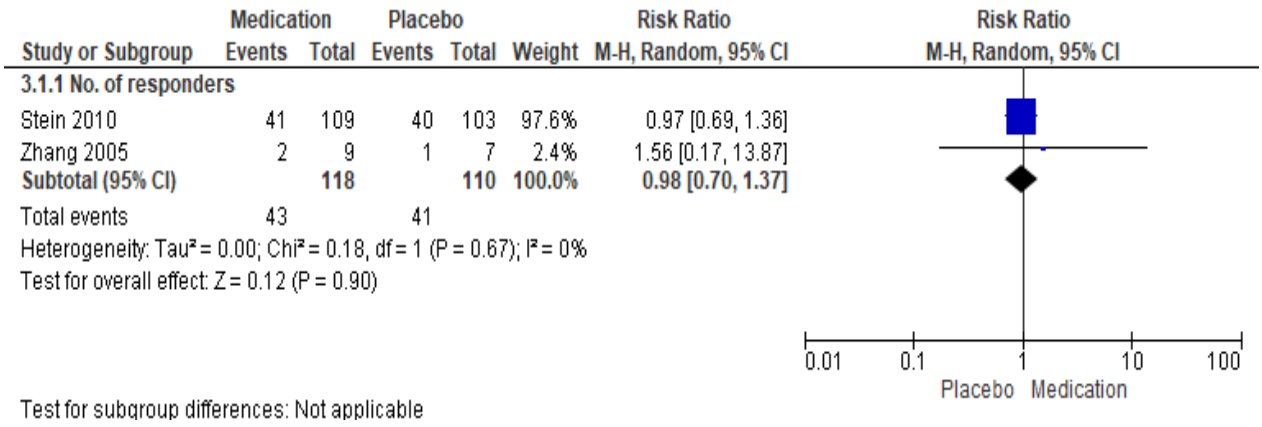
[d]Downgraded two levels due to very serious imprecision (wide confidence interval).

[e]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 3: anticonvulsant levetiracetam versus placebo

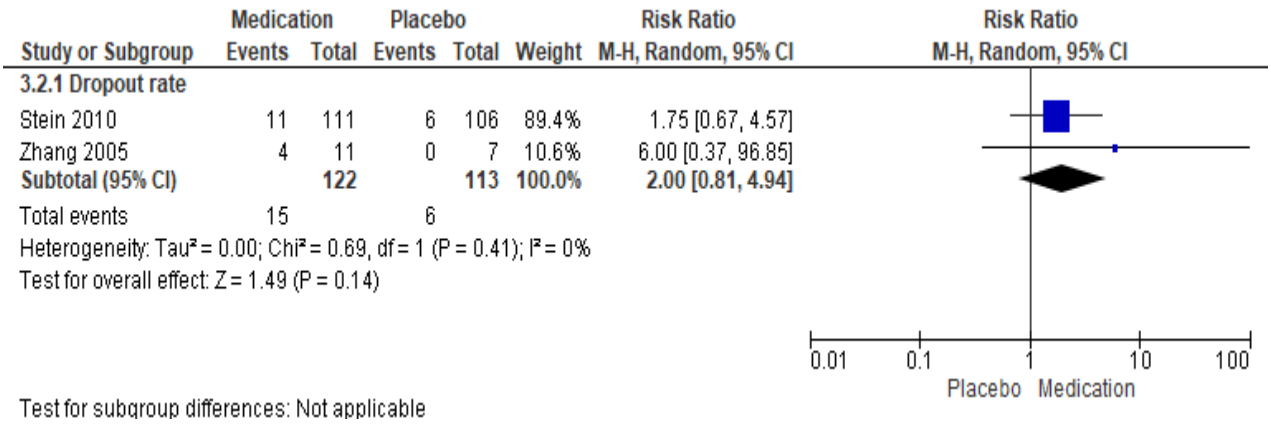
Primary outcome measures

There was no evidence of an effect of levetiracetam on treatment efficacy in participants with SAD compared to placebo (k = 2, RR 0.98; 95% CI 0.70 to 1.37, N = 228; see Analysis 3.1; Stein 2010; Zhang 2005). The evidence that was available for this outcome was of moderate quality. There was evidence of a response to treatment with the anticonvulsant levetiracetam compared to anticonvulsants with gamma-amino butyric acid (GABA) analogues (Chi^2 = 4.25, df = 1, P = 0.04; I^2 = 76.5%), the benzodiazepines (Chi^2 = 21.10, df = 1, P < 0.00001; I^2 = 95.3%), the MAOIs (Chi^2 = 5.86, df = 1, P = 0.02; I^2 = 82.9%), the RIMAs (Chi^2 = 6.76, df = 1, P = 0.009; I^2 = 85.2%), and the SSRIs (Chi^2 = 8.02, df = 1, P = 0.005; I^2 = 87.5%).



Analysis 3.1. anticonvulsant levetiracetam versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

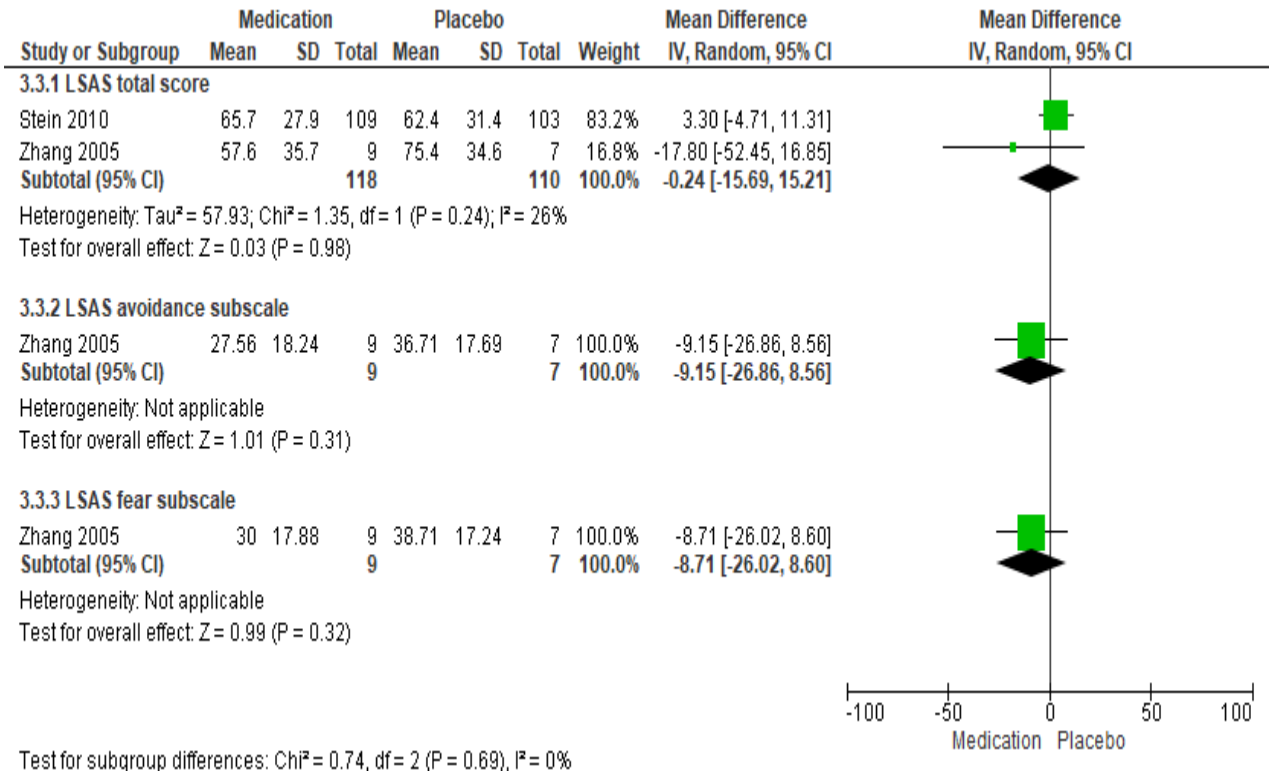
The proportion of dropouts due to adverse events was more than twice as high in participants receiving levetiracetam (15/122, 12%) relative to placebo (6/113, 5%). There was no evidence of a difference between the number of participants that dropped out due to treatment-emergent side effects (k = 2, RR 2.00; 95% CI 0.81 to 4.94; see Analysis 3.2), but the quality of the evidence is very low.



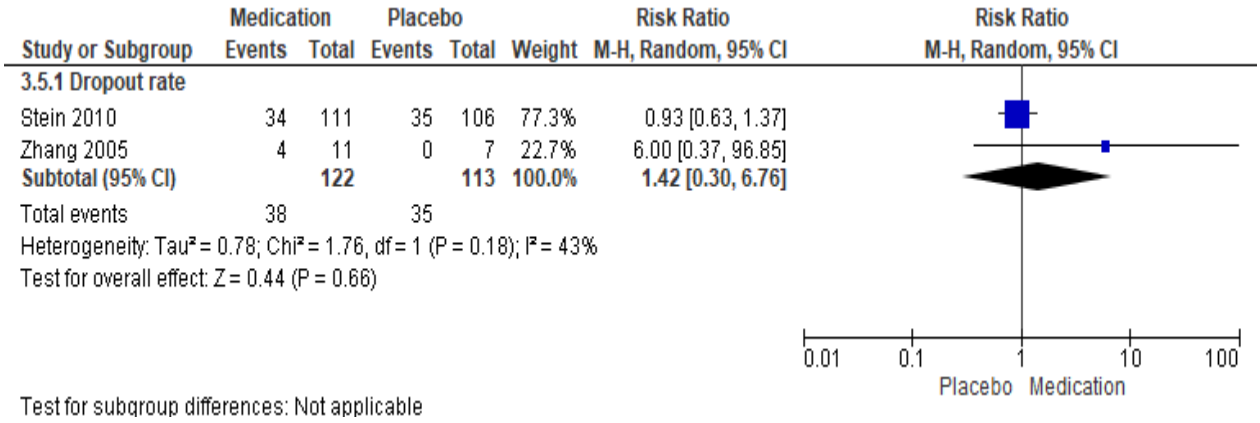
Analysis 3.2. anticonvulsant levetiracetam versus placebo. Adverse events (acute phase): Dropout rate.

Secondary outcome measures

There was no evidence of a difference for a reduction of SAD symptom severity in participants treated with levetiracetam compared to placebo on the LSAS (k = 2, MD −0.24 points, 95% CI −15.69 to 15.21, N = 228; Analysis 3.3; Stein 2010; Zhang 2005). In addition, there was no evidence of a difference between these groups in Zhang 2005 (N = 16) on either the avoidance (MD −9.15 points, 95% CI −26.86 to 8.56, Analysis 3.3) or fear subscale of the LSAS (MD −8.71 points, 95% CI −26.02 to 8.60, Analysis 3.3). The evidence that was available for the three outcomes was of very low quality. The proportion of participants dropping out due to any cause from the anticonvulsants and placebo groups was comparable (31% in both groups). The review found no evidence of a difference for levetiracetam compared to placebo for this outcome (k = 2, RR 1.42; 95% CI 0.30 to 6.76, N = 235; see Analysis 3.5; Stein 2010; Zhang 2005).



Analysis 3.3. anticonvulsant levetiracetam versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.



Analysis 3.5. anticonvulsant levetiracetam versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 3: levetiracetam versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: other anticonvulsants **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With other anticonvulsants**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 0.98** (0.70 to 1.37)	228 (2 studies)	⊕⊕⊕⊖ **Moderate**[a]	There was no evidence of an effect on the number of participants in the anticonvulsant levetiracetam groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.90).
	373 per 1000	**365 per 1000** (261 to 511)				
	Moderate					
	266 per 1000	**261 per 1000** (186 to 364)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 2.00** (0.81 to 4.94)	235 (2 studies)	⊕⊖⊖⊖ **Very low**[a,b]	The proportion of dropouts due to adverse events was high in participants receiving the anticonvulsant
	53 per 1000	**106 per 1000** (43 to 262)				
	Moderate					
	28 per 1000	**56 per 1000** (23 to 138)				

						levetiracetam (15/122, 12%) relative to placebo (6/113, 5%). There was no evidence of a difference between the number of participants that dropped out due to adverse events (P = 0.14).
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from 62.4 to 75.4	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **0.24 points lower** (15.69 lower to 15.21 higher)		228 (2 studies)	⨁⊖⊖⊖ **Very low**[a,c]	The mean LSAS total anxiety score for the anticonvulsant levetiracetam intervention groups ranged from 55 to 65 which suggests 'moderate' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 36.71	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **9.15 points lower** (26.86 lower to 8.56 higher)		16 (1 study)	⨁⊖⊖⊖ **Very low**[a,d]	The mean LSAS avoidance anxiety score for the anticonvulsant levetiracetam intervention group was 27.56 which suggests 'low' social phobia.
Reduction of anxiety symptoms -	The mean anxiety score for the control	The mean reduction of anxiety symptoms (clinician-rated: LSAS		16 (1 study)	⨁⊖⊖⊖ **Very low**[a,d]	The mean LSAS fear anxiety score for the anticonvulsant

Clinician-rated: LSAS fear subscale	group was 38.71	fear) in the intervention groups was **8.71 points lower** (26.02 lower to 8.60 higher)				levetiracetam intervention group was 30.0 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 3. Comparison 3: anticonvulsant levetiracetam versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

[c]Downgraded two levels due to very serious imprecision (wide confidence interval).

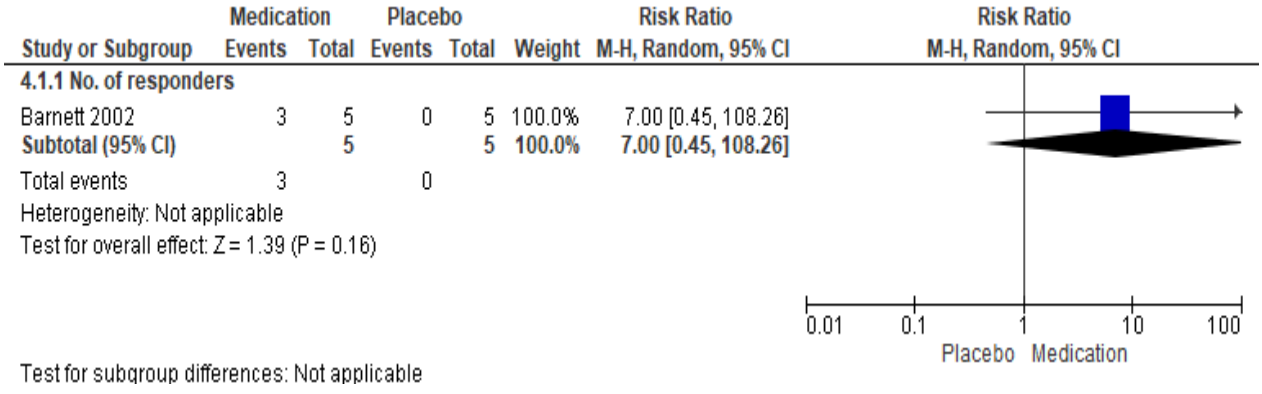
[d]Downgraded two levels due to very serious imprecision (small sample size, few events and wide confidence interval).

[e]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

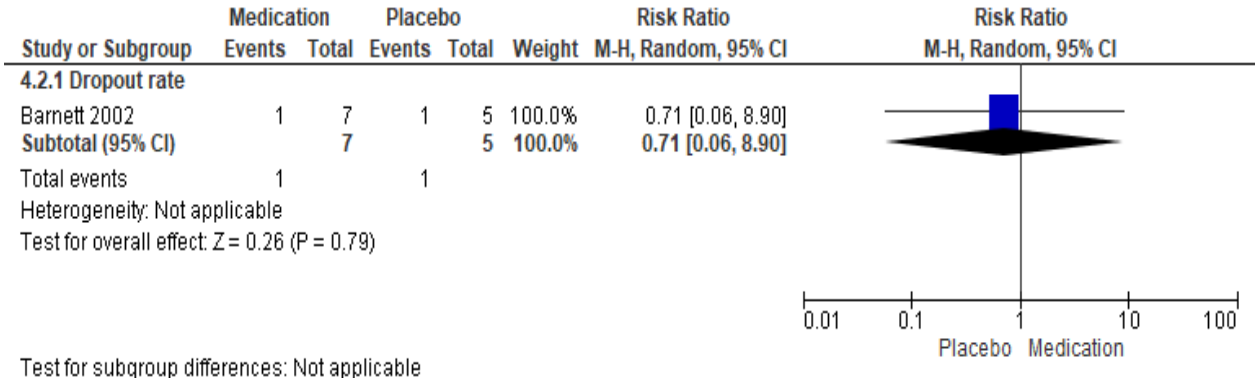
Comparison 4: antipsychotics versus placebo

Primary outcome measures

In a small RCT with 10 participants, there was no evidence of an effect for olanzapine compared to placebo on the number of participants who responded to treatment (k = 1, RR 7.00; 95% CI 0.45 to 108.26, Analysis 4.1; Barnett 2002). The data provided for this outcome was of very low quality. Of the 12 participants randomised to eight weeks of treatment with olanzapine or placebo, there was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 1, RR 0.71; 95% CI 0.06 to 8.90; see Analysis 4.2). The evidence that was available for this outcome was of very low quality.



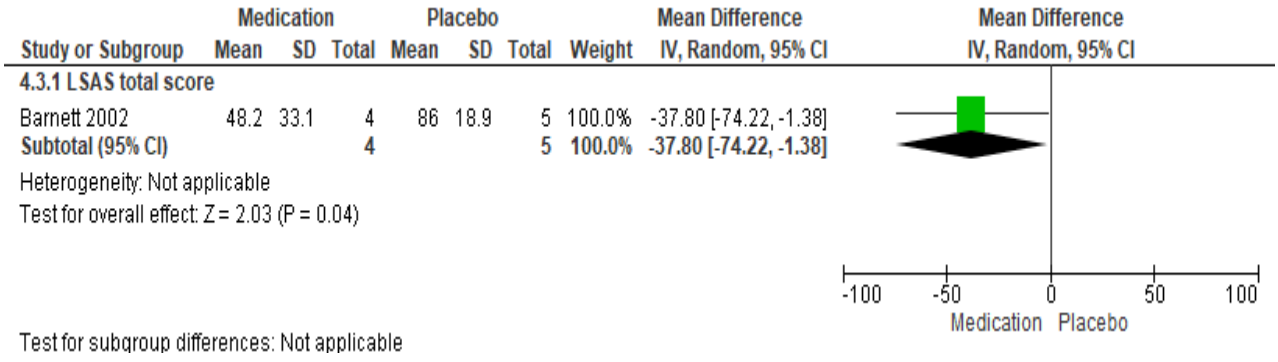
Analysis 4.1. antipsychotics versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.



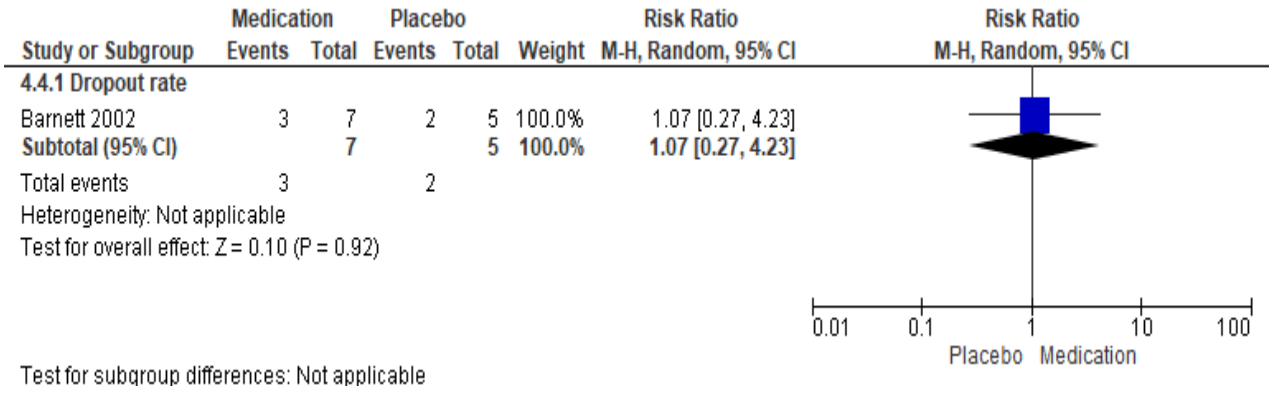
Analysis 4.2. antipsychotics versus placebo. Adverse events (acute phase): Dropout rate.

Secondary outcome measures

There was evidence of benefit for olanzapine compared to placebo in the reduction of SAD symptoms on the LSAS (k = 1, MD −37.80 points, 95% CI −74.22 to −1.38, N = 9; see Analysis 4.3; Barnett 2002), though the evidence is of very low quality. A similar proportion of participants withdrew from the olanzapine group (43%) compared to the placebo group (40%) (k = 1, RR 1.07; 95% CI 0.27 to 4.23, N = 12; see Analysis 4.4; Barnett 2002).



Analysis 4.3. antipsychotics versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score.



Analysis 4.4. antipsychotics versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 4: antipsychotics versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: antipsychotics **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With antipsychotics**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 7.00** (0.45 to 108.26)	10 (1 study)	⊕⊖⊖⊖ **Very low**[a,b]	There was no evidence of an effect on the number of participants in the antipsychotic group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.16).
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 0.71** (0.06 to 8.90)	12 (1 study)	⊕⊖⊖⊖ **Very low**[a,c]	There was no difference on the number of participants who withdrew due to adverse events (P = 0.79).
	200 per 1000	**142 per 1000** (12 to 1000)				
	Moderate					
	200 per 1000	**142 per 1000** (12 to 1000)				

Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score for the control group was 86.0	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **37.80 points lower** (74.22 lower to 1.38 lower)		9 (1 study)	⨁⊖⊖⊖ **Very low**[a,b]	The mean LSAS total anxiety score for the antipsychotic intervention group was 48.2 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 4. Comparison 4: antipsychotics versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

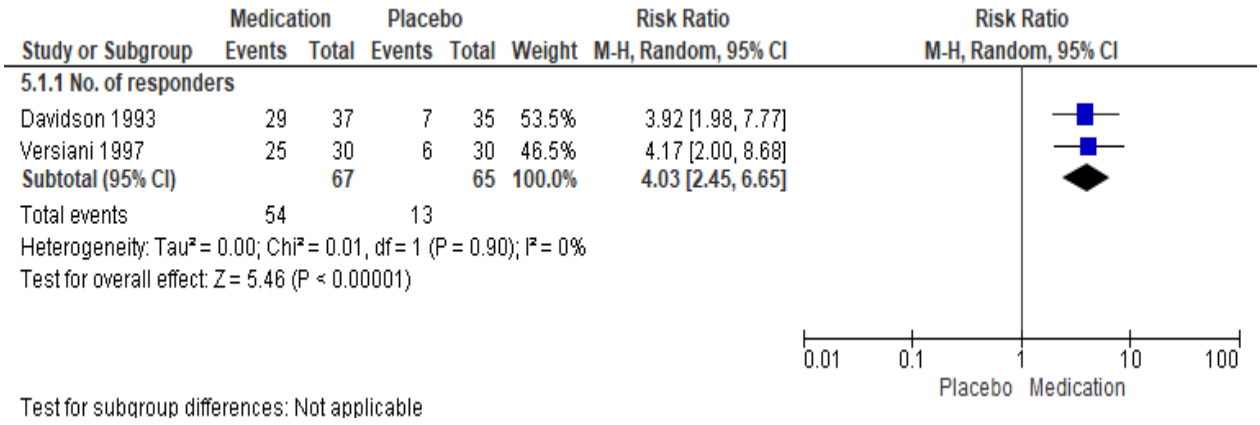
[c]Downgraded two levels due to very serious imprecision (small sample size, few events, and wide confidence interval).

[d]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 5: benzodiazepines versus placebo

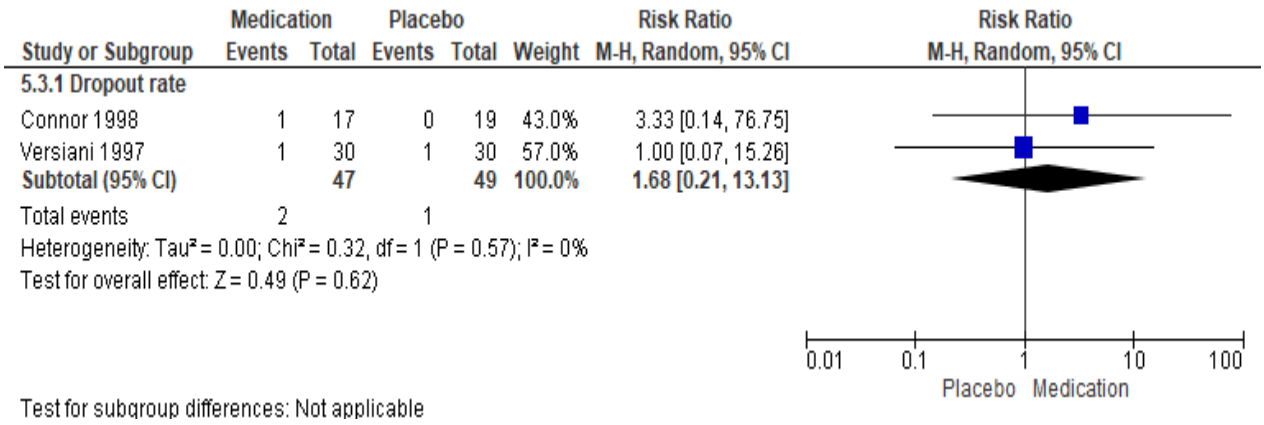
Primary outcome measures

There was evidence of a large effect of clonazepam and bromazepam on treatment efficacy in participants with SAD compared to placebo (k = 2, RR 4.03; 95% CI 2.45 to 6.65, N = 132; see Analysis 5.1; Davidson 1993; Versiani 1997), although the evidence was of low quality. The benzodiazepines demonstrated superiority with respect to treatment response relative to all the other medication classes that contained data from more than a single study, except for the MAOI phenelzine (Chi^2 = 1.67, df = 1, P = 0.20; I^2 = 40.3%).



Analysis 5.1. benzodiazepines versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

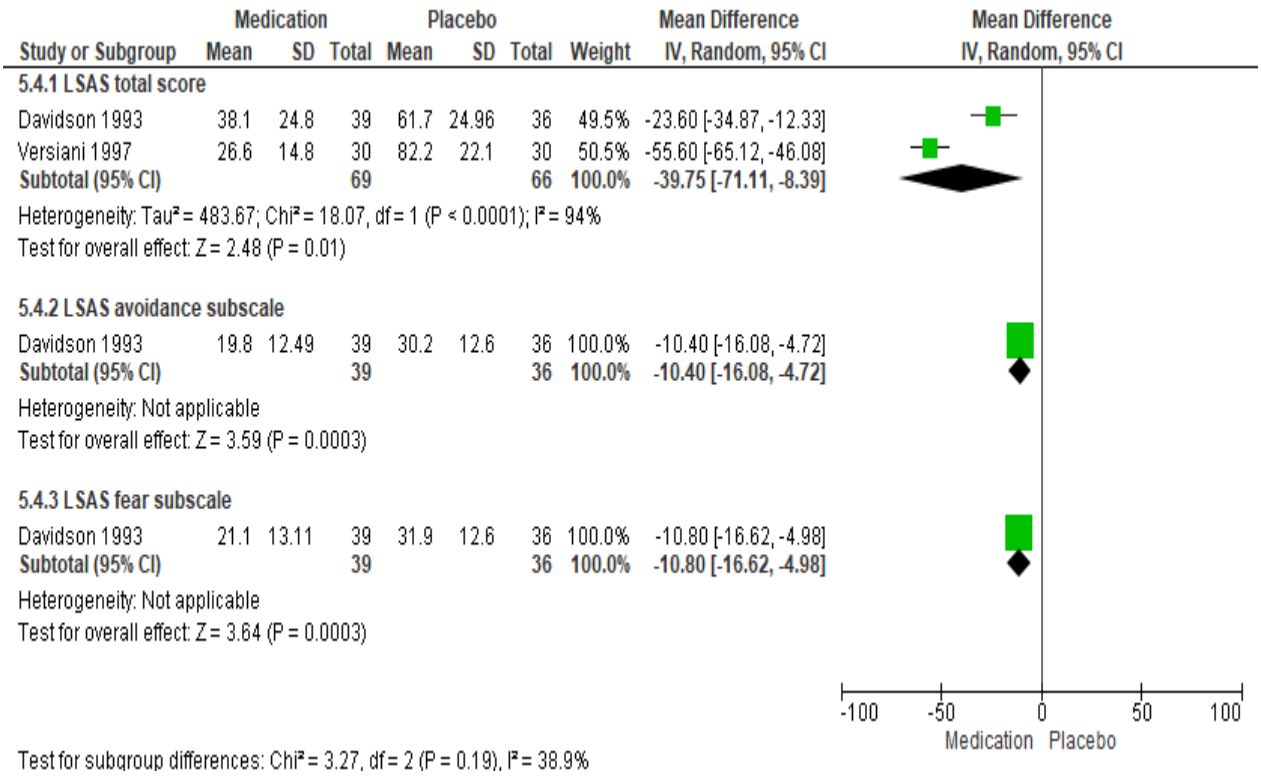
The dropout rate due to adverse events was low in RCTs of clonazepam and bromazepam (2/47; 4%) and did not differ appreciably from that observed in the placebo groups (k = 2, RR 1.68; 95% CI 0.21, 13.13, N = 96; see Analysis 5.3; Connor 1998; Versiani 1997). The evidence that was available for this outcome was of very low quality.



Analysis 5.3. benzodiazepines versus placebo. Adverse events (acute phase): Dropout rate.

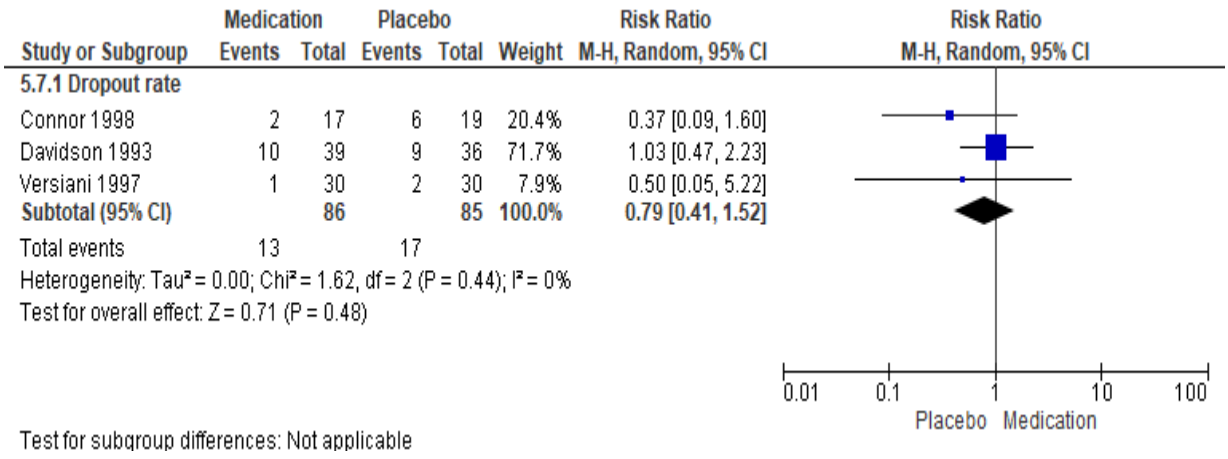
Secondary outcome measures

There was evidence of a reduction of SAD symptoms following treatment with benzodiazepines compared to placebo on the LSAS (k = 2, MD −39.75 points, 95% CI −71.11 to −8.39, N = 135, see Analysis 5.4; Davidson 1993; Versiani 1997) although the evidence was very low in quality. There was considerable heterogeneity in effect size estimates for this outcome (P < 0.001; I^2 = 94%), while effect estimates from both included RCTs demonstrated a beneficial effect of benzodiazepines relative to placebo. Clonazepam was superior to placebo on both the avoidance (MD−10.40 points, 95%CI−16.08 to−4.72, see Analysis 5.4) and fear subscale of the LSAS (MD −10.80 points, 95% CI −16.62 to −4.98, see Analysis 5.4) in one trial with 75 participants (Davidson 1993). The quality of evidence was very low for both outcomes, however.



Analysis 5.4. benzodiazepines versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Similar dropout rates were observed in the medication and placebo arms for the benzodiazepines (k = 3, RR 0.79; 95% CI 0.41 to 1.52, N = 171; see Analysis 5.7; Davidson 1993; Connor 1998; Versiani 1997).



Analysis 5.7. **benzodiazepines versus placebo**. All-cause dropouts (acute phase): Dropout rate.

Comparison 5: benzodiazepines versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: inpatient and outpatient settings **Intervention**: benzodiazepines **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With benzodiazepines**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 4.03** (2.45 to 6.65)	132 (2 studies)	⊕⊕⊖⊖ **Low**[a,b]	There was evidence of a large effect on the number of participants with SAD who responded to treatment (P < 0.00001). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the benzodiazepine groups compared to the placebo groups who responded, 'Very Much Improved' or
	200 per 1000	**806 per 1000** (490 to 1000)				
	Moderate					
	200 per 1000	**806 per 1000** (490 to 1000)				

						'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.68** (0.21 to 13.13)	96 (2 studies)	⨁⊖⊖⊖ **Very low**[a,d]	The proportion of Dropout rates due to adverse events were low in the benzodiazepine groups (2/47; 4%) and did not differ from the placebo groups (P = 0.62).
	20 per 1000	**34 per 1000** (4 to 268)				
	Moderate					
	17 per 1000	**29 per 1000** (4 to 223)				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from 61.7 to 82.2	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **39.75 points lower** (71.11 lower to 8.39 lower)		135 (2 studies)	⨁⊖⊖⊖ **Very low**[a,b,e]	The mean LSAS total anxiety score for the benzodiazepine intervention groups ranged from 26.6 to 38.1 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 30.2	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **10.40 points lower** (16.08 lower to 4.72 lower)		75 (1 study)	⨁⨁⊖⊖ **Low**[a,b]	The mean LSAS avoidance anxiety score for the benzodiazepine intervention group was 19.8 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-	The mean anxiety score for the control group was 31.9	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **10.80 points**		75 (1 study)	⨁⨁⊖⊖ **Low**[a,b]	The mean LSAS fear anxiety score for the benzodiazepine intervention group was 21.1 which

rated: LSAS fear subscale		**lower** (16.62 lower to 4.98 lower)				suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 5. Comparison 5: benzodiazepines versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (wide confidence interval).

[c]Downgraded two levels due to very serious imprecision (small sample size and wide confidence interval).

[d]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

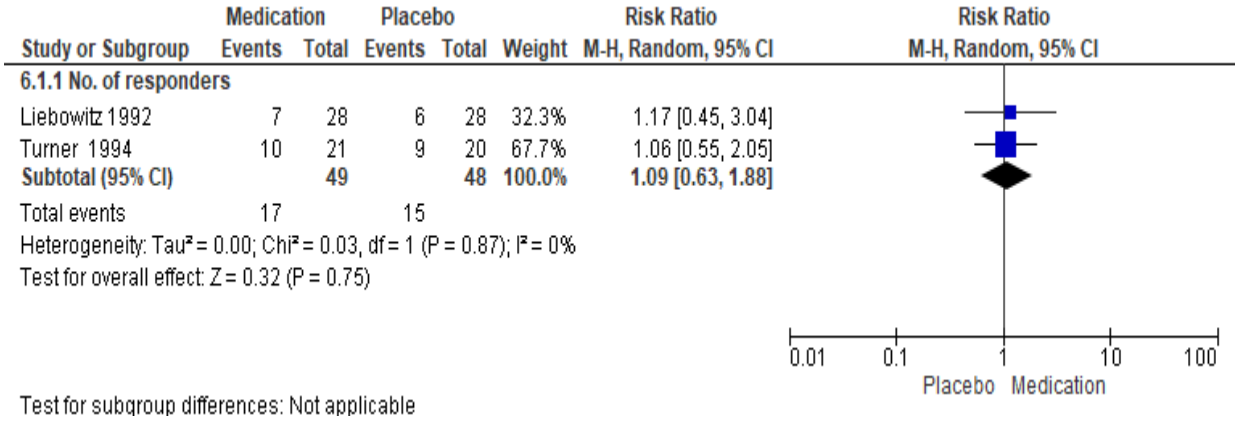
[e]Downgraded two levels due to considerable heterogeneity (I^2 of 94%).

[f]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 6: beta-blockers versus placebo

Primary outcome measures

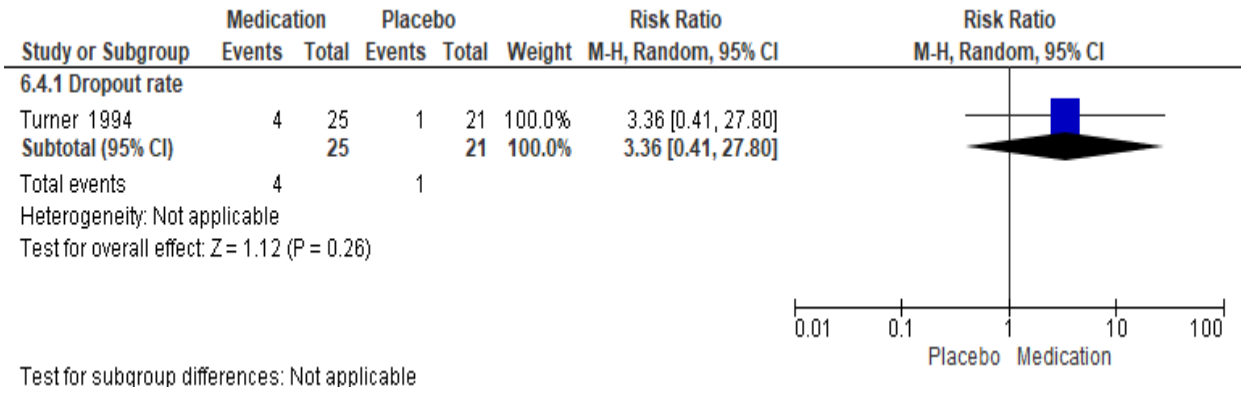
There was no evidence of an effect of atenolol on treatment efficacy in participants with SAD compared to placebo (k = 2, RR 1.09; 95% CI 0.63 to 1.88, N = 97; see Analysis 6.1; Liebowitz 1992; Turner 1994). The evidence that was available for this outcome was of very low quality. Treatment response for the beta-blockers compared to the benzodiazepines, in favour of the benzodiazepines (Chi^2 = 12.02, df = 1, P = 0.0005; I^2 = 91.7%), was observed.



Analysis 6.1. beta-blockers versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

Secondary outcome measures

The proportion of dropouts was more than three times higher in participants receiving atenolol (4/25, 16%) than placebo (1/21, 5%) in a single trial, though this difference was not statistically significant (RR 3.36; 95%CI 0.41 to 27.80; N= 46; Analysis 6.4; Turner 1994).



Analysis 6.4. beta-blockers versus placebo. All-cause dropouts (acute phase): Dropout rate.

<table>
<tr><td colspan="6">Comparison 6: beta-blockers versus placebo for social anxiety disorder (SAD)</td></tr>
<tr><td colspan="6">Patient or population: adults with SAD
Settings: inpatient and outpatient settings
Intervention: beta-blockers
Comparison: placebo</td></tr>
<tr><td rowspan="3">Outcomes</td><td colspan="2">Illustrative comparative risks* (95% CI)</td><td rowspan="3">Relative effect (95% CI)</td><td rowspan="3">No. of participants (studies)</td><td rowspan="3">Quality of the evidence (GRADE)</td><td rowspan="3">Comments</td></tr>
<tr><td>Assumed risk</td><td>Corresponding risk</td></tr>
<tr><td>With placebo</td><td>With beta-blockers</td></tr>
<tr><td rowspan="4">Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)</td><td colspan="2">Study population</td><td rowspan="4">RR 1.09
(0.63 to 1.88)</td><td rowspan="4">97
(2 studies)</td><td rowspan="4">⊕⊖⊖⊖
Very low[a,b]</td><td rowspan="4">There was no evidence of an effect on the number of participants in the beta-blocker groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.75).</td></tr>
<tr><td>312 per 1000</td><td>341 per 1000
(197 to 587)</td></tr>
<tr><td colspan="2">Moderate</td></tr>
<tr><td>332 per 1000</td><td>362 per 1000
(209 to 624)</td></tr>
<tr><td colspan="6">*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; CGI-I: Clinical Global Impressions Improvement scale; RR: risk ratio.</td></tr>
<tr><td colspan="6">GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td></tr>
</table>

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 6. Comparison 6: beta-blockers versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

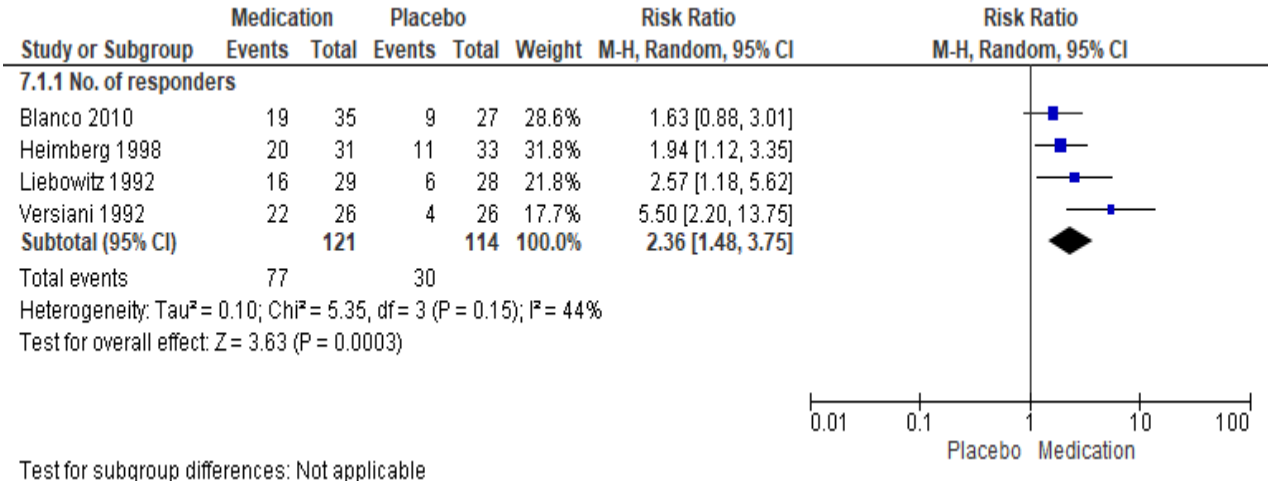
[b]Downgraded two levels due to very serious imprecision (wide confidence interval).

[c]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 7: MAOIs versus placebo

Primary outcome measures

There was evidence of an effect of phenelzine on acute treatment efficacy in participants with SAD compared to placebo (k = 4, RR 2.36; 95% CI 1.48 to 3.75, N = 235; see Analysis 7.1; Blanco 2010; Heimberg 1998; Liebowitz 1992; Versiani 1992), though the evidence was low in quality. There was data indicating greater efficacy over the long term for phenelzine compared to placebo in participants with SAD (k = 2, RR 1.84; 95% CI 1.02 to 3.33, N = 113; see Analysis 7.6; Blanco 2010; Liebowitz 1992). This conclusion was based on very low-quality evidence, however. Treatment efficacy was greater for the MAOIs compared to the anticonvulsant levetiracetam (Chi^2 = 5.86, df = 1, P = 0.02; I^2 = 82.9%) and the GW876008 (Chi^2 = 7.97, df = 1, P = 0.005; I^2 = 87.5%).

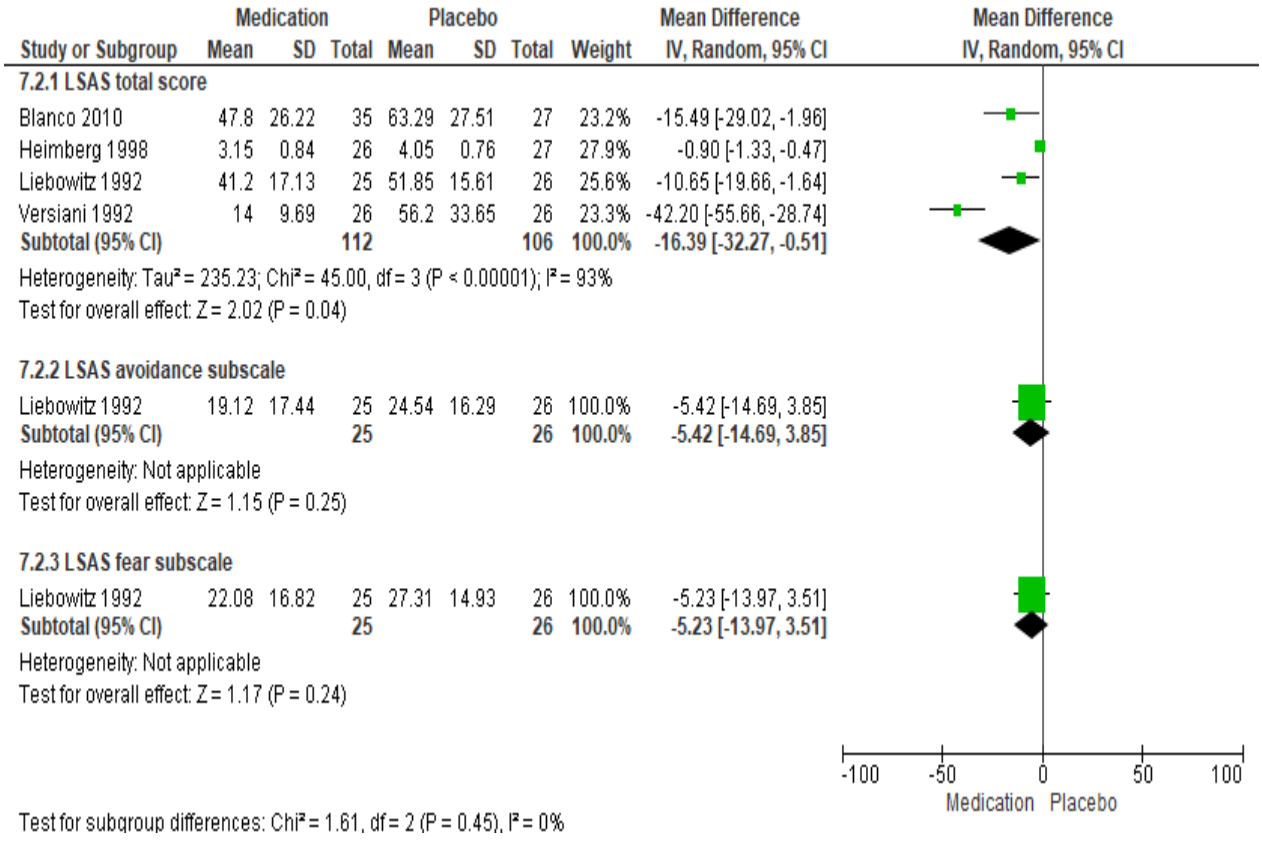


Analysis 7.1. Monoamine oxidase inhibitors versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

Secondary outcome measures

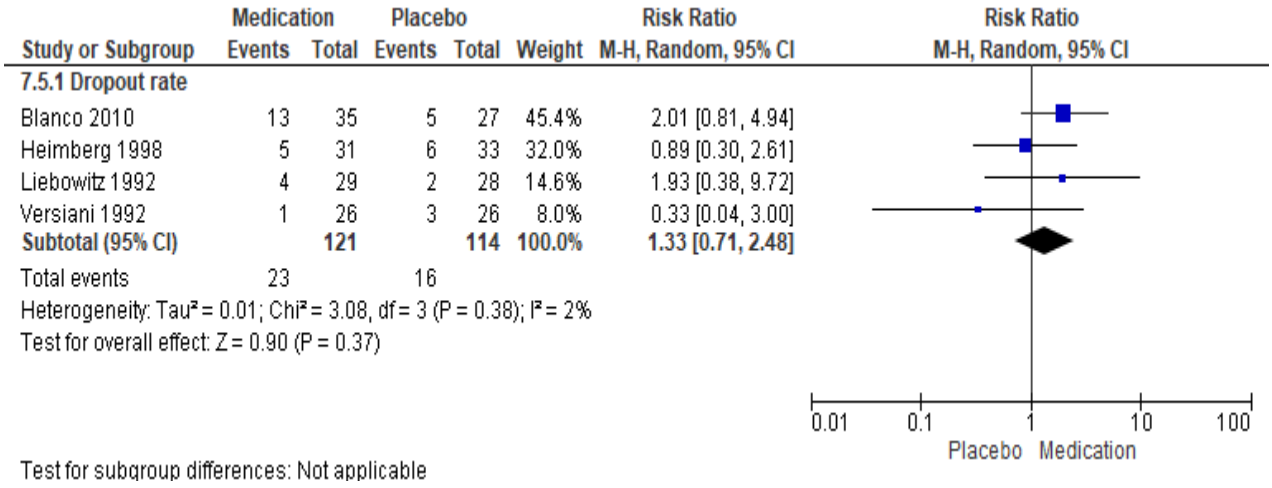
Data on the reduction of SAD symptoms were assessed, measured by the LSAS, in four studies comparing phenelzine to placebo (MD −16.39 points, 95% CI −32.27 to −0.51, N = 218; see

Analysis 7.2; Blanco 2010; Heimberg 1998; Liebowitz 1992; Versiani 1992). There was evidence of benefit even though the data were based on low-quality evidence. Considerable heterogeneity on this outcome (Chi^2 = 45.00, df = 3, P < 0.001; I^2 = 93%) partially reflected the unusually large medication effect observed in Versiani 1992 (MD −42.20 points, 95% CI −55.66 to −28.74). Removing this trial resulted in a substantially reduced and statistically non-significant treatment effect (MD −7.39 points, 95% CI −16.77 to 1.99), with considerable heterogeneity still evident across the effects for the remaining trials (Chi^2 = 8.94, df = 2, P = 0.01; I^2 = 78%). Phenelzine was not superior to placebo on either the avoidance (MD −5.42 points, 95% CI −14.69 to 3.85; see Analysis 7.2) or fear subscale of the LSAS (MD −5.23 points, 95% CI −13.97 to 3.51; see Analysis 7.2) in one trial with 51 participants (Liebowitz 1992). These outcomes were also based on very low-quality evidence, however.



Analysis 7.2. Monoamine oxidase inhibitors versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Similar dropout rates were observed in the medication and placebo arms for the MAOIs (RR 1.33; 95% CI 0.71 to 2.48; see Analysis 7.5) in four trials with 235 participants (Blanco 2010; Heimberg 1998; Liebowitz 1992; Versiani 1992).



Analysis 7.5. Monoamine oxidase inhibitors versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 7: MAOIs versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: inpatient and outpatient settings **Intervention**: MAOIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With MAOIs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 2.36** (1.48 to 3.75)	235 (4 studies)	⊕⊕⊖⊖ **Low**[a,b]	There was evidence of an effect on the number of participants with SAD who responded to treatment (P = 0.0003). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the MAOI groups compared to the placebo groups who responded, 'Very Much Improved' or
	263 per 1000	**621 per 1000** (389 to 987)				
	Moderate					
	274 per 1000	**647 per 1000** (406 to 1000)				

						'Much Improved' on the CGI-I scale.
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from 4.05 to 63.29	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **16.39 points lower** (32.27 lower to 0.51 lower)		218 (4 studies)	⨁⊖⊖⊖ **Very low**[a,c,d]	The mean LSAS total anxiety score for the MAOI intervention groups ranged from 14.0 to 47.8 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 24.54	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **5.42 points lower** (14.69 lower to 3.85 higher)		51 (1 study)	⨁⊖⊖⊖ **Very low**[a,c]	The mean LSAS avoidance anxiety score for the MAOI intervention group was 19.12 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS fear subscale	The mean anxiety score for the control group was 27.31	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **5.23 points lower** (13.97 lower to 3.51 higher)		51 (1 study)	⨁⊖⊖⊖ **Very low**[a,c]	The mean LSAS fear anxiety score for the MAOI intervention group was 22.08 which suggests 'low' social phobia.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 7. Comparison 7: MAOIs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to moderate heterogeneity (I^2 of 44%).

[c]Downgraded two levels due to very serious imprecision (wide confidence interval).

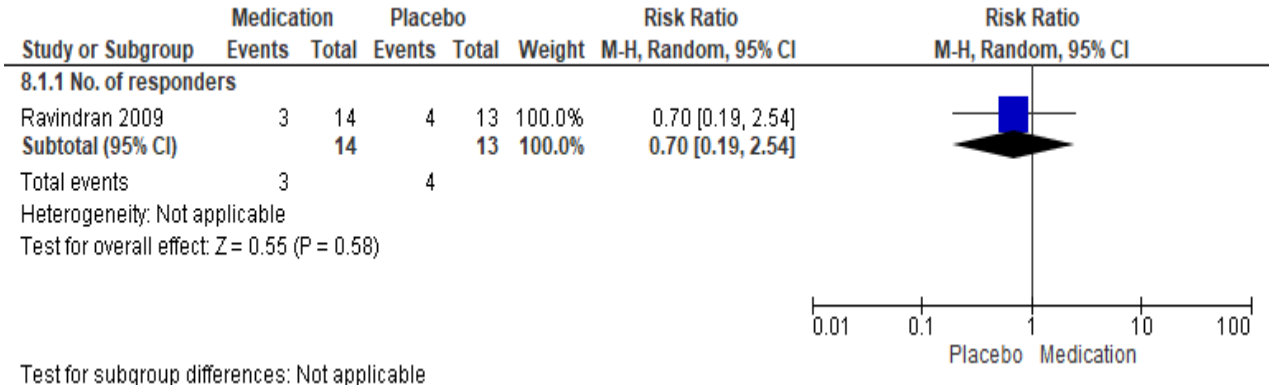
[d]Downgraded two levels due to considerable heterogeneity (I^2 of 93%).

[e]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

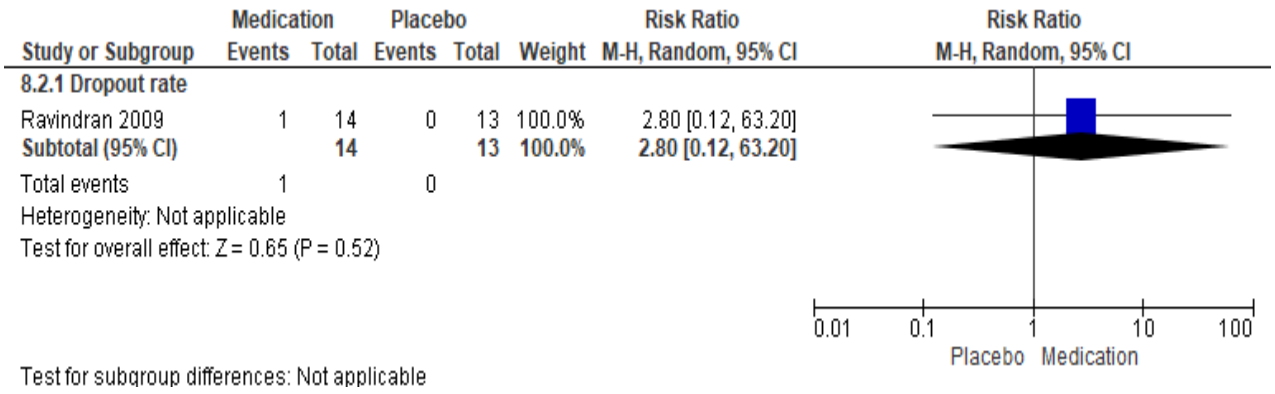
Comparison 8: NARIs versus placebo

Primary outcome measures

There was no evidence of an effect for atomoxetine on treatment efficacy in participants with SAD compared to placebo (RR 0.70; 95% CI 0.19 to 2.54, see Analysis 8.1) in one trial with 27 participants (Ravindran 2009). The evidence that was available for this outcome was of very low quality. There was evidence of an effect for the NARIs compared to the benzodiazepines, in favour of the benzodiazepines (Chi^2 = 6.17, df = 1, P = 0.01; I^2 = 83.8%). Only one of 14 (7%) participants withdrew during 10 weeks of treatment with atomoxetine (see Analysis 8.2); there was no evidence for a difference in the number of participants who withdrew due to treatment-emergent side effects. The evidence that was available for this outcome was of very low quality.



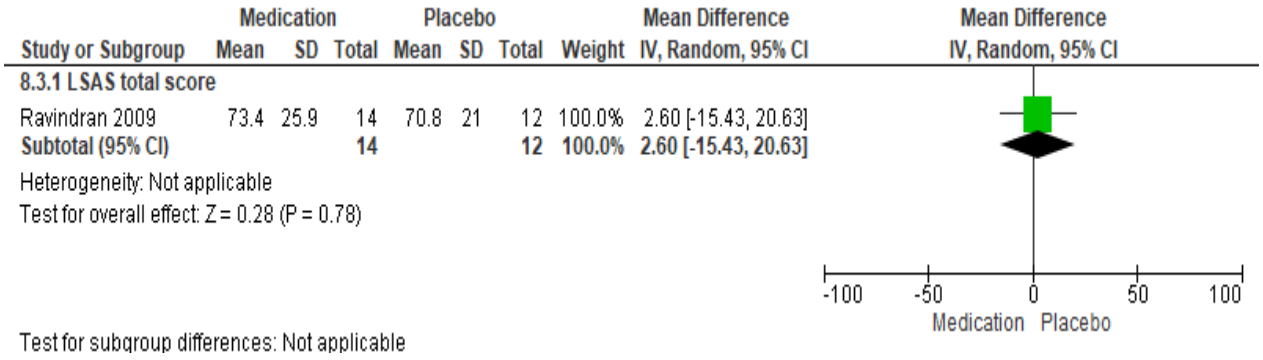
Analysis 8.1. selective noradrenaline reuptake inhibitors versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.



Analysis 8.2. selective noradrenaline reuptake inhibitors versus placebo. Adverse events (acute phase): Dropout rate.

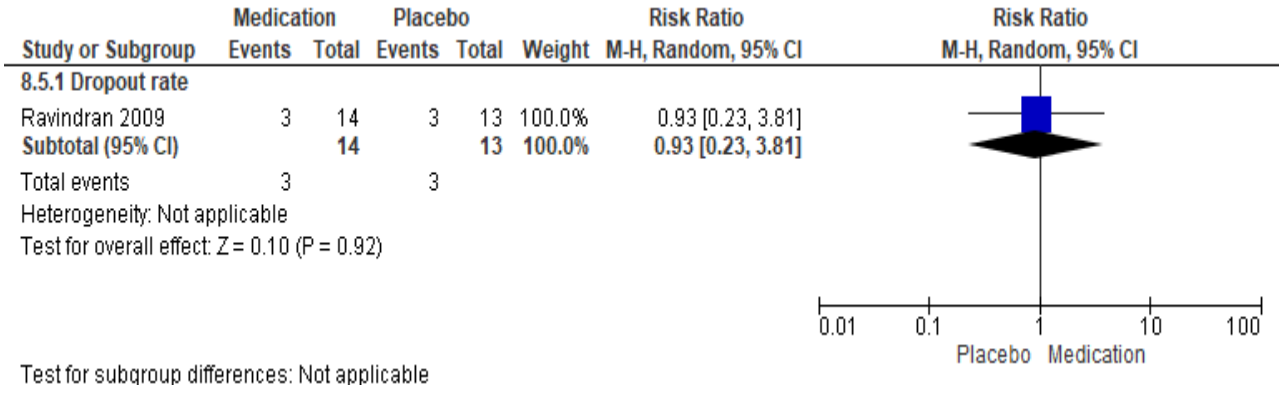
Secondary outcome measures

The review found no evidence for an effect of the single trial that provided data for the reduction of SAD symptoms (i.e. LSAS total symptom severity) when comparing atomoxetine to placebo (MD 2.60 points, 95% CI −15.43 to 20.63, N = 26; see Analysis 8.3). The evidence that was available for this outcome was of very low quality.



Analysis 8.3. selective noradrenaline reuptake inhibitors versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score.

Similar dropout rates were observed in the medication and placebo arm for the NARI (k = 1, RR 0.93; 95% CI 0.23 to 3.81, N = 27; see Analysis 8.5; Ravindran 2009).



Analysis 8.5. selective noradrenaline reuptake inhibitors versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 8: NARIs versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: NARIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With NARIs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 0.70** (0.19 to 2.54)	27 (1 study)	⊕⊖⊖⊖ **Very low**[a,b]	There was no evidence of an effect on the number of participants in the NARI group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.58).
	308 per 1000	**215 per 1000** (58 to 782)				
	Moderate					
	308 per 1000	**216 per 1000** (59 to 782)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 2.80** (0.12 to 63.20)	27 (1 study)	⊕⊖⊖⊖ **Very low**[a,c]	Only 1 of 14 (7%) participants withdrew during 10 weeks of NARI treatment. There was no evidence for a difference in the
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				

						number of participants who withdrew due to adverse events (P = 0.52).
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score for the control group was 70.8	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **2.60 points higher** (15.43 lower to 20.63 higher)		26 (1 study)	⨁⊖⊖⊖ **Very low**[a,b]	The mean LSAS total anxiety score for the NARI intervention group was 73.4 which suggests 'marked' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 8. Comparison 8: NARIs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (small sample size and wide confidence interval).

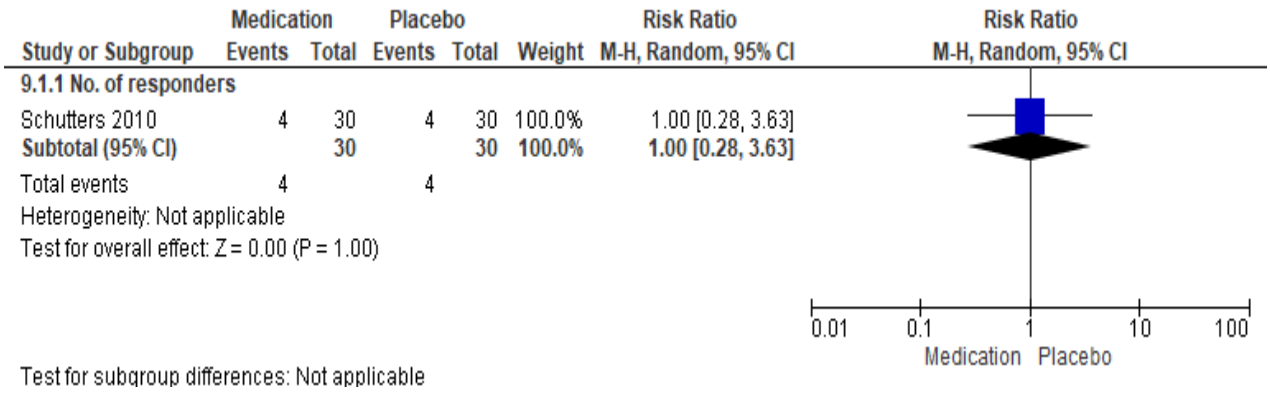
[c]Downgraded two levels due to very serious imprecision (small sample size, few events and wide confidence interval).

[d]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 9: NaSSAs versus placebo

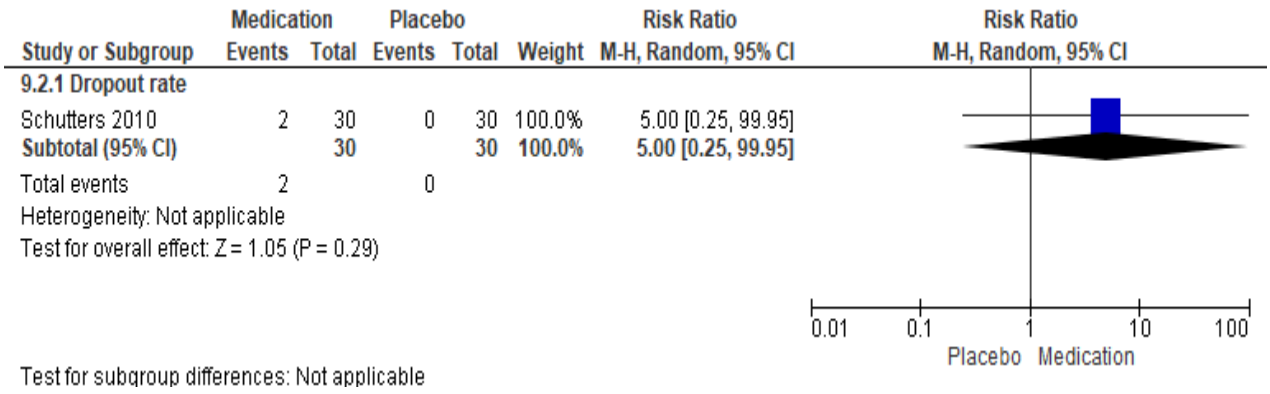
Primary outcome measures

An equal number of participants (4/30, 13%) responded to treatment in both the medication and placebo arms of a trial of mirtazapine (k = 1, RR 1.00; 95% CI 0.28 to 3.63; N = 60, see Analysis 9.1; Schutters 2010). The evidence that was available for this outcome was of very low quality.



Analysis 9.1. noradrenergic and specific serotonergic antidepressants versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

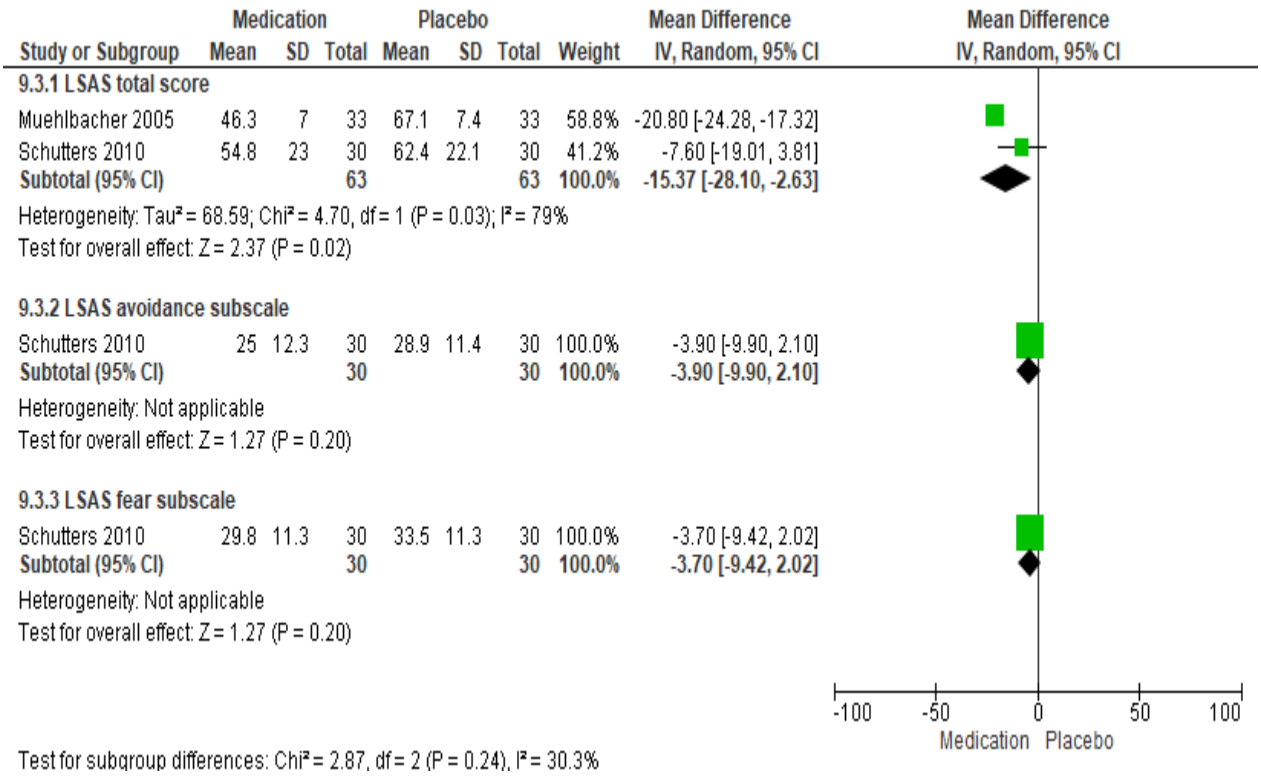
A small proportion of participants receiving mirtazapine dropped out due to adverse events (2/30, 7%) in one trial with 60 participants (Schutters 2010). Although this proportion was larger than that observed for placebo (0/30, 0%), the difference was not statistically significant (P = 0.29, see Analysis 9.2). The evidence that was available for this outcome was of very low quality.



Analysis 9.2. noradrenergic and specific serotonergic antidepressants versus placebo. Adverse events (acute phase): Dropout rate.

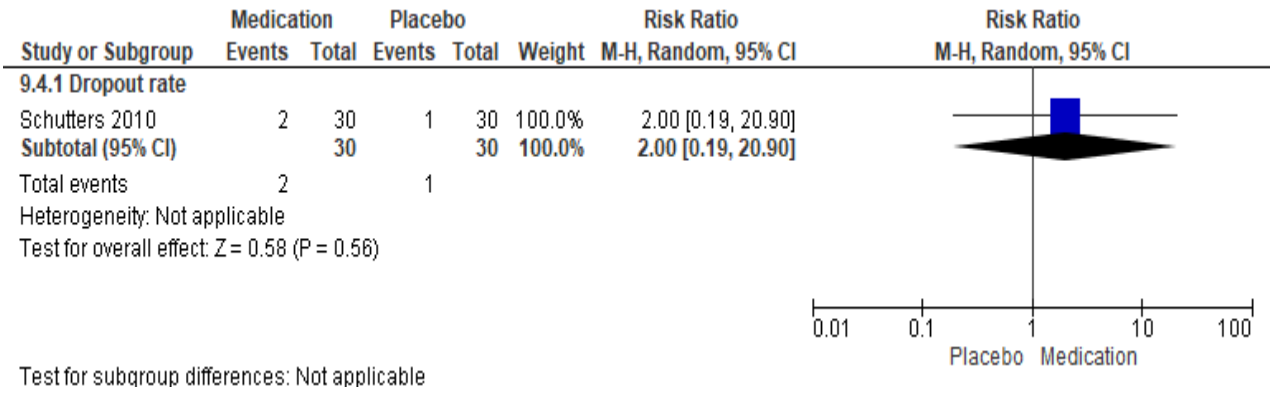
Secondary outcome measures

Evidence of an effect was found for mirtazapine compared to placebo in the reduction of total SAD symptom severity on the LSAS (k = 2, MD −15.37 points, 95%CI −28.10 to −2.63, N = 126; see Analysis 9.3; Schutters 2010; Muehlbacher 2005), even though the evidence was very low in quality. Mirtazapine was not superior to placebo on either the avoidance (MD −3.90 points, 95% CI −9.90 to 2.10, see Analysis 9.3) or fear subscale of the LSAS (MD −3.70 points, 95% CI −9.42 to 2.02, see Analysis 9.3) in one trial with 60 participants (Schutters 2010). This conclusion was based on low-quality evidence.



Analysis 9.3. noradrenergic and specific serotonergic antidepressants versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

A low proportion of participants withdrew for any cause during 12 weeks of treatment with mirtazapine (2/30, 7%), with overall dropout rates like those observed following treatment with placebo (1/30, 3%) (k = 1, RR 2.00; 95% CI 0.19 to 20.90; see Analysis 9.4; Schutters 2010).



Analysis 9.4. noradrenergic and specific serotonergic antidepressants versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 9: NaSSAs compared to placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: NaSSAs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With NaSSAs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.00** (0.28 to 3.63)	60 (1 study)	⊕⊖⊖⊖ **Very low**[a,b]	An equal number of participants (4/30, 13%) responded to treatment in both the NaSSA and placebo groups, however this difference was not statistically significant (P = 1.00).
	133 per 1000	**133 per 1000** (37 to 484)				
	Moderate					
	133 per 1000	**133 per 1000** (37 to 483)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 5.00** (0.25 to 99.95)	60 (1 study)	⊕⊖⊖⊖ **Very low**[a,b]	A small proportion of participants receiving NaSSAs dropped out due to adverse events (2/30, 7%). Although, the difference was not statistically significant (P = 0.29).
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				

Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from 62.4 to 67.1	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **15.37 points lower** (28.10 lower to 2.63 lower)		126 (2 studies)	⨁⊖⊖⊖ **Very low**[a,c,d]	The mean LSAS total anxiety score for the NaSSA intervention groups ranged from 46.3 to 54.8 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 28.9	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **3.90 points lower** (9.90 lower to 2.10 higher)		60 (1 study)	⨁⨁⊖⊖ **Low**[a,c]	The mean LSAS avoidance anxiety score for the NaSSA intervention group was 25.0 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS fear subscale	The mean anxiety score for the control group was 33.5	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **3.70 points lower** (9.42 lower to 2.02 higher)		60 (1 study)	⨁⨁⊖⊖ **Low**[a,c]	The mean LSAS fear anxiety score for the NaSSA intervention group was 29.8 which suggests 'low' social phobia.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 9. Comparison 9: NaSSAs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

[c]Downgraded two levels due to very serious imprecision (wide confidence interval).

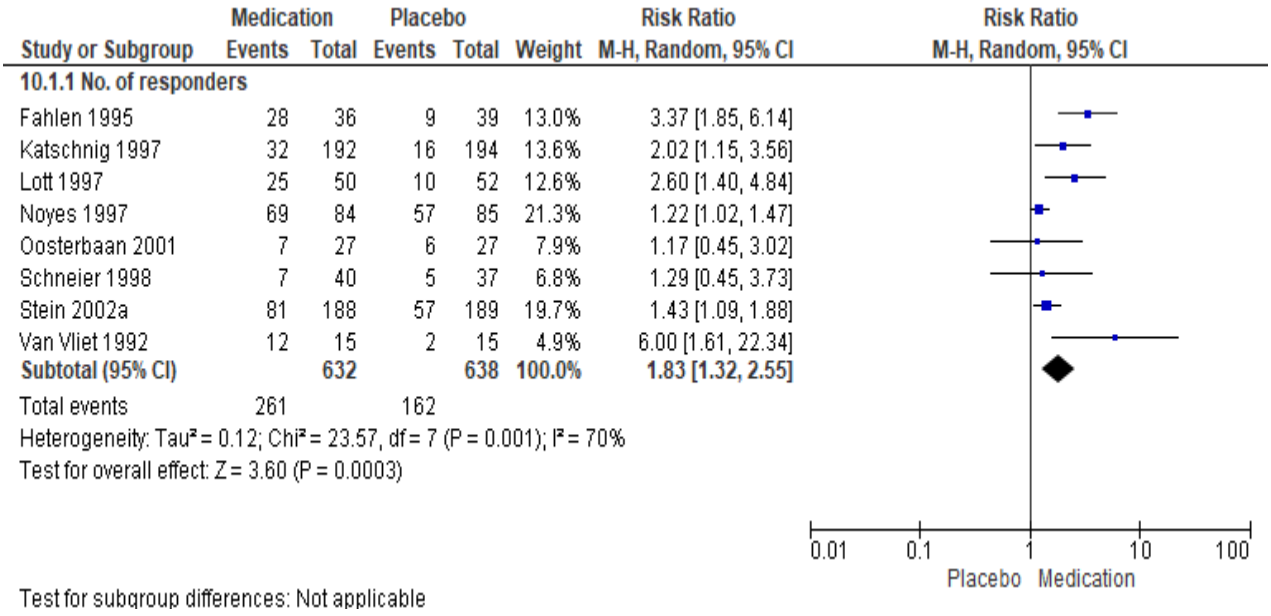
[d]Downgraded two levels due to substantial heterogeneity (I^2 of 79%).

[e]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 10: RIMAs versus placebo

Primary outcome measures

There was evidence of benefit for brofaromine and moclobemide on treatment efficacy in participants with SAD compared to placebo (k = 8, RR 1.83; 95% CI 1.32 to 2.55, N = 1270; see Analysis 10.1; Fahlen 1995; Katschnig 1997; Lott 1997; Noyes 1997; Oosterbaan 2001; Schneier 1998; Stein 2002a; Van Vliet 1992), even though the evidence was low quality. There was substantial heterogeneity in effect size estimates for this outcome (Chi 2 = 23.57, df = 7, P = 0.001; I^2 = 70%). This was partly due to large medication effects for earlier, small studies (i.e. Fahlen 1995; Van Vliet 1992), with moderate heterogeneity evident after excluding these trials (Chi^2 = 8.86, df = 5, P = 0.11; I^2 = 44%). Evidence for efficacy of the RIMAs was still apparent after removing these two studies (k = 6, RR 1.49; 95% CI 1.17 to 1.90, N = 1165).



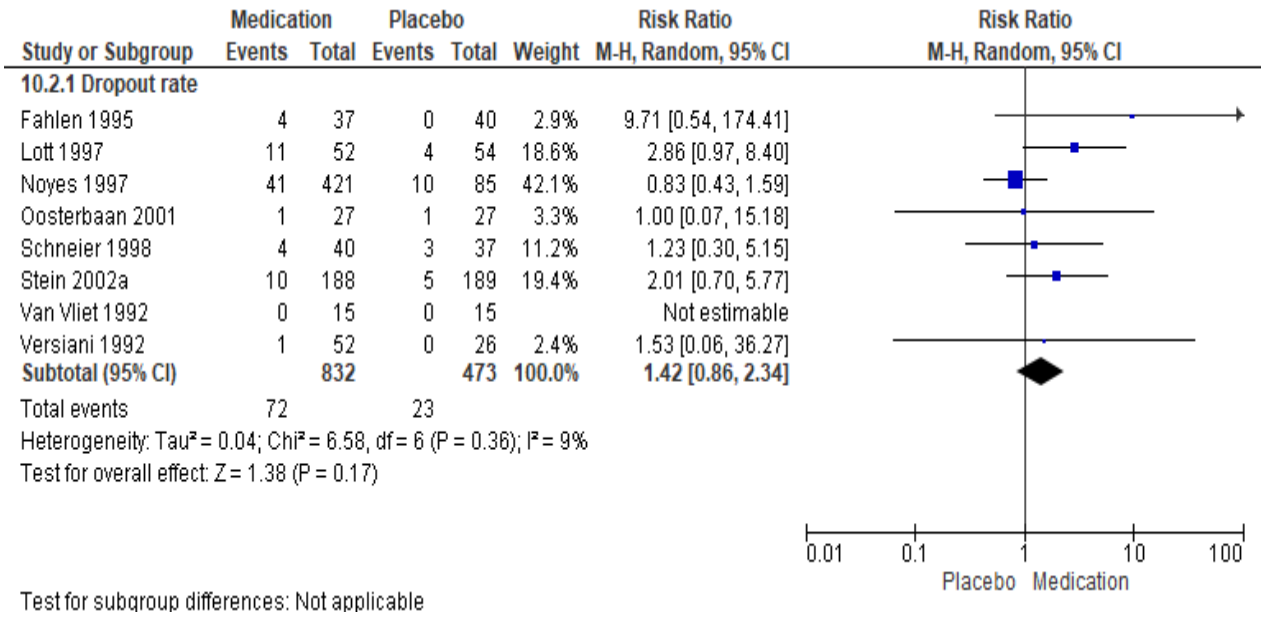
Analysis 10.1. reversible inhibitors of monoamine oxidase A versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

Given differences in the mechanism of action for moclobemide and brofaromine and the lack of availability for the latter, a post hoc analysis was conducted for moclobemide only. There

was evidence that this medication was efficacious compared to placebo (k = 5, RR 1.32; 95% CI 1.14 to 1.52, N = 1063; P < 0.001).

Comparisons between medication classes revealed that response to the RIMAs was smaller than that observed for the benzodiazepines (Chi^2 = 6.63, df = 1, P = 0.01; I^2 = 84.9%).

Dropout rates due to adverse events were low in RCTs of brofaromine and moclobemide and equivalent to those observed in the placebo arms (72/83; 9%) (k = 8, RR 1.42; 95% CI 0.86 to 2.34, N = 1305; see Analysis 10.2). The evidence that was available for this outcome was of very low quality.

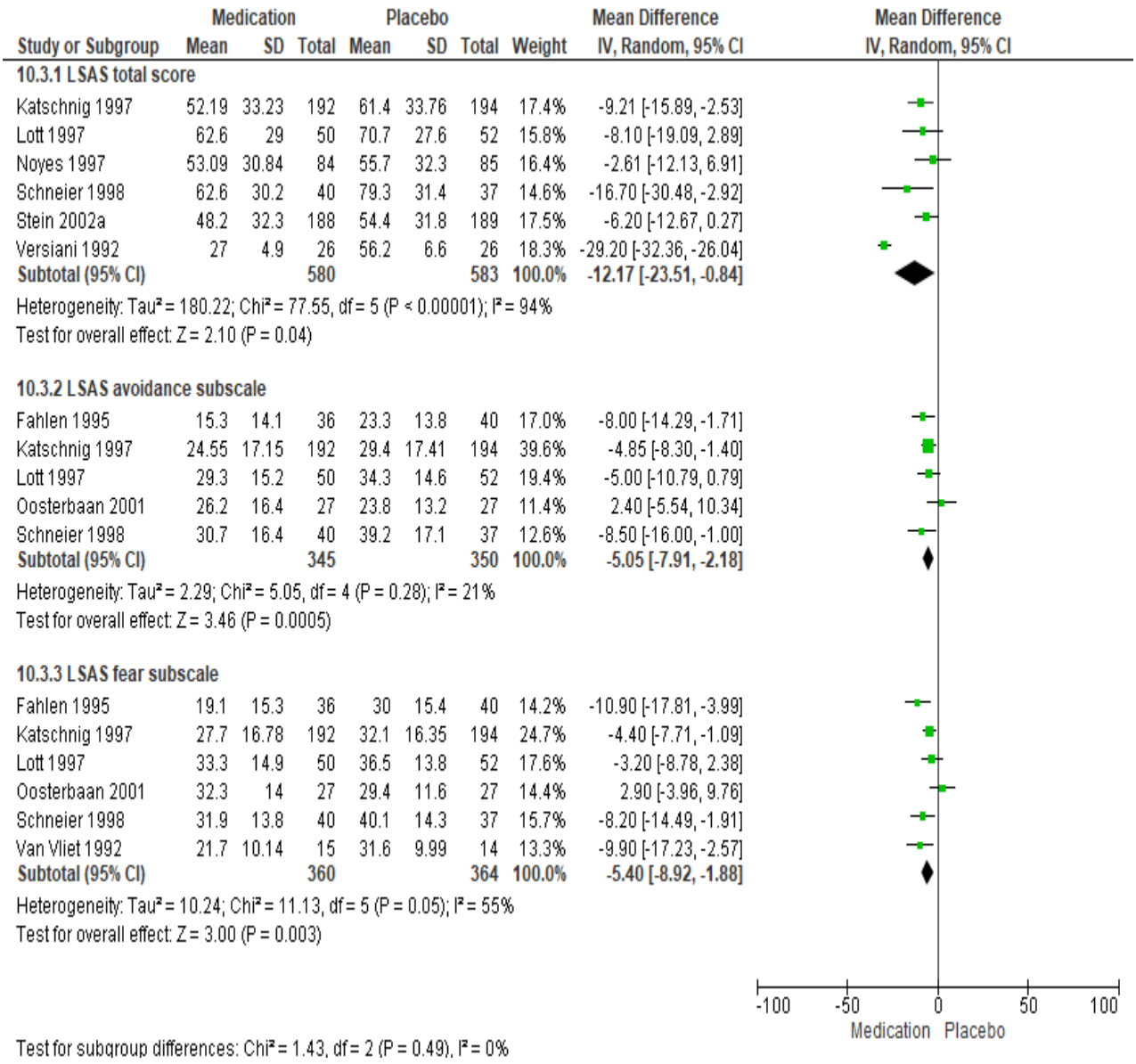


Analysis 10.2. reversible inhibitors of monoamine oxidase A versus placebo. Adverse events (acute phase): Dropout rate.

Secondary outcome measures

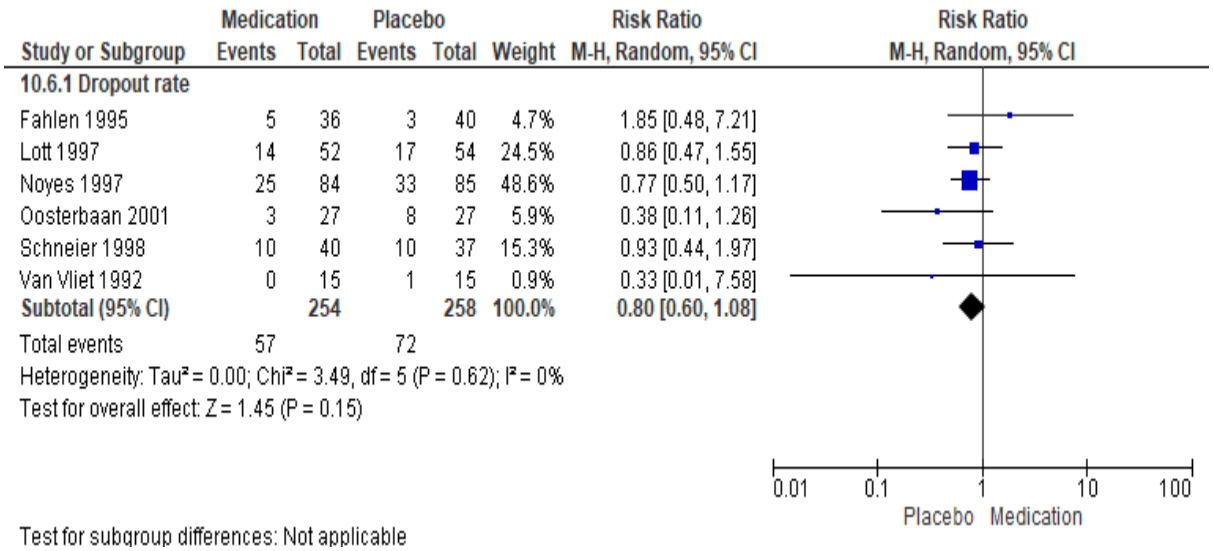
There was evidence for a reduction of SAD symptom severity on the LSAS in six studies comparing brofaromine or moclobemide to placebo (MD −12.17 points, 95% CI −23.51, −0.84,

N = 1163; see Analysis 10.3; Katschnig 1997; Lott 1997; Noyes 1997; Schneier 1998; Stein 2002a; Versiani 1992), although the quality of evidence was very low. Considerable heterogeneity was observed for this outcome (Chi^2 = 77.55, df = 5, P < 0.001; I^2 = 94%), but most disappeared after removing Versiani 1992 (Chi^2 = 3.14, df = 4, P = 0.53; I^2 = 0%), with data from the remaining five trials still supporting the efficacy of this class of medications (MD = −7.59 points, 95% CI −11.35 to −3.84). Brofaromine and moclobemide were superior to placebo on both the avoidance (k = 5, MD −5.05 points, 95%CI−7.91 to−2.18, N = 695; see Analysis 10.3; Fahlen 1995; Katschnig 1997; Lott 1997; Oosterbaan 2001; Schneier 1998) and fear subscale of the LSAS (k = 6, MD −5.40 points, 95% CI −8.92 to −1.88, N = 724; see Analysis 10.3; Fahlen 1995; Katschnig 1997; Lott 1997; Oosterbaan 2001; Schneier 1998; Van Vliet 1992). Evidence from the social subscale was low in quality. The review observed moderate to substantial variability in the effects of these agents on the fear subscale (Chi^2 = 11.13, df = 5, P = 0.05; I^2 = 55%), and the evidence was very low in quality.



Analysis 10.3. reversible inhibitors of monoamine oxidase A versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Similar dropout rates were observed in the medication and placebo arms for the RIMAs (k = 6, RR 0.80; 95% CI 0.60 to 1.08, N = 512; see Analysis 10.6; Fahlen 1995; Katschnig 1997; Lott 1997; Oosterbaan 2001; Schneier 1998; Van Vliet 1992).



Analysis 10.6. reversible inhibitors of monoamine oxidase A versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 10: RIMAs versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: inpatient and outpatient settings **Intervention**: RIMAs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With RIMAs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.83** (1.32 to 2.55)	1270 (8 studies)	⊕⊕⊖⊖ **Low**[a,b]	There was evidence of benefit on the number of participants with SAD who responded to treatment (P = 0.0003). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the RIMA groups compared to the placebo groups who responded, 'Very Much Improved' or
	254 per 1000	**465 per 1000** (335 to 647)				
	Moderate					
	207 per 1000	**379 per 1000** (273 to 528)				

						'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.42** (0.86 to 2.34)	1305 (8 studies)	⨁⊖⊖⊖ **Very low**[a,c]	Dropout rates due to adverse events were low in the RIMA groups and equivalent to those observed in the placebo groups (72/83; 9%).
	49 per 1000	**69 per 1000** (42 to 114)				
	Moderate					
	32 per 1000	**45 per 1000** (28 to 75)				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from 54.4 to 79.3	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **12.17 points lower** (23.51 lower to 0.84 lower)		1163 (6 studies)	⨁⊖⊖⊖ **Very low**[a,d,e]	The mean LSAS total anxiety score for the RIMA intervention groups ranged from 27.0 to 62.6 which suggests low to 'moderate' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score ranged across control groups from 23.3 to 39.2	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **5.05 points lower** (7.91 lower to 2.18 lower)		695 (5 studies)	⨁⨁⊖⊖ **Low**[a,e]	The mean LSAS avoidance anxiety score for the RIMA intervention groups ranged from 15.3 to 30.7 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS fear subscale	The mean anxiety score ranged across control groups from 29.4 to 40.1	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **5.40 points lower** (8.92 lower to 1.88 lower)		724 (6 studies)	⨁⊖⊖⊖ **Very low**[a,e,f]	The mean LSAS fear anxiety score for the RIMA intervention groups ranged from 19.1 to 33.3 which suggests 'low' social phobia.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.

Summary of Findings Table 10. Comparison 10: RIMAs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to substantial heterogeneity (I^2 of 70%).

[c]Downgraded two levels due to very serious imprecision (few events and wide confidence interval).

[d]Downgraded two levels due to considerable heterogeneity (I^2 of 94%).

[e]Downgraded two levels due to very serious imprecision (wide confidence interval).

[f]Downgraded two levels due to moderate heterogeneity (I^2 of 55%).

[g]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

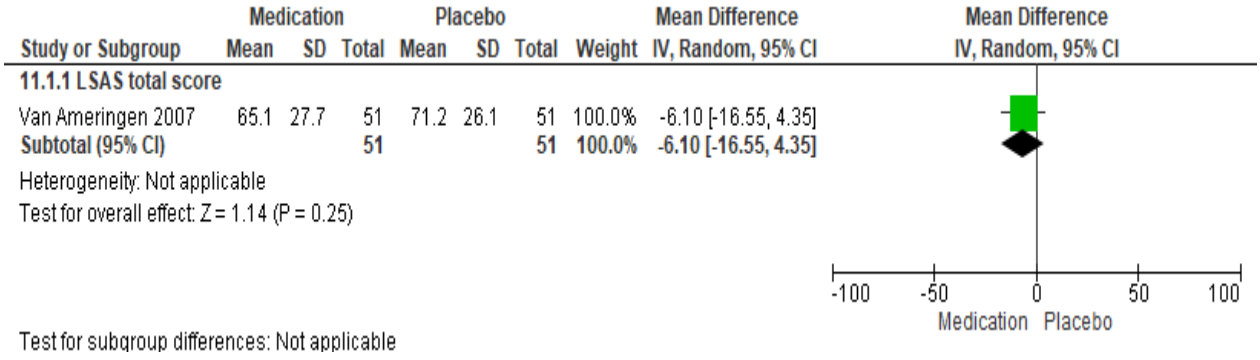
Comparison 11: SARIs versus placebo

Primary outcome measures

There were no data available to assess treatment efficacy and dropouts due to adverse events.

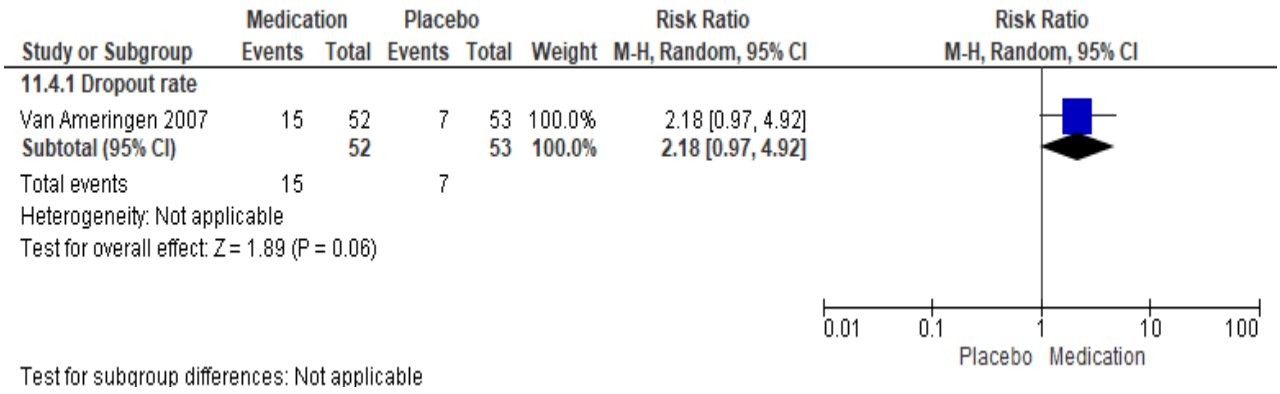
Secondary outcome measures

There was no evidence of an effect of nefazodone compared to placebo on the reduction of total SAD symptom severity on the LSAS (MD −6.10 points, 95% CI −16.55 to 4.35, see Analysis 11.1) in one trial with 102 participants (Van Ameringen 2007). The evidence that was available for this outcome was of very low quality.



Analysis 11.1. serotonin antagonist and reuptake inhibitors versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score.

The proportion of dropouts was more than twice as high in participants receiving nefazodone (15/52, 29%) compared to the placebo group (7/53, 13%), though this difference was not statistically significant (k = 1, RR 2.18; 95% CI 0.97 to 4.92; see Analysis 11.4; Van Ameringen 2007).



Analysis 11.4. serotonin antagonist and reuptake inhibitors versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 11: SARIs versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: SARIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With SARIs**				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score for the control group was 71.2	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **6.10 points lower** (16.55 lower to 4.35 higher)		102 (1 study)	⨁⊖⊖⊖ **Very low**[a,b]	The mean LSAS total anxiety score for the SARI intervention group was 65.1 which suggests 'marked' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **LSAS**: Liebowitz Social Anxiety Scale.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 11. Comparison 11: SARIs versus placebo for social anxiety disorder (SAD).

Footnotes

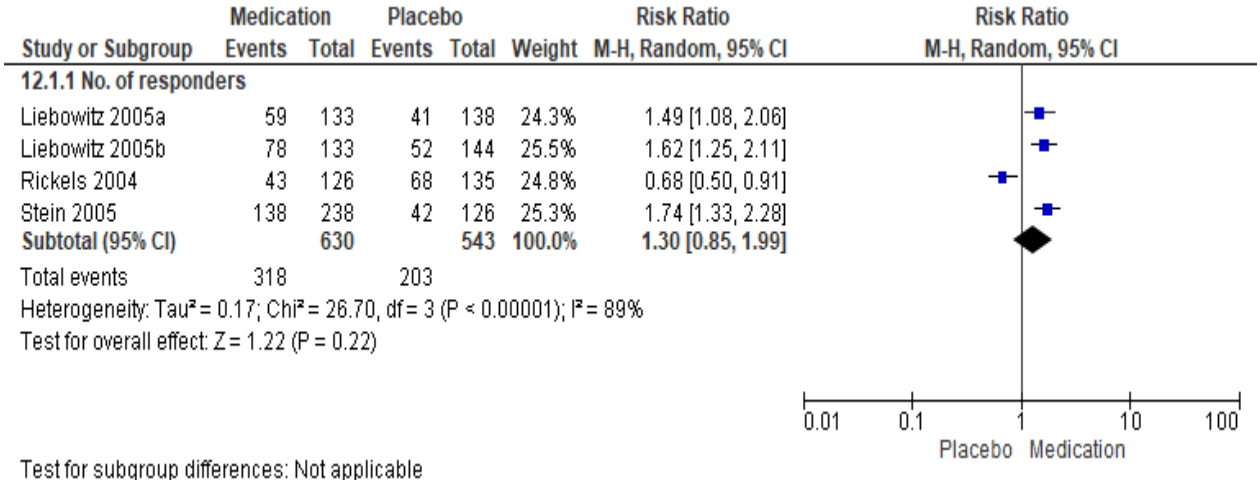
[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to very serious imprecision (wide confidence interval).

Comparison 12: SNRIs versus placebo

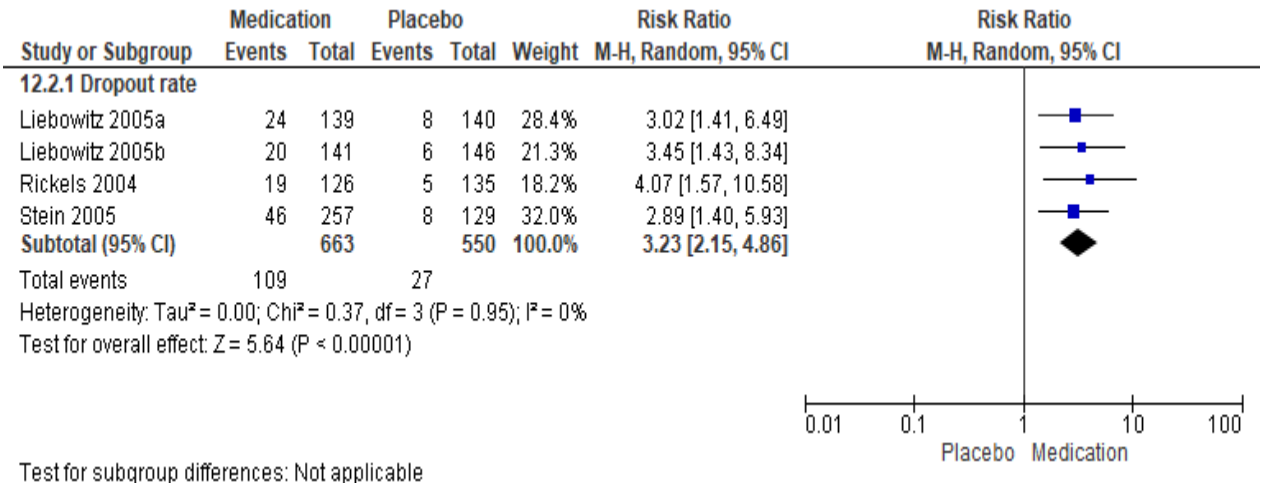
Primary outcome measures

There was no evidence of an effect of venlafaxine on treatment efficacy in participants with SAD compared to placebo (RR 1.30; 95% CI 0.85 to 1.99, see Analysis 12.1) in four trials with 1173 participants (Liebowitz 2005a; Liebowitz 2005b; Rickels 2004; Stein 2005). The evidence that was available for this outcome was of low quality. Considerable heterogeneity was observed for this outcome (Chi^2 = 26.70, df = 3, P < 0.001; I^2 = 89%). There was evidence of an effect of the SNRIs compared to the benzodiazepines (Chi^2 = 11.39, df = 1, P = 0.0007; I^2 = 91.2%) however, favouring the benzodiazepines.



Analysis 12.1. serotonin and norepinephrine reuptake inhibitors versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

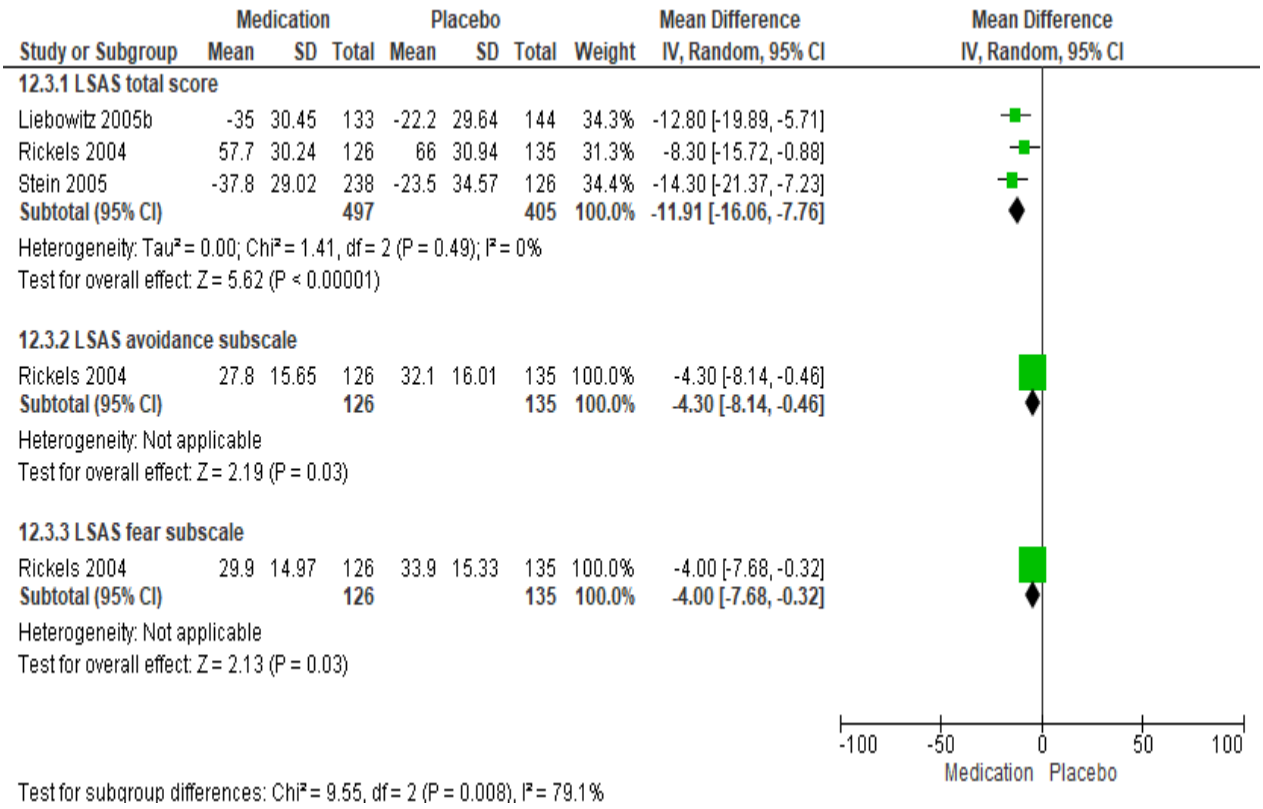
The proportion of dropouts due to adverse events was more than three times as high in participants receiving venlafaxine (109/663, 16%) compared to placebo (27/550, 5%), a statistically significant difference (k = 4, RR 3.23, 95% CI 2.15 to 4.86; Analysis 12.2). The evidence that was available for this outcome was of moderate quality.



Analysis 12.2. serotonin and norepinephrine reuptake inhibitors versus placebo. Adverse events (acute phase): Dropout rate.

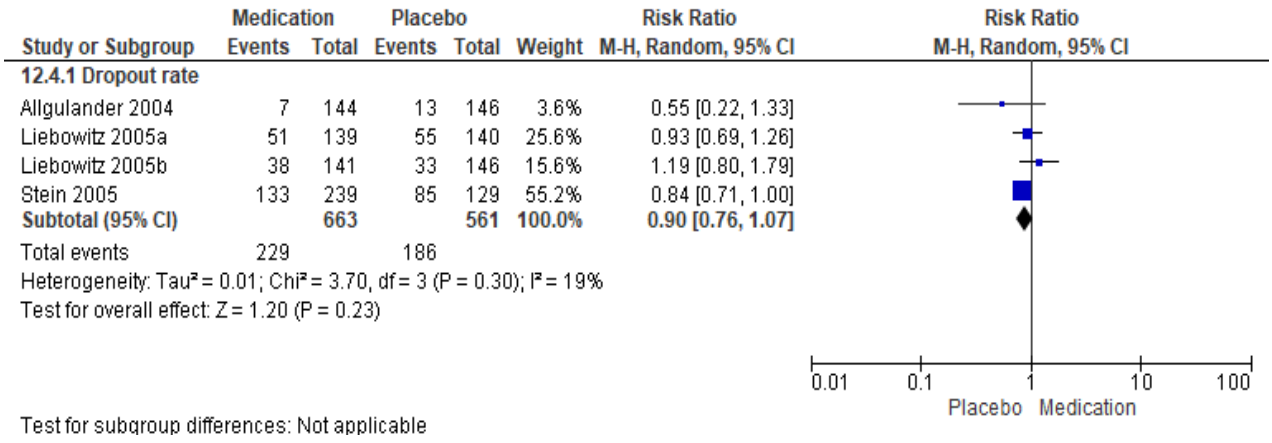
Secondary outcome measures

There was evidence of benefit for venlafaxine compared to placebo on the reduction of total SAD symptom severity on the LSAS (k = 3; MD −11.91 points, 95% CI −16.06 to −7.76) based on moderate-quality evidence. This outcome was calculated using a combination of endpoint (for Rickels 2004) and change-from baseline scores (from Liebowitz 2005b and Stein 2005) across a total of 903 participants. Venlafaxine was superior to placebo on both the avoidance (k = 1, MD −4.30 points, 95% CI −8.14 to −0.46, N = 261; see Analysis 12.3) and fear subscale of the LSAS (k = 1, MD −4.00 points, 95% CI −7.68 to −0.32, N = 261; see Analysis 12.3) for a single trial providing data on these outcomes (Rickels 2004). The evidence on the remaining outcomes of avoidance and fear was low in quality.



Analysis 12.3. serotonin and norepinephrine reuptake inhibitors versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Similar dropout rates were found in the medication and placebo arms for the SNRIs (k = 4, RR 0.90; 95% CI 0.76 to 1.07, N = 1224; see Analysis 12.4; Allgulander 2004; Liebowitz 2005a; Liebowitz 2005b; Stein 2005).



Analysis 12.4. serotonin and norepinephrine reuptake inhibitors versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 12: SNRIs compared to placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: SNRIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With SNRIs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.30** (0.85 to 1.99)	1173 (4 studies)	⊕⊕⊖⊖ **Low**[a,b]	There was no evidence of an effect on the number of participants in the SNRI groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.22).
	374 per 1000	**486 per 1000** (460 to 610)				
	Moderate					
	347 per 1000	**451 per 1000** (465 to 617)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 3.23** (2.15 to 4.86)	1213 (4 studies)	⊕⊕⊕⊖ **Moderate**[a]	The proportion of dropouts due to adverse events was more than three times as high in participants receiving SNRIs (109/663, 16%)
	49 per 1000	**159 per 1000** (106 to 239)				
	Moderate					
	49 per 1000	**158 per 1000** (105 to 238)				

						compared to placebo (27/550, 5%), a statistically significant difference (P < 0.00001).
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from -22.2 to 66.0	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **11.91 points lower** (16.06 lower to 7.76 lower)		902 (3 studies)	⨁⨁⨁⊖ **Moderate**[a]	The mean LSAS total anxiety score for the SNRI intervention groups ranged from -35.0 to 57.7 which suggests 'low' to 'moderate' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score for the control group was 32.1	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **4.30 points lower** (8.14 lower to 0.46 lower)		261 (1 study)	⨁⨁⊖⊖ **Low**[a,c]	The mean LSAS avoidance anxiety score for the SNRI intervention group was 27.8 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS fear subscale	The mean anxiety score for the control group was 33.9	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **4.00 points lower** (7.68 lower to 0.32 lower)		261 (1 study)	⨁⨁⊖⊖ **Low**[a,c]	The mean LSAS fear anxiety score for the SNRI intervention group was 29.9 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect.						

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 12. Comparison 12: SNRIs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to considerable heterogeneity (I^2 of 89%).

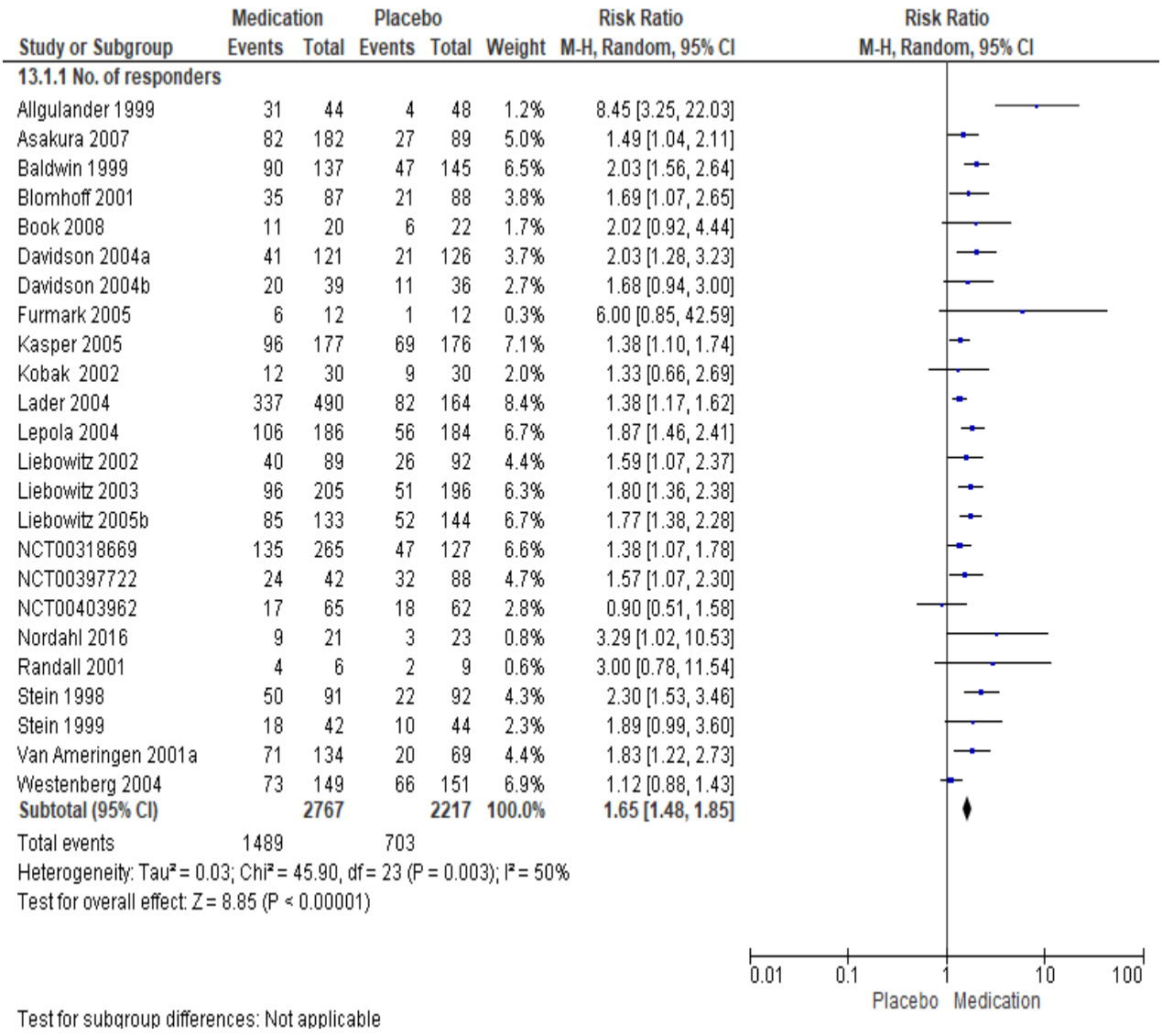
[c]Downgraded two levels due to very serious imprecision (wide confidence interval).

[d]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 13: SSRIs versus placebo

Primary outcome measures

There was evidence of treatment efficacy for paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram compared to placebo in participants with SAD (k = 24, RR 1.65; 95% CI 1.48 to 1.85, N = 4984; see Analysis 13.1; Allgulander 1999; Asakura 2007; Baldwin 1999; Blomhoff 2001; Book 2008; Davidson 2004a; Davidson 2004b; Furmark 2005; NCT00318669; NCT00403962; NCT00397722; Kasper 2005; Kobak 2002; Lader 2004; Lepola 2004; Liebowitz 2002; Liebowitz 2003; Liebowitz 2005b; Nordahl 2016; Randall 2001; Stein 1998; Stein 1999; Van Ameringen 2001a; Westenberg 2004), though the evidence was very low in quality.

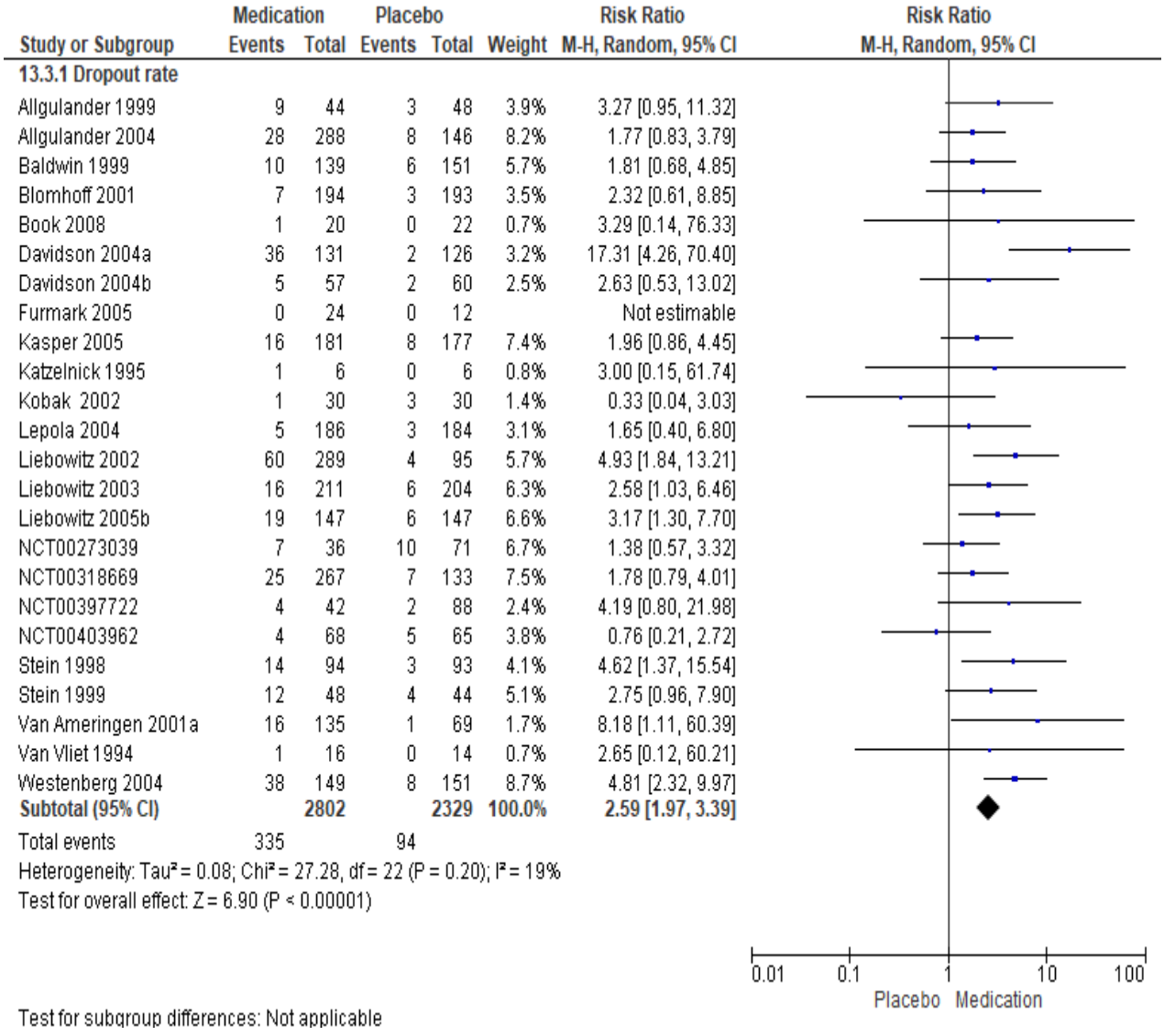


Analysis 13.1. selective serotonin reuptake inhibitors versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

There was evidence for a smaller response to treatment with the anticonvulsant levetiracetam (Chi^2 = 8.02, df = 1, P = 0.005; I^2 = 87.5%) compared to the benzodiazepines (Chi^2 = 11.58, df = 1, P = 0.0007; I^2 = 91.4%) and the GW876008 (Chi^2 = 12.28, df = 1; P = 0.0005, I^2 = 91.9%), although the response favoured the benzodiazepines.

The proportion of dropouts due to adverse events was approximately three times higher amongst participants receiving SSRIs compared to placebo. This difference was statistically

significant (RR 2.59; 95% CI 1.97 to 3.39, N = 5131; see Analysis 13.3). Twelve per cent of participants across 24 RCTs who received medication withdrew prior to study endpoint. The evidence that was available for this outcome was of low quality.

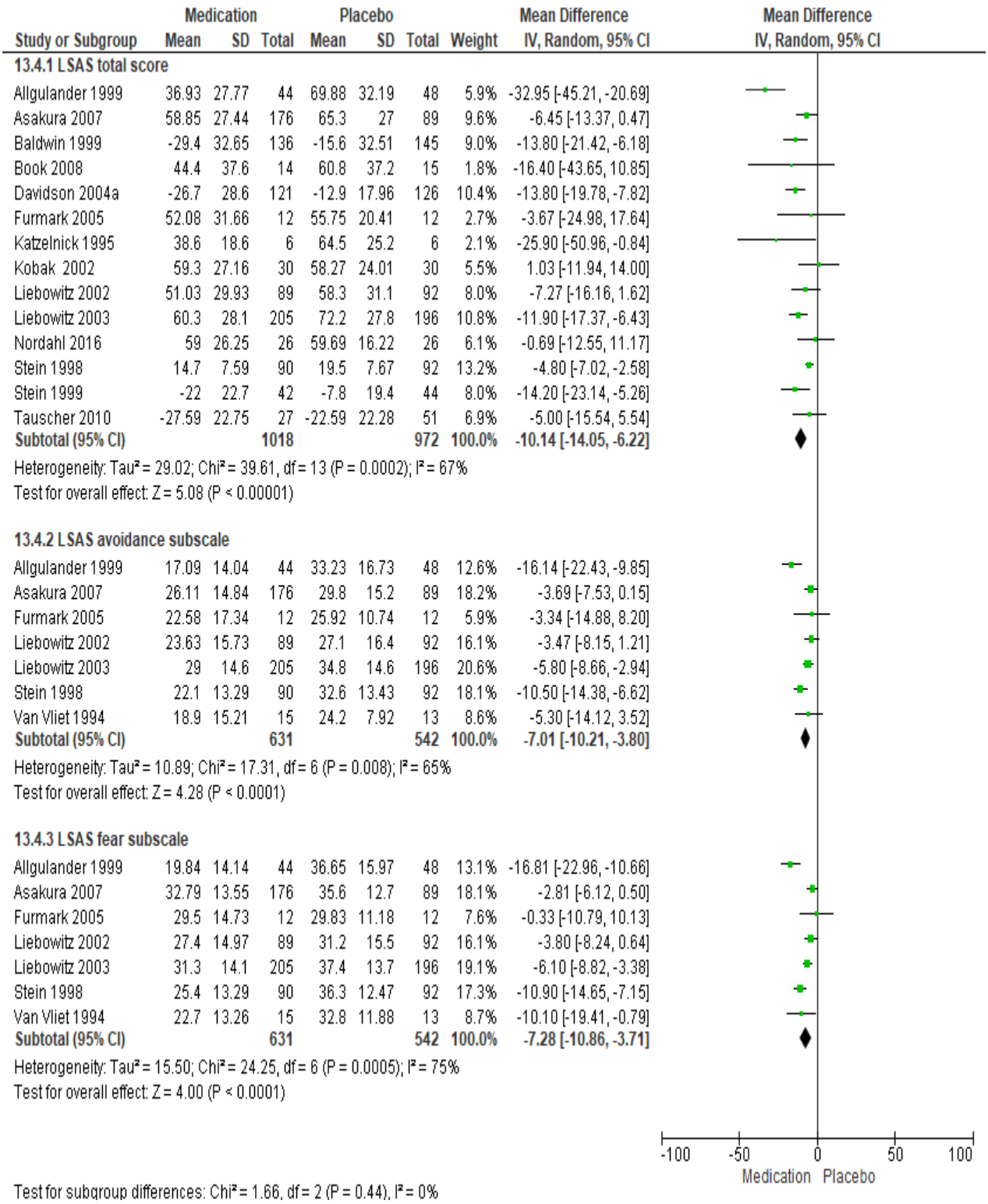


Analysis 13.3. selective serotonin reuptake inhibitors versus placebo. Adverse events (acute phase): Dropout rate.

Secondary outcome measures

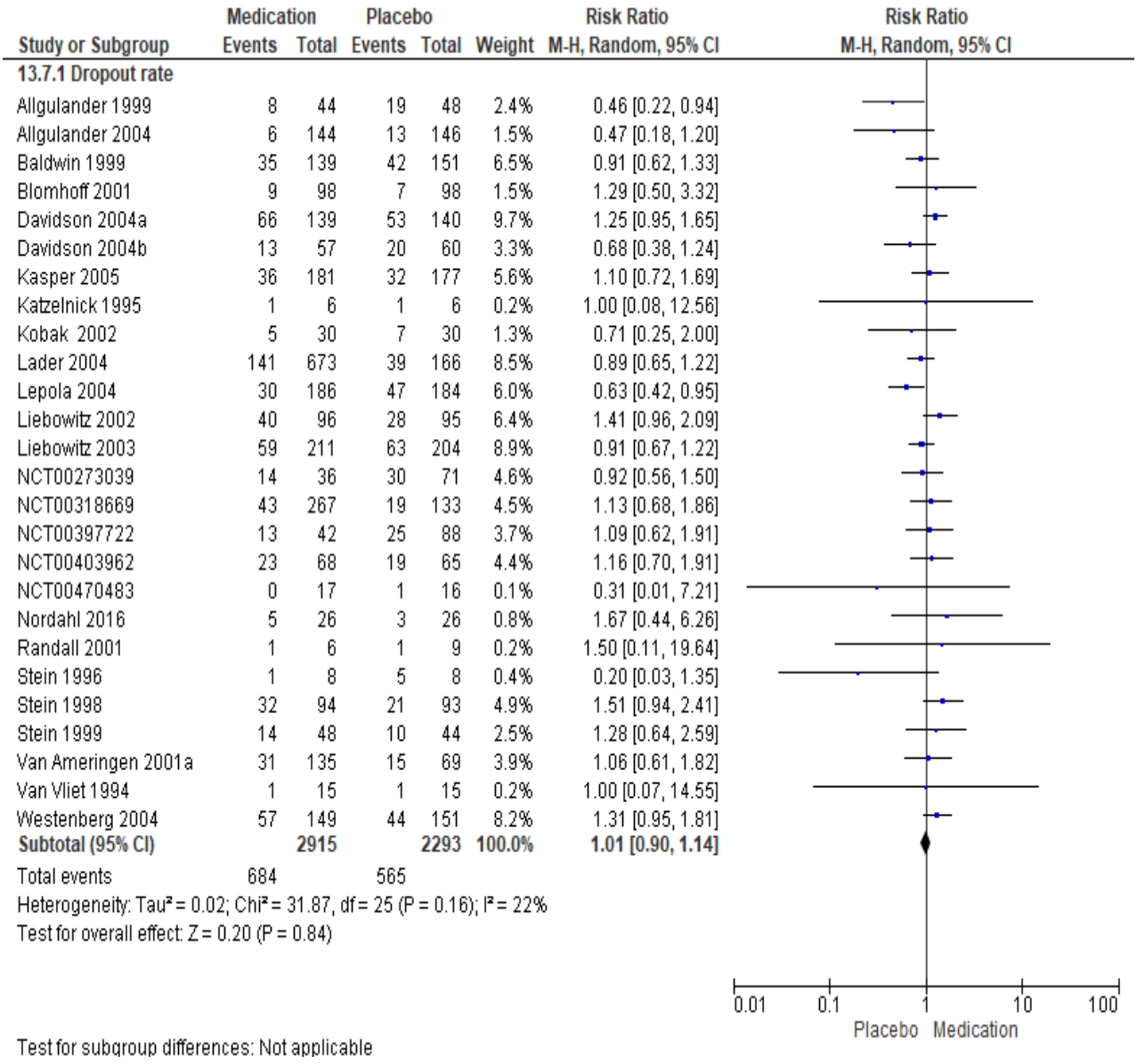
There was evidence of benefit for the SSRIs compared to placebo for reducing total SAD symptoms on the LSAS (k = 14, MD −10.14 points, 95% CI −14.05 to −6.22, N= 1990; see

Analysis 13.4; Allgulander 1999; Asakura 2007; Baldwin 1999; Book 2008; Davidson 2004a; Furmark 2005; Katzelnick 1995; Kobak 2002; Liebowitz 2002; Liebowitz 2003; Nordahl 2016; Stein 1998; Stein 1999; Tauscher 2010), though the evidence was low in quality. There was considerable heterogeneity in effect size estimates for this outcome (Chi^2 = 39.61, df = 13, P < 0.001; I^2 = 67%). This was partly due to large medication effects of Allgulander 1999. Evidence for efficacy of the SSRIs was still apparent after removing this study (k = 13, RR −8.69; 95% CI −11.83 to −5.54, N = 1898). The SSRIs were superior to placebo on both the avoidance (MD −7.01 points, 95% CI −10.21 to−3.80; see Analysis 13.4) and fear subscale of the LSAS (MD−7.28 points, 95% CI−10.86 to −3.71, see Analysis 13.4) in seven trials with 1173 participants (Allgulander 1999; Asakura 2007; Furmark 2005; Liebowitz 2002; Liebowitz 2003; Stein 1998; Van Vliet 1994). The evidence that was available for the avoidance and fear outcomes was of low quality. There was considerable to substantial heterogeneity in effect size estimates of the avoidance and fear subscales of the LSAS (Chi^2 = 17.31, df = 6, P = 0.008; I^2 = 65%; Chi^2 = 24.25, df = 6, P < 0.001; I^2 = 75%, respectively).



Analysis 13.4. selective serotonin reuptake inhibitors versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score, LSAS avoidance subscale, LSAS fear subscale.

Similar dropout rates were observed in the medication and placebo arms for the SSRIs (k = 26, RR 1.01; 95% CI 0.90 to 1.14, N = 5208; see Analysis 13.7).



Analysis 13.7. selective serotonin reuptake inhibitors versus placebo. All-cause dropouts (acute phase): Dropout rate.

<table>
<tr><td colspan="7">Comparison 13: SSRIs versus placebo for social anxiety disorder (SAD)</td></tr>
<tr><td colspan="7">Patient or population: adults with SAD
Settings: inpatient and outpatient settings
Intervention: SSRIs
Comparison: placebo</td></tr>
<tr><td rowspan="3">Outcomes</td><td colspan="2">Illustrative comparative risks* (95% CI)</td><td rowspan="3">Relative effect (95% CI)</td><td rowspan="3">No. of participants (studies)</td><td rowspan="3">Quality of the evidence (GRADE)</td><td rowspan="3">Comments</td></tr>
<tr><td>Assumed risk</td><td>Corresponding risk</td></tr>
<tr><td>With placebo</td><td>With SSRIs</td></tr>
<tr><td rowspan="5">Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)</td><td colspan="2">Study population</td><td rowspan="5">RR 1.65
(1.48 to 1.85)</td><td rowspan="5">4984
(24 studies)</td><td rowspan="5">⊕⊖⊖⊖
Very low[a,b,c]</td><td rowspan="5">There was evidence of benefit on the number of participants with SAD who responded to treatment (P < 0.00001). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the SSRI groups compared to the placebo groups who responded, 'Very Much Improved' or</td></tr>
<tr><td>317 per 1000</td><td>523 per 1000
(469 to 587)</td></tr>
<tr><td colspan="2">Moderate</td></tr>
<tr><td>290 per 1000</td><td>476 per 1000
(478 to 537)</td></tr>
<tr><td></td></tr>
</table>

						'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 2.59** (1.97 to 3.39)	5131 (24 studies)	⨁⨁⨀⨀ **Low**[a,c]	The proportion of dropouts due to adverse events was approximately three times higher amongst participants receiving SSRIs compared to placebo ((P < 0.00001).
	40 per 1000	**105 per 1000** (80 to 137)				
	Moderate					
	37 per 1000	**96 per 1000** (73 to 125)				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score ranged across control groups from -7.8 to 69.88	The mean reduction of anxiety symptoms (clinician-rated: LSAS total score) in the intervention groups was **10.14 points lower** (14.05 to 6.22 lower)		1990 (14 studies)	⨁⨁⨀⨀ **Low**[a,d]	The mean LSAS total anxiety score for the SSRI intervention groups ranged from 14.7 to 60.3 which suggests 'low' to 'moderate' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS avoidance subscale	The mean anxiety score ranged across control groups from 24.2 to 34.8	The mean reduction of anxiety symptoms (clinician-rated: LSAS avoidance) in the intervention groups was **7.01 points lower** (10.21 to 3.80 lower)		1173 (7 studies)	⨁⨁⨀⨀ **Low**[a,e]	The mean LSAS avoidance anxiety score for the SSRI intervention groups ranged from 17.09 to 26.11 which suggests 'low' social phobia.
Reduction of anxiety symptoms - Clinician-rated: LSAS fear subscale	The mean anxiety score ranged across control groups from 29.83 to 37.4	The mean reduction of anxiety symptoms (clinician-rated: LSAS fear) in the intervention groups was **7.28 points**		1173 (7 studies)	⨁⨁⨀⨀ **Low**[a,f]	The mean LSAS fear anxiety score for the SSRI intervention groups ranged from 19.84 to 32.79 which

		lower (10.86 to 3.71 lower)				suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 13. Comparison 13: SSRIs versus placebo for social anxiety disorder (SAD).

Footnotes

[a]Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b]Downgraded two levels due to moderate heterogeneity (I^2 of 50%).

[c]Downgraded two levels due to very serious publication bias (t = 2.6426, df = 22, p = 0.015).

[d]Downgraded two levels due to substantial heterogeneity (I^2 of 67%).

[e]Downgraded two levels due to substantial heterogeneity (I^2 of 65%).

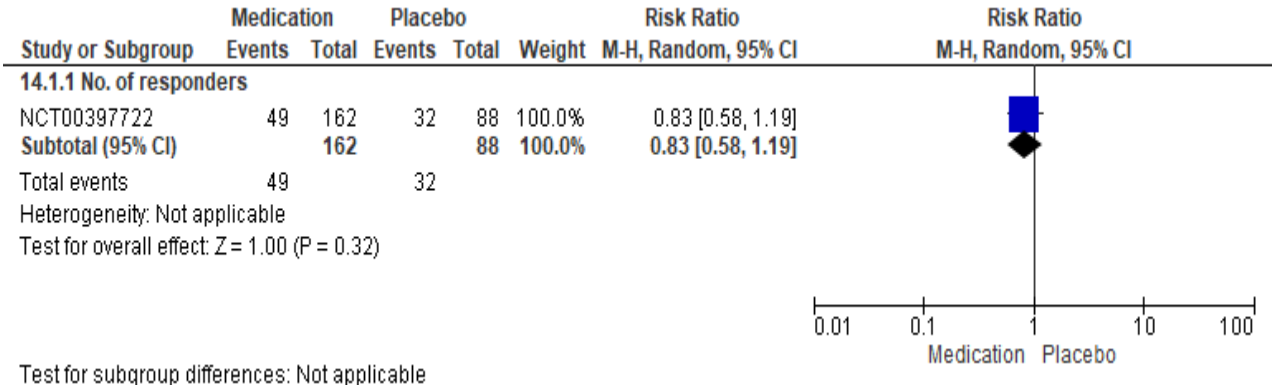
[f]Downgraded two levels due to substantial heterogeneity (I^2 of 75%).

[g]Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 14: GW876008 versus placebo

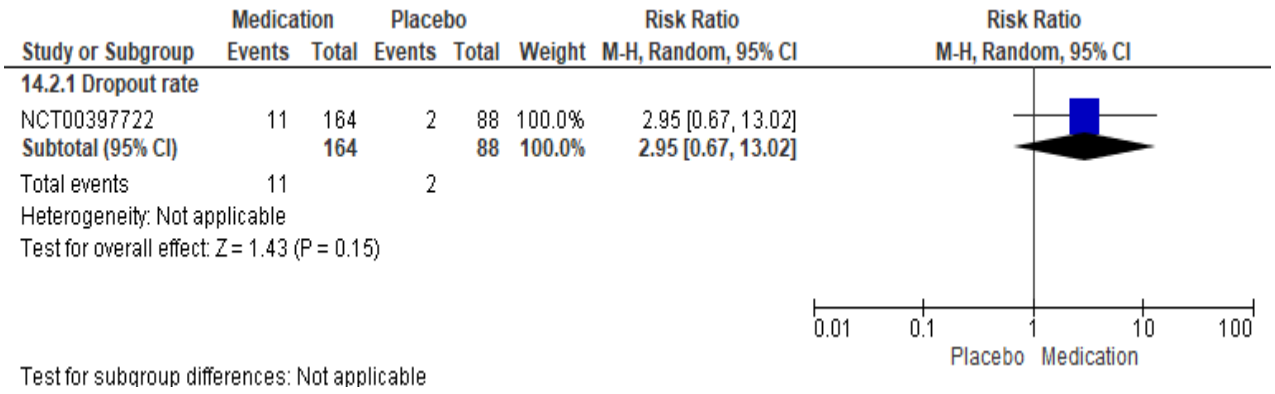
Primary outcome measures

There was no evidence of treatment efficacy for GW876008 versus placebo (RR 0.83; 95% CI 0.58 to 1.19, see Analysis 14.1) in one trial with 250 participants (NCT00397722), based on moderate quality evidence.



Analysis 14.1. GW876008 versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

Treatment dropouts were three times as high in participants receiving GW876008 (11/164, 7%) relative to placebo (2/88, 2%) (NCT00397722), though this difference was not statistically significant. There was no evidence of a difference between the number of participants that dropped out due to treatment-emergent side effects (k = 1, RR 2.95; 95% CI 0.67 to 13.02, N = 252; see Analysis 16.2) in the RCT of GW876008. The evidence that was available for this outcome was of low quality.

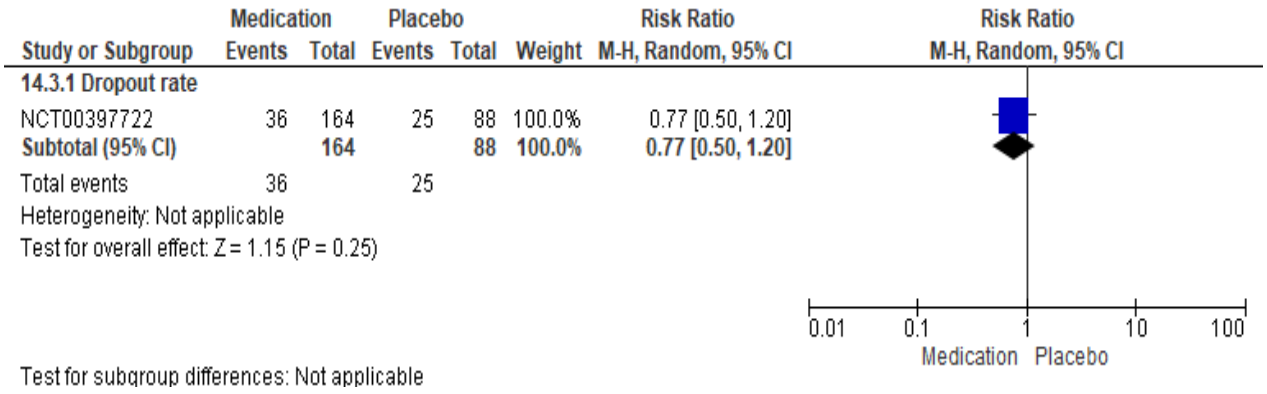


Analysis 14.2. GW876008 versus placebo. Adverse events (acute phase): Dropout rate.

The GW876008 demonstrated superiority with respect to treatment response relative to all the other medication classes that contained data from more than a single study, except for the SNRI venlafaxine (Chi^2 = 2.49, df = 1, P = 0.11; I^2 = 59.8%).

Secondary outcome measures

Similar dropout rates were observed in the medication and placebo arms in the trial of GW876008 compared to placebo (RR 0.77; 95% CI 0.50 to 1.20, N= 252; see Analysis 14.3; NCT00397722).



Analysis 14.3. GW876008 versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 14: GW876008 versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: GW876008 **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With GW876008**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 0.83** (0.58 to 1.19)	250 (1 study)	⊕⊕⊕⊖ **moderate**[1]	There was no evidence of an effect on the number of participants in the GW876008 group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.32).
	364 per 1000	**302 per 1000** (211 to 433)				
	Moderate					
	364 per 1000	**302 per 1000** (211 to 433)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 2.95** (0.67 to 13.02)	252 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The proportion of dropouts due to adverse events was approximately three times higher amongst participants receiving GW876008 (11/164,
	23 per 1000	**67 per 1000** (15 to 296)				
	Moderate					
	23 per 1000	**68 per 1000** (15 to 299)				

						7%) compared to placebo (2/88, 2%), though this difference was not statistically significant (P = 0.15).
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 14. Comparison 14: GW876008 versus placebo for social anxiety disorder (SAD).

Footnotes

[a] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

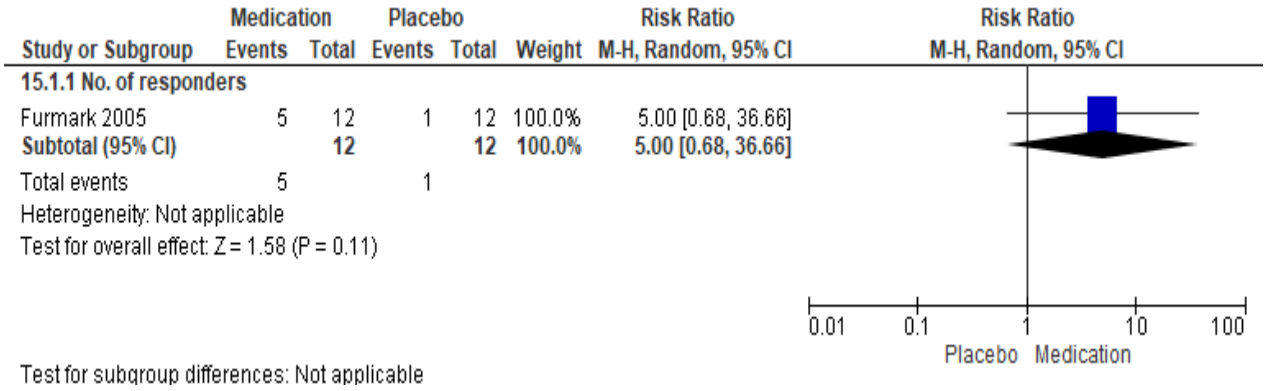
[b] Downgraded one level due to serious imprecision (wide confidence intervals).

[c] Response is defined as the number of participants with SAnD who responded to treatment, as assessed by the CGI-I or similar.

Comparison 15: NK1 receptor antagonist GR205171 versus placebo

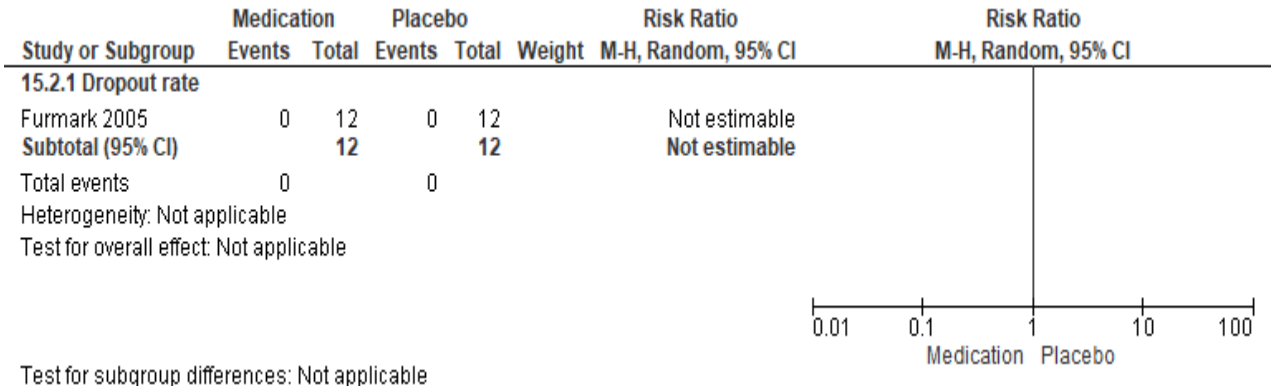
Primary outcome measures

There was no evidence of a superior treatment response to the NK1 receptor antagonist GR205171 than placebo in a single trial with 24 participants (RR 5.00; 95% CI 0.68 to 36.66, see Analysis 15.1; Furmark 2005), based on very low quality evidence.



Analysis 15.1. NK1 receptor antagonist GR205171 versus placebo. Clinical Global Impressions - Improvement (CGI-I) or similar scale (acute phase): No. of responders.

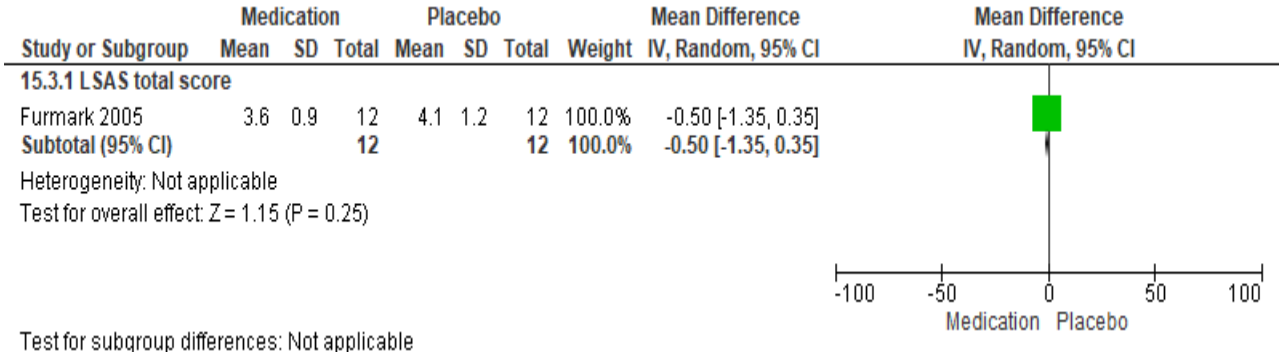
No participants withdrew due to adverse events from treatment during the six-week RCT of the NK1 receptor antagonist GR205171 (Furmark 2005; Analysis 15.2). The evidence that was available for this outcome was of moderate quality.



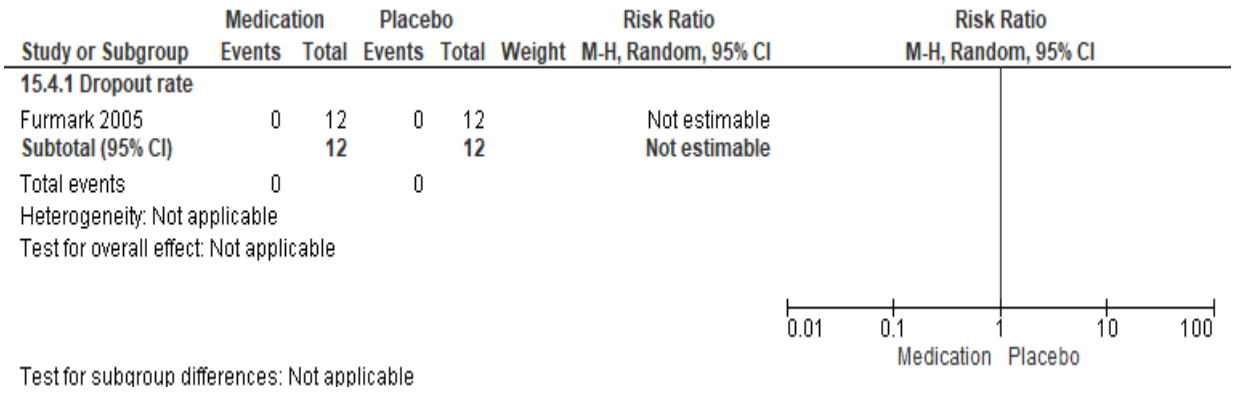
Analysis 15.2. NK1 receptor antagonist GR205171 versus placebo. Adverse events (acute phase): Dropout rate.

Secondary outcome measures

No evidence was observed for an effect of the NK1 antagonist GR205171 on total LSAS symptom severity (k = 1, MD -0.50 points, 95% CI -1.35 to 0.35, N = 24; see Analysis 15.3; Furmark 2005). This conclusion was based on data of very low quality. No participants withdrew from treatment during the six-week RCT of the NK1 receptor antagonist GR205171 (Furmark 2005; Analysis 15.4).



Analysis 15.3. NK1 receptor antagonist GR205171 versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score.



Analysis 15.4. NK1 receptor antagonist GR205171 versus placebo. All-cause dropouts (acute phase): Dropout rate.

Comparison 15: NK1 receptor antagonist GR205171 versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: NK1 receptor antagonist GR205171 **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With GR205171**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 5** (0.68 to 36.66)	24 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	There was no evidence of an effect on the number of participants in the NK1 receptor antagonist GR205171 group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.11).
	83 per 1000	**417 per 1000** (57 to 1000)				
	Moderate					
	83 per 1000	**415 per 1000** (56 to 1000)				
Dropouts due to adverse events (acute phase)	See comment	See comment	Not estimable	24 (1 study)	⊕⊕⊕⊖ **moderate**[1]	No participants withdrew due to adverse events.
Reduction of anxiety	The mean anxiety score	The mean clinician-rated: Liebowitz social		24 (1 study)	⊕⊖⊖⊖ **very low**[2]	The mean LSAS total anxiety score for the

symptoms - Clinician-rated: LSAS total score	for the control group was 4.1	anxiety scale (LSAS): reduction of anxiety symptoms - LSAS total score in the intervention groups was **0.5 points lower** (1.35 lower to 0.35 higher)				NK1 receptor antagonist GR205171 intervention group was 3.6 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **LSAS**: Liebowitz Social Anxiety Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 15. Comparison 15: NK1 receptor antagonist GR205171 versus placebo for social anxiety disorder (SAD).

Footnotes

[a] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[b] Downgraded two levels due to very serious imprecision (small sample size and wide confidence intervals).

[c] Response is defined as the number of participants with SAD who responded to treatment, as assessed by the CGI-I or similar.

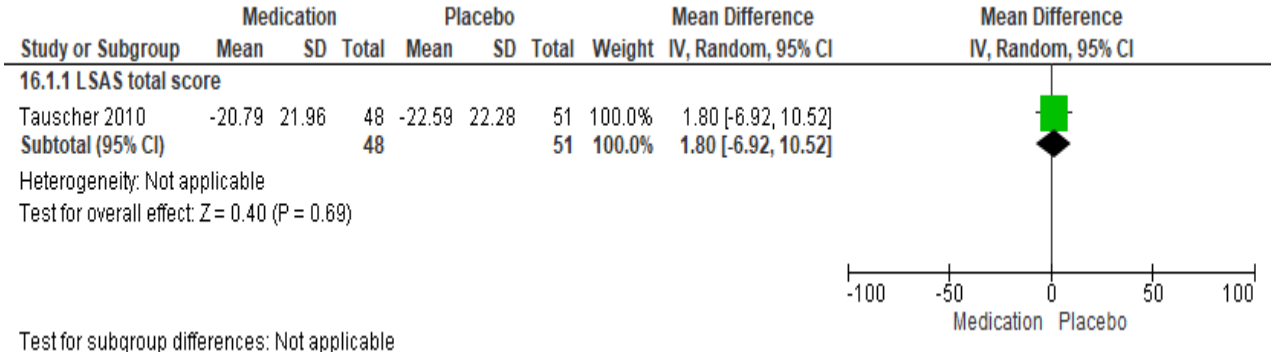
Comparison 16: LY686017 versus placebo

Primary outcome measures

There were no data available to assess treatment efficacy and dropouts due to adverse events.

Secondary outcome measures

No evidence was observed for an effect of the LY686017 on total LSAS symptom severity (k = 1, MD 1.80 points, 95%CI -6.92 to 10.52, N = 99; see Analysis 16.1; Furmark 2005; Tauscher 2010). This conclusion was based on data of very low quality.



Analysis 16.1. LY686017 versus placebo. Clinician-rated: Liebowitz Social Anxiety Scale (LSAS): reduction of anxiety symptoms: LSAS total score.

Comparison 16: LY686017 versus placebo for social anxiety disorder (SAD)						
Patient or population: adults with SAD **Settings**: outpatient settings **Intervention**: LY686017 **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With LY686017**				
Reduction of anxiety symptoms - Clinician-rated: LSAS total score	The mean anxiety score for the control group was -22.59	The mean clinician-rated: Liebowitz social anxiety scale (LSAS): reduction of anxiety symptoms - LSAS total score in the intervention groups was **1.8 points higher** (6.92 lower to 10.52 higher)		99 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	The mean LSAS total anxiety score for the LY686017 intervention group was -20.79 which suggests 'low' social phobia.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **LSAS**: Liebowitz Social Anxiety Scale.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 16. Comparison 16: LY686017 versus placebo for social anxiety disorder (SAD).

Footnotes

[a] Downgraded two levels due to serious risk of bias (concerns with randomisation procedures).

[b] Downgraded one level due to serious imprecision (wide confidence intervals).

Comparison 17: total effect of medication versus placebo

There was evidence of an effect across all medication classes (k = 51, RR 1.62; 95% CI 1.46 to 1.81, N = 8564), with substantial heterogeneity across subgroups (Chi^2 = 42.93, df = 13, P < 0.0001; I^2 = 69.7%). For this analysis data was excluded from two studies with additional arms of paroxetine to give preference to the least represented intervention in the review (i.e. GW876008 and GR205171; Furmark 2005; NCT00397722). Data from Liebowitz 1992, a phenelzine study, and from Liebowitz 2005b, a paroxetine study, was also excluded to give preference to atenolol and venlafaxine (see Analysis 17.1). There was evidence that medication class explained a substantial proportion of variability in treatment efficacy when assessed across all trials providing data on this outcome (Chi^2 = 143.17, df = 50, P < 0.00001; I^2 = 65%; see Analysis 17.1).

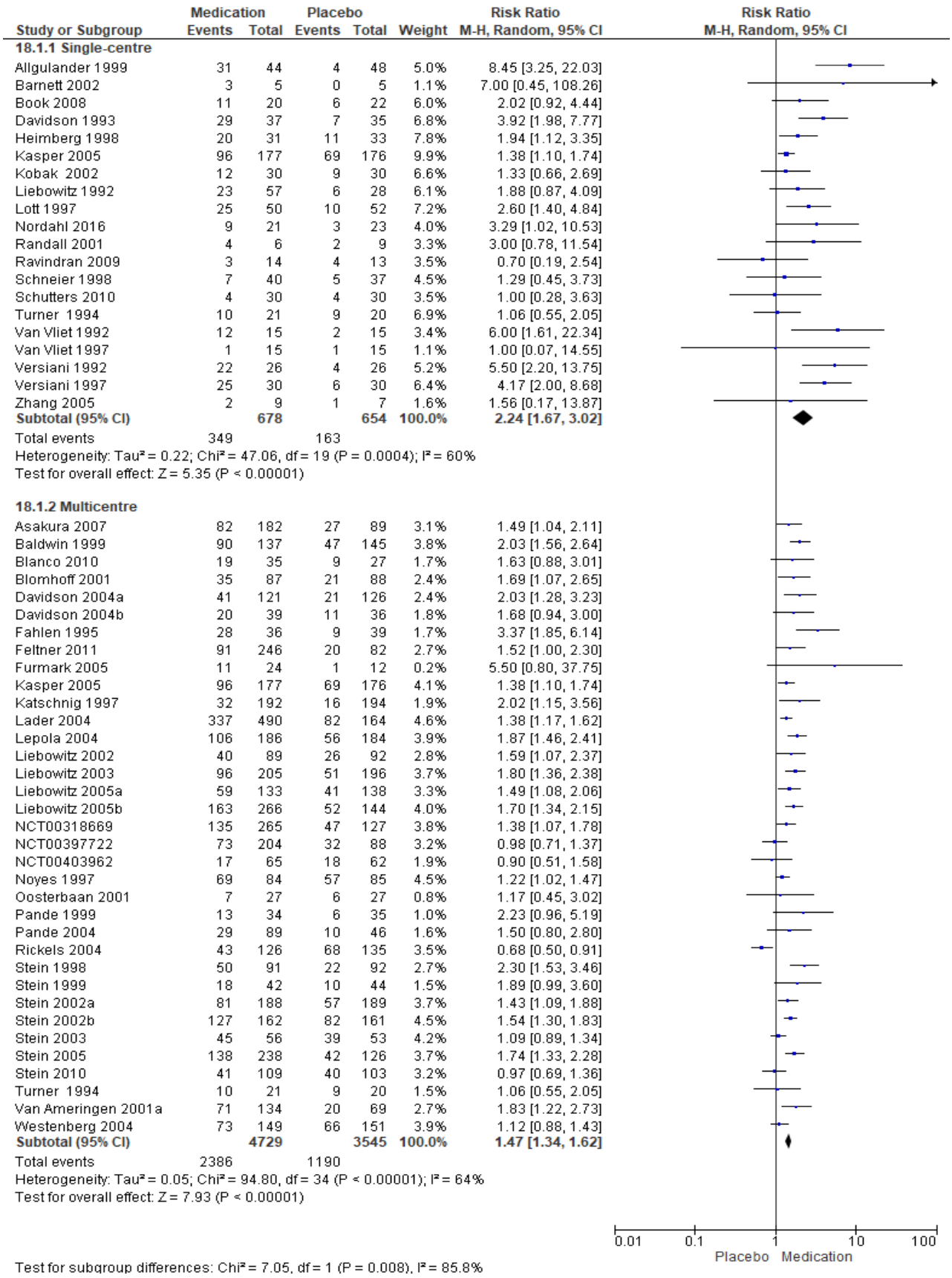
The proportion of dropouts due to adverse events was two to three times higher across all medication classes compared to placebo (k = 45, RR 2.41; 95% CI 1.99 to 2.91, N = 8751), a statistically significant difference (P < 0.001; Chi^2 = 49.24, df = 44, P = 0.27; I^2 = 11%). Nevertheless, the total proportion of dropouts due to adverse events in the medication arms (12%) is relatively low, suggesting that dropout rates may not have biased the outcomes. For this analysis data was excluded from two studies reporting data for paroxetine, as these studies also report data for the GW876008 and the NK1 receptor antagonist GR205171 (Furmark 2005; NCT00397722).

In addition, the proportion of dropouts due to any cause across both the medication and placebo groups was similar (25%) and was comparable across subgroups (Chi^2 = 13.31, df = 13, P = 0.42; I^2 = 2.3%). For this analysis data was excluded from one study with an additional arm of

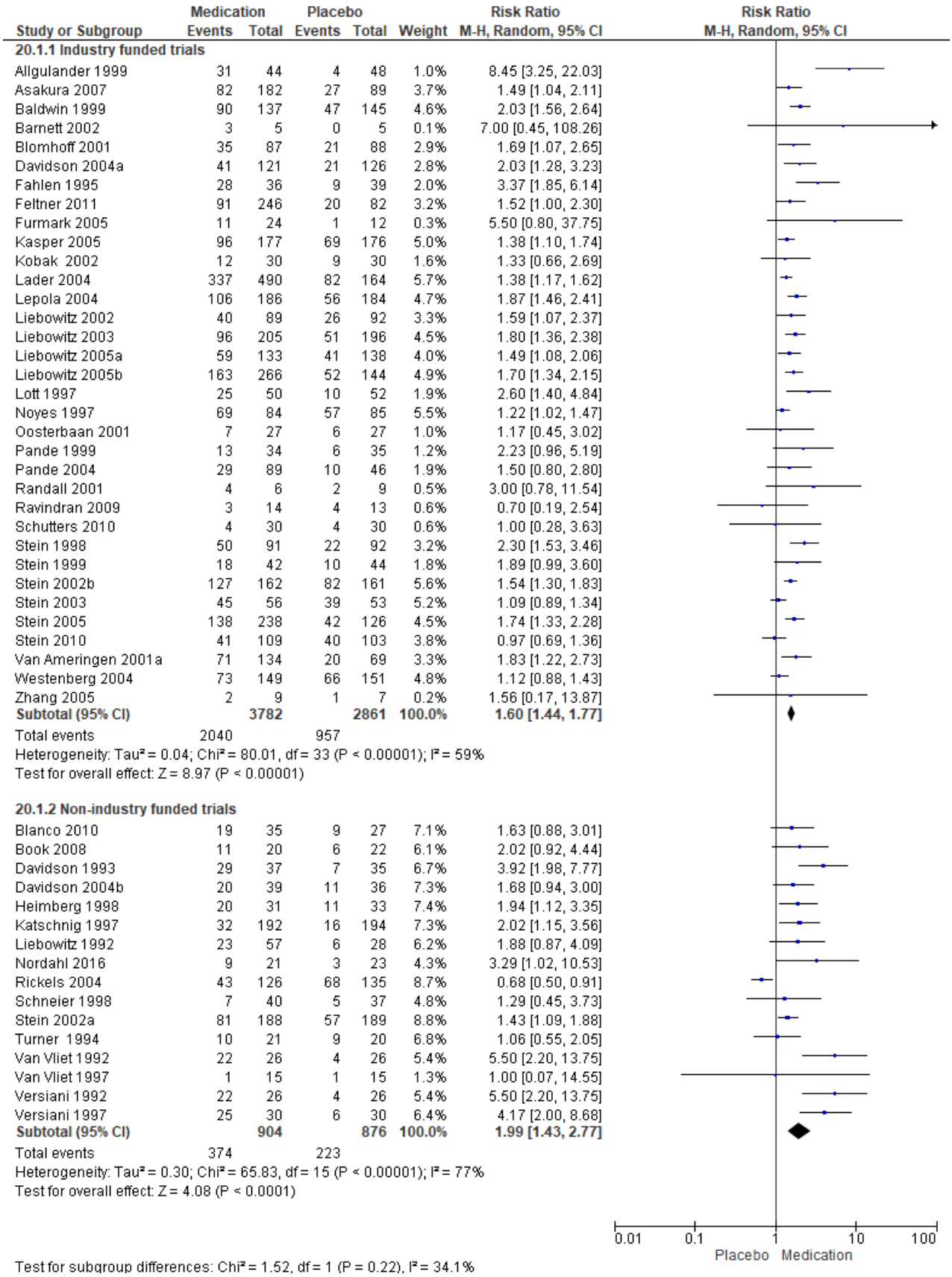
paroxetine to give preference to the experimental intervention, GR205171 (NCT00397722; see Analysis 17.3).

18. Subgroup analyses

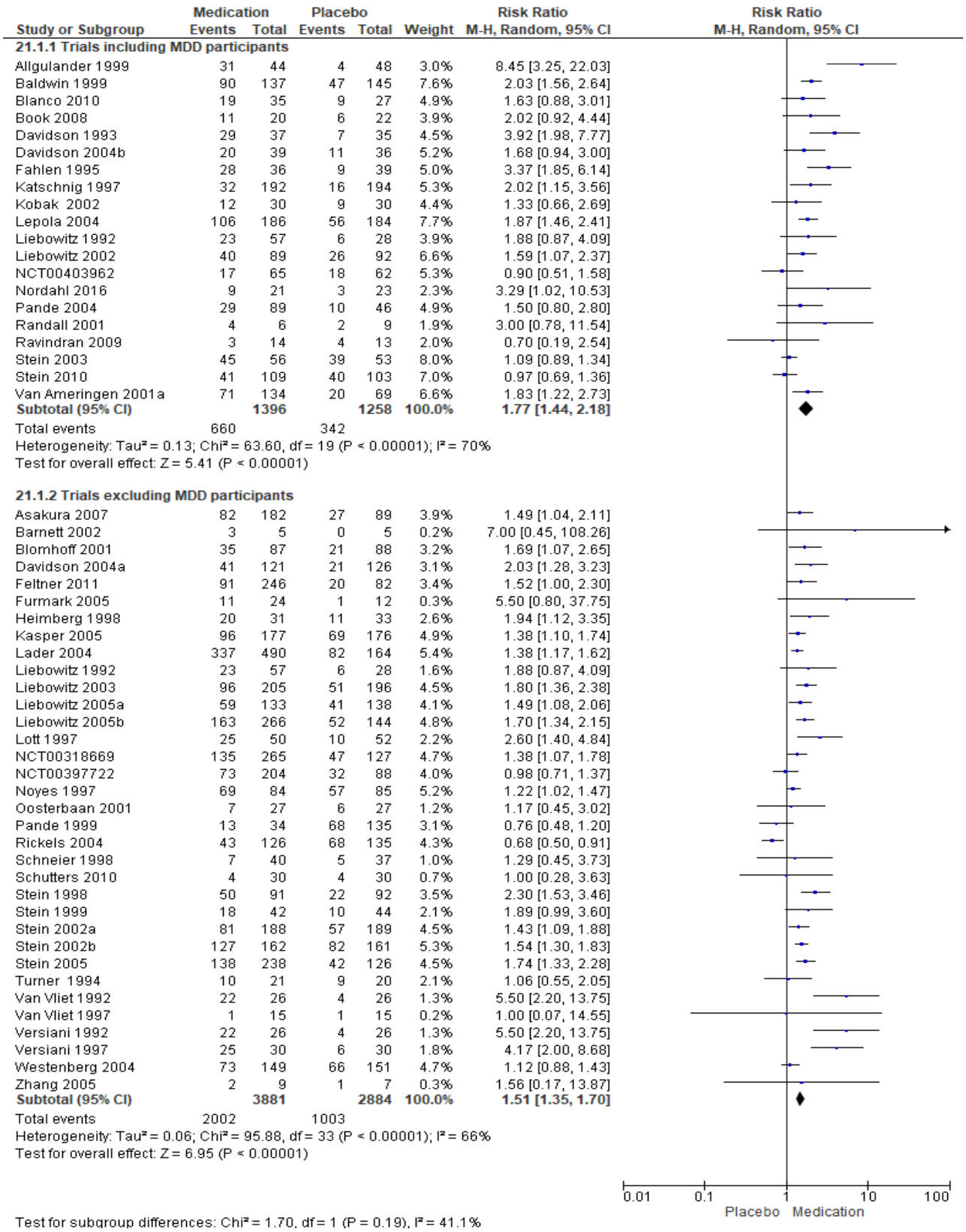
There was evidence of differences between RCTs conducted at multiple centers versus single centers (Chi^2 = 7.05, df = 1, P = 0.008; I^2 = 85.8%; see Analysis 18.1), with larger treatment effects reported for studies conducted at single centers (k = 20, RR 2.24, 95% CI 1.67 to 3.02, N = 1332). There was no evidence of a difference in treatment response based on source of funding (Chi^2 = 1.52, df = 1, P = 0.22; I^2 = 34.1%; see Analysis 20.1) or the inclusion of participants diagnosed with major depressive disorder (Chi^2 = 1.70, df = 1, P = 0.19; I^2 = 41.1%; Analysis 21.1).



Analysis 18.1. Clinical Global Impressions - Improvement (CGI-I) or similar scale: no. of responders (acute phase): Single-center, Multicenter.

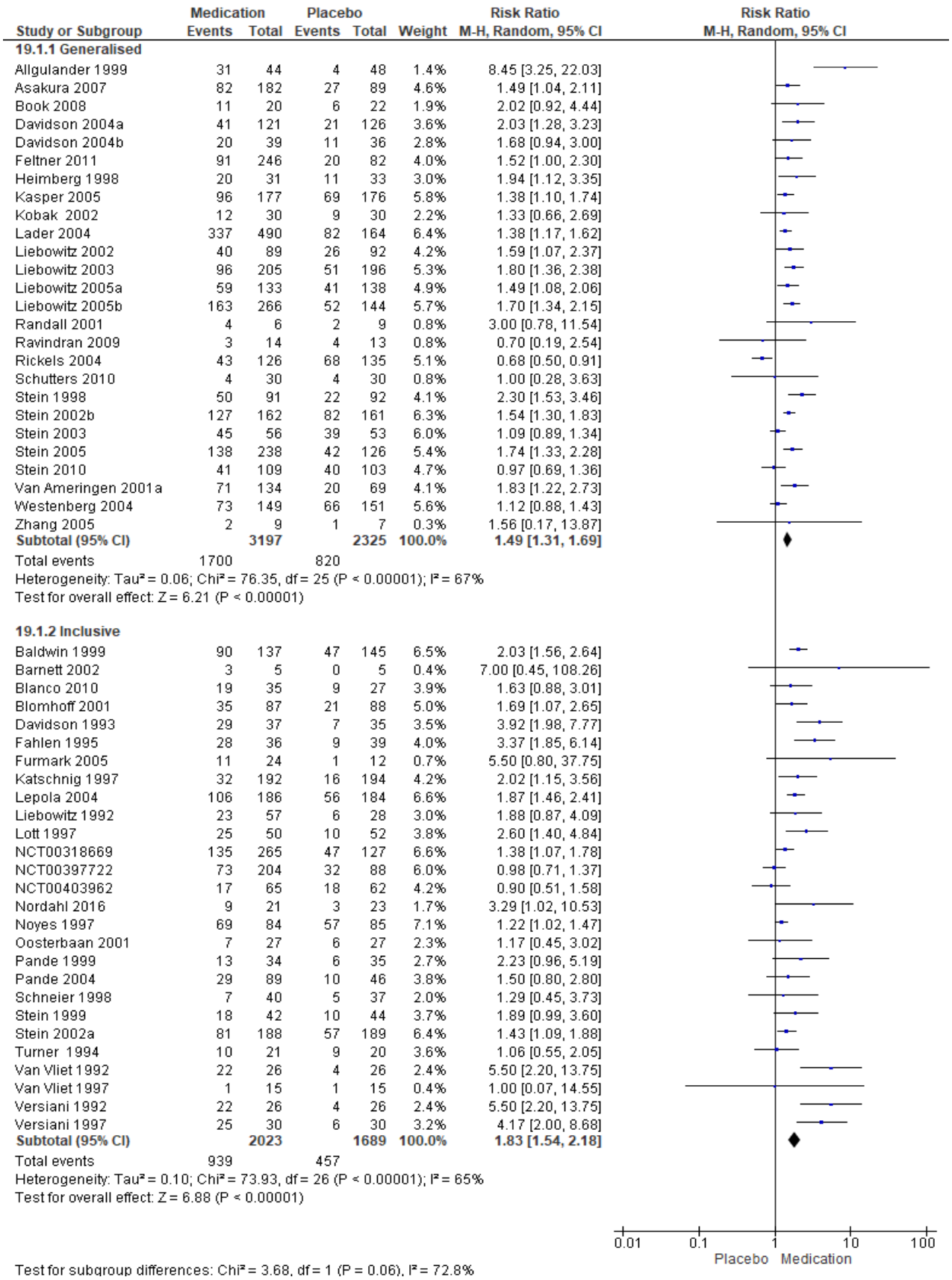


Analysis 20.1. Clinical Global Impressions - Improvement (CGI-I) or similar scale: no. of responders (acute phase): Industry funded trials, Non-industry funded trials.



Analysis 21.1. Clinical Global Impressions - Improvement (CGI-I) or similar scale: no. of responders (acute phase): Trials including MDD participants, Trials excluding MDD participants.

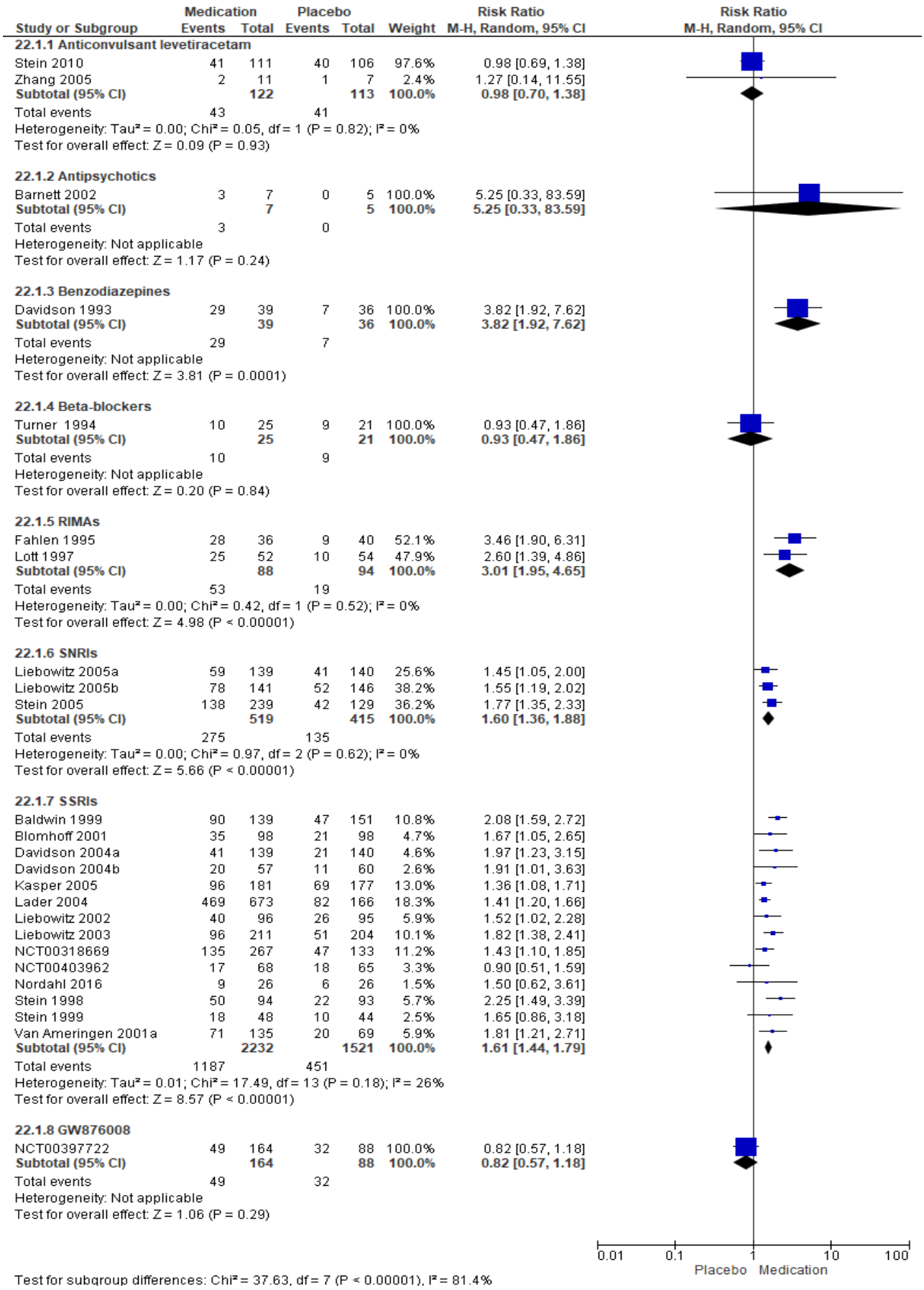
Studies that involved only participants diagnosed with generalized SAD reported smaller treatment effects (k = 26, RR 1.49, 95% CI 1.31 to 1.69, N = 5522) than trials that did not necessarily restrict inclusion to the generalized subtype (k = 27, RR 1.83, 95% CI 1.54 to 2.18, N = 3712; see Analysis 19.1). This difference was statistically significant (P < 0.001).



Analysis 19.1. Clinical Global Impressions - Improvement (CGI-I) or similar scale: no. of responders (acute phase): Generalized, Inclusive.

19. Sensitivity analyses

Twenty-four parallel RCTs failed to include all the participants randomised to the treatment groups in the responder analysis. The comparison of separate efficacy analyses in which the omitted participants were regarded as responders in either the medication or placebo groups supported the robustness of the evidence of this agent's efficacy in treating social anxiety disorder (respective results: RR 1.59, 95% CI 1.41 to 1.80, P < 0. 001, N = 5437, Analysis 22.1; and RR 1.63, 95% CI 1.44 to 1.85, P < 0. 001, N = 5215; Analysis 22.2). The review therefore considered that missing data in these trial reports did not have a significant influence on this outcome.



Analysis 22. 'Worst case' lost-to-follow-up analysis; 'Best case' lost-to-follow-up analysis.

20. Publication bias

There is evidence of possible funnel plot asymmetry providing data on response to short-term medication treatment, both for the SSRIs and all medications combined. Inspection of the contour enhanced funnel plots for the SSRIs (Figure 4) and all the trials (Figure 5) suggests that this asymmetry is due to publication bias, as trials with less precise treatment response outcomes are more likely than their higher precision counterparts to be missing from regions of the plot representing statistically non-significant treatment effects. Egger regression tests quantitatively confirmed this visual impression, providing evidence of possible publication bias for all the medication trials ($t = 2.8226$, $df = 49$, $P = 0.0069$) and for the SSRIs ($t = 2.6426$, $df = 22$, $P = 0.015$). Nevertheless, trim and fill imputation of missing effect estimates from small studies with negative results continue to provide support for the efficacy of both the SSRIs (RR 1.52, 95% CI 1.35 to 1.71) and all medications (RR = 1.48, 95% CI 1.32 to 1.66) in treating SAD. There were insufficient data to assess publication bias for the other medication classes.

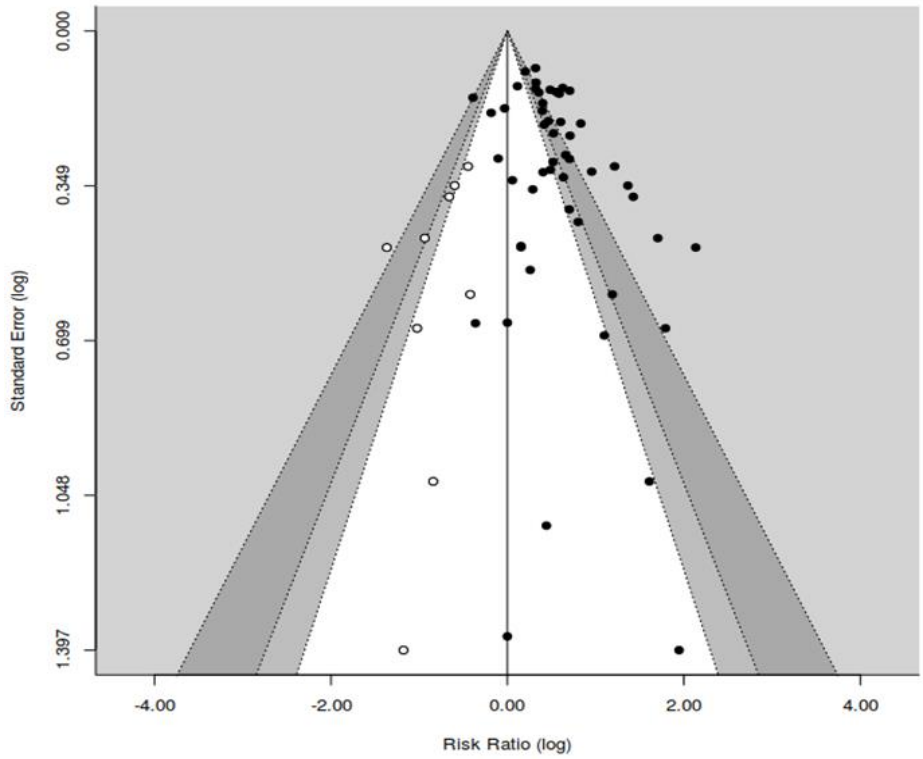


Figure 4. Contour enhanced funnel plot for treatment response on the Clinical Global Impression Scale (CGI-I) for all medication trials Filled circles = trial effect estimates; empty circles = trim and fill generated missing study estimates Contours in light-gray, gray and dark gray correspond to increasing stringent statistical boundaries (alpha = 0.1, 0.05, and 0.01, respectively). White corresponds to regions of statistical non-significance.

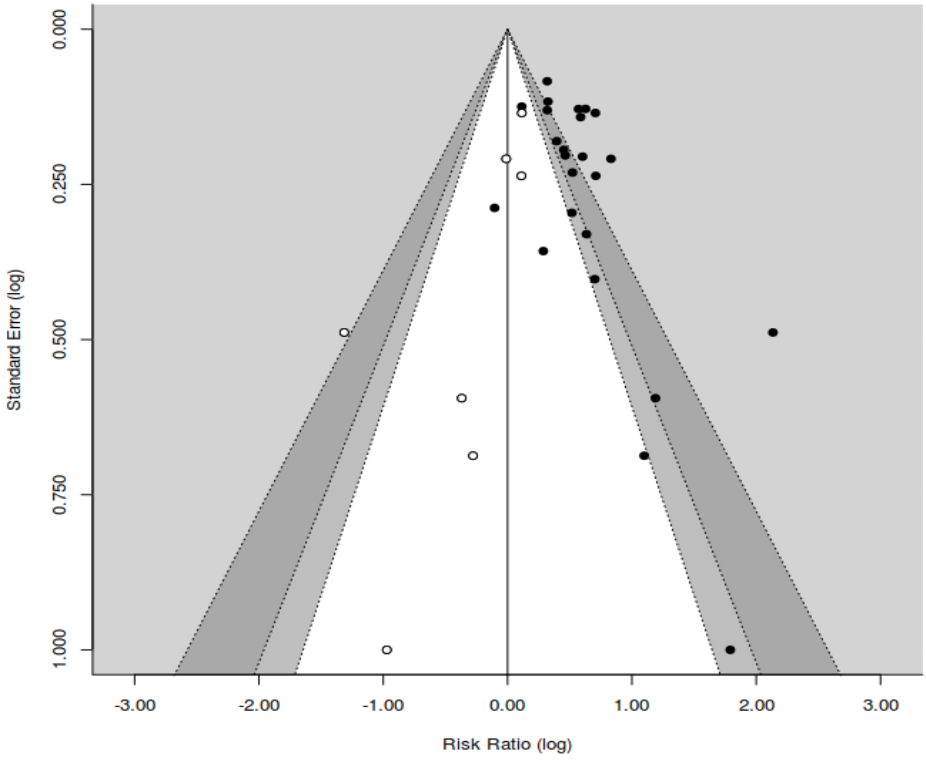


Figure 5. Contour enhanced funnel plot for treatment response on the Clinical Global Impression Scale (CGI-I) for Selective serotonin reuptake inhibitor trials Filled circles = trial effect estimates; empty circles = trim and fill generated missing study estimates Contours in light-gray, gray and dark gray correspond to increasing stringent statistical boundaries (alpha = 0.1, 0.05, and 0.01, respectively). White corresponds to regions of statistical non-significance.

DISCUSSION

Summary of main results

Evidence of an overall benefit of medication for treating SAD was found in this review. Most evidence was for the SSRIs (i.e. paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram) and was very low in quality. Similarly, low-quality evidence of efficacy for the

MAOI phenelzine, the RIMAs brofaromine and moclobemide, and the benzodiazepines clonazepam and bromazepam was found, with moderate-quality evidence of efficacy observed for the anticonvulsant/GABAs gabapentin and pregabalin. Conversely, there was no evidence in this review of a global clinical response to treatment for certain medication classes, including the 5HT1A partial agonists, the anticonvulsant levetiracetam, the antipsychotic olanzapine, the beta-blockers, the NARIs, the NaSSAs, or the SNRI venlafaxine, as well as for the experimental agents GW876008 and NK1 receptor antagonist GR205171.

Individuals diagnosed with SAD who were treated with either SSRIs or the SNRI venlafaxine were more likely to withdraw from treatment due to treatment-related adverse events. Nevertheless, the absolute proportion of individuals dropping out from treatment with these medications due to adverse events over the short term (14 weeks or less) was low (12% for SSRIs and 16% for venlafaxine). There was little evidence that any of the SSRI agents were less tolerable than any other (I^2 = 23%), as confirmed by a post hoc comparisons of dropout rates due to adverse events by agent (Chi^2 = 31.82, df = 24, P = 0.13; I^2 = 25%). The MAOIs and benzodiazepines appeared to be relatively well tolerated and showed the largest treatment response (see Summary of findings 5; Summary of findings 7). Readers should exercise great caution in any inferences about the experimental agents (GW876008, the NK1 antagonist GR20517 and LY686017), more trials with each of these agents in the future may allow better comparison of classes of medication.

For the subgroup outcomes, there was evidence that treatment response was influenced by whether RCTs took place at single or multiple centers. The size of the effect observed was also dependent on participant characteristics, with a smaller response to treatment observed in studies that restricted inclusion to participants diagnosed with generalized SAD. Nevertheless,

there was no evidence that treatment response across all medication classes varied as a function of whether trials were funded by industry or included participants diagnosed with major depressive disorder. There is also reason to believe that the effect sizes reported across all medication classes, as well as for the SSRIs, may be inflated, based on properties of the data that are consistent with publication bias. Nevertheless, the effects of medication in general and the SSRIs in particular on treatment response persist even after adjustments to account for the effect of the increased likelihood of publishing small trials if they report a positive effect of medication.

Overall completeness and applicability of evidence

Completeness of evidence

Reviews of the body of evidence for pharmacotherapy of SAD have designated SSRIs as first-line medication agents for treating SAD (Baldwin 2014; Ballenger 1998; Bandelow 2002; NICE 2011). The current review supports the efficacy of SSRIs for short-term treatment of SAD.

Importantly, although there was evidence for treatment withdrawal owing to drug-related adverse events in the SNRI and SSRI trials, dropout rates were comparable between these medication classes. This contradicts findings in a meta-analysis of the depression literature, which found venlafaxine to be more efficacious than SSRIs in increasing remission rates, but with a higher rate of withdrawal owing to treatment-related adverse events (Nemeroff 2008). Given the frequent prescription of beta-blockers for performance anxiety, the relative lack of empirical support for this intervention is surprising. The review also found evidence of heterogeneity for the MAOIs, the RIMAs, and the SSRIs when investigating the efficacy of treatment in participants with SAD. These differences may be partly accounted for by

methodological and clinical variance but may also reflect real differences in efficacy across different medications. None of the four trials of the MAOI phenelzine provide information on the number of participants who withdrew from treatment as a result of drug-related adverse events, against which to weigh the observed evidence for a response to treatment with this agent. There has been no investigation into the efficacy of other medication classes that may be considered for treating SAD, such as the tricyclic antidepressants (TCAs).

Although the SSRI trials under review used medication doses that are consistent with those advised in recent expert consensus recommendations (Ballenger 1998), there are few rigorous dose-finding studies using fixed-dose comparisons. The paroxetine database suggests that the dose-response curve of SSRIs is relatively flat in SAD, but that some participants may require higher doses (Ballenger 1998). Most SSRI studies lasted at least 12 weeks. The finding from the paroxetine database that a significant proportion of non-responders at week eight become responders by week 12 suggests that patients in clinical practice should be treated for a minimum period of 12 weeks before modifying treatment regimens due to medication non-response (Stein 2002c).

The negative 14-week trial of fluoxetine raises the question of whether all SSRIs are equally effective (Kobak 2002). The fluoxetine study included in this review had a relatively high placebo response rate and was not consistent with several early open-label reports of the value of this medication in SAD. Further work is needed to understand the differences in placebo response across the database of SAD studies (Oosterbaan 1997). In a study by Katschnig 1997, for example, placebo response was higher in participants without avoidant personality disorder, in participants with a short duration of illness, and in participants with less severe illness. Kobak 2002 found that placebo-responders had an earlier response than medication responders

and that lower severity of illness was associated with increased placebo response. These findings were similar to a recent report on two meta-analyses where bias (i.e. reporting bias) appeared to have led to significant increases in the number of positive findings in the literature (Roest 2015).

Applicability of evidence

The outcomes of this review may be generalisable to a diverse range of settings. Studies were conducted in the USA, Europe, Japan, South Africa, and Iran, in both outpatient and inpatient settings (mainly outpatient settings). The interventions targeted both men and women across a wide age range. Differences in treatment delivery, as well as the background and training of study investigators and outcome assessors, increases the likelihood that the findings of this review are applicable to a range of countries in different income brackets. However, careful consideration should be given to the specific contexts in which the trials took place, given the lack of evidence on the availability and cost-effectiveness of individual medications. The findings of this review will not apply equally to the full range of individuals presenting at clinics for the treatment of SAD. RCTs included in this review were also restricted to those assessing the effectiveness of pharmacotherapy for SAD in adults. The finding in this review that clinicians should consider medication, and in particular the SSRIs, for treating SAD, may not apply to children. Readers are referred in this regard to another Cochrane Review on the efficacy of pharmacotherapy for anxiety disorders in children and adolescents (Ipser 2009a). Most published trials of pharmacotherapy for SAD exclude individuals with concurrent psychopathology, including substance use disorders, which are highly comorbid with SAD. Although the limited RCT database suggests that medication may be equally effective in people with SAD who are dependent on alcohol (Book 2008), and certain forms of comorbidity may be prognostic of greater treatment response (Stein 2002a), firm evidence supporting

conclusions regarding whether medication is indicated for these populations is currently lacking.

Quality of the evidence

Twelve of the included RCTs possessed a high risk of bias related to at least one aspect of study design, with the most commonly observed weaknesses having to do with attrition bias (Allgulander 1999; Book 2008; Katzelnick 1995; Liebowitz 1992; Moghadam 2015; Nordahl 2016; Stein 2005; Van Ameringen 2007; Walker 2000; Zhang 2005). Lack of blinding for outcome assessors may also have influenced the detection of treatment effects (Blomhoff 2001; Moghadam 2015; Stein 2005; VanAmeringen 2007). There was also evidence for selective reporting bias in Book 2008, Nordahl 2016 and Tauscher 2010. Even though the SSRIs were the best-represented medication class, with 24 of the 51 RCTs contributing to the outcome of clinical response, most of these trials scored unclear for random sequence generation as well as for allocation concealment.

Judgements of response to treatment with the SSRIs were based on evidence rated as being of very low quality. Therefore, the review is very uncertain about the estimate (see Summary of findings 13). The RIMAs, MAOIs, and benzodiazepines were based on evidence rated as being of low quality (see Summary of findings 5; Summary of findings 7), indicating that additional data from further studies may change the size of the treatment effect estimate for these medication classes, as well as our confidence in that estimate of effect. The anticonvulsants/GABAs, on the other hand, were based on evidence rated as being of moderate quality (see Summary of findings 2; Summary of findings 12). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The most common reasons for downgrading studies were imprecise effect estimates,

low response rates, small sample size, a rating of high or unclear bias for study design (based on 50% attrition rates across groups, detection, and selective reporting bias), and inconsistency between studies (indicated by heterogeneity between the medication and placebo group). Variability in the number of sites contributing data reported in included studies could also have biased the results of the review.

A recent meta-analysis demonstrated that the size of treatment effect estimates is larger in single-center than multi-center trials, even after adjusting for sample size and various bias risk factors (Dechartres 2011). It is notable that approximately a third of the trials providing data on treatment response for this review were in single-centers. Moreover, those trials were over-represented amongst RCTs of SSRIs and in studies reporting the largest treatment effects, including more than half of the MAOI trials and both benzodiazepine RCTs. Additionally, there was a smaller treatment response in RCTs that explicitly described limiting study inclusion to people diagnosed with generalized SAD. This finding agrees with the perception that the generalized SAD subtype is more difficult to treat. It may once again have resulted in a positive bias for the MAOI, RIMA, and benzodiazepine studies, given that with the exception of a single trial of phenelzine (Heimberg 1998), all the included RCTs for these medication classes failed to specify that they restricted inclusion to the generalized subtype.

The size of the response to acute treatment with any medication and specifically with the SSRIs may be exaggerated, as possible funnel plot asymmetry for this outcome suggests (Figure 4; Figure 5). Egger regression tests quantitatively confirmed the presence of small sample bias. Although small sample bias may arise from other factors besides publication bias, the absence of smaller studies with statistically non-significant effects of treatment, as illustrated by

contour-enhanced funnel plots (Figure 4; Figure 5), does suggest that investigators are not publishing smaller studies that fail to detect treatment effects.

Potential biases in the review process

An extensive search was conducted for studies meeting rigorous inclusion criteria and repeatedly attempted to obtain missing data from the trial investigators. Nevertheless, there were insufficient data available to assess the extent to which selective publication may have introduced bias in the findings for medication classes besides the SSRIs. Furthermore, the post hoc addition of comparisons of the efficacy of 5HT partial agonists, anticonvulsants with or without GABAs, antipsychotics, NARIs, NaSSAs, and SARIs may have also introduced bias as a result of the small number of eligible RCTs for these medication classes (one to three studies).

The reliance on the LSAS, while considered the gold standard for measurement of SAD symptom severity in clinical trials, represents another potential source of bias. Treatment outcomes not assessed by standardised scales such as the LSAS also deserve more attention. For example, physiological symptoms are often a source of concern for people (symptoms such as excessive sweating may for example lead to a request for surgery), and the LSAS does not specifically record these (Davidson 1998).

Meta-analysis also has inherent problems (Bailar 1999); although indirect comparison of competing interventions usually agrees with direct ones (Song 2003), meta-analysis is by no means a substitute for direct clinical research. Furthermore, the context of general clinical practice differs from RCTs in specialised centers in many respects, not the least being the need to treat more complex participants. Conclusions about the relative efficacy of different agents

from trials with different participants require confirmation in head-to-head comparisons. An early head-to-head study of clomipramine versus diazepam suggested superiority of clomipramine, but there were relatively few participants with social phobia (Allsopp 1984). The only head-to-head comparison of an SSRI versus moclobemide did not include a placebo control but did suggest equal efficacy and tolerability, lending caution to the findings of the current review (Atmaca 2002).

Agreements and disagreements with other studies or reviews

The finding in this review of moderate to substantial variability in the response of participants with SAD to pharmacotherapy is likely to reflect real differences in efficacy across different medication and differences brought on by trial methodology and the clinical characteristics of patients. In comparing medication classes in terms of beneficial and adverse responses to medication, the data included in this review are consistent with findings from other systematic reviews and meta-analyses in identifying the SSRIs as first line agents for the treatment of SAD (Ballenger 1998; Bandelow 2002; Bandelow 2012; Bandelow 2015; Blanco 2003; Van der Linden 2000). The finding of efficacy for the SSRIs reported in this review is based on a considerably larger database of randomised controlled trials than in previous reviews and reports.

This review classified medications based on their putative mechanisms of action (taken from CCMD antidepressant classification map) (Davies 2015), and they do not necessarily map onto the drug classification schemes employed in other reviews. Nevertheless, the efficacy of the SSRIs, SNRIs, the RIMAs, and the anticonvulsants/GABAs can be confirmed in this review.

MAOIs, in the form of phenelzine, as well as certain benzodiazepines, are also effective in SAD, but in view of concerns about ease of administration (e.g. MAOIs require dietary and medication restrictions) and side effects (risk of abuse with benzodiazepines seems to be highest in individuals with a history of substance abuse (Licata 2008)), it does not seem unreasonable to view these drugs as second-line agents.

AUTHOR CONCLUSIONS

Implications for practice

Medication can be effective for the treatment of SAD, with higher rates of treatment response compared to placebo, as well as reductions in core SAD symptoms. Most evidence of efficacy in this review was for the SSRIs. Although there was evidence that treatment with SSRIs was less tolerable than placebo, the absolute proportions of participants withdrawing due to drug-related adverse events after treatment with these agents were small (< 17%). The possible influence of publication bias on the validity of conclusions regarding the efficacy overall, and the SSRIs in particular, in treating SAD, as well as the potential risk of bias for this outcome, needs to be acknowledged. Given that we only included short term trials it is also noteworthy that treatment duration increases incidence of withdrawal for the SSRI paroxetine, SSRI escitalopram and the SNRI venlafaxine, for instance (Weller, 2005). Side effects include dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, weight, sexual dysfunction, bleeding, and hyponatremia (Wang, 2018). Discontinuation of these agents is also problematic leading to inappropriate long-term use (Eveleigh, 2018).

This review also found preliminary evidence to support the use of the anticonvulsants/GABAs in treating SAD. Common side effects of anticonvulsant medications include dizziness and somnolence (Grandhe, 2017) and should be discussed with patients when prescribed. Readers

should exercise great caution in making any inferences about the experimental agents GW876008 and NK1 receptor antagonist GR205171; more trials with each of these agents in the future may allow better comparison of classes of medication.

Treatment efficacy of medication was significantly larger in trials conducted at single-centers than multiple-centers, as well as when administered to participants described as being diagnosed with generalized SAD. The findings that both RIMAs and benzodiazepines were efficacious and tolerable in treating SAD therefore needs to be interpreted in light of the observation that none of the included trials for these medications reported restricting inclusion to the generalized SAD subtype. Moreover, the RIMAs are not available in clinical practice, while findings from the small number of trials of benzodiazepines must be weighed against concerns regarding their adverse effects and their lack efficacy for common comorbid conditions that occur with SAD (Ford 2014; Licata 2008).

Trials took place in a diverse range of settings and with heterogeneous samples and should therefore currently be considered in a broad spectrum of SAD participants. Nevertheless, the review recognises that certain forms of the disorder, such as those consisting of ’pure’ public speaking fears, were not well represented in this review. Although beta-blockers are often recommended for the treatment of performance anxiety, there was insufficient evidence in this review to support the use of this medication class for people without the generalized type of SAD.

Implications for research

Differences in the efficacy of different medications deserve more attention; there are few studies directly comparing modern agents with one another. In addition, there is a paucity of

RCTs evaluating the efficacy of medications for treating SAD in people with comorbid disorders, including substance use disorders, and in people in general psychiatric and medical settings. Studies of these populations could address the question of whether early and robust pharmacotherapy of SAD can prevent subsequent morbidity and comorbidity. Further attention should also be paid to people who fall on a putative SAD spectrum of disorders, including people with performance anxiety. Finally, commonly used symptom outcomes in SAD have limitations, with more refined measures of response to treatment warranting further investigation. This would help inform the concept of remission in SAD.

Additional work is also needed to determine the best approach to people who fail to respond to pharmacotherapy; there are relatively few studies of treatment augmentation (Ipser 2009b; Pecknold 1982; Van Ameringen 1996; Stein 2001; Aarre 2003) or pharmacotherapy switching (Kelsey 1995). The current review also does not directly address the question of whether pharmacotherapy or psychotherapy has a larger effect size in SAD (Gould 1997). In clinical practice, clinicians often use exposure instructions (Gelernter 1991), while theoretically, modern understanding of SAD as involving psychobiological dysfunctions would indicate that it is unnecessary to institute false dichotomies between brain and mind, and that both kinds of intervention might be useful (Furmark 2002). Therefore, another research priority revolves around the combined use of pharmacotherapy with psychotherapy and when and if these treatments should be combined or sequenced.

In the next chapter I utilise the Cochrane standard pairwise approach in synthesising data for PTSD.

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CHAPTER 3.

Pharmacotherapy for posttraumatic stress disorder (PTSD).

Chapter three includes a comprehensive search, literature review and methodology. Cochrane risk of bias and GRADE was used to assess the quality of each trial by medication class. Data for clinical response, symptom severity (for the Clinically Administered PTSD Scale (CAPS)) and acceptability (i.e. dropouts due to side effects or dropouts due to any cause) was analysed using a standard pairwise approach, and both subgroup and sensitivity analyses were conducted to consider confounding variables that may have impacted on the overall heterogeneity and effect estimates of outcomes. Funnel plots were also generated to assess publication bias. In this dissertation, however, I only report data for acute outcomes. Therefore, I excluded any information on long-term efficacy and tolerability. Secondary outcomes for depression, anxiety and disability were also measured although I do not report this in my dissertation, keeping in mind the NMAs and to be consistent in my reporting.

BACKGROUND

In the previous chapter I looked at SAD. I now turn to PTSD. I provide information on the condition in detail, the existing trials, the interventions, and the need for additional trials.

Description of the condition

Although the phenomenon of posttraumatic stress disorder (PTSD) has long been recognised (for example as "shell shock" or "combat neurosis"), this disorder was only officially recognised in the psychiatric nomenclature in 1980 (APA 1980). Diagnostic criteria for PTSD provided by the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) encouraged research on the epidemiology, psychobiology, and treatment of PTSD.

The latest version of the Diagnostic and Statistical Manual (i.e. DSM-5) has made several notable revisions to PTSD diagnostic criteria and removed PTSD from the category of anxiety disorders. PTSD is now classified in a new category, Trauma- and Stressor-Related Disorders, in which the onset of every disorder has been preceded by exposure to a traumatic or otherwise adverse environmental event (Friedman 2016). The DSM-5 pays more attention to the behavioral symptoms that accompany PTSD and include the addition of a fourth distinct diagnostic cluster (i.e. the negative cognitions and mood cluster) (APA 2013).

The United States Department of Veterans Affairs (Friedman 2016) and the American Psychiatric Association (APA 2013) describe the following criteria ('A-H' criterion) for the diagnosis of PTSD. The "A" criterion states that a person must be exposed to a catastrophic event involving actual or threatened death or injury, or a threat to the physical integrity of him/herself or others (for example, sexual violence) for the event to be regarded as a trauma. The "B" criterion (i.e. intrusive recollection) includes symptoms that are distinctive and readily identifiable like panic, terror, dread, grief, or despair. These symptoms manifest during the daytime as intrusive images, traumatic nightmares, and flashbacks. The "C" criterion (i.e. avoidance criterion) consists of behavioural strategies PTSD patients use to reduce trauma-related events. Symptoms included in the "D" criterion reflect negative cognitions and moods that have developed after exposure to the traumatic event (i.e. blame, anger, guilt, or shame). Symptoms included in the "E" criterion are from alterations in arousal or reactivity such as hypervigilance or paranoia. In the "F" or duration criterion, it is stipulated that symptoms must persist for at least one month before PTSD may be diagnosed. Within the "G" criterion (i.e. functional significance criterion) the survivor must experience significant social, occupational, or other distress as a result of these symptoms, and in the "H" criterion (or exclusion criterion),

these symptoms cannot be due to medication use, substance use, or other illnesses (APA 2013; Friedman 2016).

Subsequent epidemiological research determined that the disorder is highly prevalent in a wide range of settings, particularly in those subjects who have been exposed to significant traumas (Breslau 1991; Davidson 1991; Kessler 1995). Estimates from the National Comorbidity Survey Replication indicates lifetime PTSD prevalence rates of 3.6% and 9.7%, among men and women in the USA, respectively (Kessler 2005). In the most recent publication of this survey these estimates are confirmed and experienced by women and men depending on the type of trauma (Kessler 2017). Higher rates have also been reported in post-conflict settings (De Jong 2001), although the South African Stress and Health (SASH) study observed lower PTSD rates than in the US surveys in South Africa (prevalence percentage: 2.3%; Herman 2009).

There is also growing evidence that PTSD results in enormous personal and societal costs; this is based on chronicity of symptoms, high comorbidity of psychiatric and medical disorders, marked functional impairment, and estimations of economic costs (Solomon 1997; Brunello 2001). Furthermore, PTSD is characterised by specific psychobiological dysfunctions (Yehuda 1995; Bonne 2004; Charney 2004) and it is possible that each criterion is mediated by different neurobiological mechanisms (Charney 1993; Bernardy 2017), which may be normalised by specific pharmacological interventions. Certainly, there is growing evidence in PTSD for rather specific dysregulations of neurotransmitter systems (including the serotonin, noradrenaline, and dopamine systems) and neuroendocrine systems (including the hypothalamus-pituitary-adrenal axis), as well as for structural and functional neuroanatomical abnormalities (Charney 1993; Yehuda 1995; Canive 1997; Connor 1998; Hull 2002; Bremner 2004; Sherin 2011).

The evidence suggests net upregulation of the noradrenergic system and its responsivity to stress in individuals with PTSD. The noradrenergic system is a central, modifiable link in a network of interconnected stress–response systems, which also includes the amygdala and its modulation by medial prefrontal cortex. Bidirectional signalling occurs between the noradrenaline and corticotropin-releasing factor (CRF) in coordinating these interconnected systems (Hendrickson & Raskind, 2016). The 2A subtype of serotonin receptors (5-HT2A receptor) are upregulated by a broad variety of stressors. Upregulation of 5-HT2A receptors during stressful events forms associations that tune the brain to environmental cues that signal danger. In life-threatening situations these receptors may activate this system and contribute to the symptoms associated with PTSD (Murnane, 2019). As for the dopamine system, this system plays an important role in many neurological processes. Dysregulated dopamine is associated with various PTSD symptoms and influence the ability to deal with stress stimuli in subjects who have been exposed to traumatic events. The dopamine system is usually dysregulated in PTSD patients to counteract or worsen the crisis response to the stressful stimuli (Kelmendi & Adams et al., 2016). If worsened, this can impact on working memory and attention impairments over time (Vicario & Felmingham, 2018). In addition, dysregulation of the HPA axis is associated with stress-related pathologies like PTSD. PTSD increases sensitivity of glucocorticoid receptors (GRs) and moderates enhanced negative feedback which decreases cortisol levels. This endocrine dysregulation is mediated by lasting neurobiological alterations caused by extreme or repeated stress exposure, where trauma exposure is directly linked to the disease development (Dirven & Homberg et al., 2017). It is also noteworthy that given the wide action of effective drugs little is known however around the mechanisms of action (Steckler & Risbrough, 2012).

Prior psychological trauma plays a causal role in PTSD, and psychotherapy has been widely employed in its management. Although psychodynamic psychotherapy has long been the mainstay of treatment, there have been few controlled studies of this modality (Brom 1989; Gersons 2000). The value of so-called psychological debriefing in the immediate aftermath of trauma remains to be proven (Rose 1998; Rose 2002). Indeed, there is evidence that acute post-trauma debriefing may worsen PTSD symptoms, prompting guidelines to advise against its use (Gist 2015). Nevertheless, there is a growing body of evidence demonstrating that cognitive-behavioural and similar psychotherapies are indeed effective in the treatment of PTSD (Keane 1989; Solomon 1992; Glynn 1995; Sherman 1998; van Etten 1998; Harvey 2003; Bisson 2005; Bradley 2005; NICE 2005; Watkins 2018).

Whereas an older model was that medications might be valuable primarily as an adjunct to psychotherapy techniques in post-traumatic reactions (Sargent 1940), contemporary psychobiological theory speculates that comorbid substance use in PTSD may represent an attempt at "self-medication" and that prescribed medication may be able to play a primary role in preventing or reversing the dysfunctions of PTSD (Charney 1993; Charney 2004). PTSD frequently includes comorbid disorders such as major affective disorders, dysthymia, alcohol or substance abuse disorders, anxiety disorders, or personality disorders (Friedman 2016). Certain of these comorbid conditions are known to respond to medication (Kessler 1995; Kessler 2005). Indeed, the position that medication treatment may be useful in PTSD seems to have gained gradually increasing acceptance (van der Kolk 1983; Wise 1983; Friedman 1988; Friedman 1991; Faustman 1989; Walker 1989; Silver 1990; Allodi 1991; Davidson 1992; Davidson 1997a; Davidson 2000; Marshall 1996; Marshall 1998a; Shalev 1996; Connor 1998; Foa 1999; Cyr 2000; Marshall 2000; Asnis 2004; Ursano 2004).

Description of the intervention

Early reports of the pharmacotherapy of PTSD focused on the tricyclic antidepressants (TCAs) and the irreversible monoamine oxidase inhibitors (MAOIs) (Hogben 1981; White 1983; Burstein 1984; Milanes 1984; Falcon 1985; Bleich 1986; Davidson 1987; Lerer 1987; Frank 1988; Shestatzky 1988; Davidson 1989; Irwin 1989; Reist 1989; Olivera 1990; Chen 1991; Kosten 1991; Basoglu 1992; Rubin 1993; Demartino 1995). More recent work has focused on the selective serotonin reuptake inhibitors (SSRIs) (Davidson 1990; Burdon 1991; McDougle 1991; De Boer 1992; Dominiak 1992; Shay 1992; Nagy 1993; Fichtner 1994; Kline 1994; van der Kolk 1994; Brady 1995; Marmar 1996; Nagy 1996; Rothbaum 1996; Connor 1998; Davidson 1998a; Marshall 1998b; Marshall 2001; Brady 2000; Hertzberg 2000; Smajkic 2001; Tucker 2001; Martenyi 2002a; Zohar 2002; Tucker 2003; Brady 2005), selective serotonin and norepinephrine reuptake inhibitors (SNRIs) (Davidson 2006a; Davidson 2006b) and the serotonin antagonists and reuptake inhibitors (SARIs) (Liebowitz 1989; Hertzberg 1996; Hertzberg 1998; Hidalgo 1999).

Several other newly introduced antidepressants have also been studied (Katz 1994; Baker 1995a; Neal 1997; Canive 1998; Davidson 1998a; Hamner 1998; Connor 1999; Davis 2000; Davis 2001; Davidson 2003). In addition, benzodiazepines (Dunner 1985; Lowenstein 1988; Braun 1990), beta-blockers (Kolb 1984; Famularo 1988), buspirone (Simpson 1991; Wells 1991; Duffy 1992; Duffy 1994; LaPorta 1992; Fichtner 1994), clonidine (Kolb 1984; Kinzie 1989; Harmon 1996) and guanfacine (Horrigan 1996), cyproheptadine (Brophy 1991; Gupta 1998), d-cycloserine (Heresco-Levy 2002), inositol (Kaplan 1996), mood-stabilizers (Kitchner 1985; Lipper 1986; Stewart 1986; van der Kolk 1987; Wolf 1988; Irwin 1989; Fichtner 1990; Fesler 1991; Szymanski 1991; Keck 1992; Forster 1994; Looff 1995; Ford 1996; Hertzberg 1999); typical (Bleich 1986; Dillard 1993) and atypical neuroleptics (Hamner 1996; Leyba

1998; Izrayelit 1998; Burton 1999; Butterfield 2001; Hamner 2003); and opioids (Glover 1993) have also received attention.

How the intervention might work

TCAs are non-specific in their actions on specific neurotransmitters, with their primary mechanism of action involving varying degrees of serotonin and norepinephrine (NE) reuptake inhibition. MAOIs, on the other hand, work by irreversibly inhibiting the enzyme, monoamine oxidase, normally involved in metabolism of serotonin and NE. Both medication classes are generally considered second or third-line treatments due to their adverse event profile and need for dietary restriction (i.e. MAOIs) (Ravindran 2009).

SSRIs and SNRIs are considered first line agents for the treatment of PTSD (Ipser 2012). These antidepressants increase serotonin output by blocking the serotonin transporter (SERT) and are effective in reducing symptoms of anxiety and fear (Stahl 2013). At this point in time there are six SSRIs currently globally available for the treatment of PTSD symptoms, namely, sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, and escitalopram. Only two (i.e. sertraline and paroxetine) are FDA approved (Ravindran 2009). Similarly, the serotonin 1A (5HT1A) partial agonist, buspirone, has potential anxiolytic actions. These could theoretically be due to this agent's 5HT1A partial agonist actions at both presynaptic and postsynaptic 5HT1A receptors, with actions at both sites resulting in enhanced serotonergic activity in projections to the amygdala, prefrontal cortex, striatum, and thalamus. SSRIs and SNRIs theoretically operate via similar mechanisms. Since the onset of anxiolytic action for buspirone is delayed, this has led to the belief that 5HT1A agonists exert their therapeutic effects by adaptive neuronal events and receptor events, rather than simply by the acute occupancy of 5HT1A receptors. In this way, the presumed mechanism of action of 5HT1A partial agonists is analogous to the SSRIs,

which also demonstrated delayed onset of action, and are also presumed to act by adaptations in neurotransmitter receptors. These delayed medication effects can be compared to the relatively rapid effect of the benzodiazepine anxiolytics, which act relatively acutely by occupying benzodiazepine receptors (Stahl 2013). The serotonin antagonist and reuptake inhibitor, nefazodone, is an older antidepressant that is thought to work through post-synaptic 5-HT2A receptor antagonism, inhibition of presynaptic serotonin and NE reuptake, and through blocking α1 receptors. Nefazodone is now rarely used due to concerns of hepatotoxicity in some patients (Ravindran 2009). Liebowitz 1989 reviewed the clinical efficacy of trazodone (50–250 mg/day) in treating 22 patients with a dual diagnosis of substance abuse and anxiety symptoms. A substantial number of subjects suffered from symptoms of posttraumatic stress disorder (PTSD). Improvement was noted in all subjects within the first month of treatment, and most reported symptomatic improvement after each dose of trazodone, resulting in an as-needed pattern of usage.

Benzodiazepines, as a class, work on the central nervous system (CNS) via their effects on the GABAA receptors. Activation at the special benzodiazepine receptor site on the GABAA receptor promotes enhanced activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), thus resulting in various effects including: anxiolysis, sedation, muscle relaxation, cognitive effects, and anticonvulsant actions. These functions, and particularly the first two, would seem to have benefits for PTSD (Ravindran 2009).

Anti-Adrenergic Agents and/or Beta-Blockers are based on putative noradrenergic alterations seen in PTSD. Clonidine, for example, is commonly used as an antihypertensive agent, and is a centrally acting α2 adrenergic agonist that works to decrease sympathetic tone. As such, it was theorised to have potential effects on the hyperarousal symptoms seen in PTSD.

Guanfacine, another α2 adrenergic agonist with a similar mechanism of action, has also been investigated. However, no benefit has been reported (Davis 2008; Neylan 2006). The use of β-adrenergic antagonists has also been investigated in PTSD, but primarily for a role in the secondary prevention of this disorder. Cahill 1994 demonstrated that a single dose of propranolol administered to healthy humans impaired subsequent recall of an emotionally arousing story but not for an emotionally neutral one, thus lending to support for the theory that memory for emotional experiences involved the β- adrenergic system. Based on this, PTSD researchers theorised that administration of a β-adrenergic antagonist in the peritraumatic period might have a beneficial effect in blocking consolidation of the traumatic memory and thus prevent development of PTSD (Ravindran 2009).

Anticonvulsant medications, with their putative anti-kindling effects, have been investigated for PTSD, although the bulk of the evidence for use of these agents (e.g. carbamazepine and divalproex) are not well researched (Ravindran 2009). Atypical antipsychotics have been controversial in their use for the treatment of various anxiety disorders and even more controversial is their use for posttraumatic stress disorder (PTSD). Anecdotal use as well as clinical evidence for utility in various anxiety disorders is probably greatest for quetiapine. More recently, central α1 receptors have been linked to potential therapeutic effects such as improvement in nightmares by the α1 antagonist prazosin in posttraumatic stress disorder (PTSD) and maybe even reduction of extrapyramidal side effects (EPS). The latter possibility is suggested by the fact that preclinical studies show that norepinephrine acting at postsynaptic α1 receptors can stimulate the same pyramidal neurons in prefrontal cortex that serotonin acting at postsynaptic 5HT2A receptors stimulates. By analogy, therefore, if blocking 5HT2A receptors reduces EPS by the downstream actions of such neurons, it may be possible that blocking α1 receptors on these same neurons would also reduce EPS. This possibility is

supported by the fact that clozapine and iloperidone both have the highest binding potencies of α1 antagonism relative to D2 antagonism among all the atypical antipsychotics; quetiapine also has potent α1 properties. All three of these agents exhibit few if any EPS in clinical use, although other atypical antipsychotics with higher EPS rates also have high α1 receptor binding. Perhaps the combination of high 5HT2A and α1 affinities is a plausible explanation for the low EPS of iloperidone and clozapine, but this is unproven and requires further research (Stahl 2013).

Only a small number of controlled trials have investigated the adjunctive use of antipsychotic agents (which include olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) in PTSD, and even fewer have explored their utility as monotherapy (Ravindran 2009). A case study on the typical neuroleptic thioridazine compared to placebo showed improved symptoms and general state of mind (Dillard 1993). Other agents like D-cycloserine (DCS), a partial agonist at the NMDA receptor, have also been investigated as a potential treatment for PTSD. Arguing that the presence of flashbacks and intrusive memories in PTSD may be a function of extinction failure, and that learning, and memory are both glutamate-dependent processes. Heresco-Levy 2002 and colleagues argued that enhancing glutamate transmission could facilitate the learning of new memories to replace the traumatic ones (as cited in Ravindran 2009). The addition of cyproheptadine, taken orally at night, has also shown to control and decrease in the intensity and frequency of nightmares (Brophy 1991; Gupta 1998). Similarly, eighteen chronic posttraumatic stress disorder combat veterans who received the opioid nalmefene showed a favourable response with a marked decrease of emotional numbing and other symptoms of PTSD, including startle response, nightmares, flashbacks, intrusive thoughts, rage and vulnerability as the dosage increases (Glover 1993). The was also evidence reported by studies assessing the mood-stabilizers carbamazepine (Lipper 1986), valproate

(Fesler 1991), lithium (Forster 1994;) and lamotrigine (Hertzberg 1999). With no significant difference found in the improvement score for inositol compared to placebo, however (Kaplan 1996).

Why it is important to do this review

A systematic review of studies of pharmacotherapy for PTSD is useful in tackling several questions for the field. Firstly, is pharmacotherapy in fact an effective form of treatment in PTSD? Given the preponderance of psychological models and evidence for the efficacy of certain forms of psychotherapy in PTSD (Bisson 2005), the role of pharmacotherapy remains debatable for many. In a recently published guideline for the treatment of PTSD, the National Institute of Clinical Evidence (NICE) recommended that preference be given to trauma-focused psychological therapy over pharmacotherapy as a routine first line treatment for this disorder (NICE 2018). For those who accept a more dominant role for pharmacotherapy, questions about appropriate dose and duration arise, with current clinical recommendations suggesting that the SSRIs, for example, are prescribed at doses that increase to maximally effective/tolerated levels over a period of at least eight weeks (Foa 1999; Ballenger 2000; Ballenger 2004).

Secondly, are particular medication classes more effective in the treatment of symptoms and/or more acceptable to the patient in terms of adverse events than others? The use of novel agents (such as the serotonergic antidepressants) for PTSD in recent years raises the question of how these compare with older agents. Some recommendations, such as the expert consensus guideline series for the treatment of posttraumatic stress disorder (Foa 1999), have suggested that the SSRIs, nefazodone, and venlafaxine are first-line medications for the treatment of PTSD, with benzodiazepines and mood-stabilisers having a role in patients with certain kinds

of symptoms. Other recommendations have highlighted paroxetine, mirtazapine, amitriptyline and phenelzine (NICE 2018). Support for such recommendations requires ongoing assessment of the literature on RCTs.

Thirdly, can a systematic review of RCTs provide information about the most important factors affecting pharmacotherapy response? Clinical factors, such as the kind of pre-existing trauma (e.g. combat-related or not), the duration of symptoms, and the presence of comorbid depression, early childhood trauma, and "secondary gain" for symptoms (for example, patients in ongoing litigation or receiving financial compensation) have all been suggested to play a role (Davidson 1993; van der Kolk 1994; Marshall 1998b; Davidson 2000). Methodological factors such as the duration of the trial or inclusion of patients with a minimal degree of symptom severity, may also affect treatment response. It is possible that the database of RCTs in PTSD may include information about some of these variables.

Several reviews of the pharmacotherapy of PTSD have indeed been published in recent years (van der Kolk 1983; Friedman 1988; Friedman 1991; Davidson 1992; Davidson 1997a; Marshall 1996; Marshall 1998a; Solomon 1992; Shalev 1996; Otto 1996; Connor 1998; Albucher 2002; Asnis 2004; Ipser 2012; Hoskins 2015). These reviews have been useful in summarising the existing research, pointing to methodological flaws, and outlining areas for future research. Nevertheless, few of these reviews have employed a systematic search strategy. It has been determined that even MEDLINE searches may miss over half of all RCTs in specialised health care journals (Hopewell 2002). Furthermore, few studies have estimated the effects of medication (Penava 1996; Davidson 1997a; van Etten 1998). Interestingly, in their meta-analysis, Penava (Penava 1996) noted that effect size correlated with increased serotonergic specificity of the antidepressant. Further reviews in this area need to adhere to

Cochrane Collaboration (Mulrow 1997) or similar (Moher 1999) guidelines for systematic identification of trials, investigation of sources of heterogeneity, measurement of methodological quality, and estimation of the effects of intervention.

In this chapter, a systematic review of RCTs of pharmacotherapy of posttraumatic stress disorder, originally published in 2006, is updated, following the guidelines and using the software of the Cochrane Collaboration (Higgins 2011; RevMan 2014).

OBJECTIVES

1. To identify and review all RCTs, including placebo controlled and comparative trials, of the pharmacotherapy of posttraumatic stress disorder (PTSD), whether published or unpublished.
2. To provide an estimate of the effects of medication in reducing PTSD symptoms.
3. To identify which factors (clinical, methodological) predict response to pharmacotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (placebo controlled and comparative trials) completed prior to the end of June 2018 were considered for inclusion. Publication is not necessarily related to study quality and indeed publication may imply certain biases (Easterbrook 1991; Dickersin 1992; Scherer 1994), so unpublished reports, abstracts, and brief and preliminary reports were also considered. Differences between trials (for example, sample size, trial duration or language)

were not used to exclude studies. Cluster-randomised controlled trials, cross-over trials and multiple treatment trials were also included in the analysis.

Types of participants

Participant characteristics

All studies of adult participants diagnosed with PTSD (as determined by the study author) were included, irrespective of diagnostic criteria and measure, duration and severity of PTSD symptoms, age, and gender. These descriptors were however tabulated in order to address the question of their possible impact on the effects of medication.

Comorbidities

No restrictions were placed on the presence of comorbid disorders secondary to PTSD.

Setting

No restrictions were placed on setting.

Subsets of participants

Studies that reported a subset of participants that met the review inclusion criteria were nevertheless excluded, to preserve randomisation.

Types of interventions

The review focused only on medication treatments, in which the comparator was a placebo (active or non-active) or other medication. A parallel review of the psychotherapy of PTSD has been completed by members of the Cochrane Collaboration (Bisson 2005). More recently, a

Cochrane review of RCTs of medication prophylaxis for PTSD has been published (Amos 2014).

This review classified medications based on their putative mechanisms of action (taken from CCMD antidepressant classification map) (Davies 2015), and they do not necessarily map onto the drug classification schemes employed in other reviews.

Experimental interventions

Specific pharmacological interventions were grouped according to medication class. The medication classes are listed below:

- Alpha-blocker (e.g. prazosin)
- Anticonvulsants (e.g. tiagabine, divalproex, lamotrigine, and topiramate)
- Antipsychotics (e.g. olanzapine, risperidone and quetiapine)
- Benzodiazepine (e.g. alprazolam)
- Dopamine beta-hydroxylase inhibitor (e.g. nepicastat)
- Experimental medications (e.g. ganaxolone, GR205171, GSK561679)
- Mono-amine oxidase inhibitor (MAOI, e.g. phenelzine)
- NK-1 receptor antagonist (e.g. orvepitant)
- NMDA receptor antagonist (e.g. ketamine)
- Noradrenaline reuptake inhibitor (NARI, e.g. reboxetine)
- Noradrenergic and specific serotonergic antidepressant (NaSSA, e.g. mirtazapine)
- Reversible inhibitor of monoamine oxidase A (RIMA, e.g. brofaromine)
- Second messenger system precursor (e.g. inositol)
- Selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram)

- Serotonin and norepinephrine reuptake inhibitor (SNRI, e.g. venlafaxine)
- Serotonin antagonist and reuptake inhibitor (SARI, e.g. nefazodone)
- Tricyclic antidepressants (TCAs, e.g. amitriptyline, desipramine and imipramine)

Comparator interventions

- Placebo (active or non-active).

No restrictions were placed on timing, dose, duration, or co-interventions.

Types of outcome measures

Primary outcomes

1. **Treatment Efficacy**

- PTSD symptom and symptom cluster response were determined from the total score on the Clinician Administered PTSD Scale (CAPS) (Blake 1990), a symptom severity measure that is increasingly used in RCTs of PTSD. The CAPS is designed to make a categorical PTSD diagnosis which corresponds to the DSM-IV criteria. A "1, 2" rule is used to determine a diagnosis whereby a frequency score of 1 (scale 0 = "none of the time" to 4 = "most or all of the time") and an intensity score of 2 (scale 0 = "none" to 4 = "extreme") is required in order to meet specific symptom criteria (Weathers 1999 as cited in the International Society for Traumatic Stress Studies).
- Treatment response (responders versus non-responders) was determined from the Clinical Global Impressions Scale - Improvement Item (CGI-I), or closely related measure such as the Duke Global Rating for PTSD scale (Davidson 1998b), or a closely related definition (Brady 2000). The CGI-I ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). In this review, responders were defined on the

CGI-I as those with a score of 1 = "very much" or 2 = "much" improved (Guy 1976). Given that the CGI-I is a widely used global outcome measure in RCTs of PTSD, this instrument served as a robust measure of the clinical value of treatment in PTSD (Davidson 1997b).

Secondary outcomes

2. Reduction of PTSD Symptoms

PTSD symptom response was assessed for those trials which used other continuous measures of symptom severity besides the CAPS (explained in primary outcomes), as well as from summary statistics from self-rated scales such as the Impact of Events Scale (IES) (Horowitz 1979), and the Davidson Trauma Scale (DTS) (Davidson 1997c). The IES evaluates the distress that is caused by traumatic events and is centred around two subscales (i.e. intrusion and avoidance). The IES is a 22-item self-report scale in which respondents choose options from 1-5. The DTS is a 17-item self-report measure that assesses the 17 DSM-IV symptoms of PTSD. Items are rated on a 5-point frequency (0 = "not at all" to 4 = "every day") and severity scale (0 = "not at all distressing" to 4 = "extremely distressing"). The scores range from 0 to 136.

Self-rated scales were frequently the only outcome measures used in older trials and may continue to have a role in clinical practice. The efficacy of medication in alleviating symptoms within the three symptom clusters characteristic of PTSD (re-experiencing/intrusion, avoidance/numbing, and hyperarousal) was determined using the CAPS-B, CAPS-C, and CAPS-D subscales of the CAPS, as well as the relevant subscales of the self-rated outcome measures.

3. Treatment tolerability

The total proportion of participants who withdrew from the RCTs due to treatment emergent adverse events was included in the analysis as a surrogate measure of medication acceptability, in the absence of other more direct indicators of acceptability. Dropout rates due to any cause were also compared in order to provide some indication of treatment effectiveness.

Search methods for identification of studies

Cochrane Specialised Register (CCMDCTR)

The Cochrane Common Mental Disorders Group maintained a comprehensive, specialised register of randomised controlled trials, the CCMDCTR (to June 2016). The register contains over 39,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with >50% of reference records tagged to c12,500 individually PICO coded study records. Reports of trials for inclusion in the register were collated from (weekly) generic searches of Medline (1950-), Embase (1974-) and PsycINFO (1967-), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials were also sourced from international trial registries, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) and Medline search is displayed below:

Electronic searches

1. CCMDCTR was searched using the following search strategy, March 2018:

Diagnosis = Post-Traumatic Stress Disorders

and

"Antidepressive Agents" OR "Monoamine Oxidase InhibitORs" OR "Selective Serotonin Reuptake InhibitORs" OR "Tricyclic Drugs" OR Acetylcarnitine OR Alaproclate OR Amersergide OR Amiflamine OR Amineptine OR Amitriptyline OR Amoxapine OR Befloxatone OR Benactyzine OR Brofaromine OR Bupropion OR Butriptyline OR Caroxazone OR ChlORpoxiten OR Cilosamine OR Cimoxatone OR Citalopram OR Clomipramine OR ClORgyline OR ClORimipramine OR Clovoxamine OR Deanol OR Demexiptiline OR Deprenyl OR Desipramine OR Dibenzipin OR Diclofensine OR Dothiepin OR Doxepin OR Duloxetine OR Escitalopram OR Etoperidone OR Femoxetine OR Fluotracen OR Fluoxetine OR Fluparoxan OR Fluvoxamine OR Idazoxan OR Imipramine OR Iprindole OR Iproniazid OR isocarboxazid OR Litoxetine OR Lofepramine OR Maprotiline OR Medifoxamine OR Melitracen OR Metapramine OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Nefazodone OR Nialamide OR Nomifensine OR NORtriptyline OR Noxiptiline OR Opipramol OR Oxaflozane OR Oxaprotiline OR Pargyline OR Paroxetine OR Phenelzine OR Piribedil OR Pirlindole OR Pivagabine OR Prosulpride OR Protriptyline OR Quinupramine OR Reboxetine OR Rolipram OR Sertraline OR Setiptiline OR Teniloxine OR Tetrindole OR Thiazesim OR Thozalinone OR Tianeptine OR Toloxatone OR Tomoxetine OR Tranylcypromine OR Trazodone OR Trimipramine OR Venlafaxine OR Viloxazine OR Viqualine OR Zimeldine.

2. Additional searches were carried out on MEDLINE (via PubMed, 1 January 2015 to 31 December 2018), PsycINFO (via EBSCOhost, 2015-2018) and The National PTSD Center Pilots database (2 May 2018).

The MEDLINE search query, as derived from a highly sensitive search strategy developed by Robinson and Dickersin (Robinson 2002), was the following:

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) AND (Stress Disorders, Post-Traumatic [mh:noexp] OR "posttraumatic stress disorder" [tw] OR "post traumatic stress disorder" [tw] OR PTSD [tw]) AND (pharmacother* [tw] OR medicat* [tw] OR drug* [tw] OR Drug Therapy [mh]).The PsycINFO search used the following search query: ("randomisation" OR "randomization") OR "controlled" AND ("post-traumatic" OR posttraumatic) AND (medication OR pharmacotherapy OR treatment).

PsycINFO includes the Dissertation Abstracts International database - a database of unpublished dissertations.

The National PTSD Center Pilots database contains published and unpublished articles on PTSD. It was searched using the following search query: (randomisation or randomization) or controlled AND (post-traumatic OR posttraumatic) AND (medication OR pharmacotherapy).

3. Unpublished trials were retrieved via the metaRegister module [mRCT] of the Controlled Trials database (http://www.controlled-trials.com, 28 June 2018). The search terms used were "PTSD", "posttraumatic stress disorder", and "post-traumatic stress disorder".

An initial broad strategy was undertaken to find not only RCTs, but also open-label trials, as well as journal and chapter reviews of the pharmacotherapy of PTSD.

Searching other resources

Reference Lists

Additional RCTs were sought in reference lists of the retrieved articles and included studies in any language.

Personal communication

Published and unpublished trials were obtained from key researchers, who were identified by the frequency with which they were cited in the bibliographies of RCTs and open-label studies.

Data collection and analysis

Review Manager 5 (RevMan 5) was used to perform all analyses reported in this review (RevMan 2014).

Selection of studies

RCTs identified from the search were independently assessed by me and my main supervisor, based on information included in the abstract and/or main body of the trial report. RCTs which were regarded as satisfying the inclusion criteria specified in the Data extraction and management and Criteria for considering studies for this review section were collated. Studies

for which additional information is required in order to determine their suitability for inclusion in the review have been listed in the Characteristics of studies awaiting classification table (see published review), pending the availability of this information. Any disagreements in assessment and collation were resolved by discussion with my co-supervisor (DS).

Data extraction and management

Spreadsheet forms were designed for the purpose of recording descriptive information, summary statistics of the outcome measures, the quality scale ratings, and associated commentary.

The following information was collated from each trial (additional information can be found in the Characteristics of included studies table):

(a) Description of the trials, including the primary researcher, the year of publication, and the source of funding.

(b) Characteristics of the interventions, including the number of participants randomised to the treatment and control groups, the number of total drop-outs per group as well as the number that dropped out due to adverse effects, the dose of medication and the period over which it was administered, and the name and class of the medication (SSRIs, TCAs, MAOIs and "other medication").

(c) Characteristics of trial methodology, including the diagnostic (e.g. DSM-IV (APA 1994)) and exclusionary criteria employed, the screening instrument used (e.g. the Structured Clinical Interview for DSM-IV (SCID) (Spitzer 1996)) for both the primary and comorbid diagnoses, the presence of comorbid major depressive disorder (MDD), the use of a placebo run-in or of

a minimal severity criterion, the number of centres involved, and the trial's methodological quality (see below).

(d) Characteristics of participants, including gender distribution and mean and range of ages, mean length of time with PTSD symptoms, whether they have been treated with the medication in the past (treatment naivety), the number of participants in the sample with MDD, the number who experienced combat trauma, and the baseline severity of PTSD, as assessed by the trial's primary outcome measure or another commonly employed scale.

(e) Outcome measures employed (primary and secondary), and summary continuous (means and standard deviations (SD)) and dichotomous (number of responders) data. Additional information included whether data reflected the intent-to-treat (ITT) with last observation carried forward (LOCF) or mixed methods (MM) sample, or whether a completer/observed cases (OC) sample was reported.

Where information was missing, investigators were contacted by email to obtain this information.

Assessment of risk of bias in included studies

Risk of bias of each included study was assessed using the Cochrane 'Risk of bias' tool (Higgins 2011) based on the consideration of the following six domains.

1. Random sequence generation: did investigators use a random number table or a computerised random number generator?

2. Allocation concealment: was the medication sequentially numbered, sealed, and placed in opaque envelopes?

3. Blinding of participants, personnel, and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated treatment or assessment adequately prevented during the study?

4. Incomplete outcome data for each main outcome or class of outcomes: were missing or excluded outcome data adequately addressed?

5. Selective outcome reporting: were the reports of the study free of suggestion of selective outcome reporting? Such a judgement could only be made based on the availability of the protocol.

6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

Risk of bias data was assessed and extracted for the included studies (by TW and JI). Any disagreements were discussed with my co supervisor (DS). Where necessary, I contacted the authors of the studies for further information. A judgement on the risk of bias for each domain within and across studies was made, based on the following three categories: 'low' risk of bias, 'unclear' risk of bias, and 'high' risk of bias. All risk of bias data is graphically presented and described in the text.

Measures of treatment effect

Categorical data

Relative risk (RR) of failure to respond to treatment was used as the summary statistic for the dichotomous outcome of interest (CGI-I or related measure).

Continuous data

Weighted mean differences (WMD) were calculated for continuous summary data obtained from studies that employed the CAPS. Alternatively, in cases in which a range of scales were employed, such as in the assessment of symptom severity on the self-rated IES and DTS scales, the standardised mean difference (SMD) was determined. This method of analysis standardises the differences between the means of the treatment and control groups in terms of the variability observed in the trial.

In the case of data from trials employing multiple fixed doses of medication, the bias introduced through comparing the summary statistics for multiple groups against the same placebo control was avoided by pooling the means and standard deviations across all the treatment arms as a function of the number of participants in each arm. In addition, when including summary statistics from the self-rated scales, preference was given to data from the DTS over the IES in trials which used both scales, given the inclusion in the former of a subscale assessing the hyperarousal symptom cluster (Weiss 1997), and concerns regarding the psychometric properties of the IES subscales (Creamer 2003).

Unit of analysis issues

Cluster-randomised trials

In cluster-randomised trials, groups of individuals are randomised to different interventions rather than individuals themselves. Analysing treatment response in cluster-randomised trials without taking these groupings into account is potentially problematic, as participants within any one cluster often tend to respond in a similar manner, and thus analyses cannot assume that participants' data are independent of the rest of the cluster. Cluster-randomised trials also face additional risk of bias issues including recruitment bias, baseline imbalance, loss of clusters, and non-comparability with trials randomising individuals (Higgins 2011). No cluster randomised trials were eligible for inclusion in this review.

Cross-over trials

Cross-over trials were only included in the calculation of summary statistics when it was (a) possible to extract medication and placebo/comparator data from the first treatment period, or (b) when the inclusion of data from both treatment periods was justified through a wash-out period of sufficient duration as to minimise the risk of carry-over effects (a minimum of two weeks or longer in the case of trials assessing the efficacy of agents with extended half-lives, such as the SSRI, fluoxetine (Gury 1999)). In the latter case, data from both periods were only included when it was possible to determine the correlation between participants' responses to the interventions in the different phases (Elbourne 2002).

Multiple treatment groups

A few trials included in this review compared more than two intervention groups or multiple doses of the same medication against placebo. Including data from the same placebo group for these studies repeatedly in the same comparison would result in a unit of analysis error (Higgins

2011). To prevent these errors for trials comparing multiple dosages of the same agent to placebo, the mean and standard deviation of the outcome of interest across dosage groups were averaged. Outcome data from multiple treatment arms were included in the same comparison if the agents tested were from different medication classes. The subtotals of the outcome were not calculated if the placebo group appeared twice in the analysis to accommodate for the second medication. In the case of trials testing multiple agents from the same classes, and in calculating the total effect across all medication classes, we restricted data from multi-arm RCTs to the agent that was least represented in the database.

Dealing with missing data

All analyses of dichotomous data were intention-to-treat (ITT) and data from trials providing information on the original group size (prior to dropouts) were included in the analyses of treatment efficacy. Preference was given within studies to the inclusion of summary statistics for continuous outcome measures derived from mixed-effects models, followed by last observation carried forward (LOCF) and observed cases (OC) summary statistics (in that order). This is in line with evidence that mixed-effects methods are more robust to bias than LOCF analyses (Verbeke 2000).

Assessment of heterogeneity

Heterogeneity of treatment response, that is whether the differences between the results of trials were greater than would be expected by chance alone, was assessed visually from the forest plot of RR. It was also determined by means of the chi-square test of heterogeneity, with a significance level of less than 0.10 interpreted as evidence of heterogeneity, given the low power of the chi squared statistic when the number of trials is small (Deeks 2003).

In addition, the I-square heterogeneity statistic reported by RevMan was used to test the robustness of the chi squared statistic to differences in the number of trials included in the groups being compared within each subgroup analysis (Higgins 2003). Differences in treatment response on the CGI-I was determined by whether the confidence intervals for the effect sizes of the subgroups overlap. This method was chosen in preference to the stratified test, due to inaccuracies in the calculation in RevMan of the chi squared statistic for dichotomous measures (Deeks 2003; Deeks 2011).

Thresholds for the interpretation of I-square can be misleading, since the importance of inconsistency depends on several factors. The review followed a rough guide for interpretation:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Funnel plots provide a graphic illustration of the effect estimates of an intervention from individual studies against some measure of the precision of that estimate. Publication bias was determined by visual inspection of a funnel plot of treatment response, with the consideration of confounding selection bias, poor methodological quality, true heterogeneity, artefact, and chance. Given that this calculation is dependent on having 10 trials per outcome, this could only be calculated for the SSRIs.

Data synthesis

Summary statistics for categorical and continuous measures were obtained from a random effects model (the random effects model includes both within-study sampling error and between-studies variation in determining the precision of the confidence interval (CI) around the overall effect size, whereas the fixed effects model takes only within-study variation into account). The summary statistics were expressed in terms of an average effect size for each subgroup, as well as by means of 95% CIs.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses (Thomson 1994) were undertaken in order to assess the degree to which methodological differences between trials might have systematically influenced differences observed in the primary treatment outcomes.

The trials were grouped according to the following methodological sources of heterogeneity:

- The involvement of participants from a single centre or multiple centres. Single-centre trials are more likely to be associated with lower sample size but less variability in clinician ratings.
- Whether or not trials were industry funded. In general, published trials which are sponsored by pharmaceutical companies appear more likely to report positive findings than trials which are not supported by for-profit companies (Als-Nielsen 2003; Baker 2003).

In addition, the following criteria were used to assess the extent of clinical sources of heterogeneity:

- Whether or not the sample included combat veterans (this subgroup has been regarded as more resistant to treatment and is arguably more likely to have more chronic and severe symptoms, to have comorbid depression, and to be male). For the purpose of this review, those trials for which 10 percent or fewer of the sample consisted of war veterans were classified as non-combat veteran RCTs.
- Whether or not the sample included patients diagnosed with major depression. Such an analysis might assist in determining the extent to which the efficacy of a medication agent in treating PTSD is independent of its ability to reduce symptoms of depression, an important consideration given the classification of many of these medications as antidepressants.

Sensitivity analysis

Sensitivity analyses, which determine the robustness of the reviewers' conclusion to methodological assumptions made in conducting the meta-analysis, were also performed. Sensitivity analyses were conducted to determine whether treatment response on the CGI-I differed as a result of:

- Treatment response versus non-response as the unit of comparison in determining medication efficacy. This comparison is regarded as necessary given concerns that the former may result in less consistent summary statistics than the latter (Deeks 2002).
- The exclusion of participants who were lost to follow up (LTF). This was determined through a "worst case/best case" scenario (Deeks 2003). In the worst case, all the missing data for the treatment group were recorded as non-responders, whereas in the best case, all missing data in the control group were treated as non-responders. (In the

case of the one SSRI (Marshall 2004) and MAOI trial (Baker 1995 a) which only reported total LTF, the ratio of participants who dropped out in the medication and placebo group was determined from the average ratio between these groups for those RCTs in the respective classes which did provide this information). Should the conclusions regarding treatment efficacy not differ between these two comparisons, it can be assumed that missing data in trial reports do not have a significant influence on outcome.

Summary of findings tables

The review author compiled 'Summary of findings' tables to summarise the best evidence for all relevant outcomes (i.e. experimental versus comparator interventions), reporting the following six elements according to a fixed format (Higgins 2011):

- A list of all important outcomes, both desirable and undesirable.
- A measure of the typical burden of these outcomes (e.g. illustrative risk, or illustrative mean, on control intervention).
- Absolute and relative magnitude of effect (if both are appropriate).
- Numbers of participants and studies addressing these outcomes.
- A grade of the overall quality of the body of evidence for each outcome.
- Space for comments.

The downgrading's of the evidence rating for outcomes were based on five factors. Reasons for downgrading the evidence were classified as 'serious' (downgrading the quality rating by one level) or 'very serious' (downgrading the quality grade by two levels).

- Limitations in the design and implementation of the trial.
- Indirectness of evidence.

- Unexplained heterogeneity or inconsistency of results.
- Imprecision of results.
- High probability of publication bias.

The review classified the quality of evidence for each outcome according to the following categories:

- High quality: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: we are very uncertain about the estimate.

RESULTS

NOTE: Due to the limited word count, certain analyses and tables for the characteristics of studies (included, excluded, awaiting publication and ongoing) can be found in the original publication which is under review. This includes all appendices.

Results of the search

A total of 9791 study reports was found through the search process (CCMDCTR 1366; EMBASE 773; PILOTS 792; PubMed 494; MEDLINE 505; PsychINFO 5000; Clinical Trials 861). Each title and abstract (if provided) was scanned for eligibility. Seven hundred and seventeen studies initially seemed relevant, but after further inspection 450 of these were excluded, leaving 267 studies that potentially met the inclusion criteria. After independent

review of the full-text studies, 204 failed to meet inclusion criteria, leaving 63 RCTs eligible for inclusion in the review (see Characteristics of included studies and Figure 1). Of the 63 trials, the review included 53 RCTs in the meta-analysis. Fifteen studies are awaiting classification, and eight studies are ongoing (see Characteristics of studies awaiting classification and Characteristics of ongoing studies).

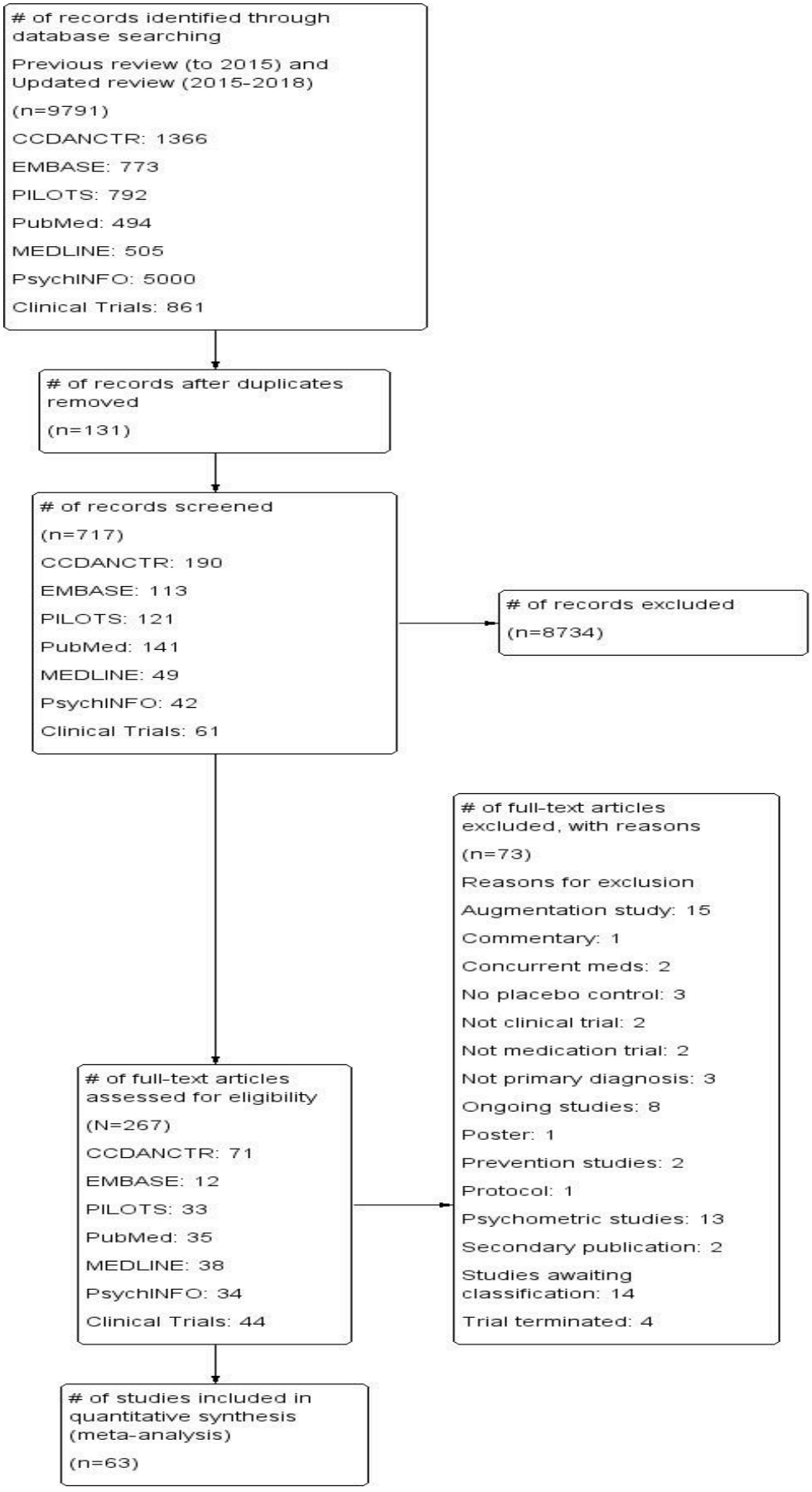


Figure 1. PRISMA Diagram

Included studies

The review included 63 RCTs of PTSD (7378 participants, age range 18-82 years), four of which contained a maintenance component (Davidson 2001a, Marshall 2007, Martenyi 2002a, van der Kolk 2007). Of the 63 trials, 55 were published, and all these publications were in English. Pharmaceutical companies contributed funding for 35 of these trials. Nineteen studies were single-centre trials, and 42 studies took place in multiple-centres. There was insufficient information to determine the setting for the SKB627 and SKB650 trial. A placebo comparison group was employed in all but six of the trials (McRae 2004 and Saygin 2002 compared nefazodone with the SSRI sertraline, while Smajkic 2001 compared the efficacy of the SSRIs sertraline, paroxetine and the SNRI venlafaxine). Chung 2004 assessed the efficacy and tolerability of mirtazapine against that of sertraline, Feder 2014 ketamine against that of midazolam (fixed 0.045 mg), and Spivak 2006 reboxetine (fixed 8 mg) against that of fluvoxamine (fixed 150 mg)). Of the remaining 57 RCTs, 28 of the trials included a SSRI treatment arm (one citalopram, dose range: 20-50 mg; eight fluoxetine, dose range: 10-80 mg; seven paroxetine, dose range: 10-60 mg; eleven sertraline, dose range: 15-200 mg), two trials a alpha-blocker intervention (prazosin, dose range: 1-15 mg), seven trials a anticonvulsant intervention (e.g. two tiagabine, dose range: 2-16 mg; two divalproex, dose range: 500-3000 mg; one lamotrigine, dose range: 25-500 mg; two topiramate, dose range: 25-400 mg), five trials a antipsychotic intervention (e.g. two olanzapine, dose range: 5-20 mg; two risperidone, dose range: 0.5-6 mg; one quetiapine, dose range: 25-800 mg), and three trials an experimental intervention (one ganaxolone, dose range: 200-600 mg; one GR205171, fixed 5 mg; one GSK561679, fixed 350 mg). The review also included two trials with a MAOI intervention (phenelzine, dose range: 15-75 mg), two trials with a RIMA intervention (brofaromine, dose range: 50-150 mg), two trials with a SNRI intervention (venlafaxine, dose range: 75-300 mg), and three trials with a TCA intervention (one amitriptyline, dose range: 50-200 mg; one

desipramine, dose range: 50-200 mg; one imipramine, dose range: 50-300 mg). Single trials included a benzodiazepine (alprazolam, dose range: 1.5-6 mg) treatment arm, a dopamine beta-hydroxylase inhibitor (nepicastat, dose range: 100-800 mg) treatment arm, a NK-1 receptor antagonist (orvepitant, fixed 60 mg) treatment arm, a NMDA receptor antagonist (ketamine, fixed 0.5 mg) treatment arm, a NaSSA (mirtazapine, dose range: 15-50 mg) treatment arm, a second messenger system precursor (inositol, fixed 12 grams) treatment arm, and a SARI (nefazodone, dose range: 50-600 mg) treatment arm.

None of the seven RCTs which employed a cross-over design (Braun 1990; Feder 2014; Kaplan 1996; Rasmusson 2017; Raskind 2007; Reist 1989; Shestatzky 1988) provided enough information for inclusion of data in the meta-analysis. These trials were all small and of poor quality, however, so their inclusion/exclusion is unlikely to have had a significant effect on the primary outcomes of the meta-analysis. In brief: Braun 1990 compared an intervention of alprazolam with placebo using a sample of 16 outpatients over a period of 12 weeks. Feder 2014 compared ketamine and midazolam over 13 days amongst 41 participants. Kaplan 1996 investigated the efficacy of inositol for a sample of 13 patients from two different outpatient clinics. Rasmusson 2017 included 112 participants in an open label trial followed by a double-blind trial investigating the experiential medication ganaxolone. Raskind 2007 assessed the efficacy of prazosin for the treatment of PTSD over eight weeks in combat veterans. Reist 1989 conducted a crossover trial of the TCA, desipramine, in treating 27 combat veterans over a period of 10 weeks. Shestatzky 1988 assessed the efficacy of the MAOI phenelzine in a 12 week trial of 13 PTSD outpatients.

In determining the long-term effects of medication, Marshall 2007 assessed whether 17 responders in the medication arm of a 10 week trial of paroxetine continued to respond after

an additional maintenance period of 12 weeks, whereas van der Kolk 2007 assessed the efficacy of fluoxetine in 59 participants over five weeks followed by a six month maintenance phase. In a relapse-prevention trial of sertraline, Davidson 2001b set out to determine whether 50 patients who were randomised to a placebo control for 28 weeks were more likely to experience clinical deterioration or relapse than those 46 patients randomised to a sertraline intervention for the same period. Participants in the relapse prevention phase of this trial had completed a 12 week acute RCT of sertraline, and had also met responder criteria following the subsequent open-label administration of this medication for a period of six months. In another relapse-prevention trial, Martenyi 2002a re-randomised 131 responders to a 12 week short-term RCT of fluoxetine to an additional 24 weeks of placebo or medication.

A great deal of clinical heterogeneity was observed across patients in the RCTs of this review. Of the 51 trials that provided information on the nature of the index trauma for PTSD, nine were composed exclusively of war veterans (Chung 2004; Davidson 1990; Hertzberg 2000; Kosten 1991; NCT00659230; Pfizer589; Raskind 2007; Raskind 2018; Reist 1989), 14 contained individuals exposed to "civilian" traumas, such as earthquakes and child molestation (Brady 2000; Brady 2005; Conner 1999; Marshall 2007; McRae 2004; NCT01000493; Padala 2006; Pfizer588; Reich 2004; Saygin 2002; Smajkic 2001; Spivak 2006; Tucker 2007; Yeh 2011) and 28 contained patients exposed to both combat-related and civilian traumas (Baker 1995 a; Braun 1990; Butterfield 2001; Davidson 2001a; Davidson 2003; Davidson 2005; Davidson 2006a; Davis 2004; Davis 2008; Dunlop 2017; Feder 2014; Hertzberg 1999; Kaplan 1996; Katz 1994; Li 2017; Marshall 2001; Martenyi 2002a; Martenyi 2007; Mathew 2011; Panahi 2011; Rasmusson 2017; Shestatzky 1988; Tucker 2001; Tucker 2003; van der Kolk 1994; van der Kolk 2007; Villarreal 2016; Zohar 2002). Of the 34 RCTs that provided information on comorbid psychopathology, 18 reported that the patients in the trials were

diagnosed with other anxiety disorders besides PTSD, as classified according to DSM III, DSM-IV or DSM-IV-TR criteria (Brady 2000; Brady 2005; Braun 1990; Butterfield 2001; Carey 2012; Davidson 1990; Davidson 2001a; Davidson 2003; Davidson 2007; Davis 2004; Dunlop 2017; Hamner 2008; Hertzberg 2000; Kaplan 1996; Li 2017; Marshall 2001; Marshall 2007; Mathew 2011; Panahi 2011; Pfizer589; Raskind 2018; Rasmusson 2017; Reich 2004; Saygin 2002; Shestatzky 1988; Tucker 2001; Tucker 2003; Tucker 2007). The most commonly reported comorbid anxiety was panic disorder with or without agoraphobia, which was reported for eight of the 12 studies that distinguished between individual anxiety disorder diagnostic categories (Braun 1990; Butterfield 2001; Davidson 1990; Davis 2004; Marshall 2001; Marshall 2007; Saygin 2002; Tucker 2003), Twenty-one studies included individuals with major depressive disorder (MDD), while MDD was an exclusion criterion for six trials. The review was unable to determine whether individuals with MDD could take part in the remaining trials due to insufficient information.

Twenty one trials assessed the primary efficacy outcome – number of participants with PTSD who responded to treatment – using the CGI–I Scale (Brady 2000; Carey 2012; Chung 2004; Davidson 1990; Davidson 2001a; Davidson 2005; Davidson 2007; Friedman 2007; GSK 29060 627; Marshall 2001; Marshall 2007; Panahi 2011; Pfizer588; Pfizer589; Raskind 2007; Raskind 2018; Saygin 2002; Shestatzky 1988; SKB627; Tucker 2001; Zohar 2002), whilst 15 other trials assessed this outcome as a secondary measure using the same scale (Baker 1995 a; Butterfield 2001; Connor 2006; Davis 2004; Feder 2014; Hamner 2008; Katz 1994; Martenyi 2002a; Martenyi 2002b; Mathew 2011; Raskind 2018; Rasmusson 2017; Tucker 2007; Villarreal 2016; Yeh 2011). Forty-five trials used the CAPS to assess the reduction of PTSD symptoms, while 21 used the CGI-S, 23 used the DTS and 14 used the IES. The most common measures used to assess depression were the HAM-D (k = 23) and the MADRS (k = 14).

Eighteen trials assessed the reduction of anxiety symptoms with the HAM-A (Braun 1990; Connor 2006; Davidson 1990; Davidson 2001a; Davis 2004; Davis 2008; Friedman 2007; Kaplan 1996; Kosten 1991; Marshall 2007; Martenyi 2002a; Martenyi 2002b; McRae 2004; Padala 2006; Reist 1989; Spivak 2006; Tucker 2007; Villarreal 2016). Only eleven trials assessed functional disability using the SDS (Carey 2012; Conner 1999; Davidson 2006a; Davidson 2006b; Davidson 2007; GSK 29060 627; Marshall 2001; Mathew 2011; McRae 2004; SKB650; Tucker 2001; Tucker 2007). Post-treatment follow-up assessments ranged from two weeks in GSK 29060 627 to six months in van der Kolk 2007. See Characteristics of included studies for more details.

Excluded studies

Seventy-three studies were excluded from the review (see Characteristics of excluded studies). The most common reason trials were considered ineligible was the augmentation of medication and or psychotherapy within groups (Aerni 2004; Back 2016; Bartzokis 2005; Becker 2007; Hamner 1997; Hamner 2003; Heresco-Levy 2002; Monnelly 2003; NCT01325168; NCT01449955; NCT01477762; Otto 2003; Raskind 2003; Stein 2002; Suris 2017). Psychometric studies were also excluded (Bremner 1997; Coupland 1997; Hamner 1999; Kanter 2001; Kellner 2000; Morgan 1995; Pitman 2002; Randall 1995; Reist 1995; Reist 2001; Southwick 1997; Vaiva 2003; van der Kolk 1989). Three trials with a primary diagnosis other than PTSD (Jacobs-Rebhun 2000; Petrakis 2006; Roache 2017) and three trials with the absence of a placebo comparator were excluded (Eftekhari 2004; Frommberger 1998; Pollack 2011). The trials by Frank 1988 and Raskind 2013 were excluded because these trials were secondary analyses of previous studies, Krystal 2007 because this trial is a commentary of another published trial, Mello 2009 because this study is a protocol, and Nagy 1996 because this study is a poster presentation with no eligible findings. PTSD prevention studies were also

excluded (Gelpin 1996; Schelling 2004). Gradus 2013 and Zatzick 2004 are not medication trials and were therefore excluded. Four trials have been withdrawn and are no longer in effect due difficulty in achieving target enrollment numbers (NCT00557622; NCT00648375; NCT00706173; NCT01664260) and were therefore excluded. The trials by Neylan 2006 and Pitman 2002 were excluded because the participants in the trials were on concurrent medication. Finally, a qualitative study by NCT03302312 was excluded including the trials by Kline 1994 and Pivac 2004 given that they are not clinical trials. See Characteristics of excluded studies for more details.

Studies awaiting classification

Fourteen trials are awaiting classification (Fluoxetine, Davidson; Fluoxetine, Lilly; NCT00413296; NCT00641511; NCT00672776; NCT01517711; Nefazodone 1, BMS; Nefazodone 2, BMS; Olanzapine, Davidson; Paroxetine 2 - SB; Paroxetine 3 - SB; Sertraline 2, Pfizer; Sertraline 3, Pfizer; Sertraline 4, Pfizer). NCT00413296 conducted a study on the effectiveness of levetiracetam in 16 subjects with PTSD. NCT00641511 assessed nepicastat compared to placebo in patients with PTSD, and NCT00672776 paroxetine. PET measurement of brain activation before and after paroxetine or placebo treatment also took place in the NCT00672776 trial. NCT01517711 assessed tramadol and placebo in 40 patients with PTSD, as measured by the CAPS, CGI-S and various other secondary scales. There was insufficient information provided on the remaining studies awaiting classification and therefore the review does not have anything to report. See Characteristics of studies awaiting classification and Figure 1 for more details.

Ongoing studies

Eight studies are ongoing (Davis 2003; Mechoulam (THC); Mithoefer 2005; NCT01221792; NCT02637895; NCT02709018; NCT02933606; Tucker 2004). NCT01221792 will compare carvedilol versus placebo using the DTS and the CAPS to determine levels of PTSD severity in PTSD patients, whereas NCT02637895 will compare vortioxetine to placebo for 12 weeks on the CAPS. NCT02709018 will assess the efficacy of losartan, and NCT02933606 will compare BNC210 to placebo for treating PTSD in male or female patients between 18 and 70 years of age. There was little information provided on characteristics of the remaining ongoing studies (Davis 2003; Mechoulam (THC); Mithoefer 2005; Tucker 2004). See Characteristics of ongoing studies and Figure 1 for more details.

Risk of bias in included studies

Risk of bias was assessed using the Cochrane 'Risk of bias' tool for allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. Fifteen of the included studies were rated as being at high risk for at least one type of bias (see Figure 2 and Figure 3).

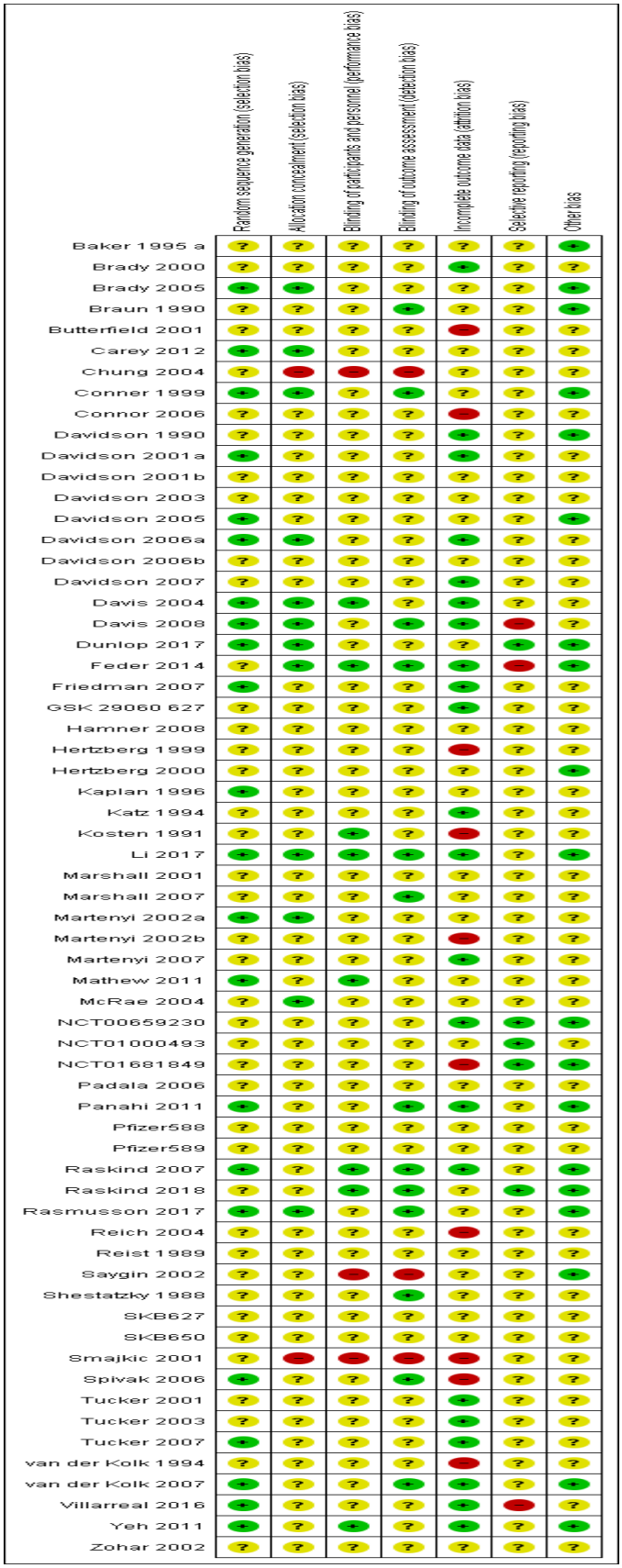


Figure 2. Risk of bias summary: review author judgements about each risk of bias item for each included study.

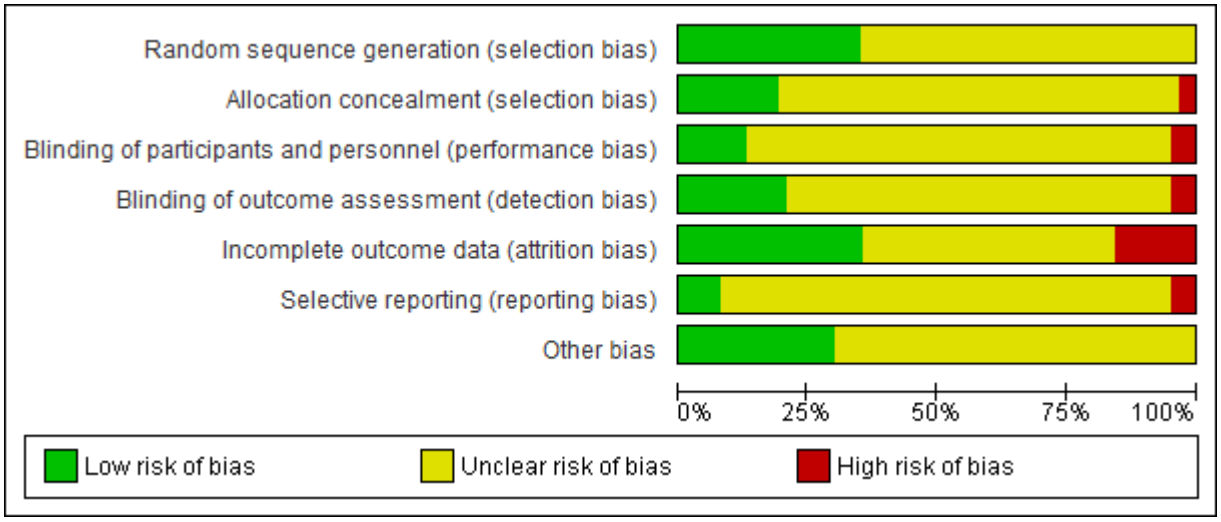


Figure 3. Risk of bias graph: review author judgements about each risk of bias item presented as percentages across all included studies.

Allocation (selection bias)

Randomisation

The randomisation procedure employed was described in 22 trials (Brady 2005; Carey 2012; Conner 1999; Davidson 2001a; Davidson 2005; Davidson 2006a; Davis 2004; Davis 2008; Dunlop 2017; Friedman 2007; Kaplan 1996; Li 2017; Martenyi 2002a; Mathew 2011; Panahi 2011; Raskind 2007; Rasmusson 2017; Spivak 2006; Tucker 2007; van der Kolk 2007; Villarreal 2016; Yeh 2011). Computer generated random codes were employed in ten of these trials (Conner 1999; Davidson 2001a; Davis 2008; Friedman 2007; Li 2017; Martenyi 2002a; Spivak 2006; Tucker 2007; Villarreal 2016; Yeh 2011), while an urn randomisation procedure was followed in Brady 2005. Permuted blocks were generated by computer programs for seven trials (Carey 2012; Davidson 2006a; Dunlop 2017; Mathew 2011; Raskind 2007; Rasmusson 2017; van der Kolk 2007) and prearranged random codes were used by Kaplan 1996, as well as a preassigned set of random numbers by Davidson 2005. The review classified all these studies as being at low risk for selection bias, while risk of bias was designated as unclear in the remaining studies.

Allocation concealment

Of the 63 RCTs, only 12 trials described adequate allocation concealment (Brady 2005; Carey 2012; Conner 1999; Davidson 2006a; Davis 2004; Davis 2008; Dunlop 2017; Feder 2014; Li 2017; Martenyi 2002a; McRae 2004; Rasmusson 2017) and were classified as low for risk of bias. A pharmacist or sponsor who prepared and supplied the study medication maintained allocation concealment in ten trials (Brady 2005; Carey 2012; Conner 1999; Davidson 2006a; Davis 2004; Davis 2008; Dunlop 2017; Feder 2014; Li 2017; McRae 2004). One study maintained concealment with the use of sealed envelopes (Martenyi 2002a), and another with bottles with numbers and codes generated by a computer program (Rasmusson 2017). One trial was classified as being at high risk of bias because it was an open label trial with no allocation concealment information (Smajkic 2001). The remaining trials were classified as unclear because the trials did not provide enough information to determine the adequacy of the concealment used.

Blinding (performance bias and detection bias)

Blinding of participants and personnel

Eight studies included in the review were classified as being at low risk for performance bias, as participants and personnel were explicitly described as blinded in the study report (Davis 2004; Feder 2014; Kosten 1991; Li 2017; Mathew 2011; Raskind 2007; Raskind 2018; Yeh 2011). Two trials were classified as being at high risk of bias because each trial did not blind their participants and personnel (Chung 2004; Smajkic 2001). The review classified risk of bias for the remaining trials as unclear, despite investigators describing them in the study reports as double-blinded, as they did not specify the actual parties blinded.

Blinding of outcome assessors

Although most of the trials were described as "double-blind", only 13 of the trials explicitly described the assessment of outcome as blinded (Braun 1990; Conner 1999; Davis 2008; Feder 2014; Li 2017; Marshall 2007; Panahi 2011; Raskind 2007; Raskind 2018; Rasmusson 2017; Shestatzky 1988; Spivak 2006; van der Kolk 2007). The extent to which blinding was preserved in those flexible dose trials which adjusted dosage based on tolerability is unclear, however. Indeed, the outcome was assessed independently of medication administration and side-effect evaluation in only one RCT (Marshall 2007). Two comparative RCTs did not employ any form of blinding (Chung 2004; Smajkic 2001), whereas it is not clear whether blinding was undertaken in another (Saygin 2002). The remaining studies were classified as being at unclear risk.

Incomplete outcome data (attrition bias)

Thirty one studies failed to provide sufficient information to determine whether the medication and placebo groups were comparable with respect to dropout proportions, or in terms of the demographic and clinical characteristics of those who withdrew (Baker 1995 a; Brady 2005; Braun 1990; Carey 2012; Chung 2004; Conner 1999; Davidson 2001a; Davidson 2003; Davidson 2005; Davidson 2006b; Dunlop 2017; Hamner 2008; Hertzberg 2000; Kaplan 1996; Marshall 2001; Marshall 2007; Martenyi 2002a; Mathew 2011; McRae 2004; NCT01000493; Padala 2006; Pfizer588; Pfizer589; Raskind 2018; Rasmusson 2017; Reist 1989; Saygin 2002; Shestatzky 1988; SKB627; SKB650; Zohar 2002). The risk of attrition bias was rated as unclear for these trials. Substantial differences in the proportion of study dropouts between the medication and placebo groups for 10 trials were observed (Butterfield 2001; Connor 2006; Hertzberg 1999; Kosten 1991; Martenyi 2002b; NCT01681849; Reich 2004; Smajkic 2001; Spivak 2006; van der Kolk 1994), justifying a rating of high risk. The review rated the

remaining 21 studies as being at low risk for this domain, because of comparable dropout rates in each comparison group and no difference in the demographic characteristics. Intention-to-treat data for all outcomes were assessed in 30 studies, using LOCF (k = 34), completers (k = 19), observed cases (k = 2) and mixed-effect models (k = 3) to account for missing data. Four studies did not specify how they addressed the issue of missing data.

Selective reporting (reporting bias)

It was unclear whether selective reporting took place in 55 trials because the study protocols were not available for the study. Five studies were rated as being at low risk for selective reporting because authors reported on all outcomes as specified in their respective trial protocols (Dunlop 2017; NCT00659230; NCT01000493; NCT01681849; Raskind 2018). In Davis 2008, Feder 2014, and Villarreal 2016, the pre-specified secondary outcomes in the protocol did not appear in the study report, meriting a classification of high risk.

Other potential sources of bias

Nineteen studies were classified as being at low risk for other potential sources of bias (Baker 1995 a; Brady 2005; Braun 1990; Conner 1999; Davidson 1990; Davidson 2005; Dunlop 2017; Feder 2014; Hertzberg 2000; Li 2017; NCT00659230; NCT01681849; Panahi 2011; Raskind 2007; Raskind 2018; Rasmusson 2017; Saygin 2002; van der Kolk 2007; Yeh 2011). The review rated the risk of other bias for the remaining studies as unclear due to industry involvement, whether through funding or provision of study medication.

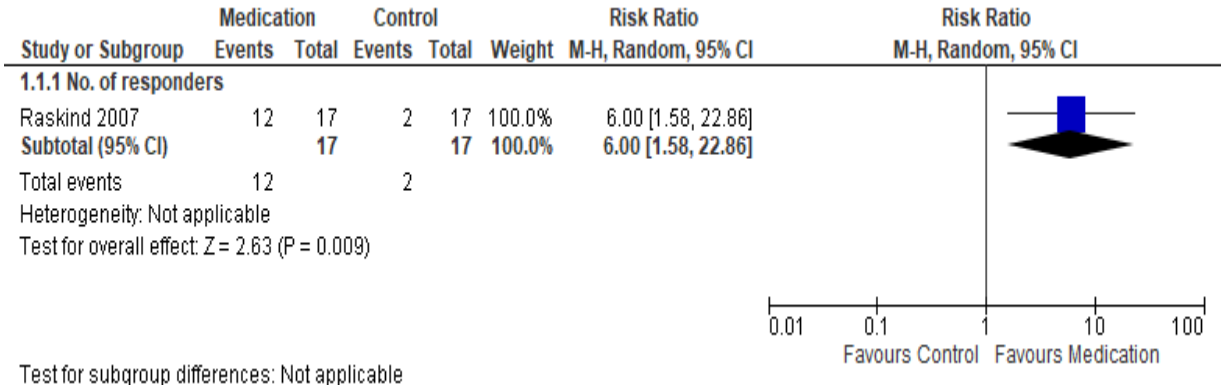
Effects of interventions

See 'Summary of findings' tables for the main comparisons of medication classes compared to placebo for treating PTSD, and Types of outcome measures for a description of the scoring systems used in included studies.

Comparison 1: Alpha-blockers versus placebo

Primary outcome measures

There was evidence of benefit of prazosin compared to placebo on the number of participants with PTSD who responded to treatment (k = 1, RR 6.00 ; 95% CI 1.58 to 22.86, N = 34; see Analysis 1.1; Raskind 2007). The evidence that was available for this outcome was of low quality.

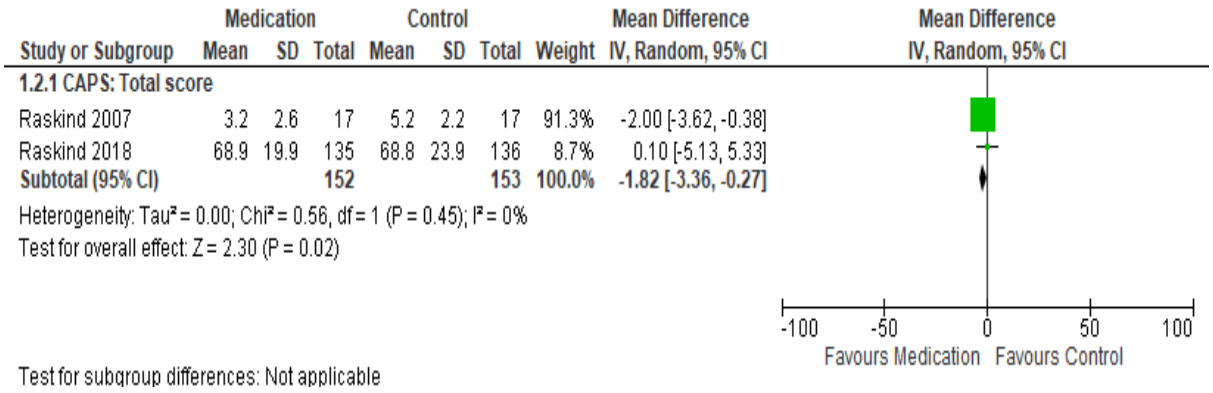


Analysis 1.1. Alpha-blockers versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

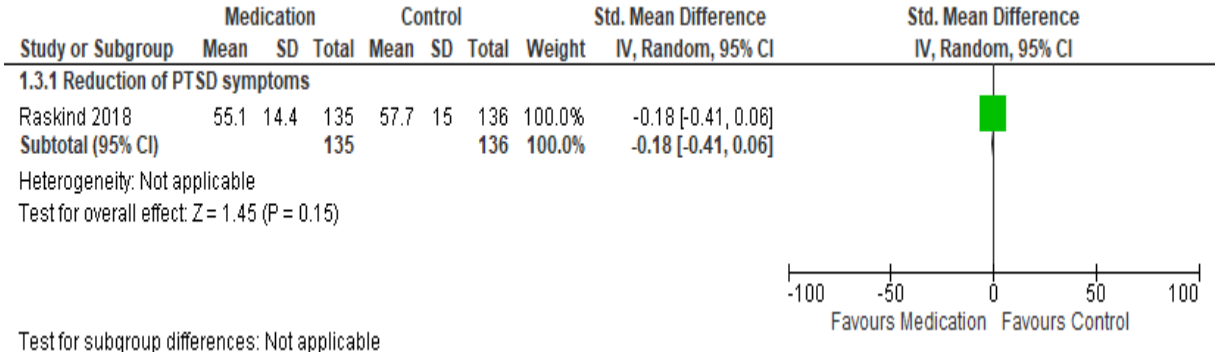
Secondary outcomes measures

There was evidence of benefit of prazosin compared to placebo in the reduction of PTSD symptoms on the CAPS (total score; k = 2, MD −1.82 points, 95% CI −3.36 to −0.27, N = 9; see Analysis 1.2; Raskind 2007; Raskind 2018), though the evidence is of low quality. No evidence of an effect for prazosin versus placebo was found for one trial that provided data for

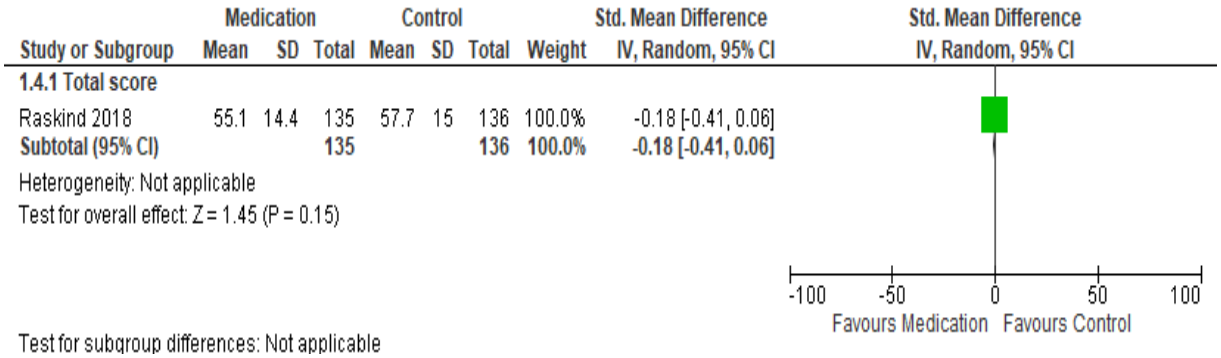
the reduction of PTSD symptoms (SMD -0.18 points, 95% CI −0.41 to 0.06, N = 271; Analysis 1.3; Analysis 1.4; Raskind 2018) on the self rated PTSD Checklist–Military Version (PCL-M).



Analysis 1.2. Alpha-blockers versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score.

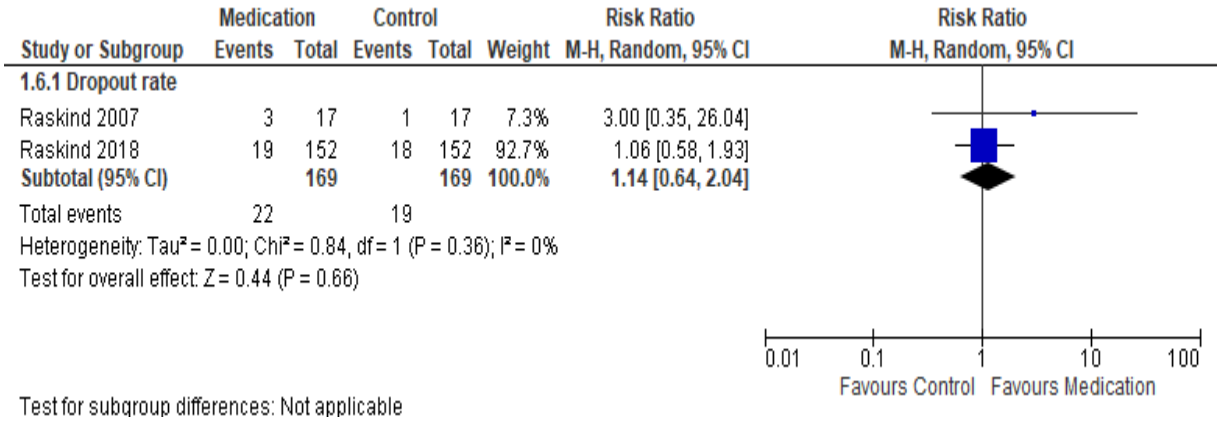


Analysis 1.3. Alpha-blockers versus placebo. Symptom severity: Other measures.

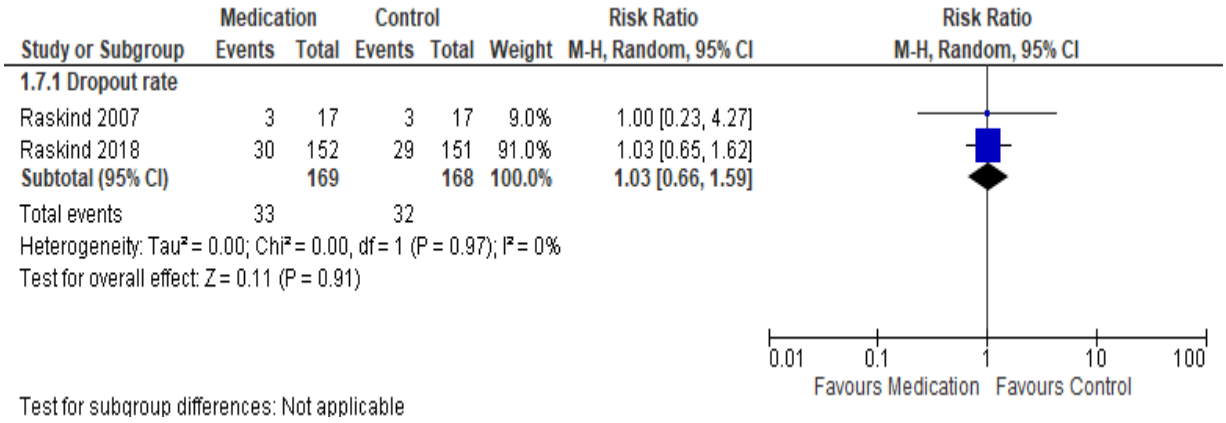


Analysis 1.3. Alpha-blockers versus placebo. Self-rated scales: Total score.

There was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 2, RR 1.14; 95% CI 0.64 to 2.04, N = 338; see Analysis 1.6; Raskind 2007; Raskind 2018). The evidence that was available for this outcome was of low quality. A similar proportion of participants withdrew from the prazosin groups (20%) compared to the placebo groups (19%) (k = 2, RR 1.03; 95% CI 0.66 to 1.59, N = 337; see Analysis 1.7; Raskind 2007; Raskind 2018).



Analysis 1.6. Alpha-blockers versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 1.7. Alpha-blockers versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 1: Alpha-blockers versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single and multi-center trials **Intervention**: alpha-blockers **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With alpha-blockers**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 6** (1.58 to 22.86)	34 (1 study)	⨁⨁⊖⊖ **low**[1,2]	There was evidence of a large effect on the number of participants with PTSD who responded to treatment (P = 0.009). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the
	118 per 1000	**706 per 1000** (186 to 1000)				
	Moderate					
	118 per 1000	**708 per 1000** (186 to 1000)				

						alpha-blocker group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.14** (0.64 to 2.04)	338 (2 studies)	⨁⨁⊖⊖ **low**[1,2]	No difference in dropout rates were found in the alpha-blocker group (22/169; 13%) and placebo group (19/169; 11%) (P = 0.66).
	112 per 1000	**128 per 1000** (72 to 229)				
	Moderate					
	89 per 1000	**101 per 1000** (57 to 182)				
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: Total score in the intervention groups was **1.82 points lower** (3.36 to 0.27 lower)		305 (2 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the alpha-blocker intervention group is 1.82 points which suggests 'mild/ minimal' PTSD.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.

Summary of Findings Table 1. Alpha-blockers versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

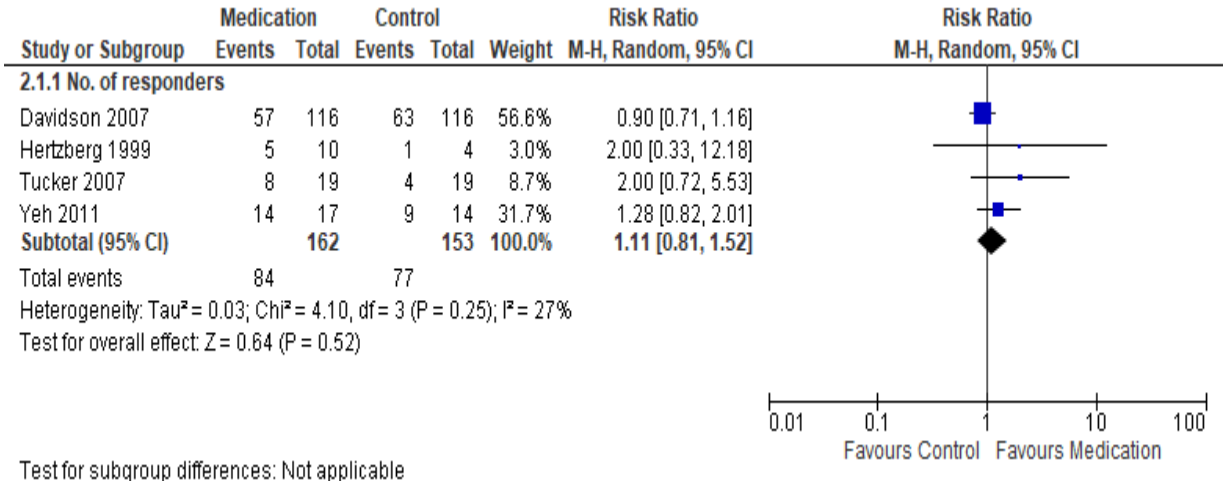
[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

Comparison 2: Anticonvulsants versus placebo

Primary outcome measures

There was no evidence of an effect of lamotrigine, tiagabine and topiramate on treatment efficacy in participants with PTSD compared to placebo (RR 1.11; 95% CI 0.81 to 1.52, see Analysis 2.1) in four trials with 315 participants (Davidson 2007; Hertzberg 1999; Tucker 2007; Yeh 2011). The evidence that was available for this outcome was of moderate quality.

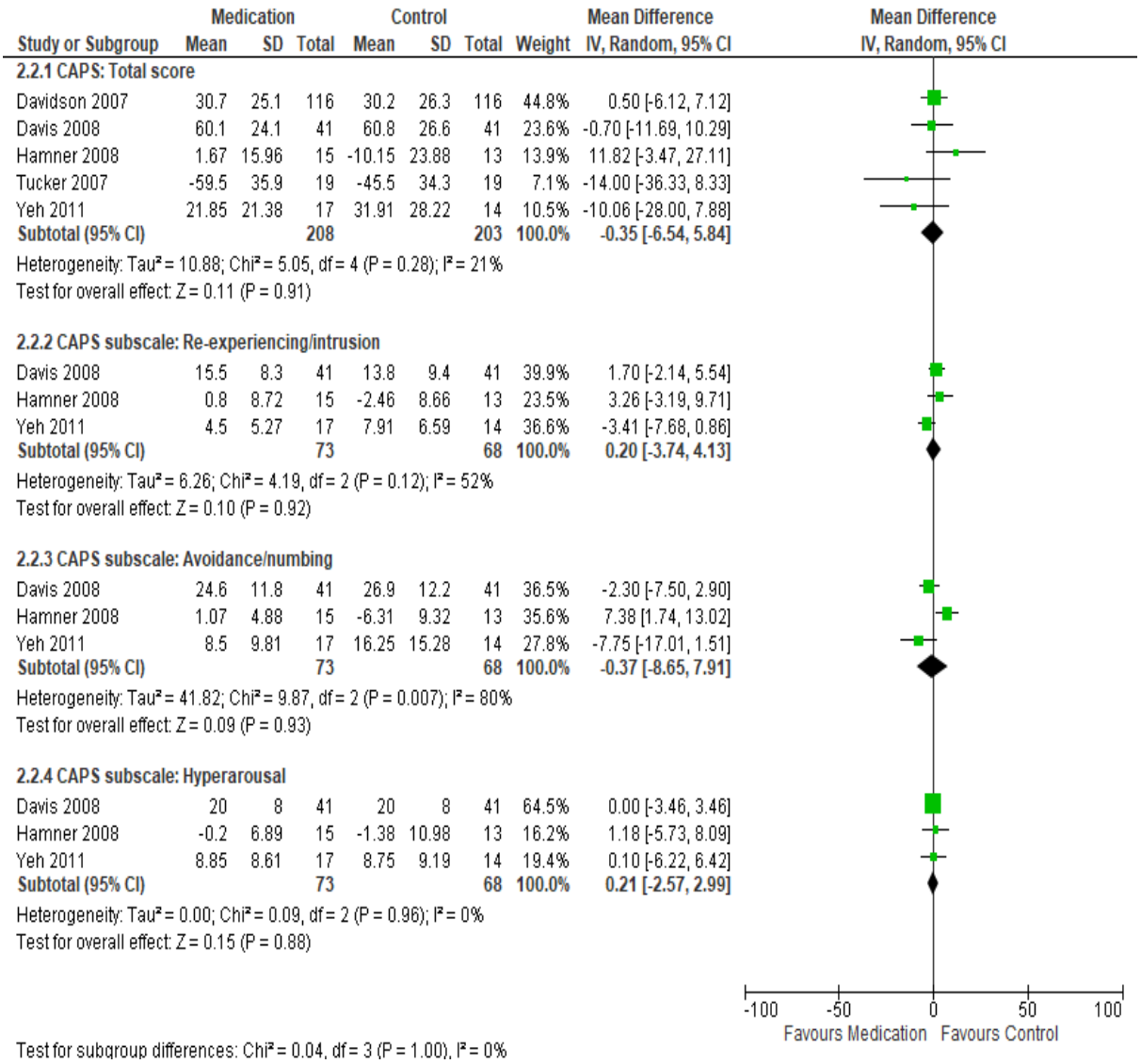


Analysis 2.1. Anticonvulsants versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

Secondary outcomes measures

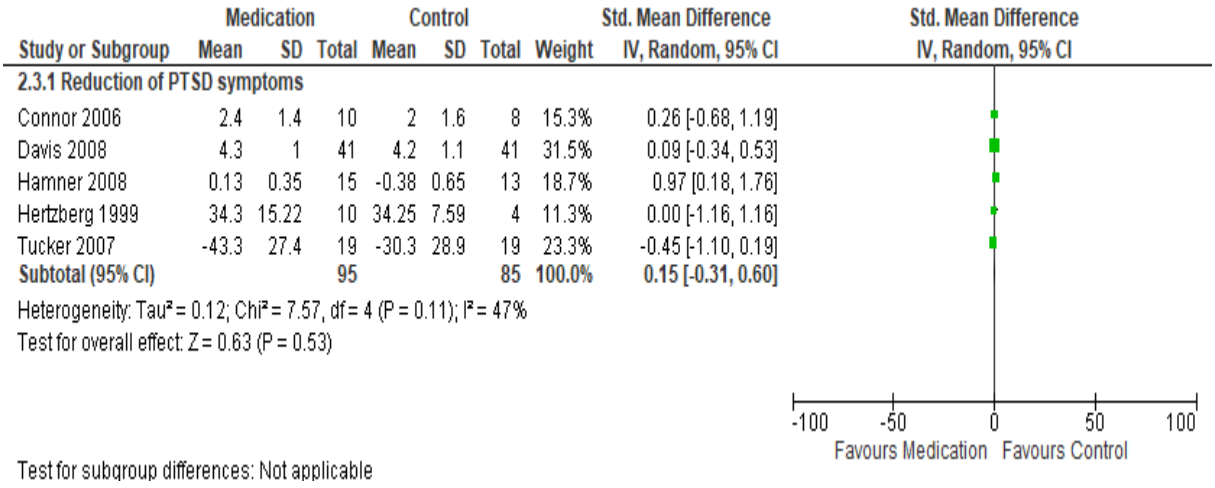
Data was assessed on the reduction of PTSD symptoms, measured by the CAPS (total score), in five studies comparing divalproex, tiagabine and topiramate to placebo (MD −0.35 points, 95% CI −6.54 to −5.84, N = 411; see Analysis 2.2; Davidson 2007; Davis 2008; Hamner 2008; Tucker 2007; Yeh 2011), and no evidence of benefit was found (P = 0.61). This outcome was based on low quality evidence. Divalproex and topiramate was not superior to placebo on either the re-experiencing/intrusion (MD −0.20 points, 95% CI −3.74 to 4.13; see Analysis 2.2), avoidance/numbing (MD −0.37 points, 95% CI −8.65 to 7.91; see Analysis 2.2), and

hyperarousal (MD 0.21 points, 95% CI −2.57 to 2.99; see Analysis 2.2) subscale of the CAPS in three trials with 141 participants (Davis 2008; Hamner 2008; Yeh 2011). Substantial and considerable heterogeneity was found for the re-experiencing/intrusion and avoidance/numbing subscale, respectively (Chi^2 = 4.19, df = 2 (P = 0.12); I^2 = 52%; Chi^2 = 9.87, df = 2 (P = 0.007); I^2 = 80%). This is further confirmed by the very low to low-quality evidence for these outcomes.

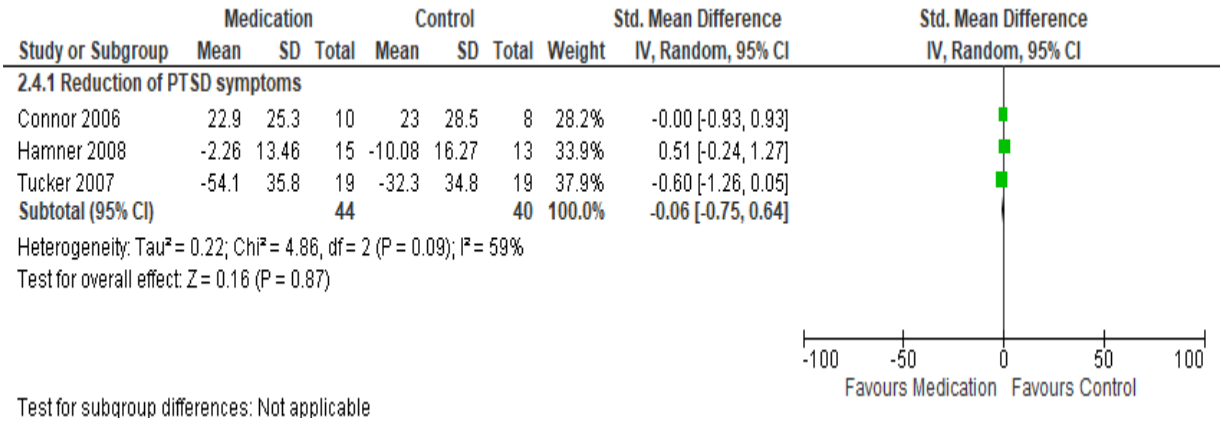


Analysis 2. Anticonvulsants versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

Furthermore, no evidence was found of an effect of divalproex, lamotrigine, tiagabine and topiramate versus placebo for the reduction of PTSD symptoms on the other symptom severity scales such as the CGI-S and DGRP (k = 5, SMD -0.02 points, 95% CI −0.32 to 0.28, N = 180; see Analysis 2.3; Connor 2006; Davis 2008; Hamner 2008; Hertzberg 1999; Tucker 2007), and on the self-rated DTS and IES (k = 3, SMD -0.06 points, 95% CI −0.75 to 0.64, N = 84; see Analysis 2.4; Connor 2006; Hamner 2008; Tucker 2007), with substantial heterogeneity found for the self-rated measures (Chi² = 4.86, df = 2 (P = 0.09); I² = 59%).

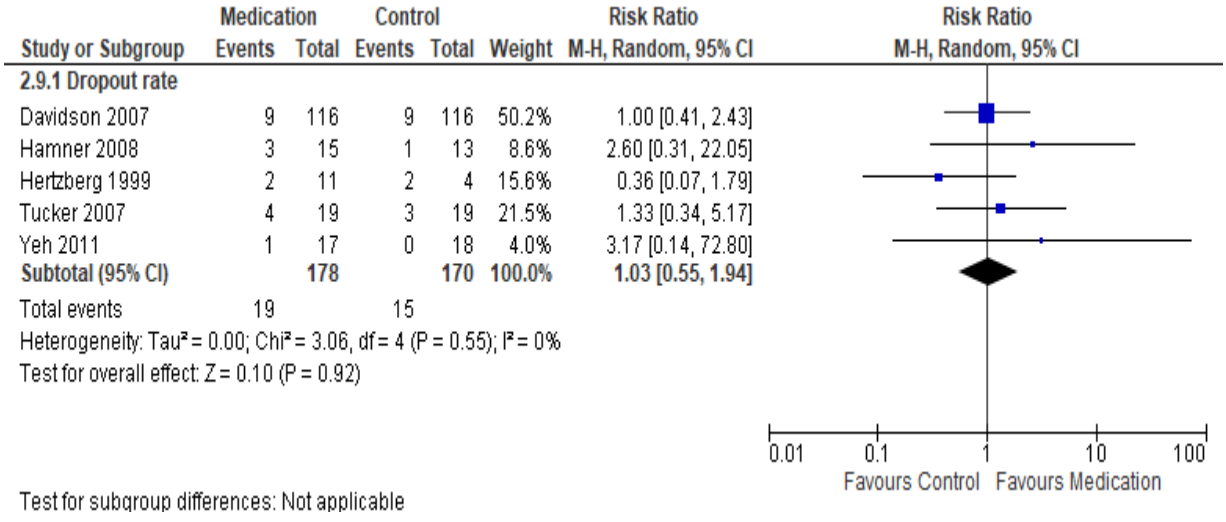


Analysis 2.3. Anticonvulsants versus placebo. Symptom severity: Other measures.

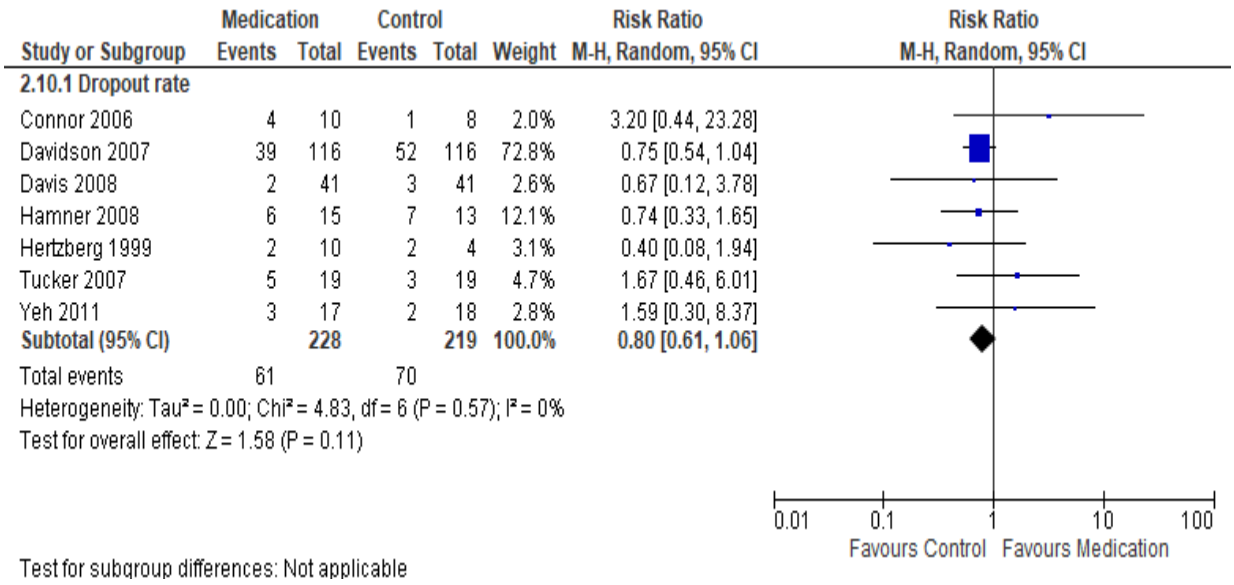


Analysis 2.4. Anticonvulsants versus placebo. Self-rated scales: Total score.

Dropout rates due to adverse events were low in RCTs of divalproex, lamotrigine, tiagabine and topiramate and comparable to those observed in the placebo arms (19/178, 11%; 15/170, 9%72/83; 9%, respectively) (k = 5, RR 1.03; 95% CI 0.55 to 1.94, N = 348; see Analysis 2.9; Davidson 2007; Hamner 2008; Hertzberg 1999; Tucker 2007; Yeh 2011). The evidence that was available for this outcome was of low quality. Similar dropout rates due to any cause were observed in the medication and placebo arms for the anticonvulsants (k = 7, RR 0.80; 95% CI 0.61 to 1.06, N = 447; see Analysis 2.10; Connor 2006; Davidson 2007; Davis 2008; Hamner 2008; Hertzberg 1999; Tucker 2007; Yeh 2011).



Analysis 2.9. Anticonvulsants versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 2.10. Anticonvulsants versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 2: Anticonvulsants versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single and multi-center trials **Intervention**: anticonvulsants **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With anticonvulsants**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.11** (0.81 to 1.52)	315 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	There was no evidence of an effect on the number of participants in the anticonvulsant groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.52).
	503 per 1000	**559 per 1000** (408 to 765)				
	Moderate					
	397 per 1000	**441 per 1000** (322 to 603)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.03** (0.55 to 1.94)	348 (5 studies)	⊕⊕⊖⊖ **low**[1,2]	No difference in dropout rates were found in the anticonvulsant groups
	88 per 1000	**91 per 1000** (49 to 171)				
	Moderate					

	78 per 1000	**80 per 1000** (43 to 151)				(19/170; 11%) and placebo group (15/170; 9%) (P = 0.92).
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was **0.35 points lower** (6.54 lower to 5.84 higher)		411 (5 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the anticonvulsant intervention groups is 0.35 points which suggests 'no' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **0.2 points higher** (3.74 lower to 4.13 higher)		141 (3 studies)	⨁⊖⊖⊖ **very low**[1,2,3]	The mean CAPS Re-experiencing/intrusion PTSD score for the anticonvulsant intervention groups is 0.2 points which suggests 'no' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **0.37 points lower**		141 (3 studies)	⨁⊖⊖⊖ **very low**[1,2,4]	The mean CAPS Avoidance/numbing PTSD score for the anticonvulsant intervention groups is 0.37 points which suggests 'no' PTSD.

		(8.65 lower to 7.91 higher)				
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **0.21 points higher** (2.57 lower to 2.99 higher)		141 (3 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Hyperarousal PTSD score for the anticonvulsant intervention groups is 0.21 points which suggests 'no' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 2. Comparison 2: Anticonvulsants versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

1 Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

2 Downgraded one level due to serious imprecision (wide confidence interval).

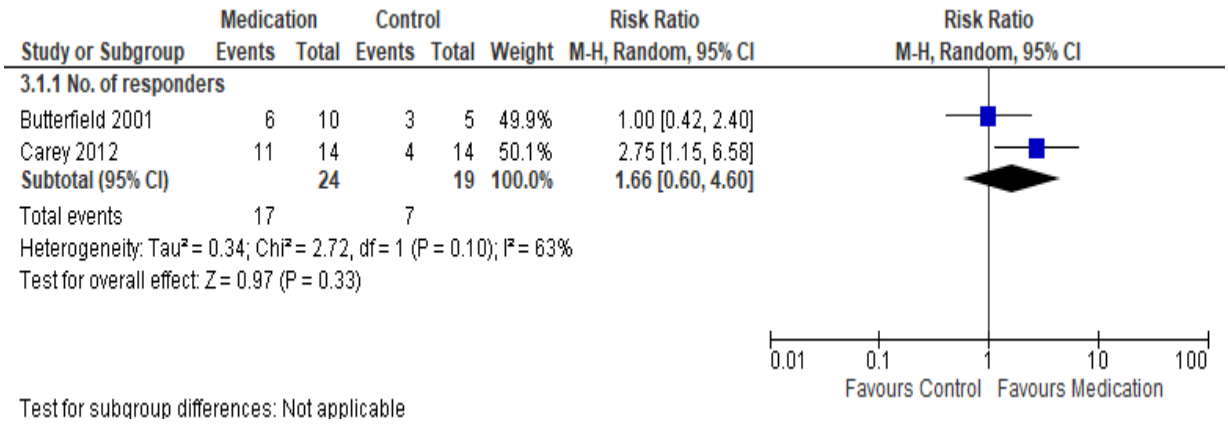
3 Downgraded two levels due to moderate heterogeneity (I^2 of 52%).

4 Downgraded two levels due to substantial heterogeneity (I^2 of 80%).

Comparison 3: Antipsychotics versus placebo

Primary outcome measures

There was no evidence of an effect of olanzapine on treatment efficacy in participants with PTSD compared to placebo (RR 1.66; 95% CI 0.60 to 4.60, see Analysis 3.1) in two trials with 43 participants (Butterfield 2001; Carey 2012). The evidence that was available for this outcome was of low quality.

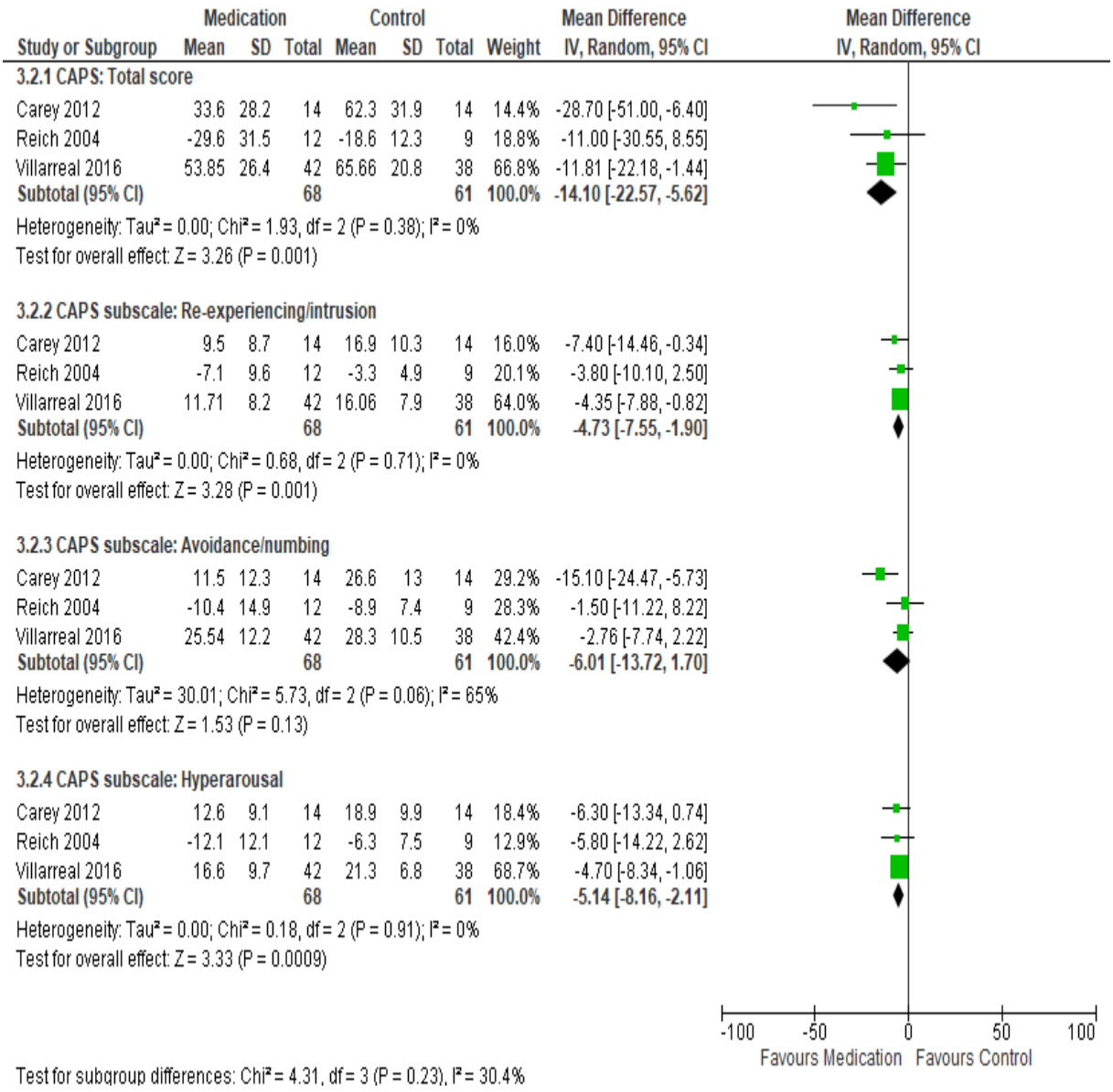


Analysis 3.1. Antipsychotics versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

Secondary outcomes measures

There was evidence of a reduction of PTSD symptoms following treatment with olanzapine, risperidone and quetiapine compared to placebo for CAPS total (k = 3, MD −14.10 points, 95% CI −22.57 to −5.62, N = 129, see Analysis 3.2; Carey 2012; Reich 2004; Villarreal 2016), although the evidence was low in quality. There was also evidence of a reduction of PTSD symptoms for this outcome on the re-experiencing/intrusion (MD −4.73 points, 95% CI −7.55 to -1.90; see Analysis 3.2) and hyperarousal (MD -5.14 points, 95% CI −8.16 to -2.11; see Analysis 3.2) subscale of the CAPS (Carey 2012; Reich 2004; Villarreal 2016). The evidence that was available for the two subscales was of low quality. There was however no evidence of

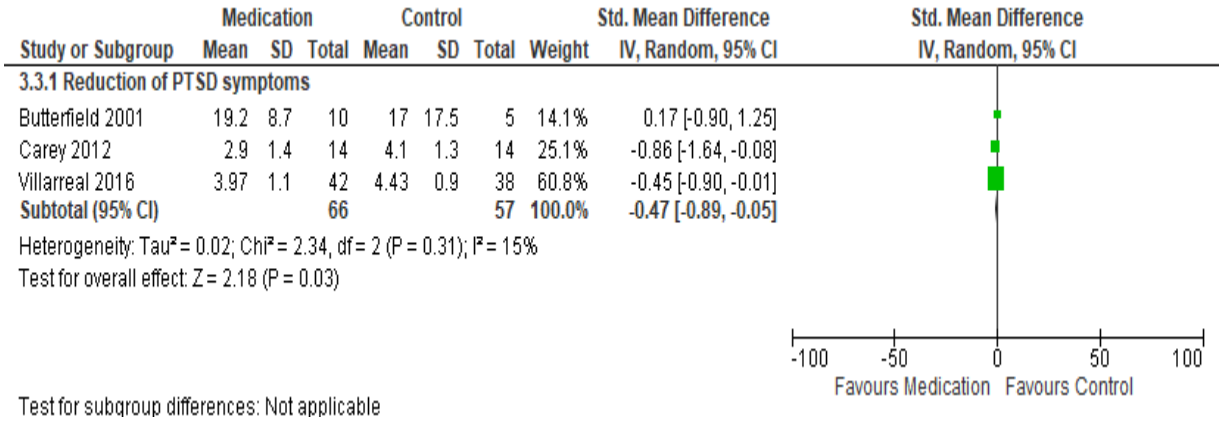
a reduction of PTSD symptoms on the avoidance/numbing (MD −6.01 points, 95% CI −13.72 to 1.70; see Analysis 3.2) subscale of the CAPS (Carey 2012; Reich 2004; Villarreal 2016). The evidence for this subscale was very low in quality and confirmed by the substantial heterogeneity found for this subscale ($Chi^2 = 5.73$, df = 2 (P = 0.06); $I^2 = 65\%$). The substantial heterogeneity on this outcome is partially reflected by the unusually large medication effect observed in Carey 2012 (MD −15.10 points, 95% CI −24.47 to −5.73). Removing this trial resulted in a substantially reduced and statistically non-significant treatment effect (MD −2.50 points, 95% CI −6.93 to 1.93), with no heterogeneity observed across the effects for the remaining trials ($Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$).



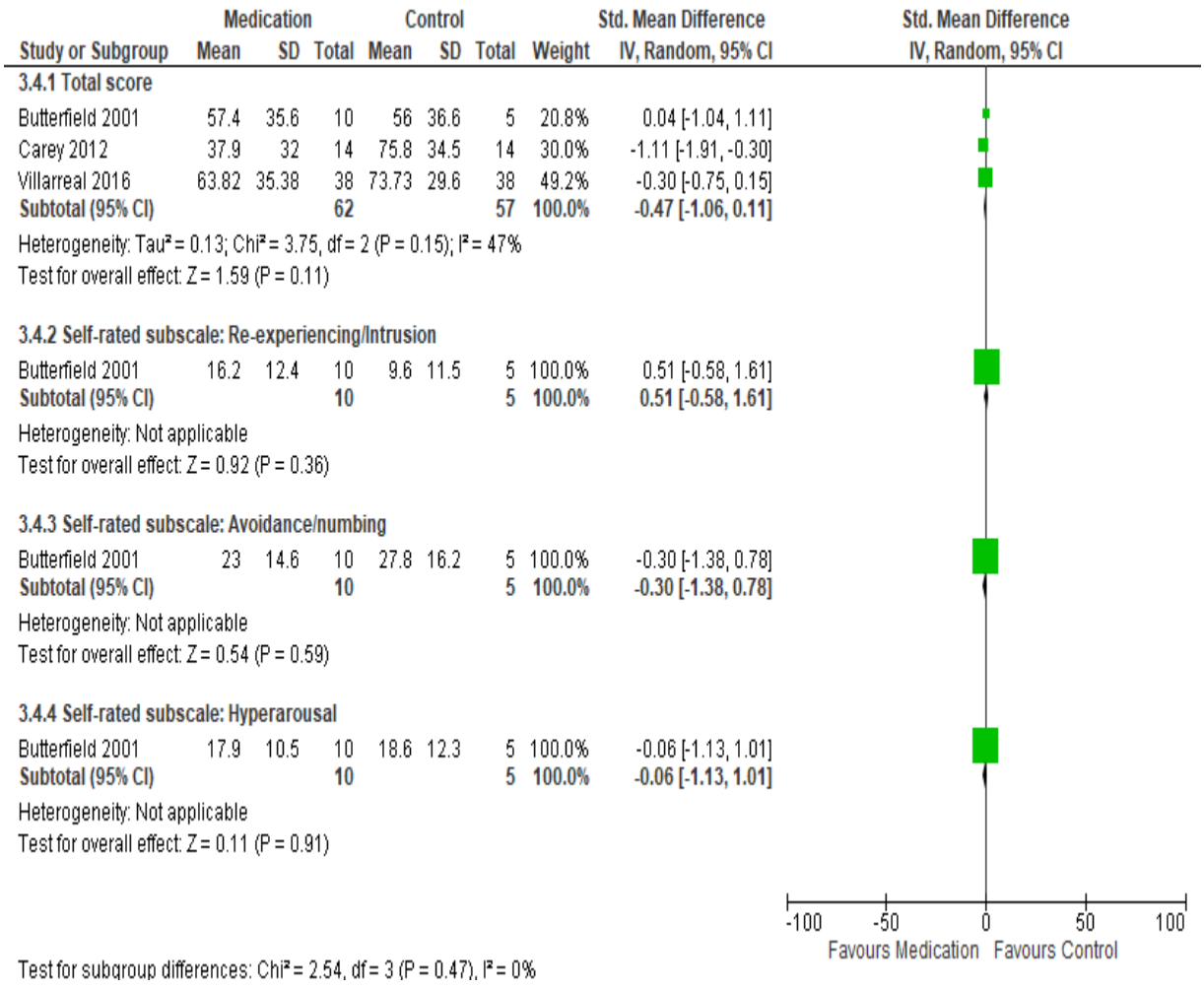
Analysis 3.2. Antipsychotics versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

Furthermore, evidence of an effect of olanzapine and quetiapine compared to placebo was found for the reduction of PTSD symptoms on other symptom severity scales such as the CGI-S and SIP (k = 3, SMD -0.47 points, 95% CI −0.89 to -0.05, N = 123; see Analysis 3.3; Butterfield 2001; Carey 2012; Villarreal 2016), with no evidence of an effect on the self-rated DTS (k = 3, SMD -0.47 points, 95% CI −1.06 to 0.11, N = 123; see Analysis 3.4; Butterfield

2001; Carey 2012; Villarreal 2016), including the re-experiencing/intrusion (k = 1, MD 0.51 points, 95% CI −0.58 to 1.61, N = 15; see Analysis 3.4), avoidance/numbing (k = 1, MD −0.30 points, 95% CI −1.38 to 0.78, N = 15; see Analysis 3.4) and hyperarousal (k = 1, MD -0.06 points, 95% CI −1.13 to 1.01, N = 15; see Analysis 3.4) subscale of the DTS (Butterfield 2001). In addition, moderate heterogeneity was also found for the total score on the self-rated measures (Chi^2 = 3.75, df = 2 (P = 0.15); I^2 = 47%).

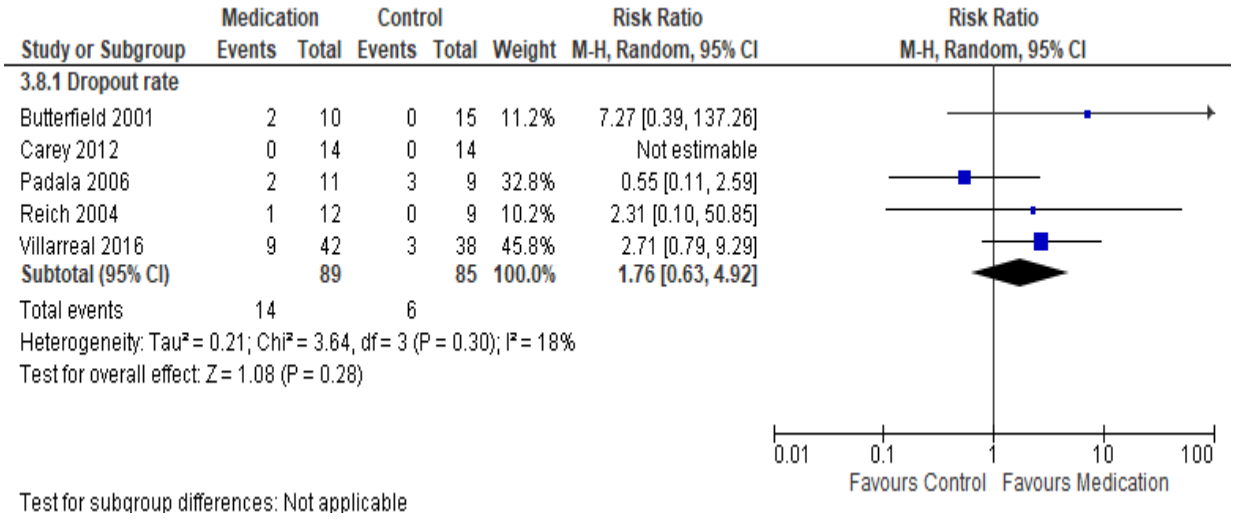


Analysis 3.3. Antipsychotics versus placebo. Symptom severity: Other measures.

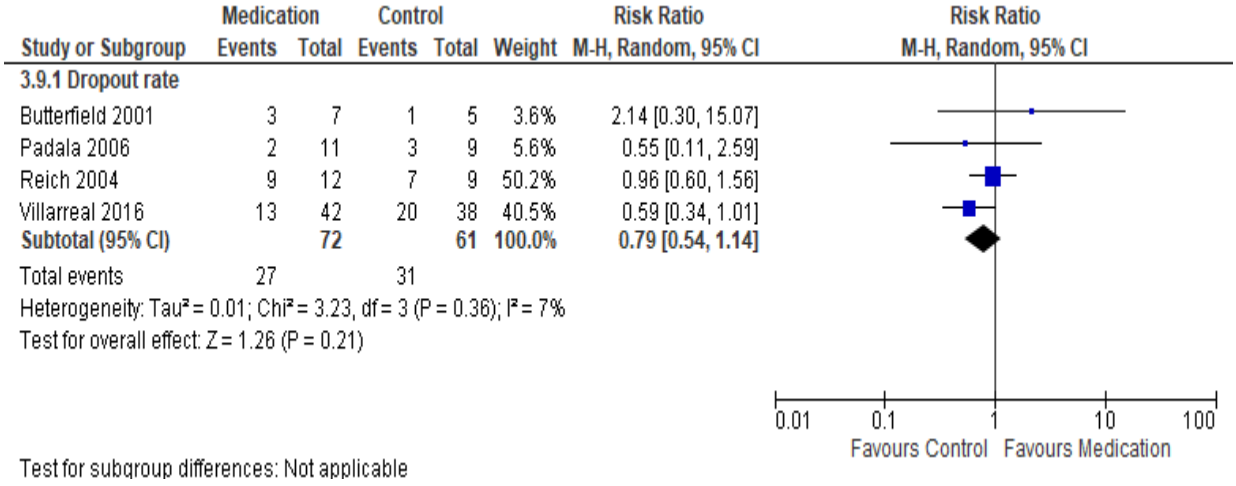


Analysis 3.4. Antipsychotics versus placebo. Self-rated scales: Total score, Self-rated subscale Re-experiencing/Intrusion, Self-rated subscale Avoidance/numbing, Self-rated subscale Hyperarousal.

Twice as many participants withdrew due to treatment-emergent side effects from the antipsychotic intervention arm compared to the placebo arm, however no difference between groups were found (k = 5, RR 1.76; 95% CI 0.63 to 4.92, N = 174; see Analysis 3.8; Butterfield 2001; Carey 2012; Padala 2006; Reich 2004; Villarreal 2016). The evidence that was available for this outcome was of low quality. Similar dropout rates due to any cause in the medication and placebo arms were also observed in four trials with 133 participants (RR 0.79; 95% CI 0.54 to 1.14; see Analysis 3.9; Butterfield 2001; Padala 2006; Reich 2004; Villarreal 2016).



Analysis 3.8. Antipsychotics versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 3.9. Antipsychotics versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 3: Antipsychotics versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single and multi-center trials **Intervention**: antipsychotics **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With antipsychotics**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.66** (0.6 to 4.6)	43 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,4]	There was no evidence of an effect on the number of participants in the antipsychotic groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.33).
	368 per 1000	**612 per 1000** (221 to 1000)				
	Moderate					
	443 per 1000	**735 per 1000** (266 to 1000)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.76** (0.63 to 4.92)	174 (5 studies)	⊕⊕⊖⊖ **low**[1,2]	Twice as many patients withdrew from the antipsychotic groups (14/89; 16%)
	71 per 1000	**124 per 1000** (44 to 347)				
	Moderate					

	0 per 1000	**0 per 1000** (0 to 0)				compared to the placebo groups (6/85; 7%), however no difference in dropout rates were found (P = 0.28).
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was **14.1 lower** (22.57 to 5.62 lower)		129 (3 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the antipsychotic intervention groups is 14.1 points which suggests 'extreme' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **4.73 lower** (7.55 to 1.9 lower)		129 (3 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Re-experiencing/intrusion PTSD score for the antipsychotic intervention groups is 4.73 points which suggests 'extreme' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **6.01 lower**		129 (3 studies)	⨁⊖⊖⊖ **very low**[1,2,3]	The mean CAPS Avoidance/numbing PTSD score for the antipsychotic intervention groups is 6.01 points which suggests 'extreme' PTSD.

		(13.72 lower to 1.7 higher)				
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **5.14 lower** (8.16 to 2.11 lower)		129 (3 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Hyperarousal PTSD score for the antipsychotic intervention groups is 5.14 points which suggests 'extreme' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 3. Comparison 3: Antipsychotics versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

1 Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

2 Downgraded one level due to serious imprecision (wide confidence interval).

3 Downgraded two levels due to substantial heterogeneity (I^2 of 65%).

4 Downgraded two levels due to substantial heterogeneity (I^2 of 63%).

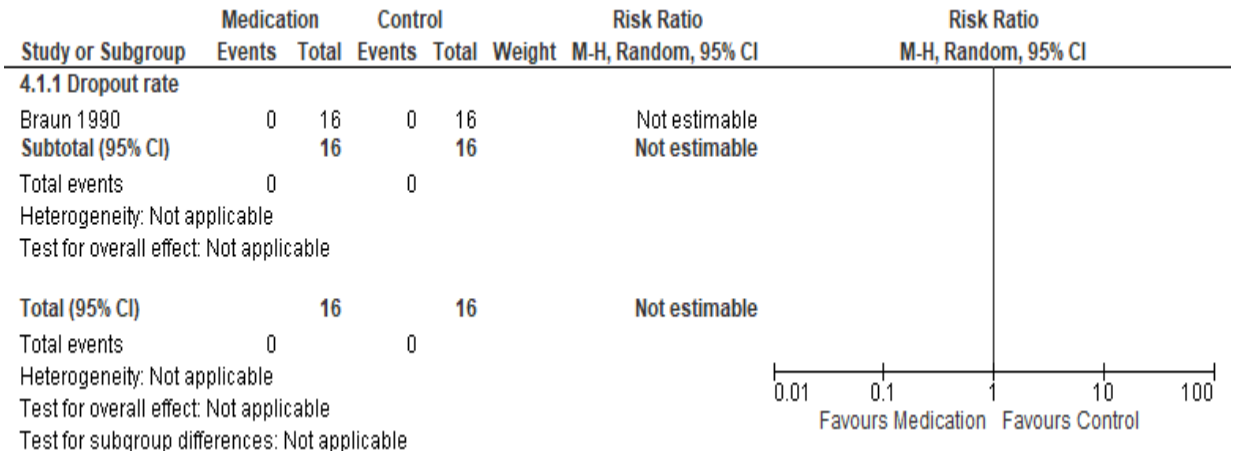
Comparison 4: Benzodiazepines versus placebo

Primary outcome measures

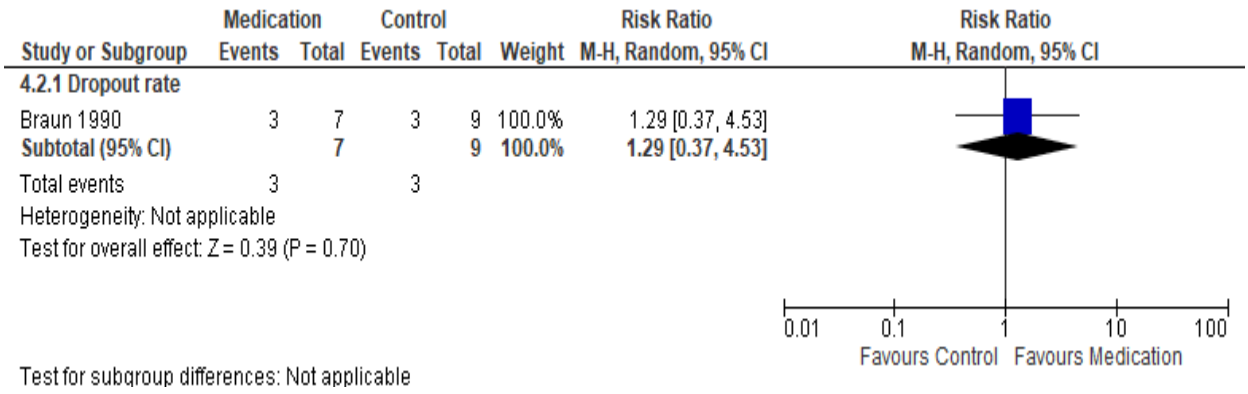
There were no data available to assess the number of participants who responded to alprazolam versus placebo.

Secondary outcomes measures

No participants dropped out due to treatment emergent side effects in the alprazolam and placebo group (see Analysis 4.1; Braun 1990). The evidence that was available for this outcome was of moderate quality. There was also no difference in the number of participants who withdrew due to any cause (k = 1, RR 1.29; 95% CI 0.37 to 4.53, N = 16; see Analysis 4.2; Braun 1990). The dropout rate was similar for the alprazolam (3/7, 43%) and placebo group (3/9, 33%).



Analysis 4.1. Benzodiazepines versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 4.2. Benzodiazepines versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 4: Benzodiazepines versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single-center trial **Intervention**: benzodiazepine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With benzodiazepines**				
Dropouts due to adverse events (acute phase)	See comment	See comment	Not estimable	32 (1 study)	⊕⊕⊕⊖ **moderate**[1]	No dropouts were reported for the benzodiazepine and placebo group.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 4. Comparison 4: Benzodiazepines versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

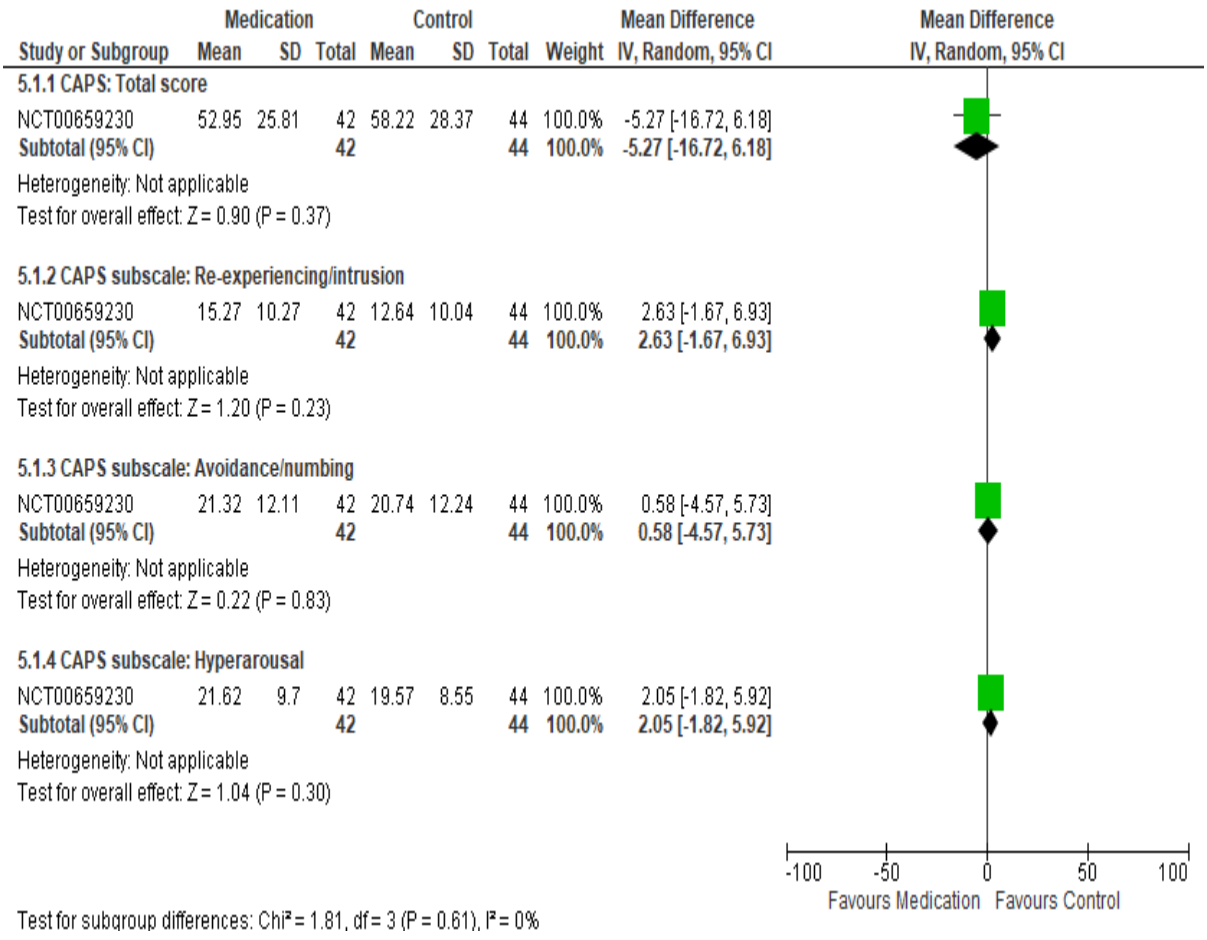
Comparison 5: Dopamine beta-hydroxylase inhibitors versus placebo

Primary outcome measures

There were no data available to assess the number of participants who responded to nepicastat versus placebo.

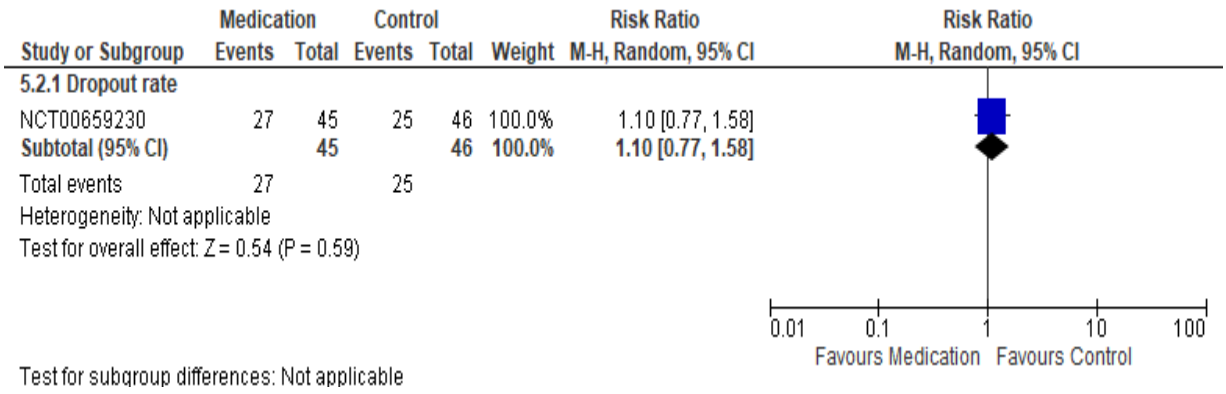
Secondary outcomes measures

The review observed no evidence of an effect of nepicastat on CAPS total symptom severity (MD -5.27 points, 95% CI -16.72 to 6.18; see Analysis 5.1), as well as on the re-experiencing/intrusion (MD 2.63 points, 95% CI −1.67 to 6.93; see Analysis 5.1), avoidance/numbing (MD 0.58 points, 95% CI −4.57 to 5.73; see Analysis 5.1), and hyperarousal (MD 2.05 points, 95% CI −1.82 to 5.92; see Analysis 5.1) subscale of the CAPS in one trial with 88 participants (NCT00659230). This conclusion was based on data of low quality.

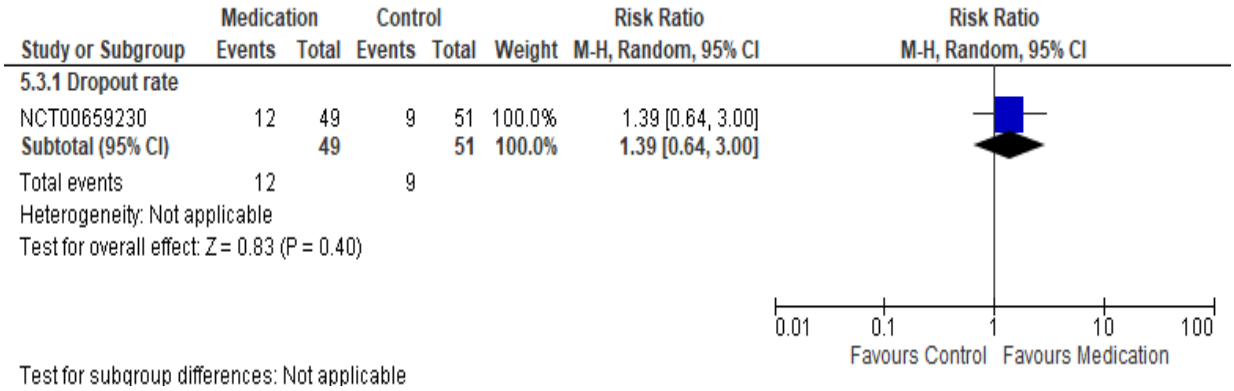


Analysis 5.1. Dopamine beta-hydroxylase inhibitors versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

There was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 1, RR 1.10; 95% CI 0.77 to 1.58, N = 91; see Analysis 5.2; NCT00659230). The evidence that was available for this outcome was of moderate quality. There was also no difference in the number of participants who withdrew due to any cause (k = 1, RR 1.39; 95% CI 0.64 to 3.00, N = 100; see Analysis 5.3; NCT00659230). Overall there were 12 (24%) dropouts in the nepicastat group and nine (18%) dropouts in the placebo group.



Analysis 5.2. Dopamine beta-hydroxylase inhibitors versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 5.3. Dopamine beta-hydroxylase inhibitors versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 5: Dopamine beta-hydroxylase inhibitors versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: multi-center trial **Intervention**: dopamine beta-hydroxylase inhibitor **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With Dopamine beta-hydroxylase inhibitors**				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.1** (0.77 to 1.58)	91 (1 study)	⊕⊕⊕⊖ **moderate**[1]	No difference in dropout rates were found in the dopamine beta-hydroxylase group (27/45; 60%) and placebo group (25/46; 54%) (P = 0.59), however dropout rates were above 50% in each group.
	543 per 1000	**598 per 1000** (418 to 859)				
	Moderate					
	544 per 1000	**598 per 1000** (419 to 860)				
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was		86 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the dopamine beta-hydroxylase inhibitor intervention group is 5.27 points which

		5.27 lower (16.72 lower to 6.18 higher)				suggests 'extreme' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **2.63 higher** (1.67 lower to 6.93 higher)		86 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Re-experiencing/intrusion PTSD score for the dopamine beta-hydroxylase inhibitor intervention group is 2.63 points which suggests 'moderate' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **0.58 higher** (4.57 lower to 5.73 higher)		86 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Avoidance/numbing PTSD score for the dopamine beta-hydroxylase inhibitor intervention group is 0.58 points which suggests 'no' PTSD.
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **2.05 higher** (1.82 lower to 5.92 higher)		86 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Hyperarousal PTSD score for the dopamine beta-hydroxylase intervention group is 2.05 points which suggests 'moderate' PTSD.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.

Summary of Findings Table 5. Comparison 5: Dopamine beta-hydroxylase inhibitors versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

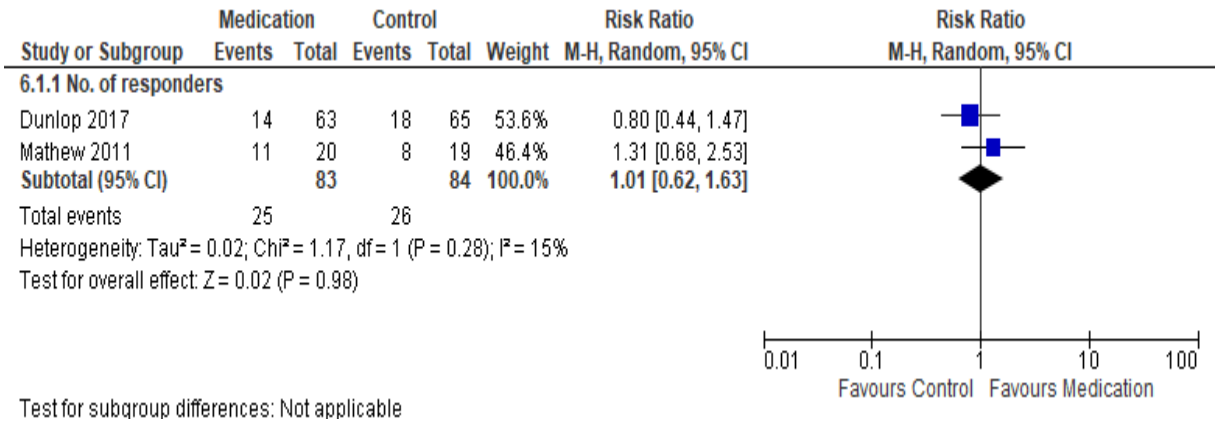
[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

Comparison 6: Experimental medications versus placebo

Primary outcome measures

There was no evidence of an effect for the GSK561679 and the GR205171 experimental medication on treatment efficacy in participants with PTSD compared to placebo (RR 1.01; 95% CI 0.62 to 1.63, see Analysis 6.1) in two trials with 167 participants (Dunlop 2017; Mathew 2011). The evidence that was available for this outcome was of moderate quality.

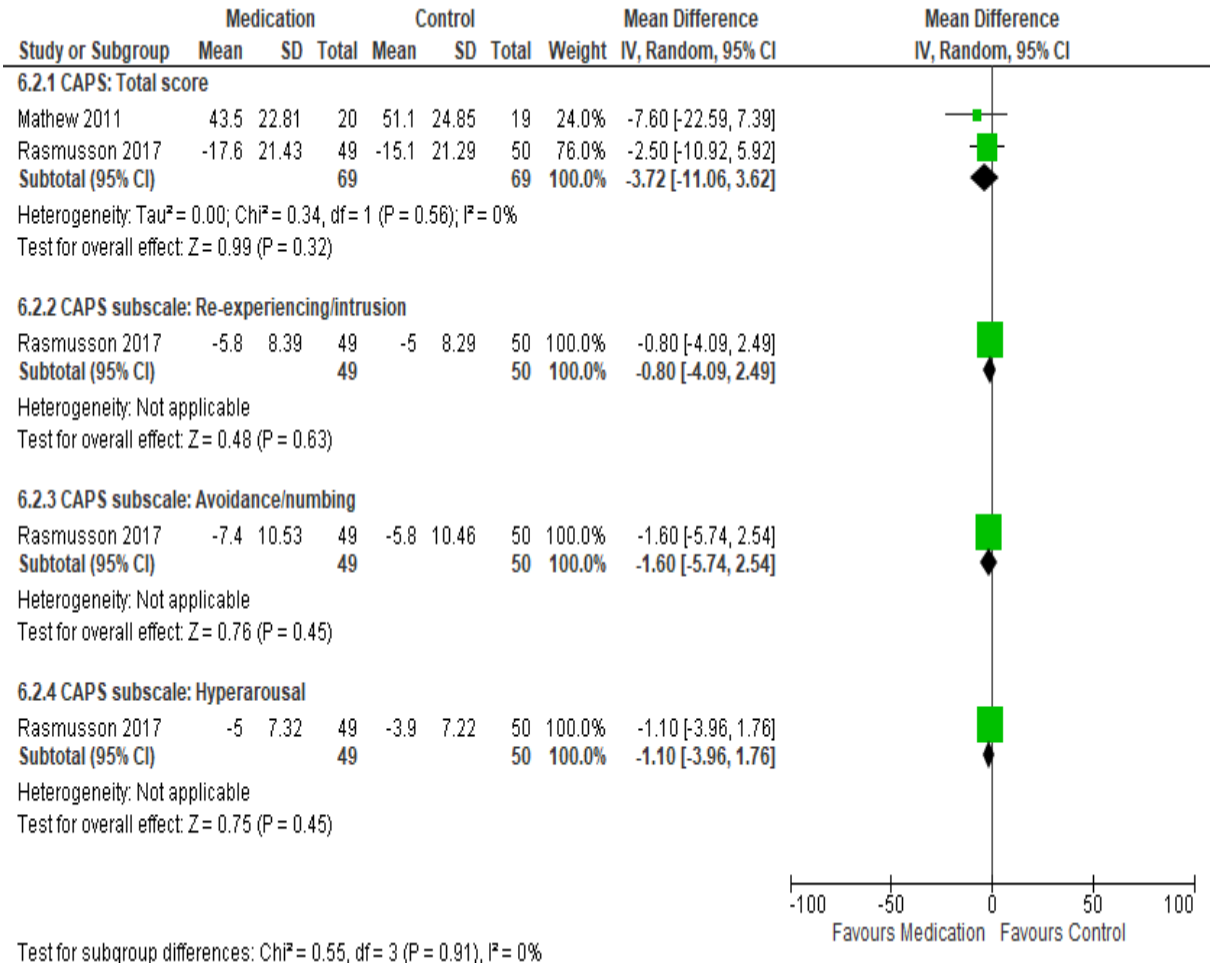


Analysis 6.1. Experimental medications versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

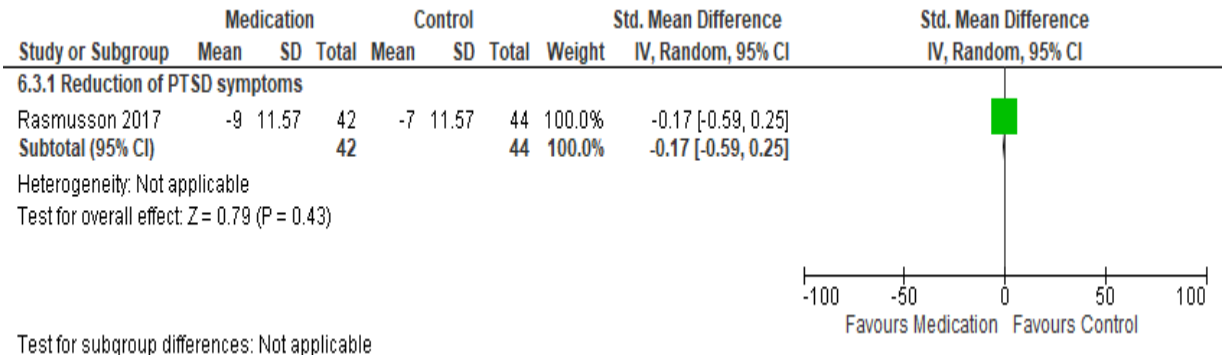
Secondary outcomes measures

No evidence was observed for an effect of GR205171 medication and ganaxolone on total CAPS symptom severity (k = 2, MD -3.72 points, 95% CI -11.06 to 3.62, N = 138; see Analysis 6.2; Mathew 2011; Rasmusson 2017), as well as for the study by Rasmusson 2017 investigating ganaxolone versus placebo on the re-experiencing/intrusion (MD -0.80 points, 95% CI −4.09 to 2.49, N = 99; see Analysis 6.2), avoidance/numbing (MD -1.60 points, 95% CI −5.74 to 2.54, N = 99; see Analysis 6.2), and hyperarousal (MD -1.10 points, 95% CI −3.96 to 1.76, N = 99; see Analysis 6.3) subscale on the CAPS. These outcomes were based on data of low quality. Similarly, no evidence of an effect for ganaxolone versus placebo was observed for the

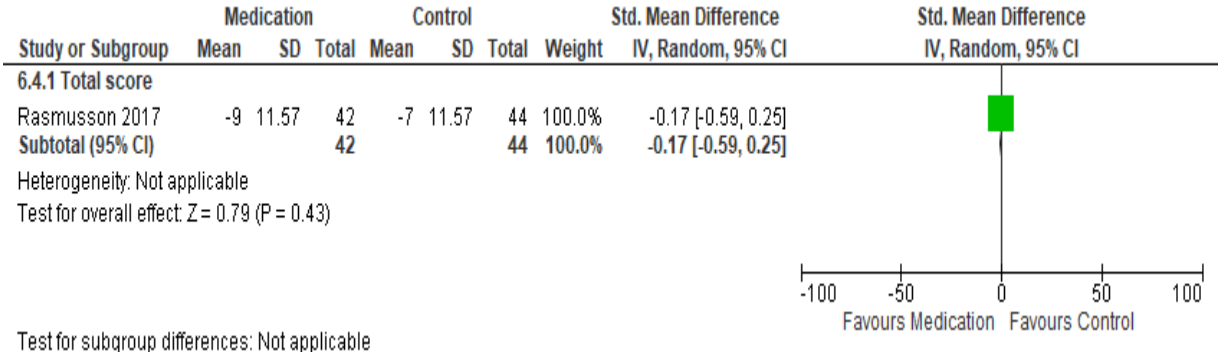
reduction of PTSD symptoms on the PCL scale (self-rated measure) (k = 1, SMD -0.17 points, 95% CI −0.59 to 0.25, N = 86; see Analysis 6.3; Analysis 6.4; Rasmusson 2017).



Analysis 6.2. Experimental medications versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

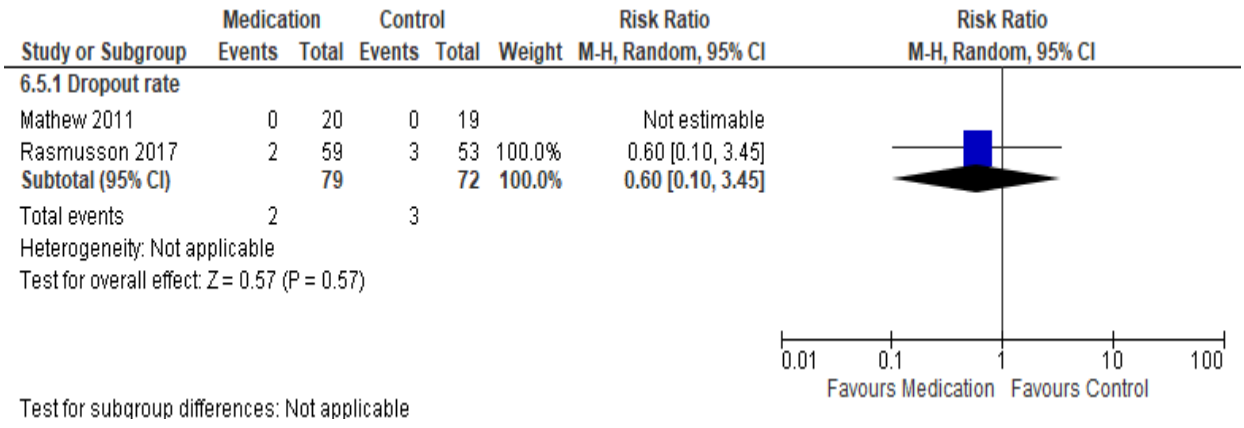


Analysis 6.3. Experimental medications versus placebo. Symptom severity: Other measures.

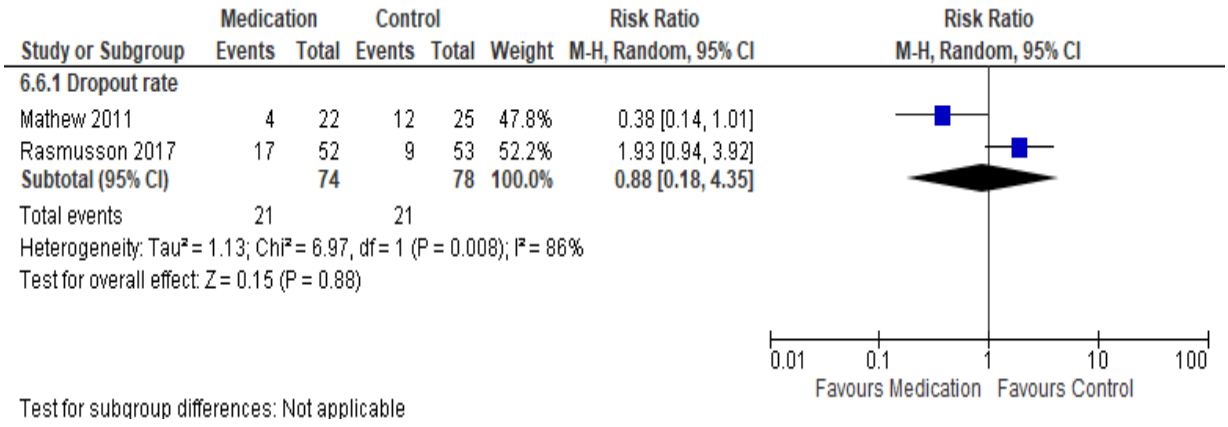


Analysis 6.4. Experimental medications versus placebo. Self-rated scales: Total score.

There was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 2, RR 0.60; 95% CI 0.10 to 3.45, N = 151; see Analysis 6.5; Mathew 2011; Rasmusson 2017). However, similar dropouts were observed for the participants who withdrew due to any cause from the experimental intervention arm compared to the placebo arm (k = 2, RR 0.88; 95% CI 0.18 to 4.35, N = 152; see Analysis 6.6; Mathew 2011; Rasmusson 2017).



Analysis 6.5. Experimental medications versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 6.6. Experimental medications versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 6: Experimental medications versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: multi-center trials **Intervention**: experimental medications **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With experimental medications**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.01** (0.62 to 1.63)	167 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	There was no evidence of an effect on the number of participants in the experimental medication groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.98).
	310 per 1000	**313 per 1000** (192 to 505)				
	Moderate					
	349 per 1000	**352 per 1000** (216 to 569)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 0.6** (0.1 to 3.45)	151 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	Dropout rates due to adverse events were low in the experimental
	42 per 1000	**25 per 1000** (4 to 144)				
	Moderate					

	28 per 1000	**17 per 1000** (3 to 97)				medication and placebo groups (2/79, 3%; 3/72, 4%).
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was **3.72 lower** (11.06 lower to 3.62 higher)		138 (2 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the experimental medication groups is 3.72 points which suggests 'severe' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **0.8 lower** (4.09 lower to 2.49 higher)		99 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Re-experiencing/intrusion PTSD score for the experimental medication groups is 0.8 points which suggests 'no' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups		99 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Avoidance/numbing PTSD score for the experimental medication groups is 1.6 points which suggests 'mild/ minimal' PTSD.

		was **1.6 lower** (5.74 lower to 2.54 higher)				
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **1.1 lower** (3.96 lower to 1.76 higher)		99 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Hyperarousal PTSD score for the experimental medication groups is 1.1 points which suggests 'mild/ minimal' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 6. Comparison 6: Experimental medications versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

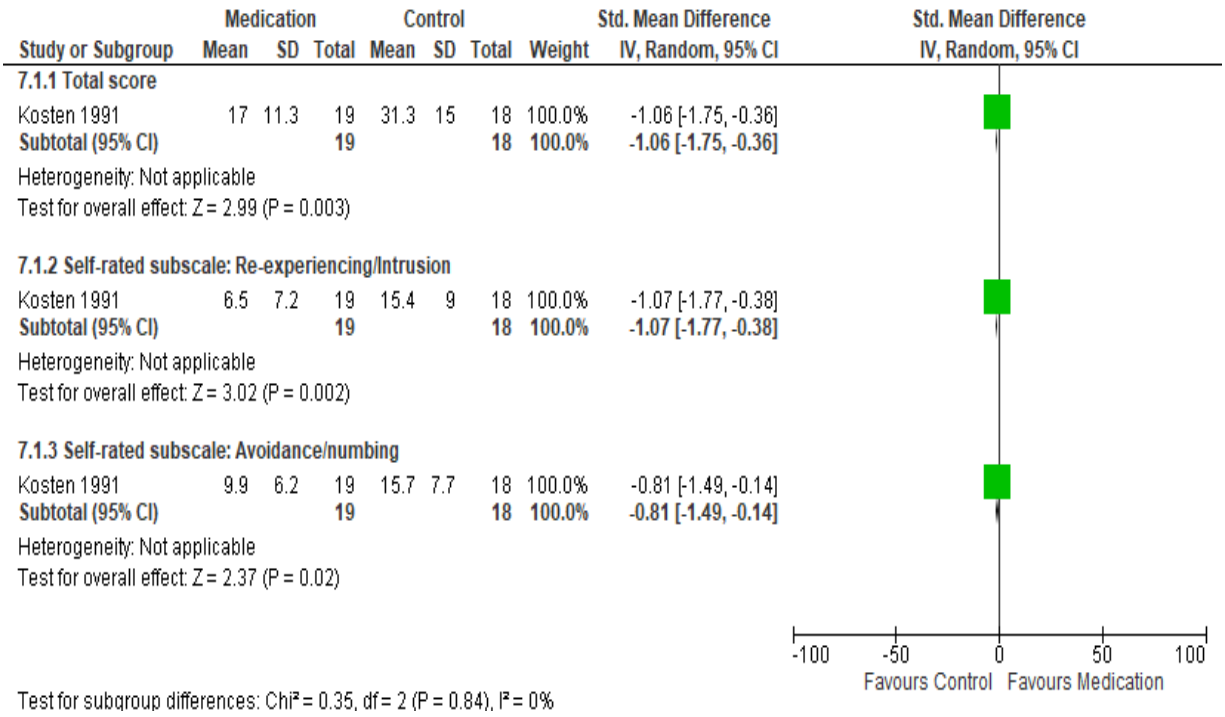
Comparison 7: MAOIs versus placebo

Primary outcome measures

There were no data available to assess the number of participants who responded to phenelzine versus placebo.

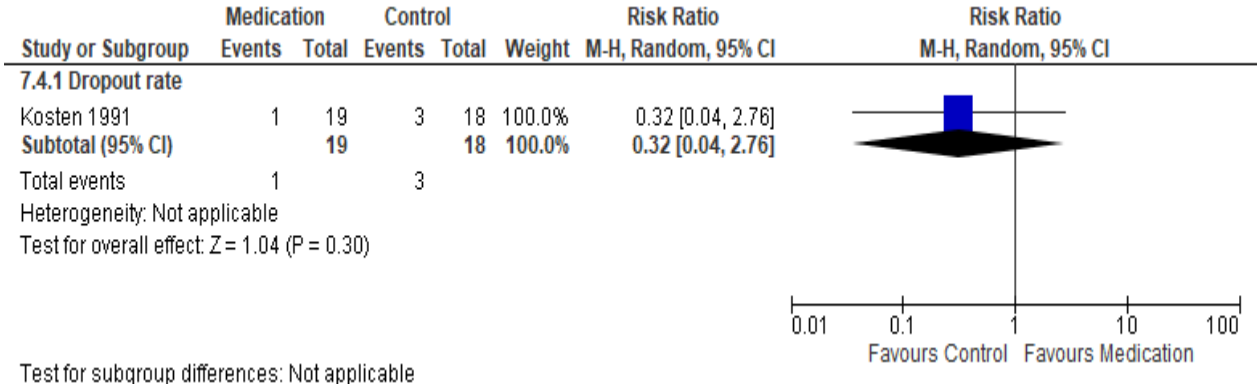
Secondary outcomes measures

There was evidence of benefit for the MAOI phenelzine compared to placebo for reducing total PTSD symptoms on the IES (SMD −1.06 points, 95% CI −1.75 to −0.36; see Analysis 7.1) for one trial with 37 participants (Kosten 1991). This benefit was also found for the re-experiencing/intrusion (k = 1, SMD -1.07 points, 95% CI −1.77 to -0.38, N = 37; see Analysis 7.1; Kosten 1991) and avoidance/numbing (k = 1, SMD −0.81 points, 95% CI −1.49 to -0.14, N = 37; see Analysis 7.1; Kosten 1991) subscale on the IES.

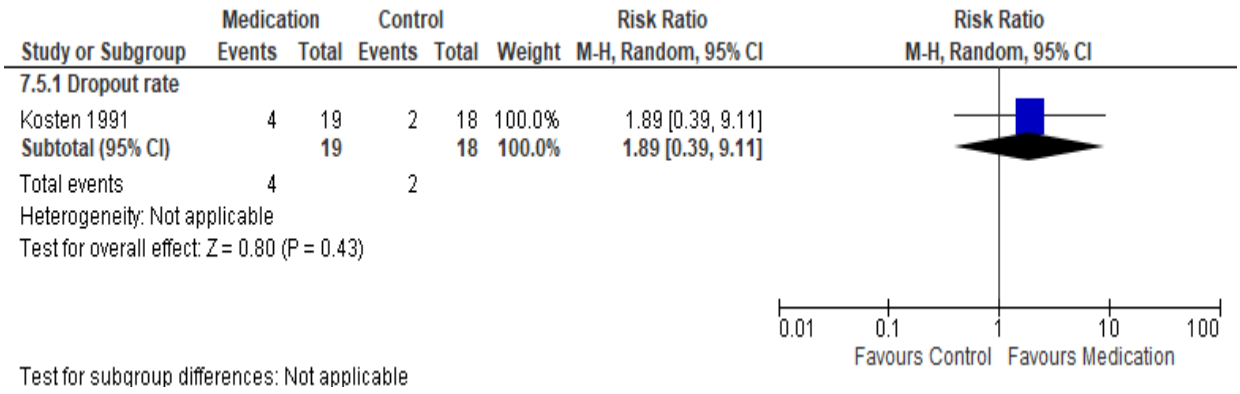


Analysis 7.1. Monoamine oxidase inhibitors versus placebo. Self-rated scales: Total score, Self-rated subscale Re-experiencing/Intrusion, Self-rated subscale Avoidance/numbing.

More patients dropped out in the placebo group (3/18; 17%) compared to the phenelzine group (1/19; 5%) due to treatment-emergent side effects, although no difference in dropout rates were found (k = 1, RR 0.32; 95% CI 0.04 to 2.76, N = 37; Analysis 7.4; Kosten 1991). The evidence that was available for this outcome was of low quality. No evidence of a difference was also found for dropouts due to any cause (k = 1, RR 1.89; 95% CI 0.39 to 9.11, N = 37; Analysis 7.5; Kosten 1991).



Analysis 7.4. Monoamine oxidase inhibitors versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 7.5. Monoamine oxidase inhibitors versus placebo. Drop-out rate due to any cause:

Dropout rate.

Comparison 7: MAOIs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: multi-center trial **Intervention**: MAOIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With MAOIs**				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 0.32** (0.04 to 2.76)	37 (1 study)	⨁⨁⊖⊖ **low**[1,2]	More patients dropped out in the placebo group (3/18; 17%) compared to the MAOI group (1/19; 5%). However, no difference in dropout rates were found (P = 0.30).
	167 per 1000	**53 per 1000** (7 to 460)				
	Moderate					
	167 per 1000	**53 per 1000** (7 to 461)				
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 7. Comparison 7: MAOIs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

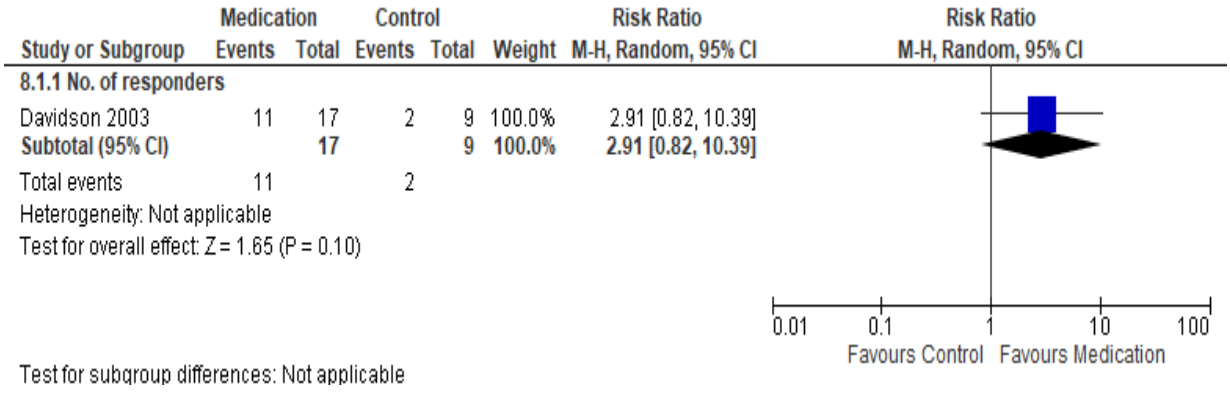
[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

Comparison 8: NaSSAs versus placebo

Primary outcome measures

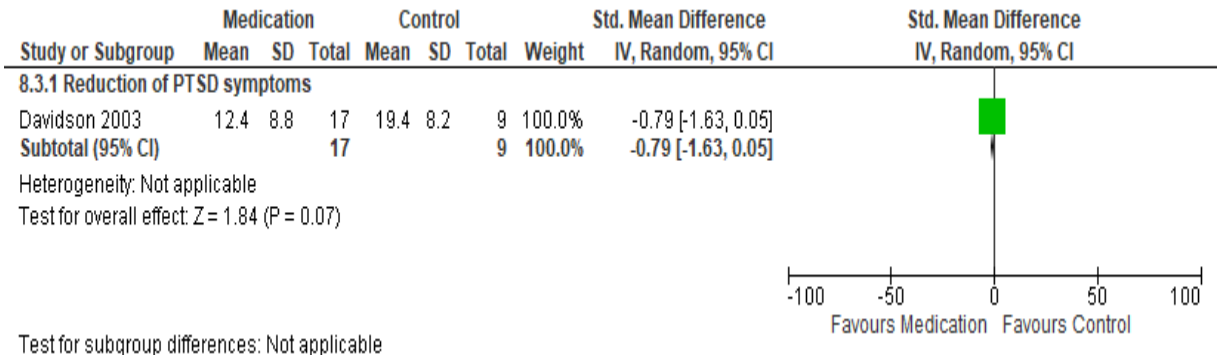
There was no evidence of an effect of mirtazapine on treatment efficacy in participants with PTSD compared to placebo (RR 2.91; 95% CI 0.82 to 10.39, see Analysis 8.1) in one trial with 26 participants (Davidson 2003). The evidence that was available for this outcome was of low quality.



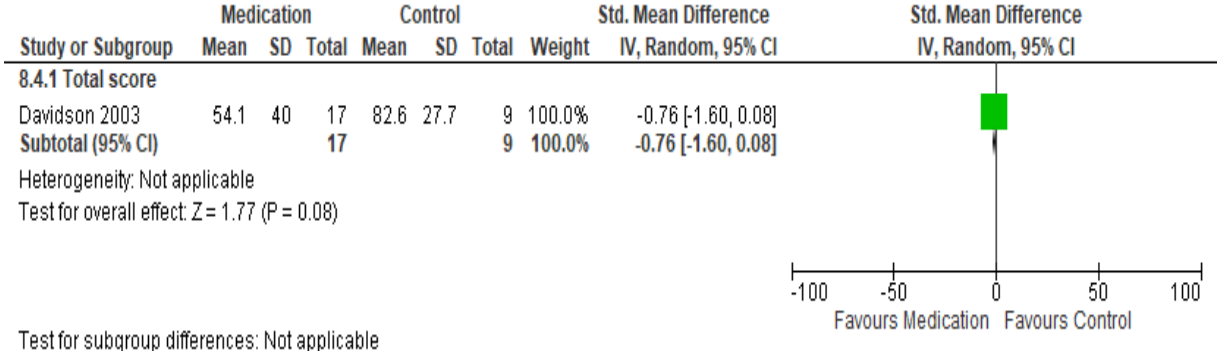
Analysis 8.1. Noradrenergic and specific serotonergic antidepressants versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

Secondary outcomes measures

There was no evidence of an effect of mirtazapine for reducing PTSD symptoms on the SPRINT (k = 1, SMD -0.79 points, 95% CI −1.63 to 0.05, N = 26; see Analysis 8.2; Davidson 2003) and on the self rated DTS (k = 1, SMD -0.76 points, 95% CI −1.60 to 0.08, N = 26; see Analysis 8.3; Davidson 2003).

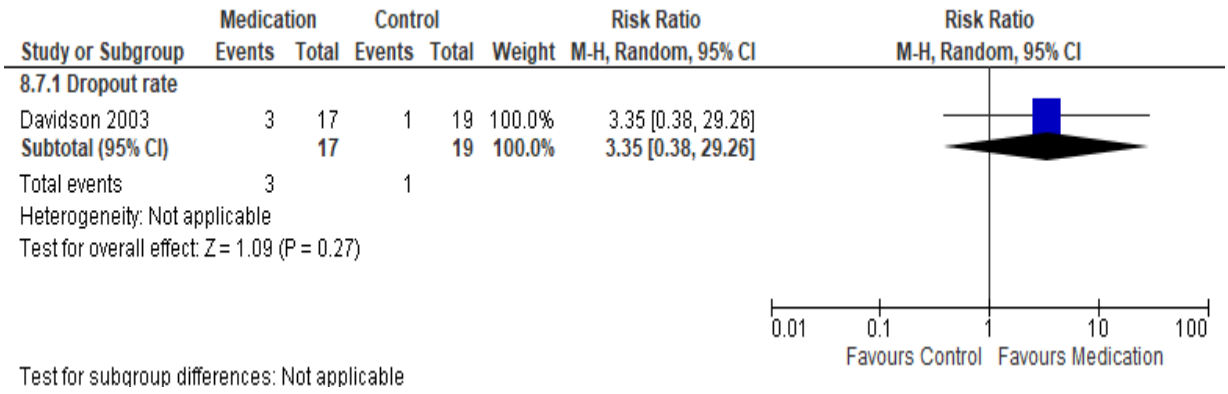


Analysis 8.2. Noradrenergic and specific serotonergic antidepressants versus placebo. Symptom severity: Other measures.



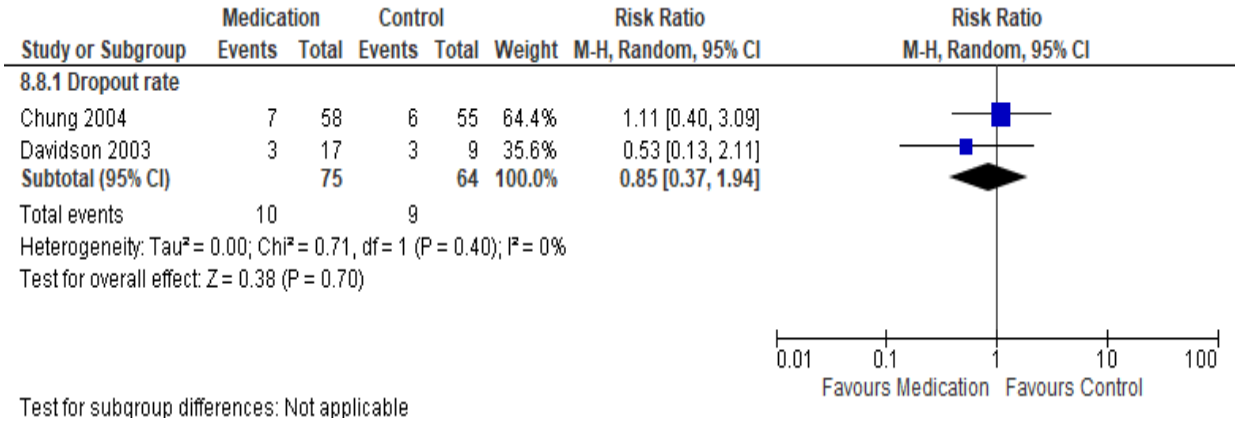
Analysis 8.3. Noradrenergic and specific serotonergic antidepressants versus placebo. Self-rated scales: Total score.

There was also no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 1, RR 3.35; 95% CI 0.38 to 29.26, N = 36; see Analysis 8.6; Davidson 2003) and dropouts due to any cause (k = 1, RR 0.85; 95% CI 0.37 to 1.94, N = 139; see Analysis 8.7; Davidson 2003; Chung 2004). The evidence for the outcome withdrawal due to treatment-emergent side effects was of low quality.



Analysis 8.6. Noradrenergic and specific serotonergic antidepressants versus placebo.

Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 8.7. Noradrenergic and specific serotonergic antidepressants versus placebo.

Drop-out rate due to any cause: Dropout rate.

Comparison 8: NaSSAs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single-center trial **Intervention**: NaSSA **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With NaSSAs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 2.91** (0.82 to 10.39)	26 (1 study)	⊕⊕⊖⊖ **low**[1,2]	There was no evidence of an effect on the number of participants in the NaSSA group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.10).
	222 per 1000	**647 per 1000** (182 to 1000)				
	Moderate					
	222 per 1000	**646 per 1000** (182 to 1000)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 3.35** (0.38 to 29.26)	36 (1 study)	⊕⊕⊖⊖ **low**[1,2]	The proportion of dropouts due to adverse events was high in
	53 per 1000	**176 per 1000** (20 to 1000)				
	Moderate					

	53 per 1000	**178 per 1000** (20 to 1000)				participants receiving the NaSSA (3/17; 18%) relative to placebo (1/19; 5%). There was no evidence of a difference between the number of participants that dropped out due to adverse events (P = 0.27).
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 8. Comparison 8: NaSSAs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

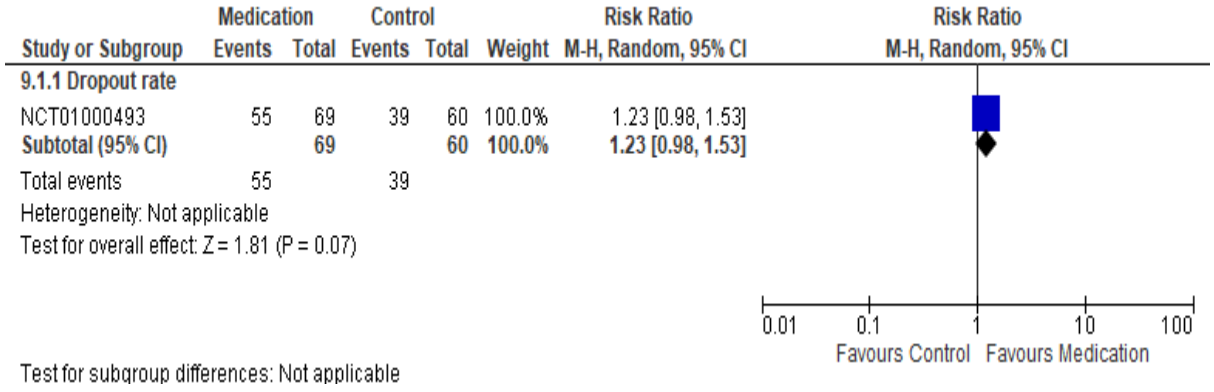
Comparison 9: NK-1 receptor antagonists versus placebo

Primary outcome measures

There were no data available to assess the number of participants who responded to orvepitant versus placebo.

Secondary outcomes measures

The proportion of dropouts was high in participants receiving orvepitant (55/69, 78%) and placebo (39/60, 65%), although this difference was not statistically significant (k = 1, RR 1.23; 95% CI 0.98 to 1.53, N = 129; see Analysis 9.1; NCT01000493).

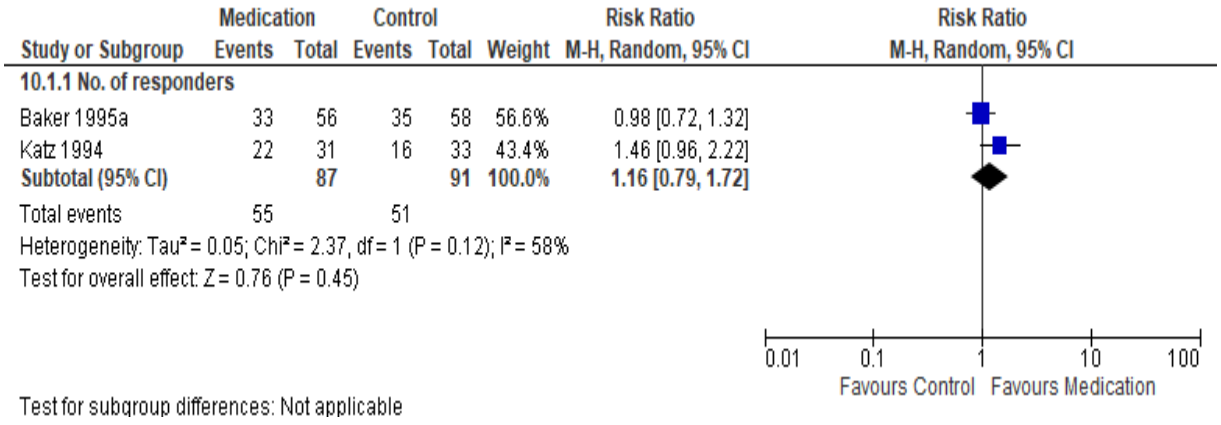


Analysis 9.1. NK-1 receptor antagonists versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 10: RIMAs versus placebo

Primary outcome measures

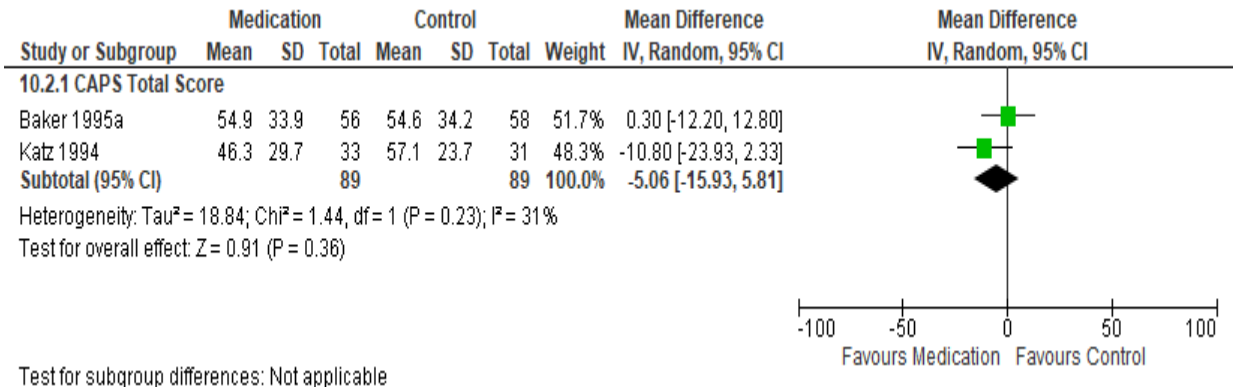
There was no evidence of benefit for brofaromine on treatment efficacy in participants with PTSD compared to placebo (k = 2, RR 1.16; 95% CI 0.79 to 1.72, N = 178; see Analysis 10.1; Baker 1995 a; Katz 1994). This conclusion was based on very low quality evidence.



Analysis 10.1. Reversible inhibitors of monoamine oxidase A versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

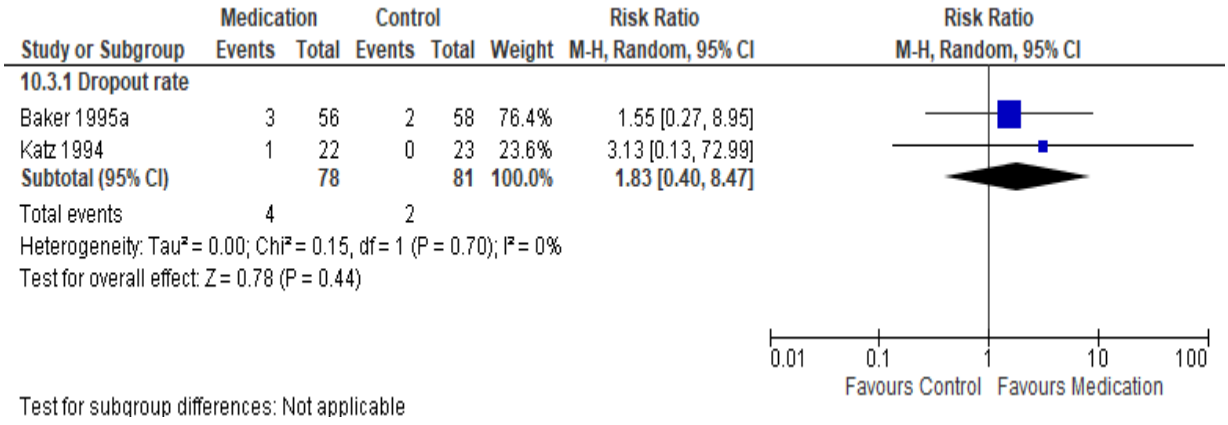
Secondary outcomes measures

There was no evidence of a reduction of PTSD symptoms following treatment with brofaromine compared to placebo for CAPS total (k = 2, MD −5.06 points, 95% CI −15.93 to 5.81, N = 178, see Analysis 10.2; Baker 1995 a; Katz 1994), based on low quality evidence.

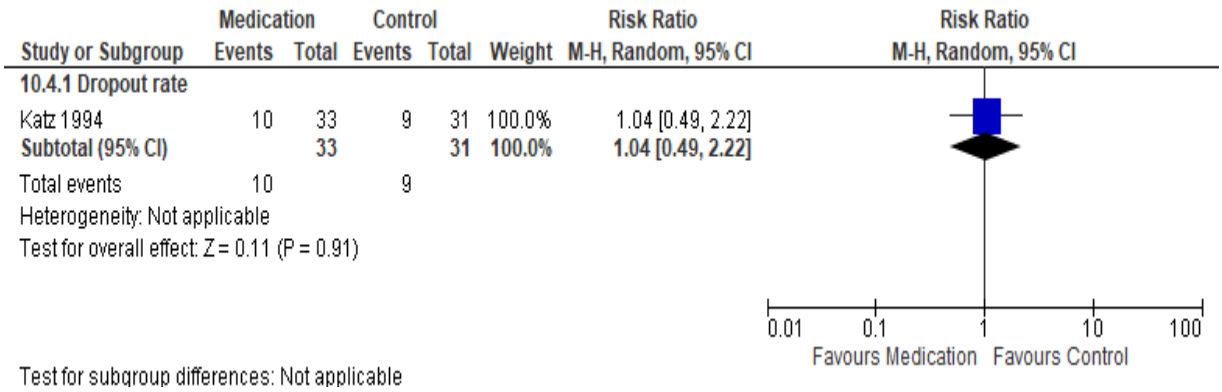


Analysis 10.2. Reversible inhibitors of monoamine oxidase A versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total Score.

There was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 2, RR 1.83; 95% CI 0.40 to 8.47, N = 159; see Analysis 10.3; Baker 1995 a; Katz 1994) and dropouts due to any cause (k = 1, RR 1.04; 95% CI 0.49 to 2.22, N = 64; see Analysis 10.4; Katz 1994). The evidence for the outcome withdrawal due to treatment-emergent side effects was of low quality.



Analysis 10.3. Reversible inhibitors of monoamine oxidase A versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 10.4. Reversible inhibitors of monoamine oxidase A versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 9: RIMAs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: multi-center trials **Intervention**: RIMAs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With RIMAs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.16** (0.79 to 1.72)	178 (2 studies)	⊕⊖⊖⊖ **very low**[1,3]	There was no evidence of an effect on the number of participants in the RIMA groups compared to the placebo groups who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale (P = 0.45).
	560 per 1000	**650 per 1000** (443 to 964)				
	Moderate					
	544 per 1000	**631 per 1000** (430 to 936)				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.83** (0.4 to 8.47)	159 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	Dropout rates due to adverse events were low and similar in the
	25 per 1000	**45 per 1000** (10 to 209)				
	Moderate					

	17 per 1000	**31 per 1000** (7 to 144)				RIMA and placebo groups (4/78, 5%; 2/81, 2%).
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS total score in the intervention groups was **5.06 lower** (15.93 lower to 5.81 higher)		178 (2 studies)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS total PTSD score for the RIMA groups is 5.06 points which suggests 'extreme' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 9. Comparison 9: RIMAs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

[3] Downgraded two levels due to moderate heterogeneity (I^2 of 58%).

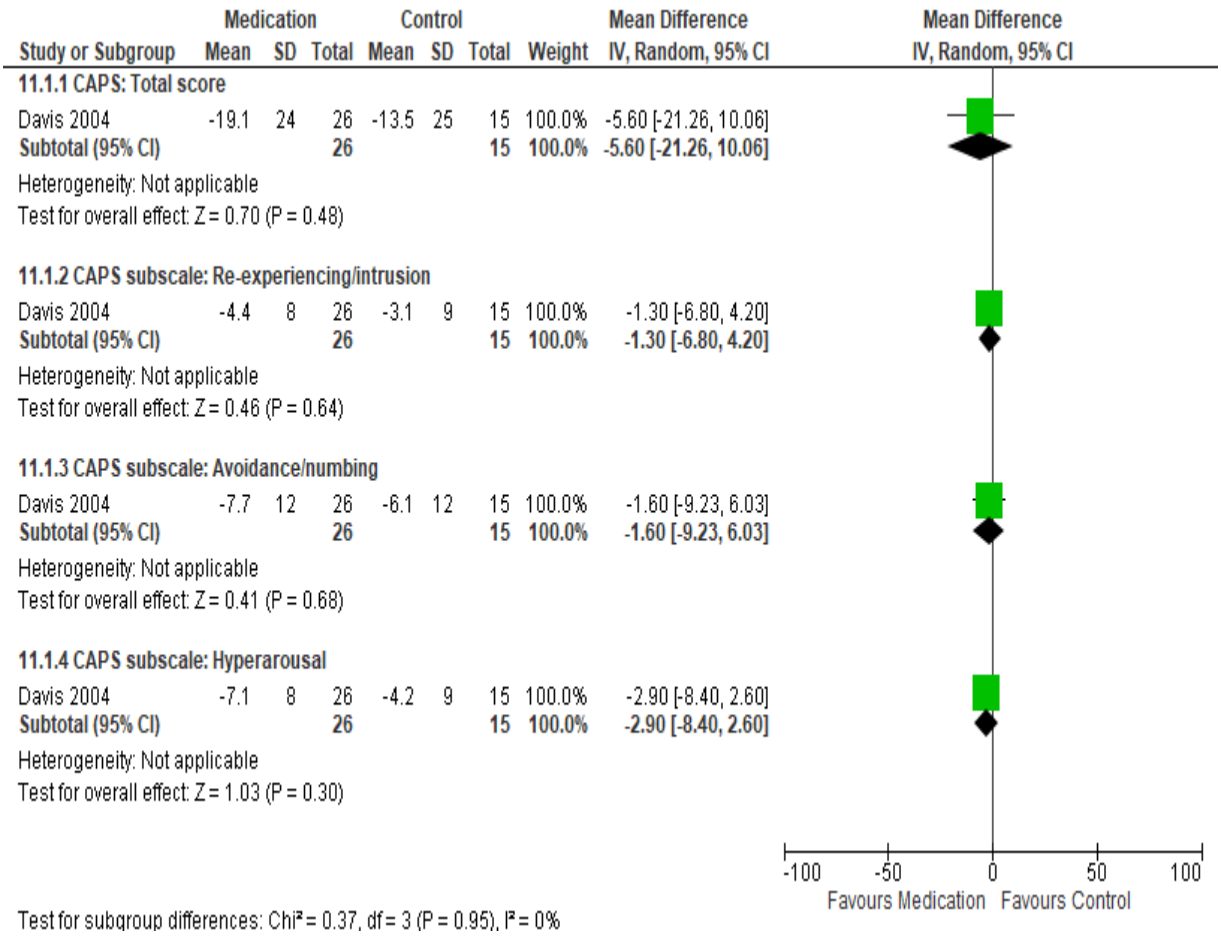
Comparison 11: SARIs versus placebo

Primary outcome measures

There were no data available to assess the number of participants who responded to nefazodone versus placebo.

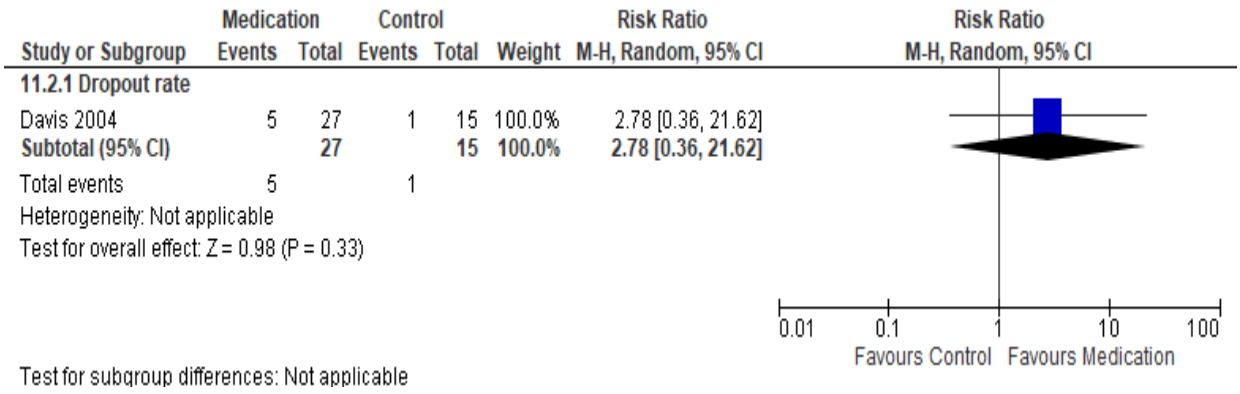
Secondary outcomes measures

The review observed no evidence of an effect of nefazodone on total CAPS symptom severity (k = 1, MD -5.60 points, 95% CI -21.26 to 10.06, N = 41; see Analysis 11.1; Davis 2004), as well as for the re-experiencing/intrusion (MD -1.30 points, 95% CI −6.80 to 4.20, N = 41; see Analysis 11.1; Davis 2004), avoidance/numbing (MD -1.60 points, 95% CI −9.23 to 6.03, N = 41; see Analysis 11.1; Davis 2004), and hyperarousal (MD -2.90 points, 95% CI −8.40 to 2.60, N = 41; see Analysis 11.1; Davis 2004) subscale on the CAPS. These outcomes were based on data of low quality.

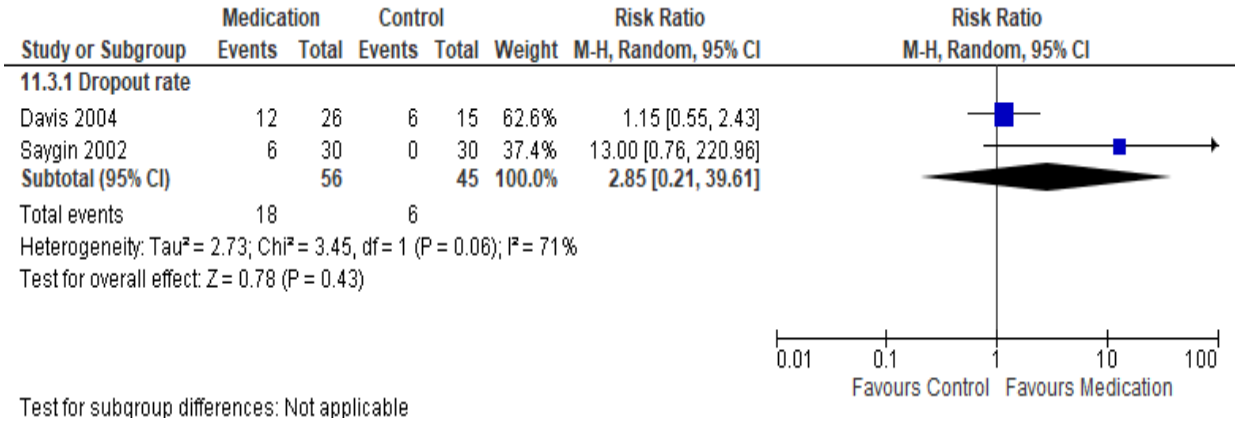


Analysis 11.1. Serotonin antagonist and reuptake inhibitors versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

More patients dropped out of the nefazodone group due to treatment-emergent side effects (19%) and dropouts due to any cause (32%), although no difference in dropout rates were found, respectively (k = 1, RR 2.78; 95% CI 0.36 to 21.62, N = 42; Analysis 11.2; Davis 2004; k = 2, RR 2.85; 95% CI 0.21 to 39.61, N = 101; Analysis 11.3; Davis 2004; Saygin 2002). The evidence for the outcome withdrawal due to treatment-emergent side effects was of low quality and considerable heterogeneity was found for the outcome dropouts due to any cause (Chi^2 = 3.45, df = 1 (P = 0.06); I^2 = 71%).



Analysis 11.2. Serotonin antagonist and reuptake inhibitors versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 11.3. Serotonin antagonist and reuptake inhibitors versus placebo. Drop-out rate due to any cause: Dropout rate.

<table>
<tr><td colspan="6">Comparison 11: SARIs versus placebo for posttraumatic stress disorder (PTSD)</td></tr>
<tr><td colspan="6">Patient or population: adults with PTSD
Settings: multi-center trial
Intervention: SARI
Comparison: placebo</td></tr>
<tr><td>Outcomes</td><td colspan="2">Illustrative comparative risks* (95% CI)
Assumed risk
With placebo</td><td>Relative effect (95% CI)</td><td>No. of participants (studies)</td><td>Quality of the evidence (GRADE)</td><td>Comments
Corresponding risk
With SARIs</td></tr>
<tr><td rowspan="4">Dropouts due to adverse events (acute phase)</td><td colspan="2">Study population</td><td rowspan="4">RR 2.78
(0.36 to 21.62)</td><td rowspan="4">42
(1 study)</td><td rowspan="4">⊕⊕⊖⊖
low[1,2]</td><td rowspan="4">More patients withdrew from the SARI group (5/27; 19%) compared to the placebo group (1/15; 7%), however no difference in dropout rates were found (P = 0.33).</td></tr>
<tr><td>67 per 1000</td><td>185 per 1000
(24 to 1000)</td></tr>
<tr><td colspan="2">Moderate</td></tr>
<tr><td>67 per 1000</td><td>186 per 1000
(24 to 1000)</td></tr>
<tr><td>Clinically Administered PTSD Scale (CAPS): CAPS Total score</td><td></td><td>The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was 5.6 lower (21.26 lower to 10.06 higher)</td><td></td><td>41
(1 study)</td><td>⊕⊕⊖⊖
low[1,2]</td><td>The mean CAPS total PTSD score for the SARI intervention group is 5.6 points which suggests 'extreme' PTSD.</td></tr>
</table>

CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **1.3 lower** (6.8 lower to 4.2 higher)		41 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Re-experiencing/intrusion PTSD score for the SARI intervention group is 1.3 points which suggests 'mild/minimal' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **1.6 lower** (9.23 lower to 6.03 higher)		41 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Avoidance/numbing PTSD score for the SARI intervention group is 1.6 points which suggests 'mild/minimal' PTSD.
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **2.9 lower** (8.4 lower to 2.6 higher)		41 (1 study)	⨁⨁⊖⊖ **low**[1,2]	The mean CAPS Hyperarousal PTSD score for the SARI intervention group is 2.9 points which suggests 'moderate' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect.						

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 10. Comparison 10: SARIs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

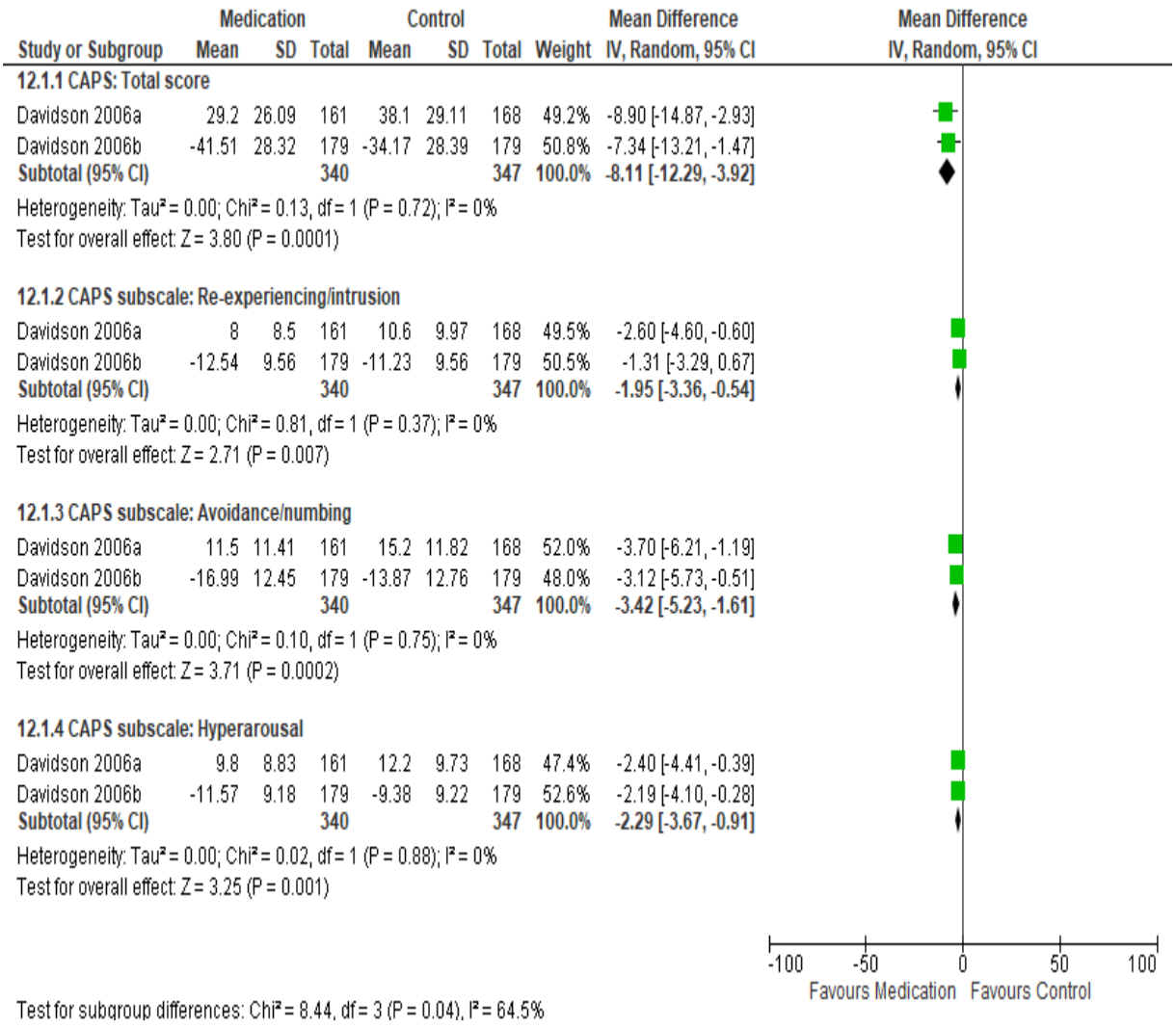
Comparison 12: SNRIs versus placebo

Primary outcome measures

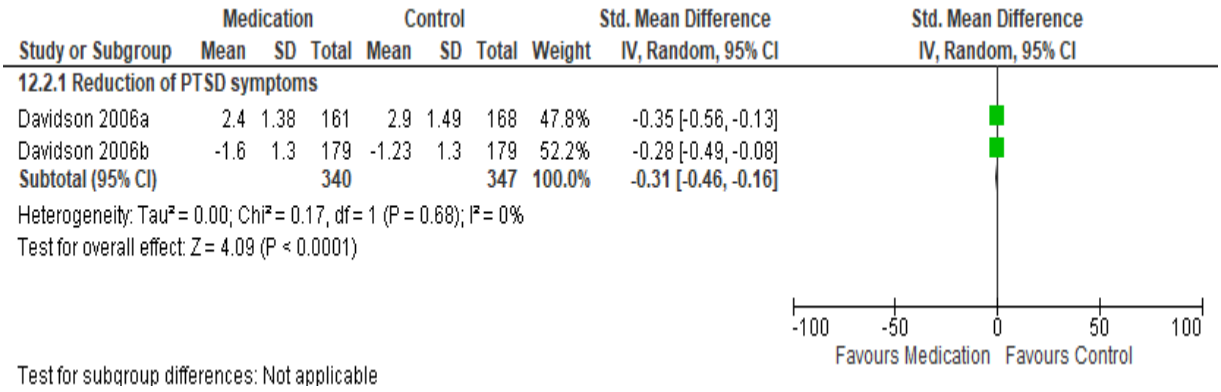
There were no data available to assess the number of participants who responded to venlafaxine versus placebo.

Secondary outcomes measures

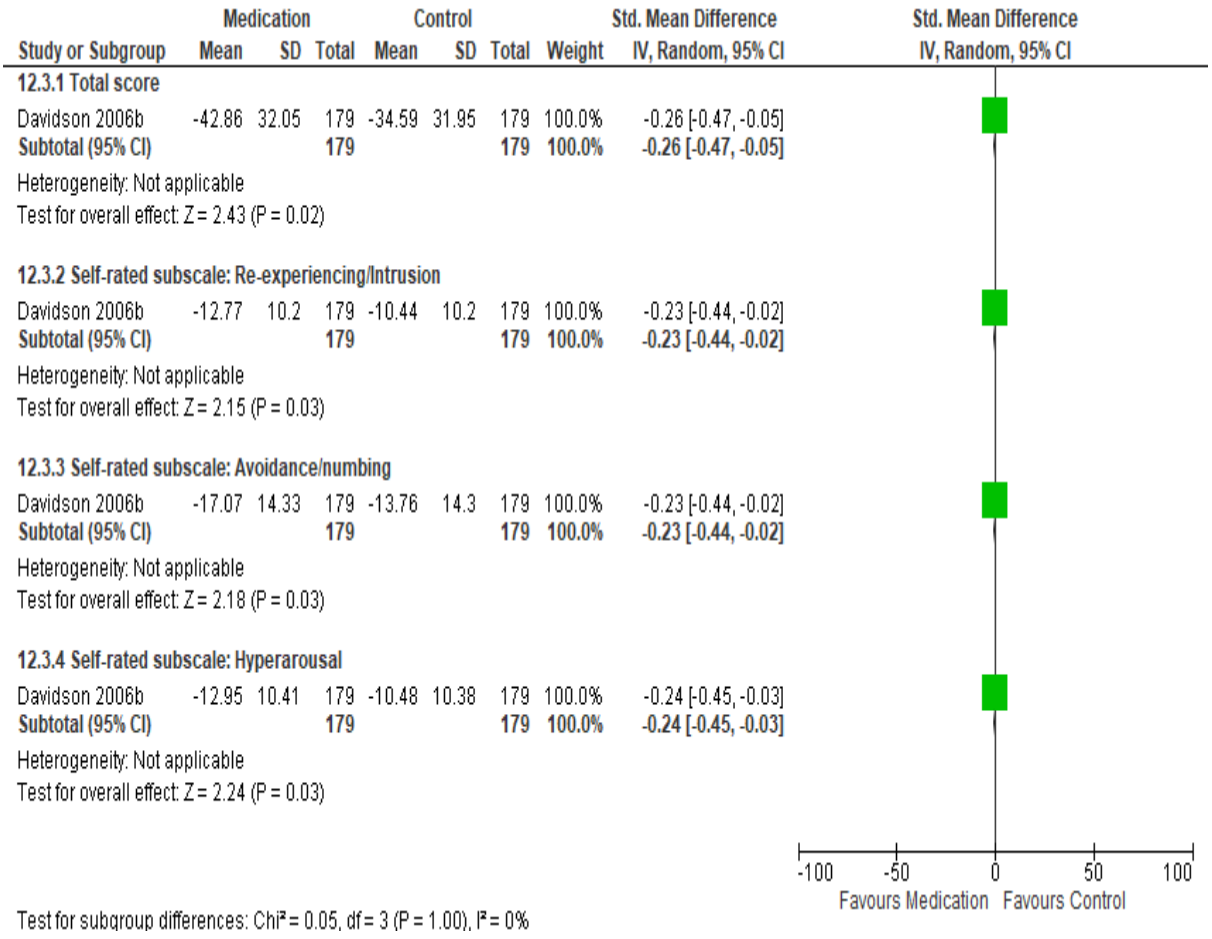
There was evidence of benefit for the SNRI venlafaxine compared to placebo for reducing total PTSD symptoms on the CAPS (k = 2, MD −8.11 points, 95% CI −12.29 to −3.92, N = 687; see Analysis 12.1; Davidson 2006a; Davidson 2006b), re-experiencing/intrusion (k = 2, MD −1.95 points, 95% CI −3.36 to −0.54, N = 687; see Analysis 12.1; Davidson 2006a; Davidson 2006b), avoidance/numbing (k = 2, MD −3.42 points, 95% CI −5.23 to −1.61, N = 687; see Analysis 12.1; Davidson 2006a; Davidson 2006b), and hyperarousal (k = 2, MD −2.29 points, 95% CI −3.67 to −0.91, N = 687; see Analysis 12.1; Davidson 2006a; Davidson 2006b) subscale of the CAPS. The evidence that was available for these outcomes was of moderate quality. Evidence of benefit of venlafaxine compared to placebo was also found for reducing PTSD symptoms on the CGI-S (k = 2, SMD −0.31 points, 95% CI −0.46 to −0.16, N = 687; see Analysis 12.2; Davidson 2006a; Davidson 2006b). Moreover, evidence of an effect of venlafaxine on total DTS symptom severity (k = 1, SMD -0.26 points, 95% CI -0.47 to -0.05, N = 358; see Analysis 12.3; Davidson 2006b) was observed, as well as for the re-experiencing/intrusion (k = 1, MD -0.23 points, 95% CI −0.44 to -0.02, N = 358; see Analysis 12.3; Davidson 2006b), avoidance/numbing (k = 1, MD -0.23 points, 95% CI −0.44 to -0.02, N = 358; see Analysis 12.3; Davidson 2006b), and hyperarousal (k = 1, MD -0.24 points, 95% CI −0.45 to -0.03, N = 358; see Analysis 12.3; Davidson 2006b) subscale on the DTS.



Analysis 12.1. Serotonin and norepinephrine reuptake inhibitors versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.



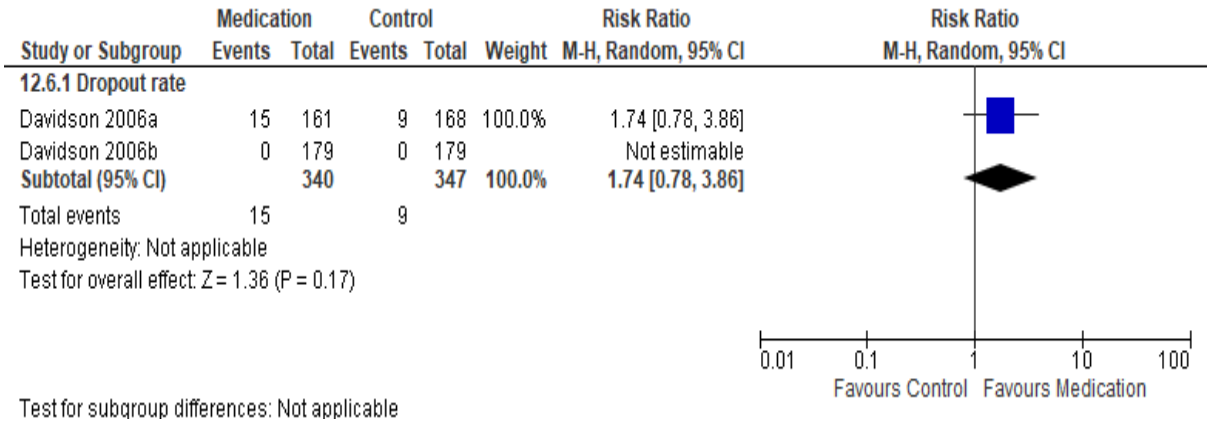
Analysis 12.2. Serotonin and norepinephrine reuptake inhibitors versus placebo. Symptom severity: Other measures.



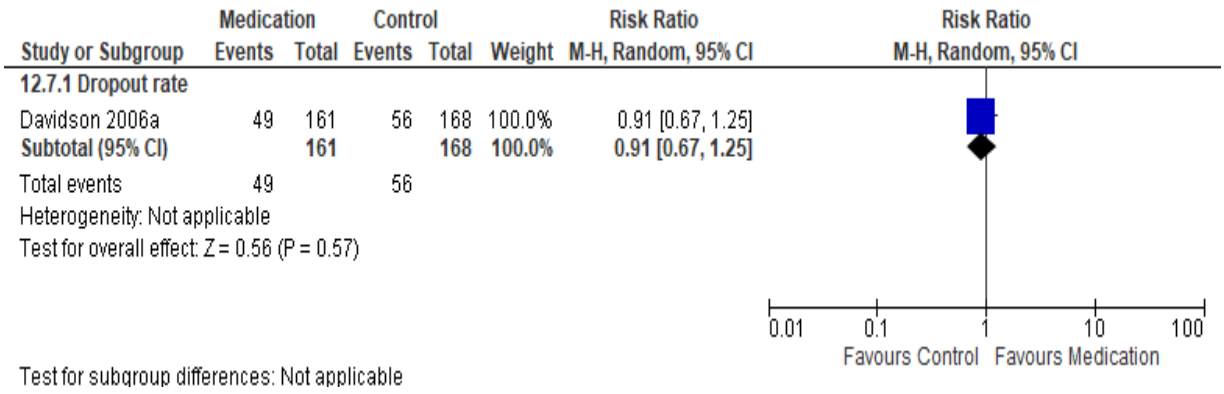
Analysis 12.3. Serotonin and norepinephrine reuptake inhibitors versus placebo. Self-rated scales: Total score, Self-rated subscale Re-experiencing/Intrusion, Self-rated subscale Avoidance/numbing, Self-rated subscale Hyperarousal.

In addition, there was no difference in the number of participants who withdrew due to treatment-emergent side effects (k = 2, RR 1.74; 95% CI 0.78 to 3.86, N = 687; see Analysis 12.6; Davidson 2006a; Davidson 2006b). This conclusion was based on moderate quality evidence. No difference in the number of participants who withdrew due to any cause (k = 1,

RR 0.91; 95% CI 0.67 to 1.25, N = 329; see Analysis 12.7; Davidson 2006a) was also found, which is confirmed by the similar dropout rates in both groups (30% versus 33%).



Analysis 12.6. Serotonin and norepinephrine reuptake inhibitors versus placebo. Dropout rate due to treatment emergent adverse effects: Dropout rate.



Analysis 12.7. Serotonin and norepinephrine reuptake inhibitors versus placebo. Dropout rate due to any cause: Dropout rate.

Comparison 12: SNRIs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: multi-center trials **Intervention**: SNRIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With SNRIs**				
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.74** (0.78 to 3.86)	687 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	Dropout rates due to adverse events were low in the SNRI and placebo groups (15/340, 4%; 9/347, 3%).
	26 per 1000	**45 per 1000** (20 to 100)				
	Moderate					
	27 per 1000	**47 per 1000** (21 to 104)				
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was **8.11 lower** (12.29 to 3.92 lower)		687 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	The mean CAPS total PTSD score for the SNRI intervention groups is 8.11 points which suggests 'extreme' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean clinically administered PTSD scale (CAPS): reduction		687 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	The mean CAPS Re-experiencing/intrusion PTSD score for the

		of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **1.95 lower** (3.36 to 0.54 lower)				SNRI intervention groups is 1.95 points which suggests 'mild/minimal' PTSD.
CAPS subscale: Avoidance/numbing		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **3.42 lower** (5.23 to 1.61 lower)		687 (2 studies)	⨁⨁⨁⊖ **moderate**[1]	The mean CAPS Avoidance/numbing PTSD score for the SNRI intervention groups is 3.42 points which suggests 'severe' PTSD.
CAPS subscale: Hyperarousal		The mean clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **2.29 lower** (3.67 to 0.91 lower)		687 (2 studies)	⨁⨁⨁⊖ **moderate**[1]	The mean CAPS Hyperarousal PTSD score for the SNRI intervention groups is 2.29 points which suggests 'moderate' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the						

estimate.
Very low quality: we are very uncertain about the estimate.

Summary of Findings Table 11. Comparison 11: SNRIs versus placebo for posttraumatic stress disorder (PTSD).

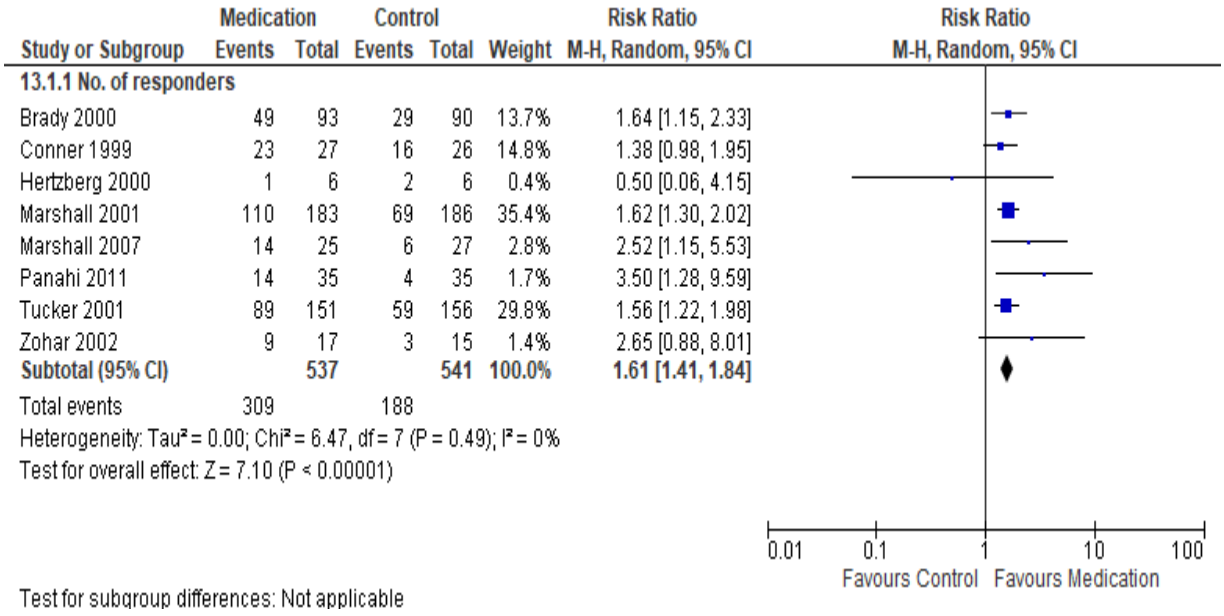
Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

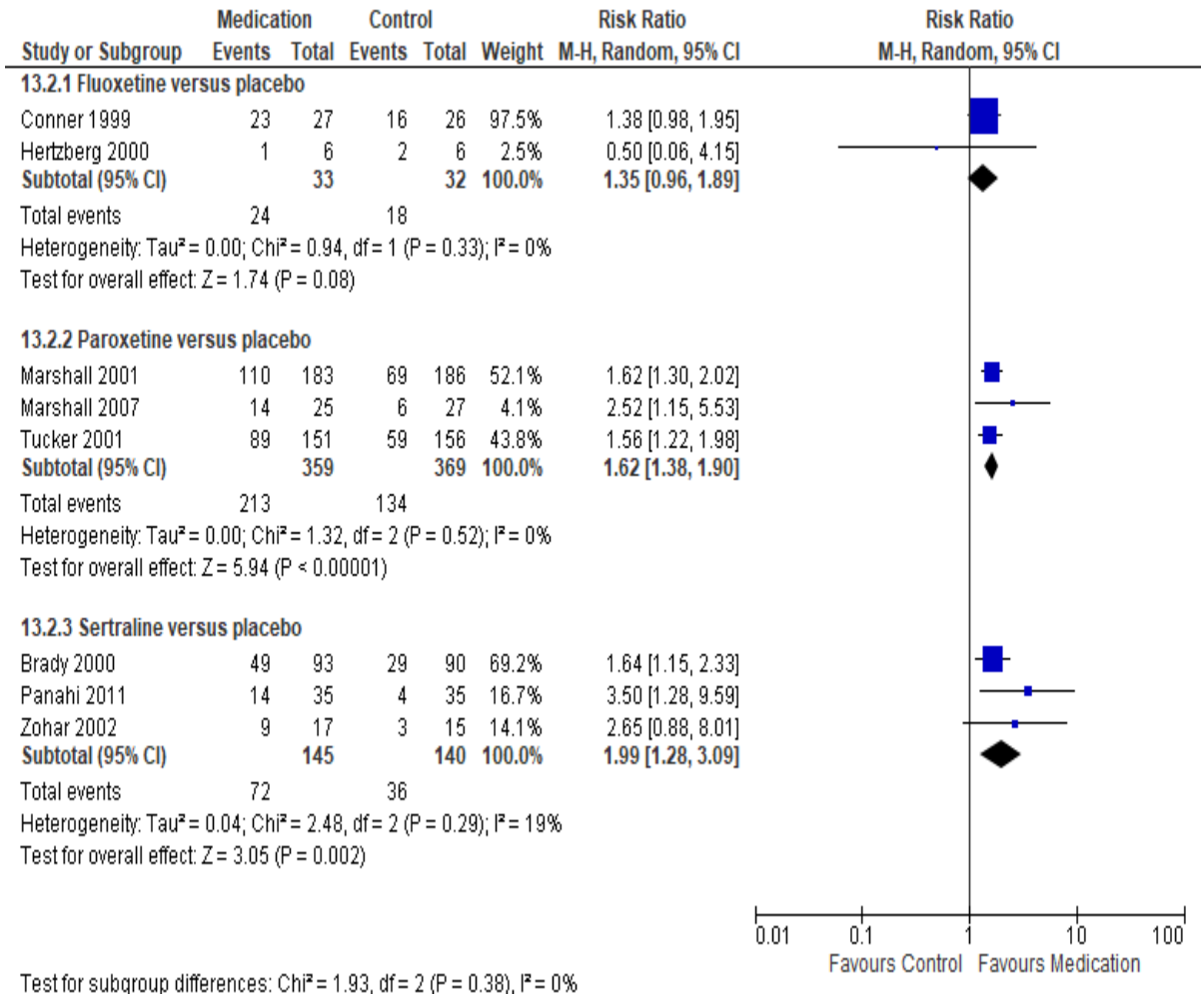
Comparison 13: SSRIs versus placebo

Primary outcome measures

There was evidence of treatment efficacy for fluoxetine, paroxetine and sertraline compared to placebo in participants with PTSD (k = 8, RR 1.61; 95% CI 1.41 to 1.84, N = 1078; see Analysis 13.1; Brady 2000; Conner 1999; Hertzberg 2000; Marshall 2001; Marshall 2007; Panahi 2011; Tucker 2001; Zohar 2002), based on moderate quality evidence. A larger effect was also observed for the number of participants who responded to treatment for the individual SSRI paroxetine (N = 3, RR 1.62, 95% CI 1.38 to 1.90, N = 728; Analysis 13.2; Marshall 2001; Marshall 2007; Tucker 2001) and to a lesser extent, sertraline (N = 3, RR 1.99, 95% CI 1.28 to 3.09, N = 285; Analysis 13.2; Brady 2000; Panahi 2011; Zohar 2002), but not fluoxetine (N = 2, RR 1.35, 95% CI 0.96 to 1.89, N = 65; Analysis 13.2; Conner 1999; Hertzberg 2000). The failure to detect a treatment effect for fluoxetine presumably reflects the small samples, and hence low power, of this comparison.



Analysis 13.1. Selective serotonin reuptake inhibitors versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

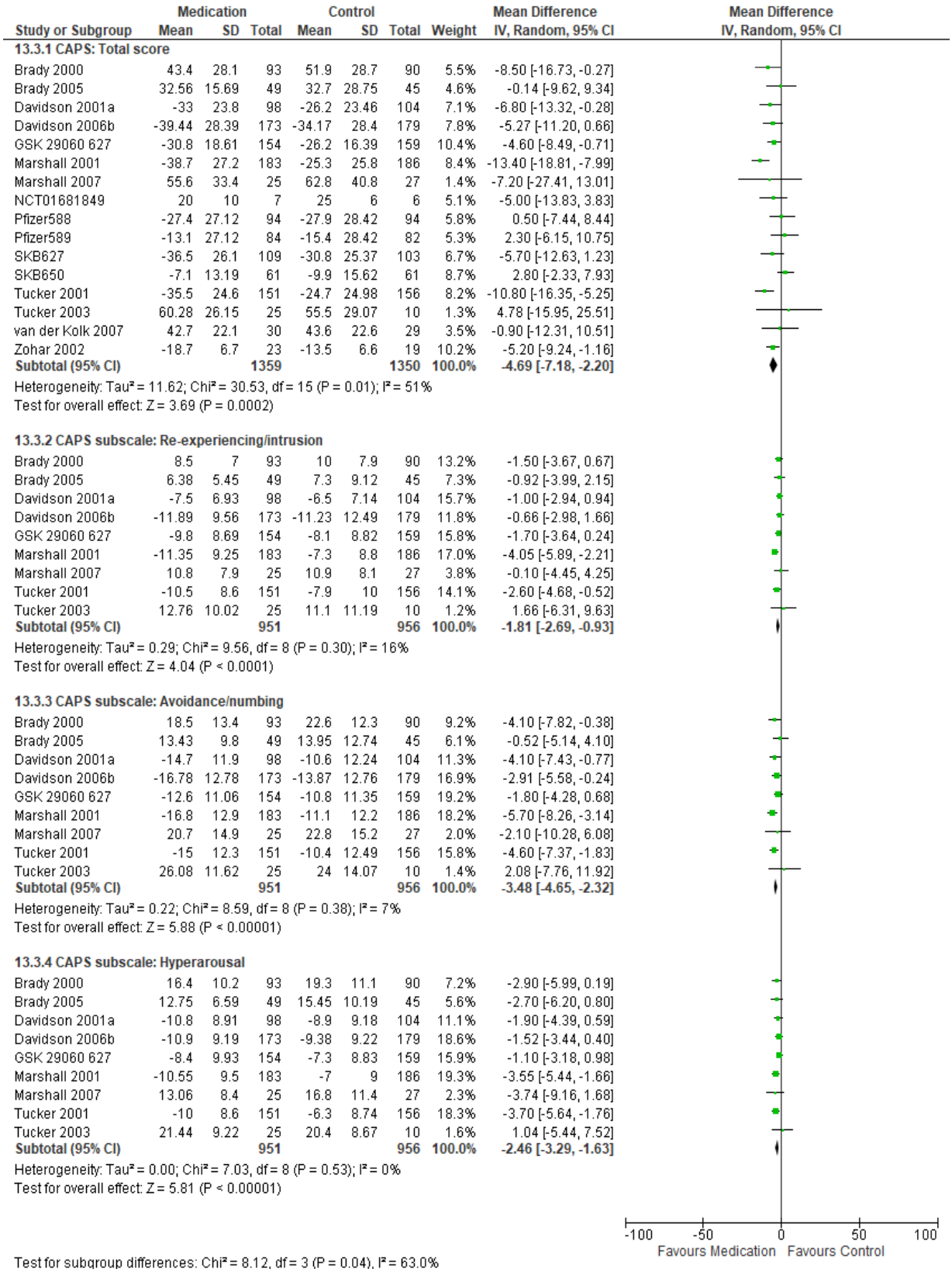


Analysis 13.2. Selective serotonin reuptake inhibitors versus placebo. Clinical Global Impressions: Individual selective serotonin reuptake inhibitors agents.

Secondary outcomes measures

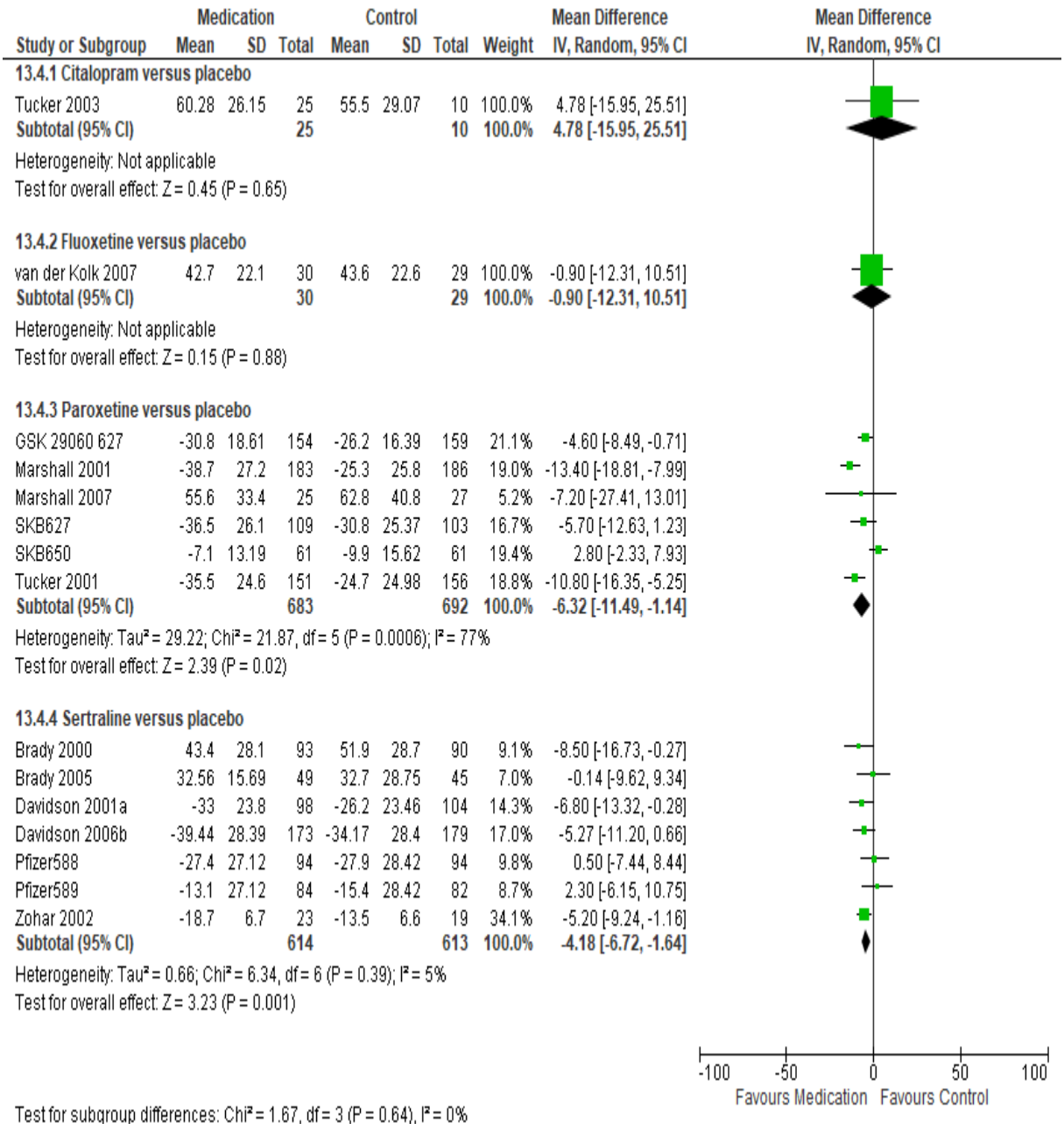
There was evidence of benefit for the SSRIs compared to placebo for reducing total PTSD symptoms on the CAPS (k = 14, MD −4.69 points, 95% CI −7.18 to −2.20, N = 2709; see Analysis 13.3; Davidson 2001a; Davidson 2006b; GSK 29060 627; Marshall 2001; Marshall 2007; NCT01681849; Pfizer588; Pfizer589; SKB627; SKB650; Tucker 2001; Tucker 2003; van der Kolk 2007; Zohar 2002), though the evidence was very low in quality. There was considerable heterogeneity in effect size estimates for this outcome (Chi^2 = 30.53, df = 15 (P = 0.01); I^2 = 51%). The SSRIs were superior to placebo on both the e-experiencing/intrusion (MD

-1.81 points, 95% CI −2.69 to -0.93; see Analysis 13.3), avoidance/numbing (MD -3.48 points, 95% CI −4.65 to -2.32; see Analysis 13.3), and hyperarousal (MD -2.46 points, 95% CI −3.29 to -1.63; see Analysis 13.3) subscale on the CAPS in nine trials with 1907 participants (Brady 2000; Brady 2005; Davidson 2001a; Davidson 2006b; GSK 29060 627; Marshall 2001; Marshall 2007; Tucker 2001; Tucker 2003). The evidence that was available for these outcomes was of moderate quality.



Analysis 13.3. Selective serotonin reuptake inhibitors versus placebo. Clinically Administered PTSD Scale (CAPS): CAPS Total score, CAPS subscale Re-experiencing/intrusion, CAPS subscale Avoidance/numbing, CAPS subscale Hyperarousal.

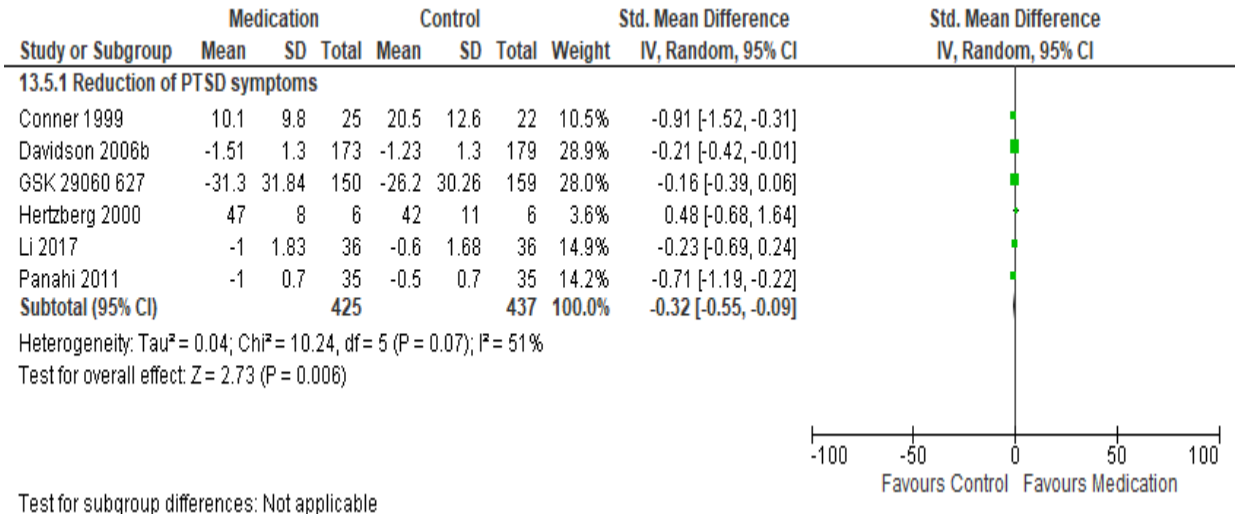
The pattern of symptom severity on the CAPS for the separate SSRI medications was similar to that observed for treatment efficacy, with both paroxetine (N = 6, MD -6.32 points, 95% CI -11.49 to -1.14, N = 1375; see Analysis 13.4; GSK 29060 627; Marshall 2001; Marshall 2007; SKB627; SKB650; Tucker 2001) and sertraline (N = 7, MD -4.18 points, 95% CI -6.72 to -1.64, N = 1227; see Analysis 13.4; Brady 2000; Brady 2005; Davidson 2001a; Davidson 2006b; Pfizer588; Pfizer589; Zohar 2002) demonstrating a reduction in PTSD symptoms. There was once again insufficient evidence to determine whether fluoxetine was effective in reducing total PTSD (N = 1, MD -0.90 points, 95% CI -12.31 to 10.51, N = 59; see Analysis 13.4; van der Kolk 2007), as well as citalopram (N = 1, MD 4.78 points, 95% CI -15.95 to 25.51, N = 35; see Analysis 13.4; Tucker 2003), relative to placebo.



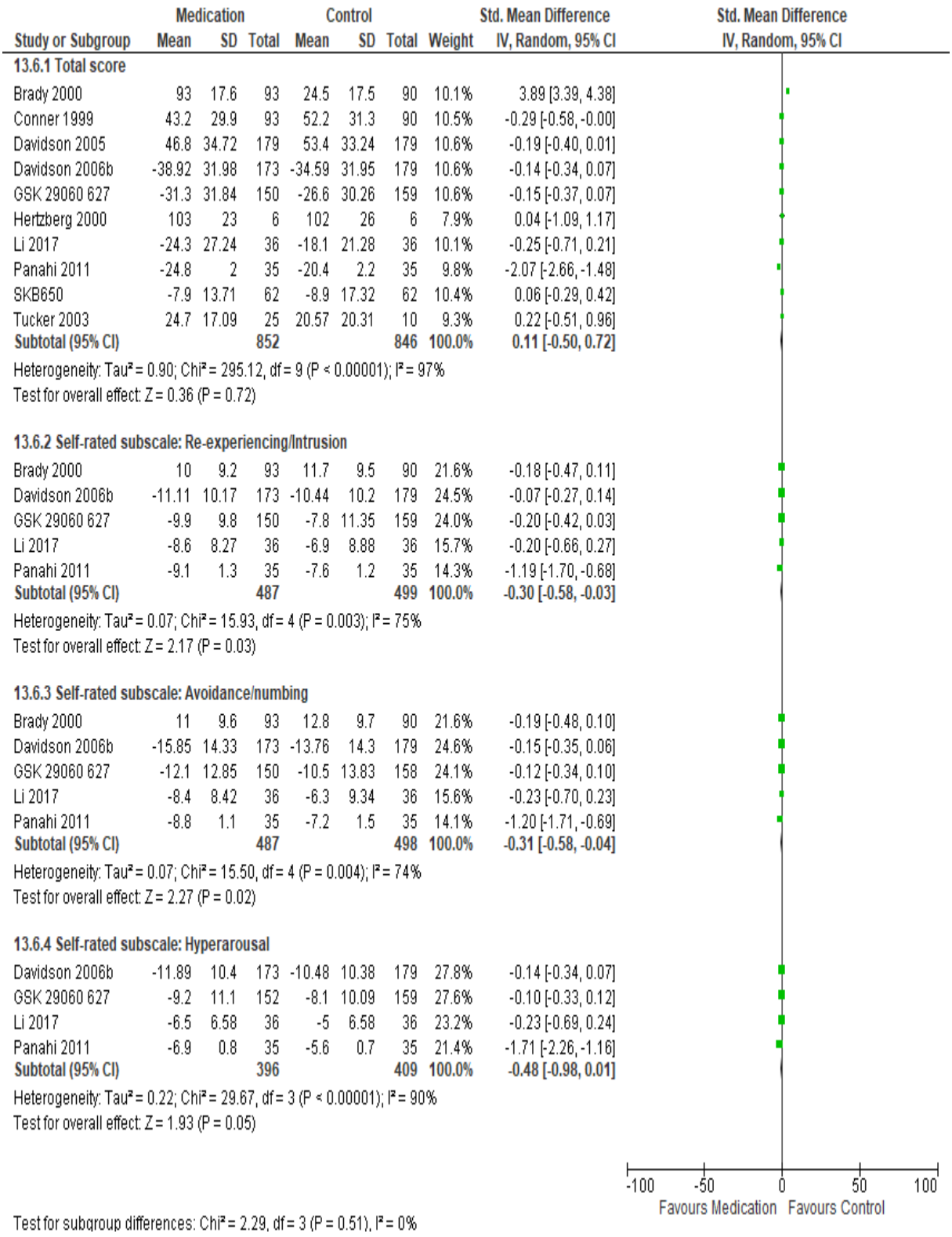
Analysis 13.4. Selective serotonin reuptake inhibitors versus placebo. The Clinically Administered PTSD Scale (CAPS): Individual SSRI agents.

Furthermore, there was evidence of benefit for the SSRIs fluoxetine, paroxetine and sertraline compared to placebo for the reduction in PTSD symptoms on the CGI-S (N = 6, SMD -0.32 points, 95% CI -0.55 to -0.09, N = 862; see Analysis 13.5; Conner 1999; Davidson 2006b; GSK 29060 627; Hertzberg 2000; Li 2017; Panahi 2011). There was considerable

heterogeneity in effect size estimates for this outcome (Chi² = 10.24, df = 5 (P = 0.07); I² = 51%), however. There was no evidence of an effect for the SSRIs compared to placebo for the reduction in total PTSD symptoms on the DTS (N = 10, SMD 0.11, 95% CI -0.50 to 0.72, N = 1698; see Analysis 13.6; Brady 2000; Conner 1999; Davidson 2005; Davidson 2006b; GSK 29060 627; Hertzberg 2000; Li 2017; Panahi 2011; SKB650; Tucker 2003), and is confirmed by the substantial heterogeneity found between trials (Chi² = 295.12, df = 9 (P < 0.00001); I² = 97%). The review did however observe evidence of an effect of paroxetine and sertraline for the re-experiencing/intrusion (k = 5, MD -0.30 points, 95% CI −0.58 to -0.03, N = 986; see Analysis 13.6; Brady 2000; Davidson 2006b; GSK 29060 627; Li 2017; Panahi 2011), avoidance/numbing (k = 5, MD -0.31 points, 95% CI −0.58 to -0.04, N = 986; see Analysis 13.6; Brady 2000; Davidson 2006b; GSK 29060 627; Li 2017; Panahi 2011), and hyperarousal (k = 4, MD -0.48 points, 95% CI −0.98 to 0.01, N = 805; see Analysis 13.6; Davidson 2006b; GSK 29060 627; Li 2017; Panahi 2011) subscale on the DTS, although substantial heterogeneity was found for each subscale (I² = 75%, I² = 74%, I² = 90%; respectively).

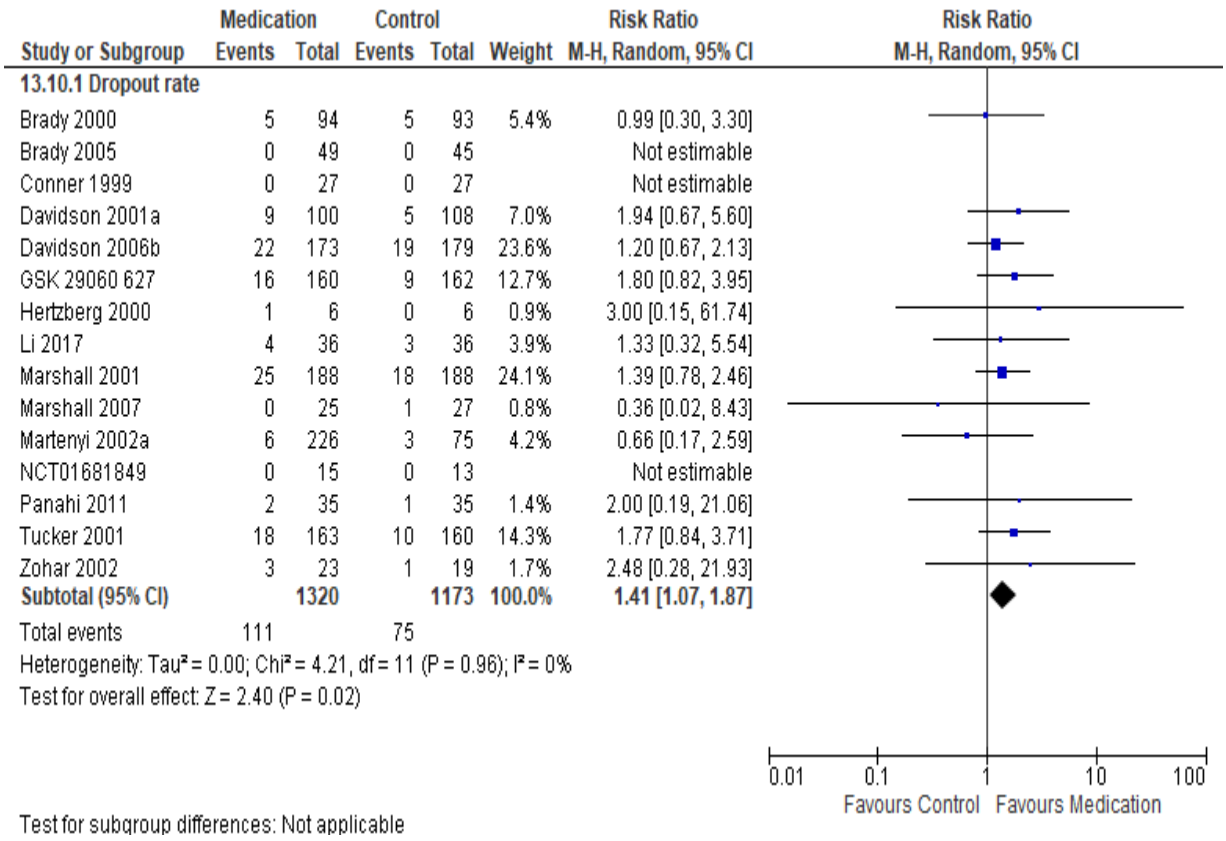


Analysis 13.5. Selective serotonin reuptake inhibitors versus placebo. Symptom severity: Other measures.

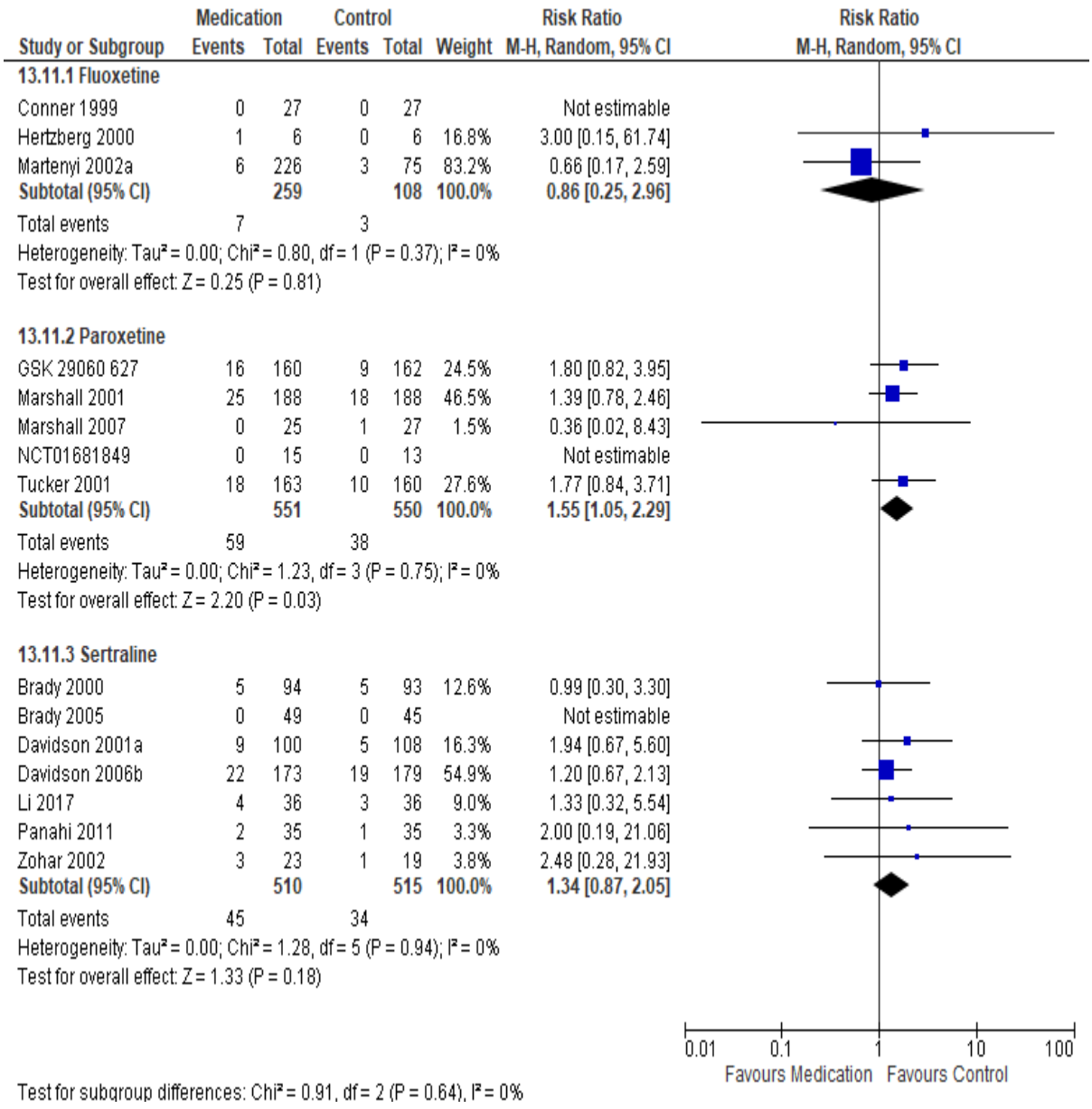


Analysis 13.6. Selective serotonin reuptake inhibitors versus placebo. Self-rated scales: Total score, Self-rated subscale Re-experiencing/Intrusion, Self-rated subscale Avoidance/numbing, Self-rated subscale Hyperarousal.

The proportion of dropouts due to adverse events was similar amongst participants receiving the SSRIs fluoxetine, paroxetine and sertraline (111/1320, 8%) compared to placebo (75/1173, 6%), although a significant difference in dropouts were found (k = 15, RR 1.41; 95% CI 1.07 to 1.87, N = 2493; see Analysis 13.10; Brady 2000; Brady 2005; Conner 1999; Davidson 2001a; Davidson 2006b; GSK 29060 627; Hertzberg 2000; Li 2017; Marshall 2001; Marshall 2007; Martenyi 2002a; NCT01681849; Panahi 2011; Tucker 2001; Zohar 2002). This conclusion was based on moderate quality evidence. This difference in treatment-emergent side effects was also evident for the separate SSRI paroxetine (k = 5, RR 1.55; 95% CI 1.05 to 2.29, N = 1101; see Analysis 13.11; GSK 29060 627; Marshall 2001; Marshall 2007; NCT01681849; Tucker 2001), but not for the SSRI fluoxetine (k = 3, RR 0.86; 95% CI 0.25 to 2.96, N = 367; see Analysis 13.11; Conner 1999; Hertzberg 2000; Martenyi 2002a) and the SSRI sertraline (k = 7, RR 1.34; 95% CI 0.87 to 2.05, N = 1025; see Analysis 13.11; Brady 2000; Brady 2005; Davidson 2001a; Davidson 2006b; Li 2017; Panahi 2011; Zohar 2002).

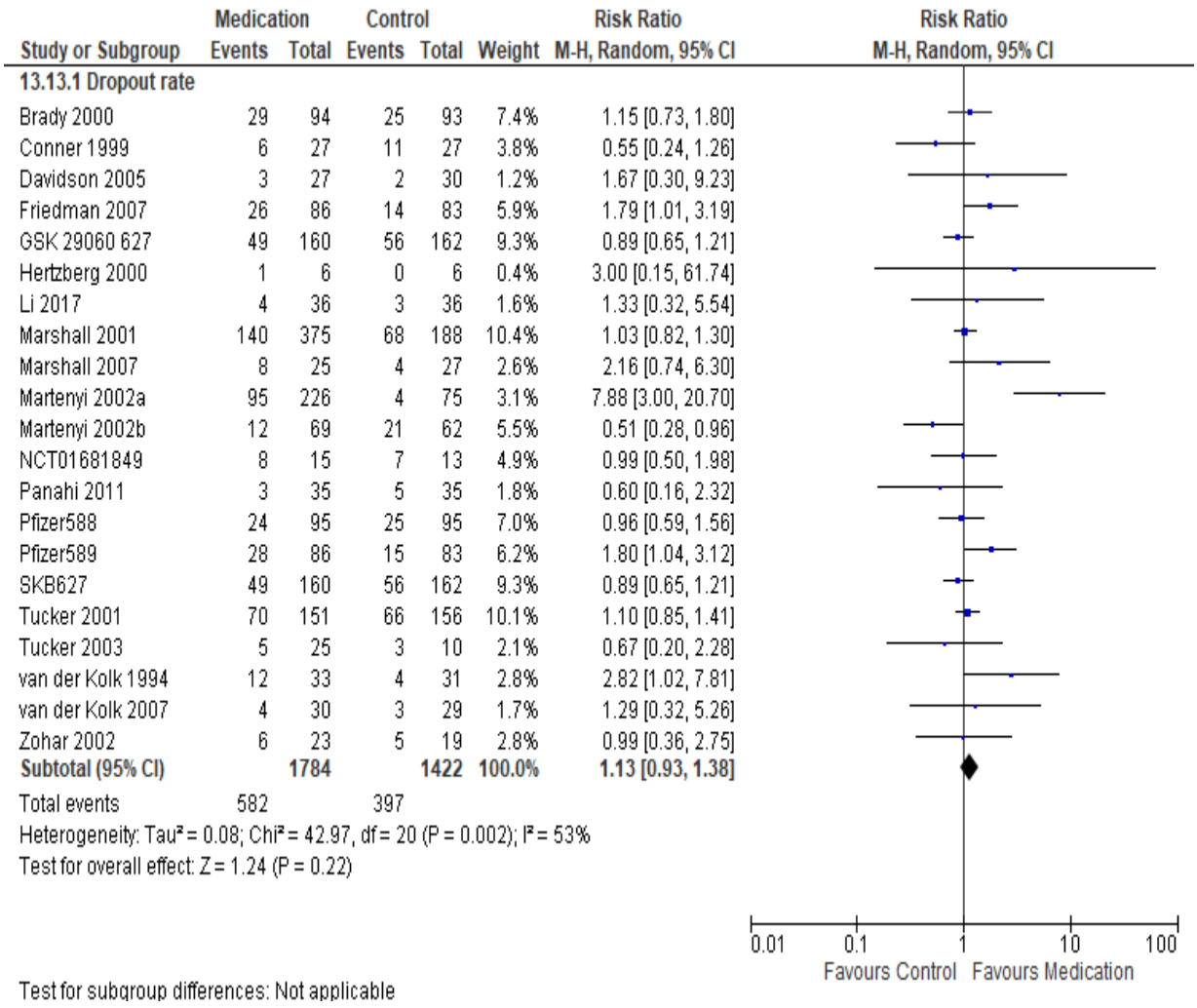


Analysis 13.10. Selective serotonin reuptake inhibitors versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 13.11. Selective serotonin reuptake inhibitors versus placebo. Drop-out rate due to treatment emergent adverse effects: Individual SSRI agents.

In addition, similar dropout rates were observed in the medication and placebo arms for the SSRIs (k = 21, RR 1.13; 95% CI 0.93 to 1.38, N = 3206; see Analysis 13.13). Considerable heterogeneity in effect size estimates for this outcome (Chi^2 = 42.97, df = 20 (P = 0.002); I^2 = 53%) was also observed.



Analysis 13.13. Selective serotonin reuptake inhibitors versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 13: SSRIs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single and multi-center trials **Intervention**: SSRIs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With SSRIs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 1.61** (1.41 to 1.84)	1078 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	There was evidence of benefit on the number of participants with PTSD who responded to treatment (P < 0.00001). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the SSRI groups compared to the placebo groups who responded, 'Very
	348 per 1000	**559 per 1000** (490 to 639)				
	Moderate					
	328 per 1000	**528 per 1000** (462 to 604)				

						Much Improved' or 'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.41** (1.07 to 1.87)	2493 (15 studies)	⨁⨁⨁⨀ **moderate**[1]	A similar proportion withdrew due to treatment adverse events, a significant difference between group were found (P = 0.02).
	42 per 1000	**25 per 1000** (4 to 144)				
	Moderate					
	46 per 1000	**65 per 1000** (49 to 86)				
Clinically Administered PTSD Scale (CAPS): CAPS Total score		The mean 1.1 clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS: total score in the intervention groups was **4.69 lower** (7.18 to 2.2 lower)		2709 (16 studies)	⨁⨀⨀⨀ **very low**[1,2,3]	The mean CAPS total PTSD score for the SSRI intervention groups is 4.69 points which suggests 'extreme' PTSD.
CAPS subscale: Re-experiencing/intrusion		The mean 1.1 clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: re-experiencing/intrusion in the intervention groups was **1.81 lower** (2.69 to 0.93 lower)		1907 (9 studies)	⨁⨁⨁⨀ **moderate**[1]	The mean CAPS Re-experiencing/intrusion PTSD score for the SSRI intervention groups is 1.81 points which suggests 'mild/minimal' PTSD.
CAPS subscale: Avoidance/numbing		The mean 1.1 clinically administered PTSD scale (CAPS):		1907 (9 studies)	⨁⨁⨁⨀ **moderate**[1]	The mean CAPS Avoidance/numbing PTSD score for the

		reduction of PTSD symptoms - CAPS subscale: avoidance/numbing in the intervention groups was **3.48 lower** (4.65 to 2.32 lower)				SSRI intervention groups is 3.48 points which suggests 'severe' PTSD.
CAPS subscale: Hyperarousal		The mean 1.1 clinically administered PTSD scale (CAPS): reduction of PTSD symptoms - CAPS subscale: hyperarousal in the intervention groups was **2.46 lower** (3.29 to 1.63 lower)		1907 (9 studies)	⨁⨁⨁⊖ **moderate**[1]	The mean CAPS Hyperarousal PTSD score for the SSRI intervention groups is 2.46 points which suggests 'moderate' PTSD.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **CAPS:** Clinically Administered PTSD Scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 12. Comparison 12: SSRIs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

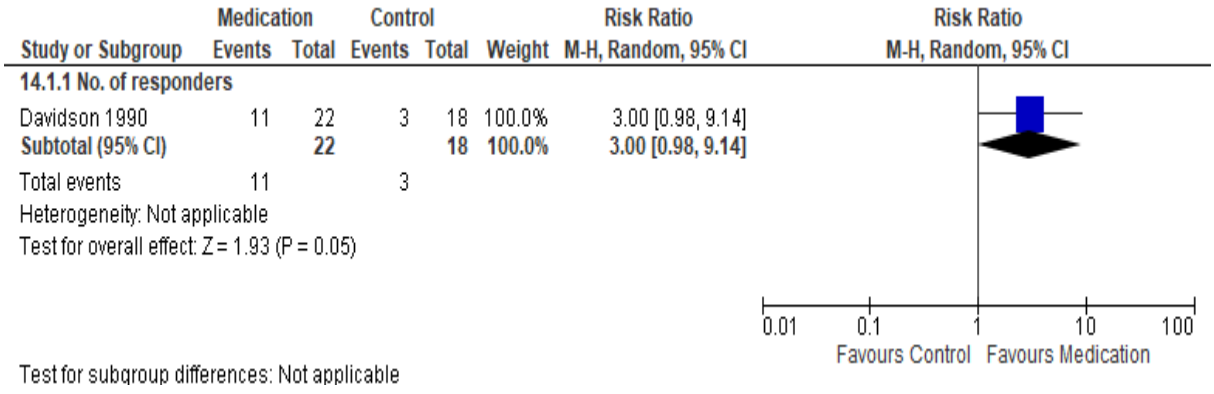
[2] Downgraded two levels due to moderate heterogeneity (I^2 of 51%).

[3] Downgraded one level due to serious imprecision (wide confidence interval).

Comparison 14: TCAs versus placebo

Primary outcome measures

There was evidence of an effect of amitriptyline on treatment efficacy in participants with PTSD compared to placebo (RR 3.00; 95% CI 0.98 to 9.14, see Analysis 14.1) in one trial with 40 participants (Davidson 1990). The evidence that was available for this outcome was of low quality.

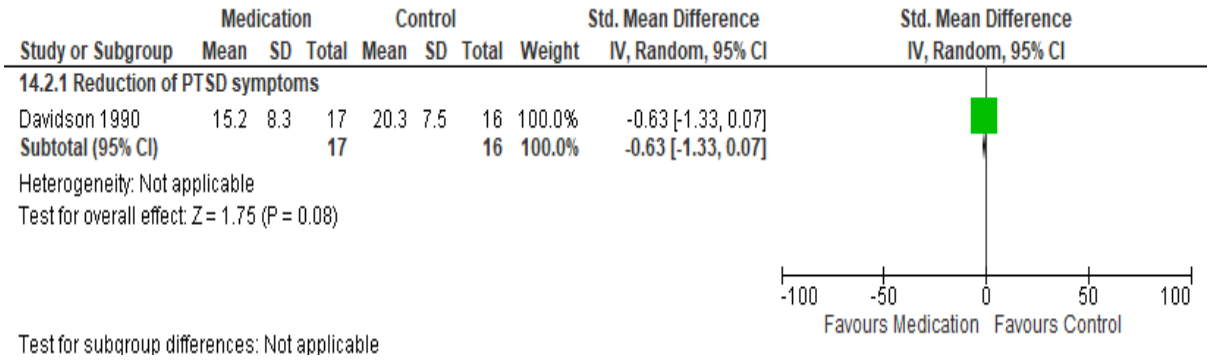


Analysis 14.1. Tricyclic antidepressants versus placebo. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

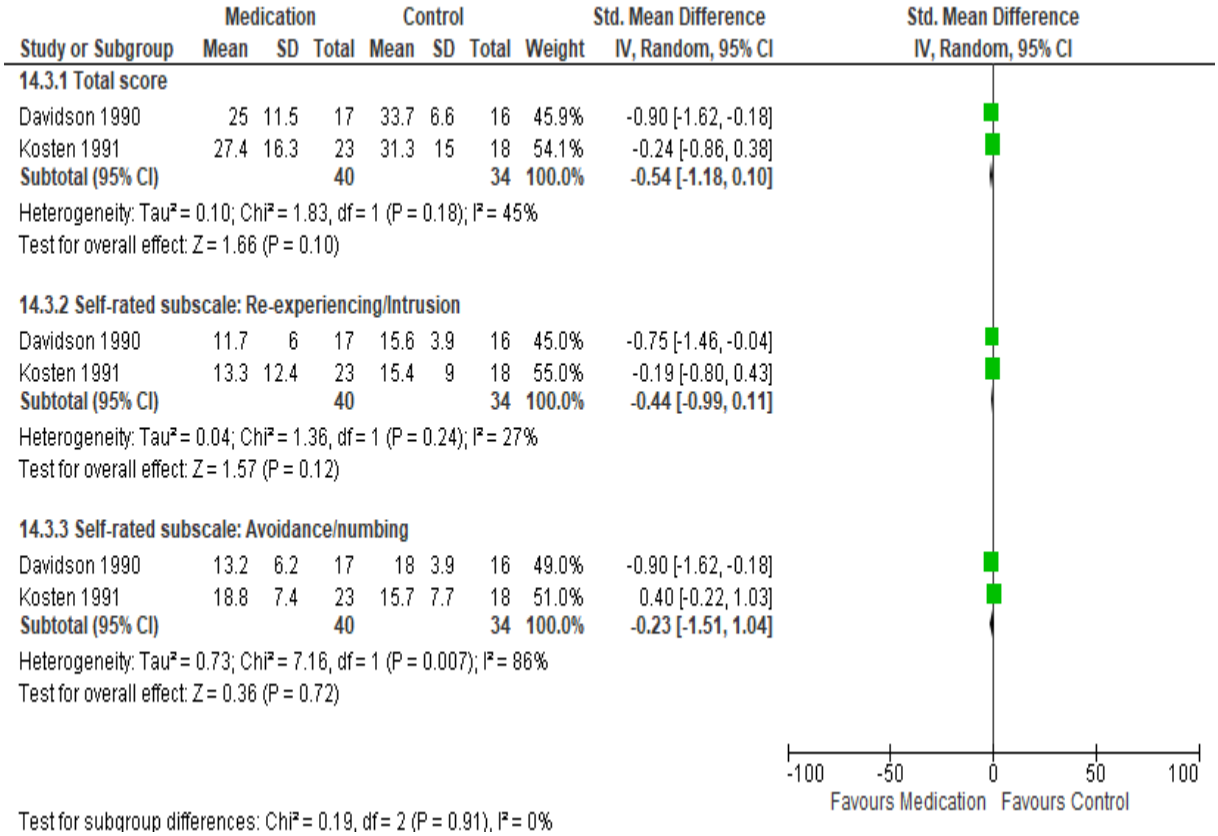
Secondary outcomes measures

No evidence of an effect of amitriptyline on the SI-PTSD checklist for symptom severity was observed (k = 1, SMD -0.63 points, 95% CI -1.33 to 0.07, N = 33; see Analysis 14.2; Davidson 1990). The review also found no evidence of benefit of amitriptyline and imipramine compared to placebo for reducing total IES symptom severity (k = 2, SMD -0.54 points, 95% CI −1.18 to 0.10, N = 74; see Analysis 14.3; Davidson 1990; Kosten 1991), as well as for the re-experiencing/intrusion (k = 2, SMD -0.44 points, 95% CI −0.99 to 0.11, N = 74; see Analysis 14.3; Davidson 1990; Kosten 1991) and avoidance/numbing (k = 2, SMD -0.23 points, 95% CI −1.51 to 1.04, N = 74; see Analysis 14.3; Davidson 1990; Kosten 1991) subscale on the IES. Moderate heterogeneity was found for the total IES symptom severity outcome (Chi² =

1.83, df = 1 (P = 0.18); I^2 = 45%) and substantial heterogeneity for the avoidance/numbing subscale of the IES (Chi^2 = 7.16, df = 1 (P = 0.007); I^2 = 86%).

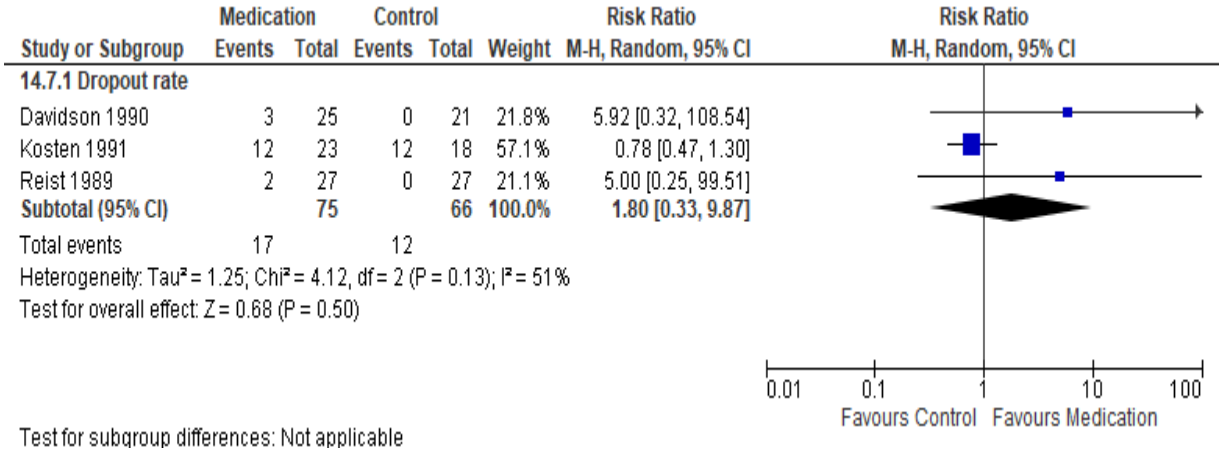


Analysis 14.2. Tricyclic antidepressants versus placebo. Symptom severity: Other measures.

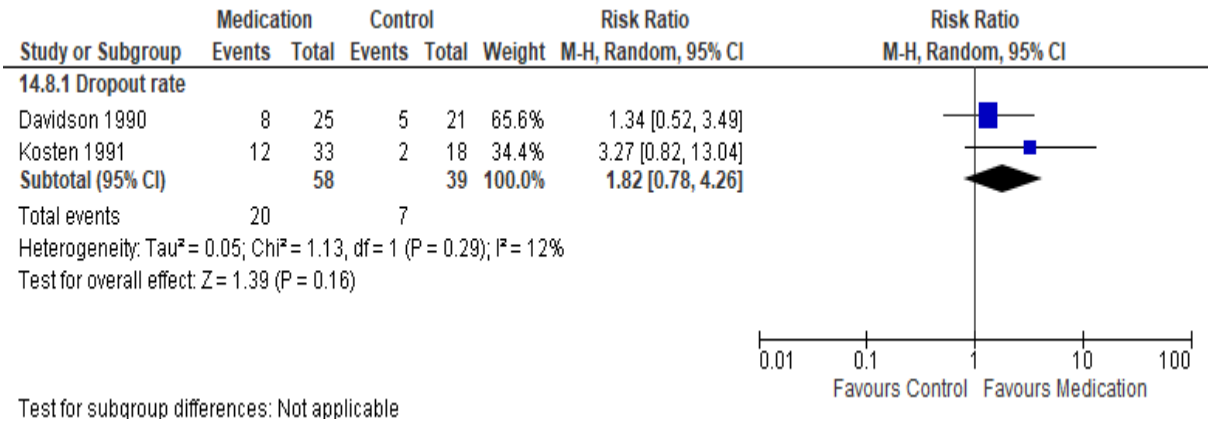


Analysis 14.3. Tricyclic antidepressants versus placebo. Self-rated scales: Total score, Self-rated subscale Re-experiencing/Intrusion, Self-rated subscale Avoidance/numbing.

In addition, there was no difference in the number of participants who withdrew due to treatment-emergent side effects in the amitriptyline, desipramine and imipramine groups compared to the placebo groups (k = 3, RR 1.80; 95% CI 0.33 to 9.87, N = 141; see Analysis 14.7; Davidson 1990; Kosten 1991; Reist 1989). This conclusion was based on very low quality evidence. Moderate heterogeneity was found for this outcome (Chi^2 = 4.12, df = 2 (P = 0.13); I^2 = 51%). More patients dropped out of the amitriptyline and imipramine groups (34%) compared to the placebo groups (18%) due to any cause dropouts. However, no difference in dropout rates were found (k = 2, RR 1.82; 95% CI 0.78 to 4.26, N = 97; Analysis 14.8; Davidson 1990; Kosten 1991).



Analysis 14.7. Tricyclic antidepressants versus placebo. Drop-out rate due to treatment emergent adverse effects: Dropout rate.



Analysis 14.8. Tricyclic antidepressants versus placebo. Drop-out rate due to any cause: Dropout rate.

Comparison 14: TCAs versus placebo for posttraumatic stress disorder (PTSD)						
Patient or population: adults with PTSD **Settings**: single and multi-center trials **Intervention**: TCAs **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	With placebo	**With TCAs**				
Global Impressions scale change item (CGI-I or similar): no. of responders (acute phase)	**Study population**		**RR 3** (0.98 to 9.14)	40 (1 study)	⊕⊕⊖⊖ **low**[1,2]	There was evidence of benefit on the number of participants with PTSD who responded to treatment (P = 0.05). A RR score greater than 1 and 95% CI that does not overlap with 1 indicates that there were a statistically significantly greater number of people in the
	167 per 1000	**500 per 1000** (163 to 1000)				
	Moderate					
	167 per 1000	**501 per 1000** (164 to 1000)				

						TCA group compared to the placebo group who responded, 'Very Much Improved' or 'Much Improved' on the CGI-I scale.
Dropouts due to adverse events (acute phase)	**Study population**		**RR 1.8** (0.33 to 9.87)	141 (3 studies)	⨁⊖⊖⊖ **very low**[1,2,3]	No difference in dropout rates were found in the anticonvulsant groups (17/75; 23%) and placebo group (12/66; 18%) (P = 0.50).
	182 per 1000	**327 per 1000** (60 to 1000)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **CGI-I**: Clinical Global Impressions Improvement scale; **RR**: risk ratio.						
GRADE Working Group grades of evidence **High quality**: further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: we are very uncertain about the estimate.						

Summary of Findings Table 13. Comparison 13: TCAs versus placebo for posttraumatic stress disorder (PTSD).

Footnotes

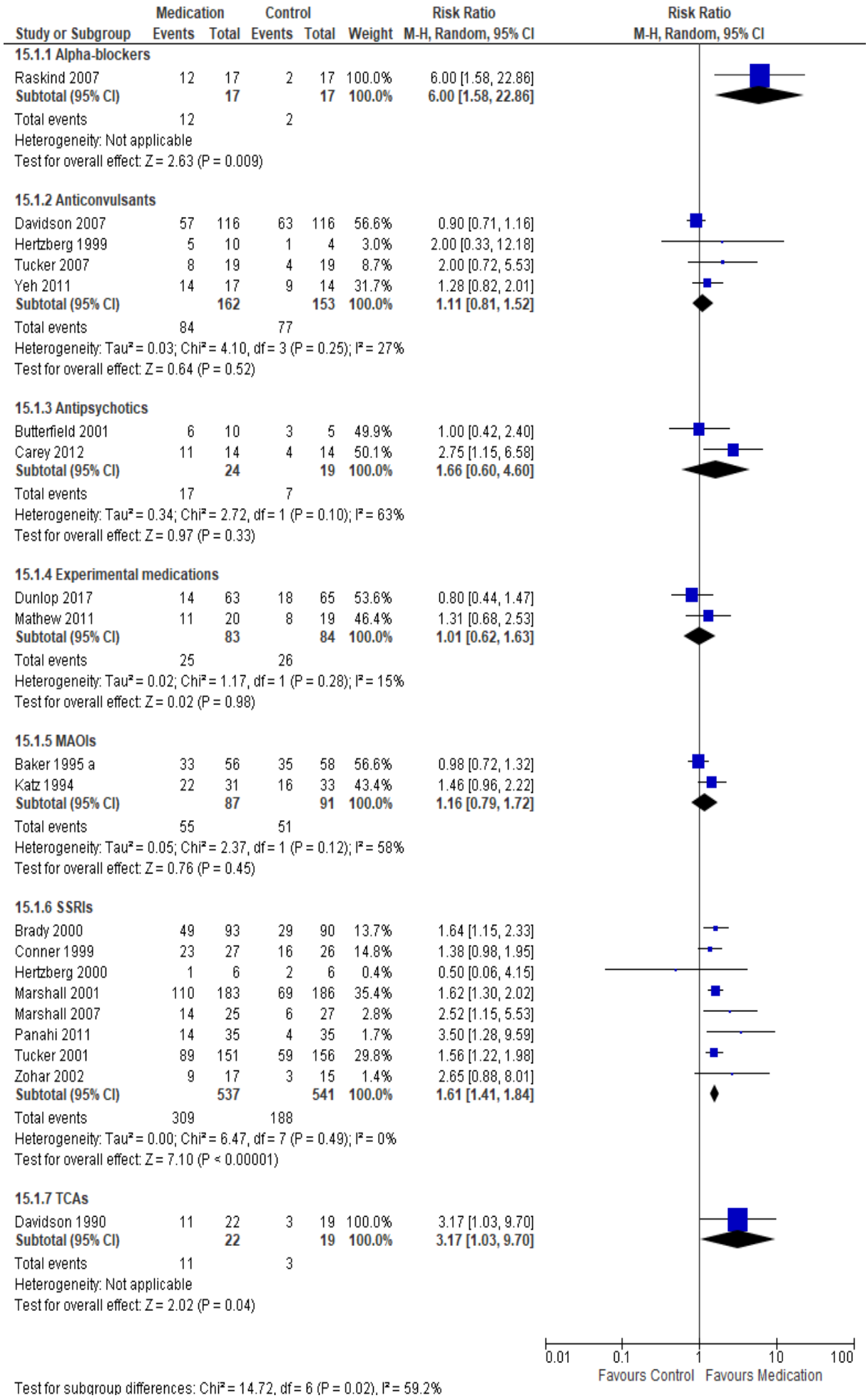
[1] Downgraded one level due to serious risk of bias (concerns with randomisation procedures).

[2] Downgraded one level due to serious imprecision (wide confidence interval).

[3] Downgraded two levels due to moderate heterogeneity (I^2 of 51%).

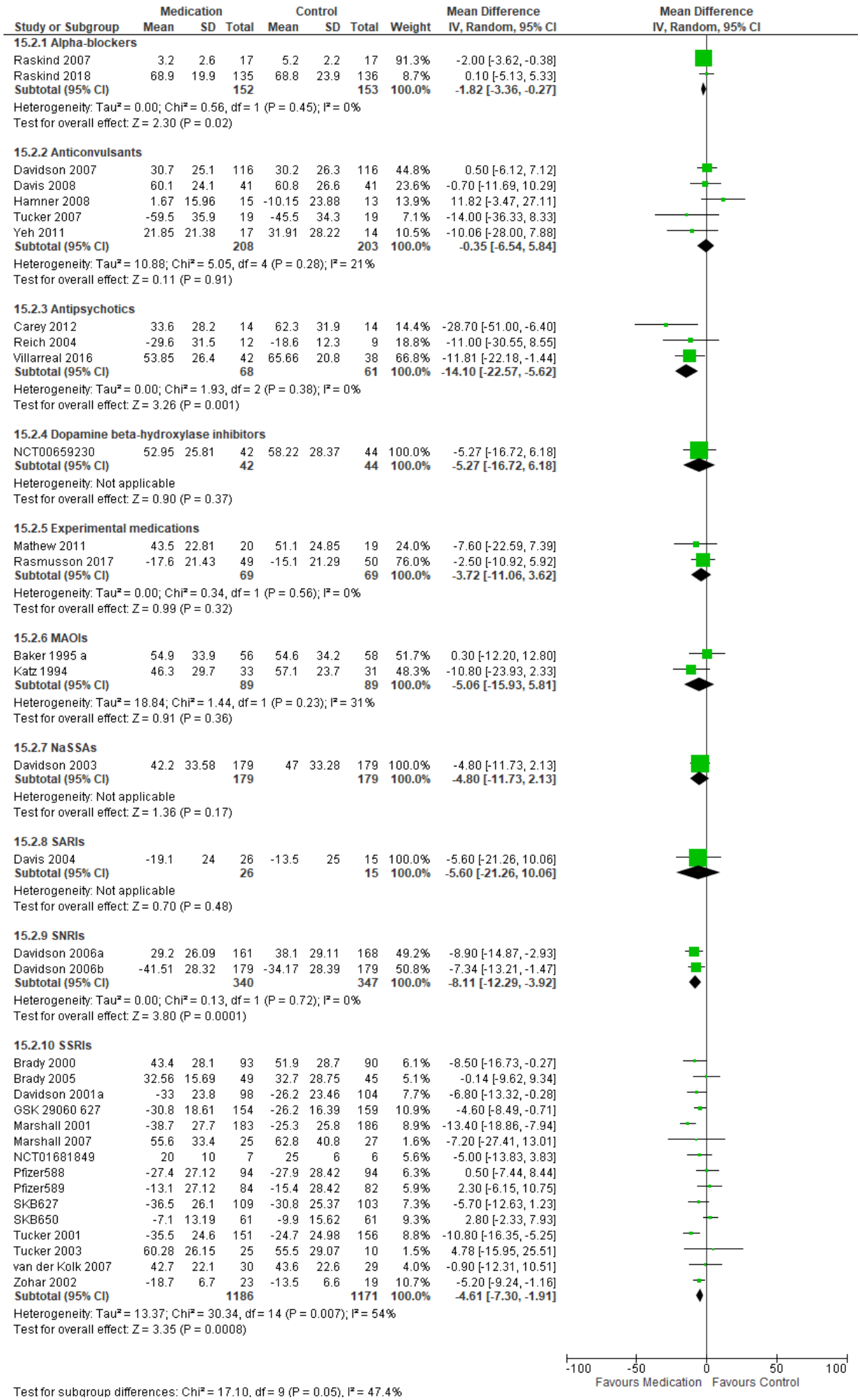
Comparison 15: total effect of medication versus placebo

There was evidence of an effect across all medication classes (k = 20, RR 1.45; 95% CI 1.22 to 1.73, N = 1856; see Analysis 15.1), with moderate heterogeneity across subgroups (Chi^2 = 14.72, df = 6 (P = 0.02), I^2 = 59.2%; see Analysis 15.1). There was also evidence that medication class explained a moderate proportion of variability in treatment efficacy when assessed across all trials providing data on this outcome (Chi^2 = 42.18, df = 19 (P = 0.002); I^2 = 55%; see Analysis 15.1).


Medication
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
15.1.1 Alpha-blockers
Raskind 2007 12 17 2 17 100.0% 6.00 [1.58, 22.86]
Subtotal (95% CI) 17 17 100.0% 6.00 [1.58, 22.86]
Total events 12 2
Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.009)
15.1.2 Anticonvulsants
Davidson 2007 57 116 63 116 56.6% 0.90 [0.71, 1.16]
Hertzberg 1999 5 10 1 4 3.0% 2.00 [0.33, 12.18]
Tucker 2007 8 19 4 19 8.7% 2.00 [0.72, 5.53]
Yeh 2011 14 17 9 14 31.7% 1.28 [0.82, 2.01]
Subtotal (95% CI) 162 153 100.0% 1.11 [0.81, 1.52]
Total events 84 77
Heterogeneity: Tau² = 0.03; Chi² = 4.10, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 0.64 (P = 0.52)
15.1.3 Antipsychotics
Butterfield 2001 6 10 3 5 49.9% 1.00 [0.42, 2.40]
Carey 2012 11 14 4 14 50.1% 2.75 [1.15, 6.58]
Subtotal (95% CI) 24 19 100.0% 1.66 [0.60, 4.60]
Total events 17 7
Heterogeneity: Tau² = 0.34; Chi² = 2.72, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.97 (P = 0.33)
15.1.4 Experimental medications
Dunlop 2017 14 63 18 65 53.6% 0.80 [0.44, 1.47]
Mathew 2011 11 20 8 19 46.4% 1.31 [0.68, 2.53]
Subtotal (95% CI) 83 84 100.0% 1.01 [0.62, 1.63]
Total events 25 26
Heterogeneity: Tau² = 0.02; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 0.02 (P = 0.98)
15.1.5 MAOIs
Baker 1995 a 33 56 35 58 56.6% 0.98 [0.72, 1.32]
Katz 1994 22 31 16 33 43.4% 1.46 [0.96, 2.22]
Subtotal (95% CI) 87 91 100.0% 1.16 [0.79, 1.72]
Total events 55 51
Heterogeneity: Tau² = 0.05; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.76 (P = 0.45)
15.1.6 SSRIs
Brady 2000 49 93 29 90 13.7% 1.64 [1.15, 2.33]
Conner 1999 23 27 16 26 14.8% 1.38 [0.98, 1.95]
Hertzberg 2000 1 6 2 6 0.4% 0.50 [0.06, 4.15]
Marshall 2001 110 183 69 186 35.4% 1.62 [1.30, 2.02]
Marshall 2007 14 25 6 27 2.8% 2.52 [1.15, 5.53]
Panahi 2011 14 35 4 35 1.7% 3.50 [1.28, 9.59]
Tucker 2001 89 151 59 156 29.8% 1.56 [1.22, 1.98]
Zohar 2002 9 17 3 15 1.4% 2.65 [0.88, 8.01]
Subtotal (95% CI) 537 541 100.0% 1.61 [1.41, 1.84]
Total events 309 188
Heterogeneity: Tau² = 0.00; Chi² = 6.47, df = 7 (P = 0.49); I² = 0%
Test for overall effect: Z = 7.10 (P < 0.00001)
15.1.7 TCAs
Davidson 1990 11 22 3 19 100.0% 3.17 [1.03, 9.70]
Subtotal (95% CI) 22 19 100.0% 3.17 [1.03, 9.70]
Total events 11 3
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)
0.01
0.1
1
10
100
Favours Control
Favours Medication
Test for subgroup differences: Chi² = 14.72, df = 6 (P = 0.02), I² = 59.2%

Analysis 15.1. Clinical Global Impressions scale improvement item (CGI-I): No. of responders.

Significant reductions in symptom severity were observed for patients who received medication in 34 short term trials from which it was possible to retrieve data for this outcome (MD -4.51; 95% CI -6.26 to -2.75, N = 4690; see Analysis 15.2). Moderate heterogeneity was observed for this outcome ($Chi^2 = 59.95$, df = 33 (P = 0.003); $I^2 = 45\%$; see Analysis 15.2). For this analysis data from one study reporting data for sertraline was excluded, because this study also reported data for the SNRI venlafaxine (Davidson 2006b).


Medication
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
15.2.1 Alpha-blockers
Raskind 2007 3.2 2.6 17 5.2 2.2 17 91.3% -2.00 [-3.62, -0.38]
Raskind 2018 68.9 19.9 135 68.8 23.9 136 8.7% 0.10 [-5.13, 5.33]
Subtotal (95% CI) 152 153 100.0% -1.82 [-3.36, -0.27]
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)
15.2.2 Anticonvulsants
Davidson 2007 30.7 25.1 116 30.2 26.3 116 44.8% 0.50 [-6.12, 7.12]
Davis 2008 60.1 24.1 41 60.8 26.6 41 23.6% -0.70 [-11.69, 10.29]
Hamner 2008 1.67 15.96 15 -10.15 23.88 13 13.9% 11.82 [-3.47, 27.11]
Tucker 2007 -59.5 35.9 19 -45.5 34.3 19 7.1% -14.00 [-36.33, 8.33]
Yeh 2011 21.85 21.38 17 31.91 28.22 14 10.5% -10.06 [-28.00, 7.88]
Subtotal (95% CI) 208 203 100.0% -0.35 [-6.54, 5.84]
Heterogeneity: Tau² = 10.88; Chi² = 5.05, df = 4 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.11 (P = 0.91)
15.2.3 Antipsychotics
Carey 2012 33.6 28.2 14 62.3 31.9 14 14.4% -28.70 [-51.00, -6.40]
Reich 2004 -29.6 31.5 12 -18.6 12.3 9 18.8% -11.00 [-30.55, 8.55]
Villarreal 2016 53.85 26.4 42 65.66 20.8 38 66.8% -11.81 [-22.18, -1.44]
Subtotal (95% CI) 68 61 100.0% -14.10 [-22.57, -5.62]
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)
15.2.4 Dopamine beta-hydroxylase inhibitors
NCT00659230 52.95 25.81 42 58.22 28.37 44 100.0% -5.27 [-16.72, 6.18]
Subtotal (95% CI) 42 44 100.0% -5.27 [-16.72, 6.18]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)
15.2.5 Experimental medications
Mathew 2011 43.5 22.81 20 51.1 24.85 19 24.0% -7.60 [-22.59, 7.39]
Rasmusson 2017 -17.6 21.43 49 -15.1 21.29 50 76.0% -2.50 [-10.92, 5.92]
Subtotal (95% CI) 69 69 100.0% -3.72 [-11.06, 3.62]
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)
15.2.6 MAOIs
Baker 1995 a 54.9 33.9 56 54.6 34.2 58 51.7% 0.30 [-12.20, 12.80]
Katz 1994 46.3 29.7 33 57.1 23.7 31 48.3% -10.80 [-23.93, 2.33]
Subtotal (95% CI) 89 89 100.0% -5.06 [-15.93, 5.81]
Heterogeneity: Tau² = 18.84; Chi² = 1.44, df = 1 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.91 (P = 0.36)
15.2.7 NaSSAs
Davidson 2003 42.2 33.58 179 47 33.28 179 100.0% -4.80 [-11.73, 2.13]
Subtotal (95% CI) 179 179 100.0% -4.80 [-11.73, 2.13]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)
15.2.8 SARIs
Davis 2004 -19.1 24 26 -13.5 25 15 100.0% -5.60 [-21.26, 10.06]
Subtotal (95% CI) 26 15 100.0% -5.60 [-21.26, 10.06]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
15.2.9 SNRIs
Davidson 2006a 29.2 26.09 161 38.1 29.11 168 49.2% -8.90 [-14.87, -2.93]
Davidson 2006b -41.51 28.32 179 -34.17 28.39 179 50.8% -7.34 [-13.21, -1.47]
Subtotal (95% CI) 340 347 100.0% -8.11 [-12.29, -3.92]
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
15.2.10 SSRIs
Brady 2000 43.4 28.1 93 51.9 28.7 90 6.1% -8.50 [-16.73, -0.27]
Brady 2005 32.56 15.69 49 32.7 28.75 45 5.1% -0.14 [-9.62, 9.34]
Davidson 2001a -33 23.8 98 -26.2 23.46 104 7.7% -6.80 [-13.32, -0.28]
GSK 29060 627 -30.8 18.61 154 -26.2 16.39 159 10.9% -4.60 [-8.49, -0.71]
Marshall 2001 -38.7 27.7 183 -25.3 25.8 186 8.9% -13.40 [-18.86, -7.94]
Marshall 2007 55.6 33.4 25 62.8 40.8 27 1.6% -7.20 [-27.41, 13.01]
NCT01681849 20 10 7 25 6 6 5.6% -5.00 [-13.83, 3.83]
Pfizer588 -27.4 27.12 94 -27.9 28.42 94 6.3% 0.50 [-7.44, 8.44]
Pfizer589 -13.1 27.12 84 -15.4 28.42 82 5.9% 2.30 [-6.15, 10.75]
SKB627 -36.5 26.1 109 -30.8 25.37 103 7.3% -5.70 [-12.63, 1.23]
SKB650 -7.1 13.19 61 -9.9 15.62 61 9.3% 2.80 [-2.33, 7.93]
Tucker 2001 -35.5 24.6 151 -24.7 24.98 156 8.8% -10.80 [-16.35, -5.25]
Tucker 2003 60.28 26.15 25 55.5 29.07 10 1.5% 4.78 [-15.95, 25.51]
van der Kolk 2007 42.7 22.1 30 43.6 22.6 29 4.0% -0.90 [-12.31, 10.51]
Zohar 2002 -18.7 6.7 23 -13.5 6.6 19 10.7% -5.20 [-9.24, -1.16]
Subtotal (95% CI) 1186 1171 100.0% -4.61 [-7.30, -1.91]
Heterogeneity: Tau² = 13.37; Chi² = 30.34, df = 14 (P = 0.007); I² = 54%
Test for overall effect: Z = 3.35 (P = 0.0008)
-100 -50 0 50 100
Favours Medication Favours Control
Test for subgroup differences: Chi² = 17.10, df = 9 (P = 0.05), I² = 47.4%

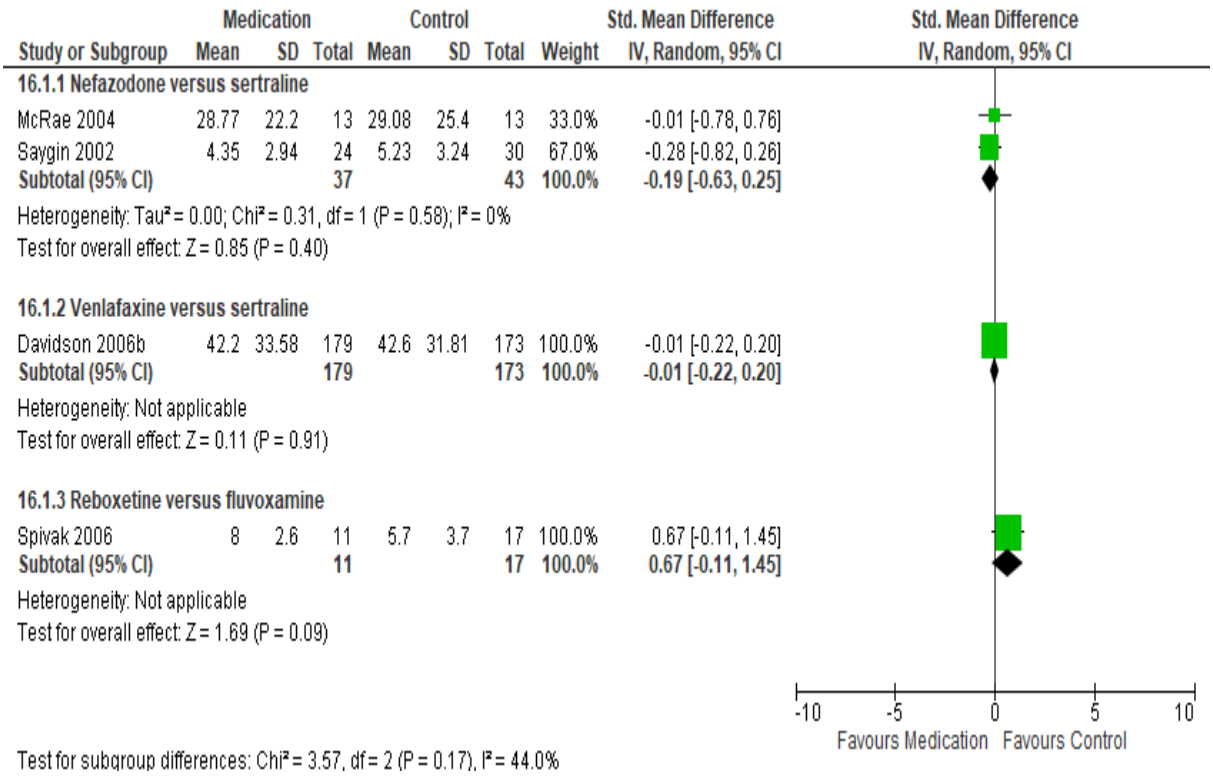
Analysis 15.2. Clinically Administered PTSD Scale (CAPS): CAPS Total score.

The proportion of dropouts due to adverse events was statistically significant across all medication classes compared to placebo (k = 39, RR 1.24; 95% CI 1.04 to 1.48, N = 4340; see Analysis 15.3), even though the dropout rate was low in the medication (10%) and placebo arm (7%). For this analysis data from one study reporting data for sertraline was excluded, because this study also reported data for the SNRI venlafaxine (Davidson 2006b).

In addition, the proportion of dropouts due to any cause across both the medication and placebo groups was similar (32% and 29%, respectively) and was comparable across subgroups (Chi^2 = 12.29, df = 12 (P = 0.42), I^2 = 2.3%; see Analysis 15.4). For this analysis data from one study was excluded with an additional arm of phenelzine to give preference to imipramine (Kosten 1991).

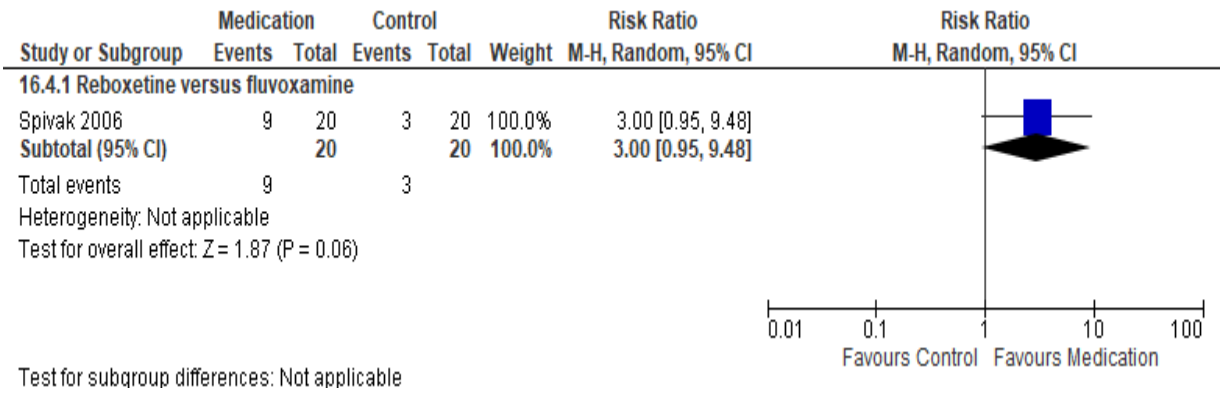
Comparison 16: Head-to-head comparisons

With regards to direct comparisons, no difference in the reduction of symptom severity was observed in the two head-to-head comparisons of nefazodone and sertraline (SMD -0.19 points, 95% CI -0.63 to 0.25, N = 80; see Analysis 16.1; McRae 2004; Saygin 2002), nor in the single trial comparing venlafaxine and sertraline (SMD -0.01 points, 95% CI -0.22 to 0.20, N = 352; see Analysis 16.1; Davidson 2006b) and the single trial comparing reboxetine and fluvoxamine (SMD 0.67 points, 95% CI -0.11 to 1.45, N = 28; see Analysis 16.1; Spivak 2006).



Analysis 16.1. Clinician administered scales: Symptom severity.

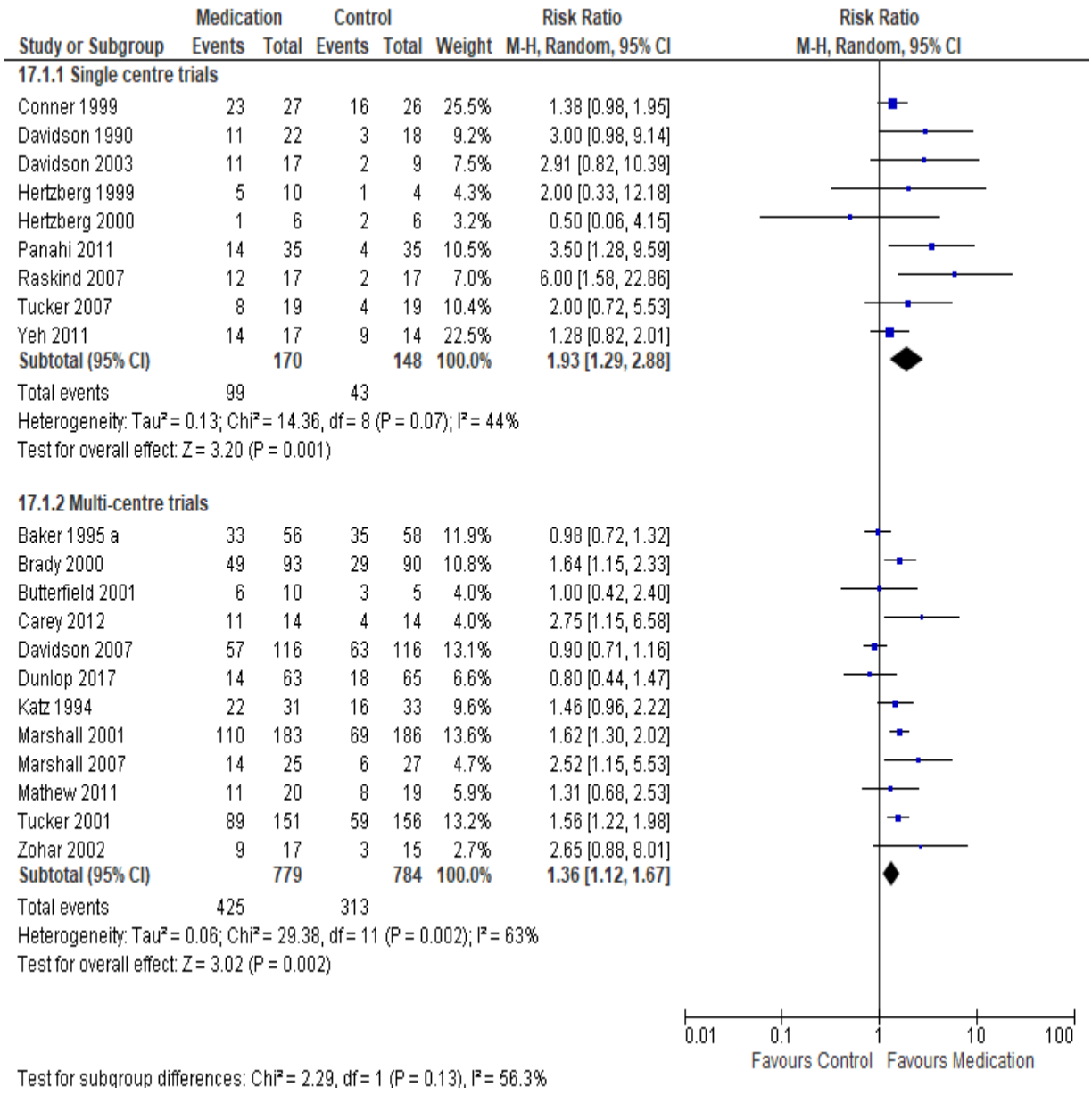
More patients dropped out of the reboxetine group (9/20, 45%) compared to the fluvoxamine group (3/20, 15%) due to treatment-emergent side effects, although no difference in dropout rates were found (k = 1, RR 3.00; 95% CI 0.95 to 9.48, N = 40; see Analysis 16.4; Spivak 2006).



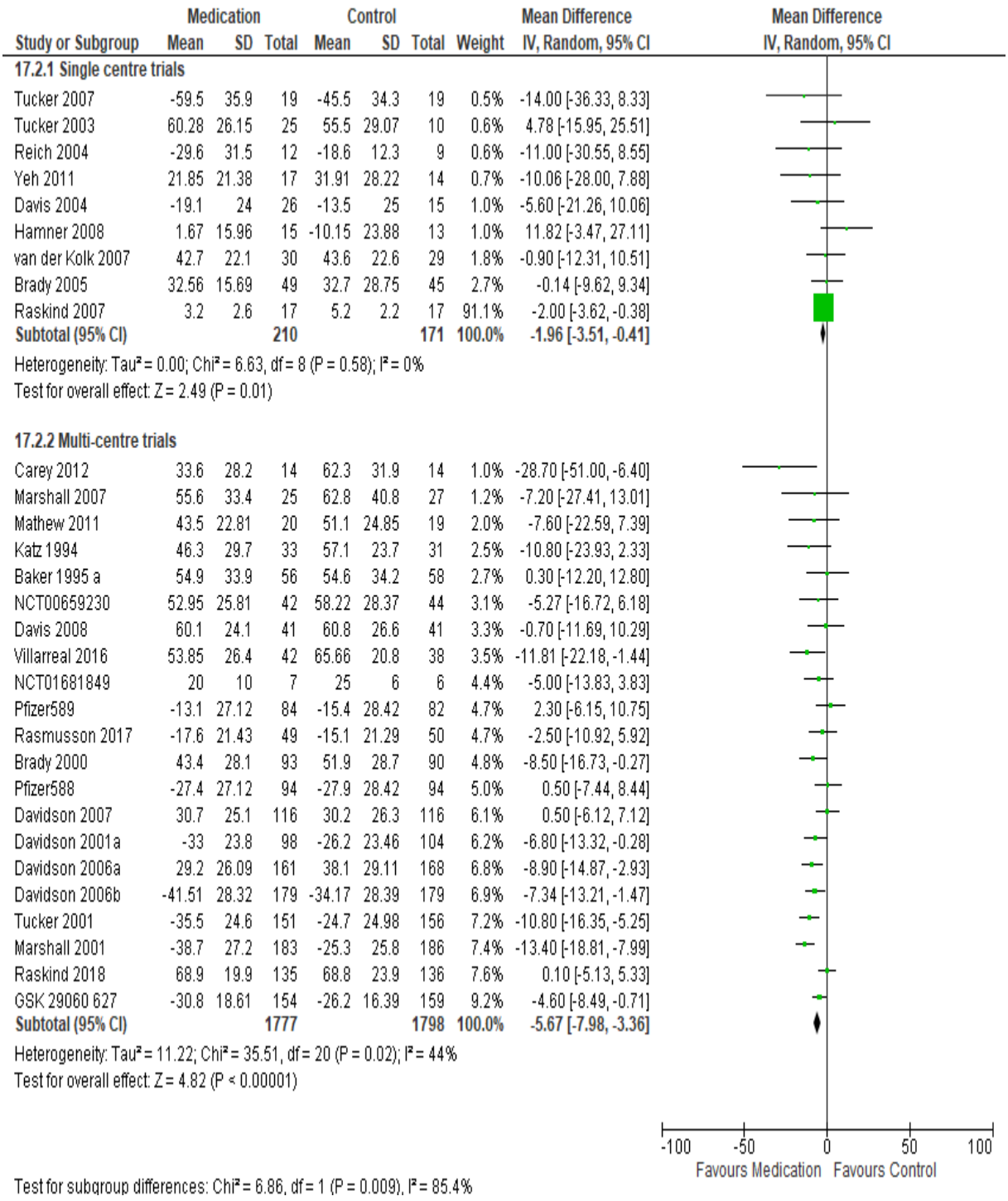
Analysis 16.4. Drop-out rate due to treatment emergent adverse effects: Reboxetine versus fluvoxamine.

17. Subgroup analyses - Methodological criteria

No evidence was observed in the analysis of treatment response for single centre trials (k = 9, RR 1.93; 95% CI 1.29 to 2.88, N = 318; see Analysis 17.1) and for multi-centre trials (k = 12, RR 1.36; 95% CI 1.12 to 1.67, N = 1563; see Analysis 17.1). Symptom severity in the 21 trials which took place across multiple centres for which the CAPS total score was available was reduced to a greater extent (Chi^2 = 35.51, df = 20 (P = 0.02); I^2 = 44%; see Analysis 17.2) than the nine trials conducted within single centres (Chi^2 = 6.63, df = 8 (P = 0.58); I^2 = 0%; see Analysis 17.2).



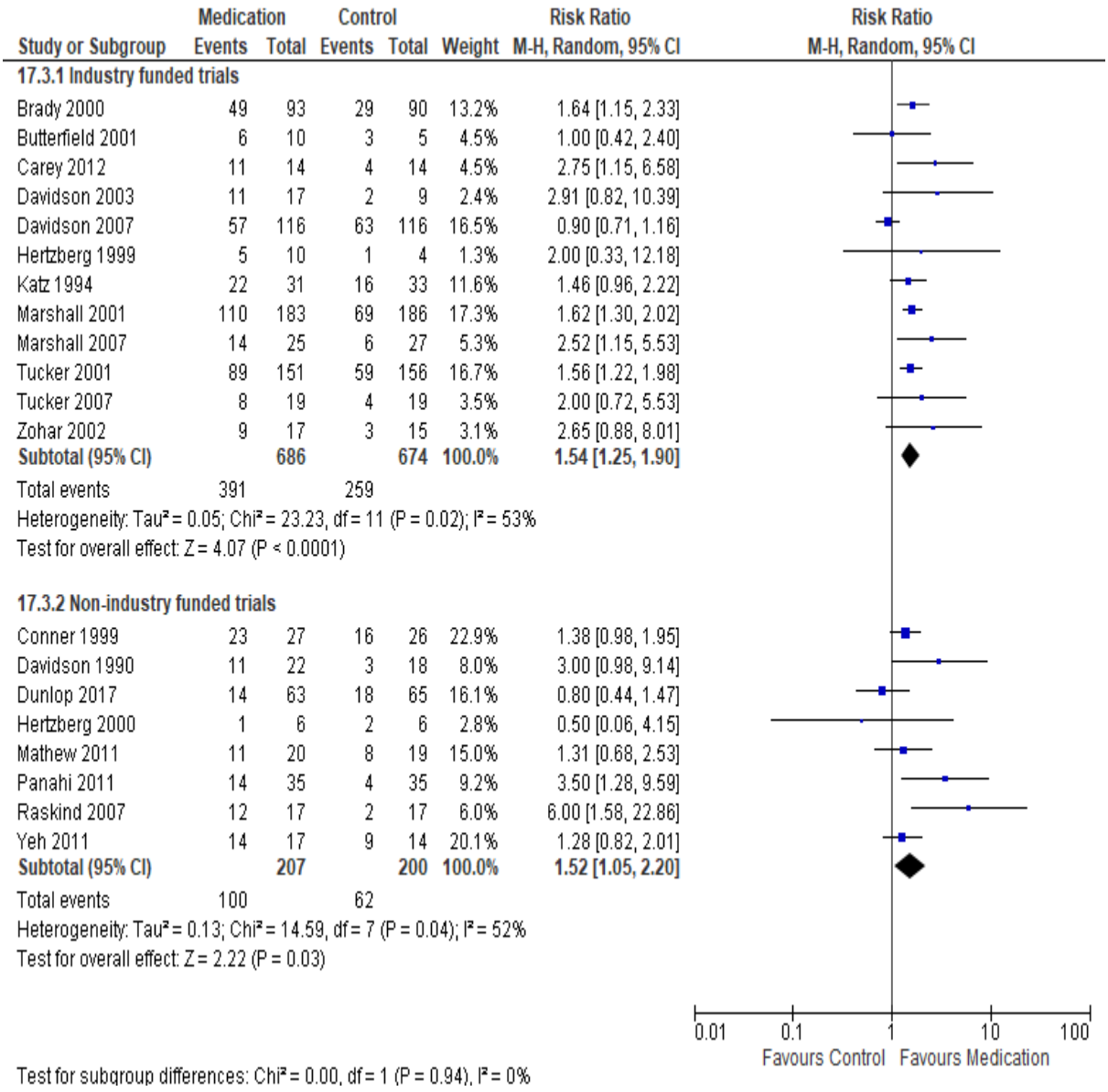
Analysis 17.1. Single versus multi-center trials (The Clinical Global Impressions: No. of responders).



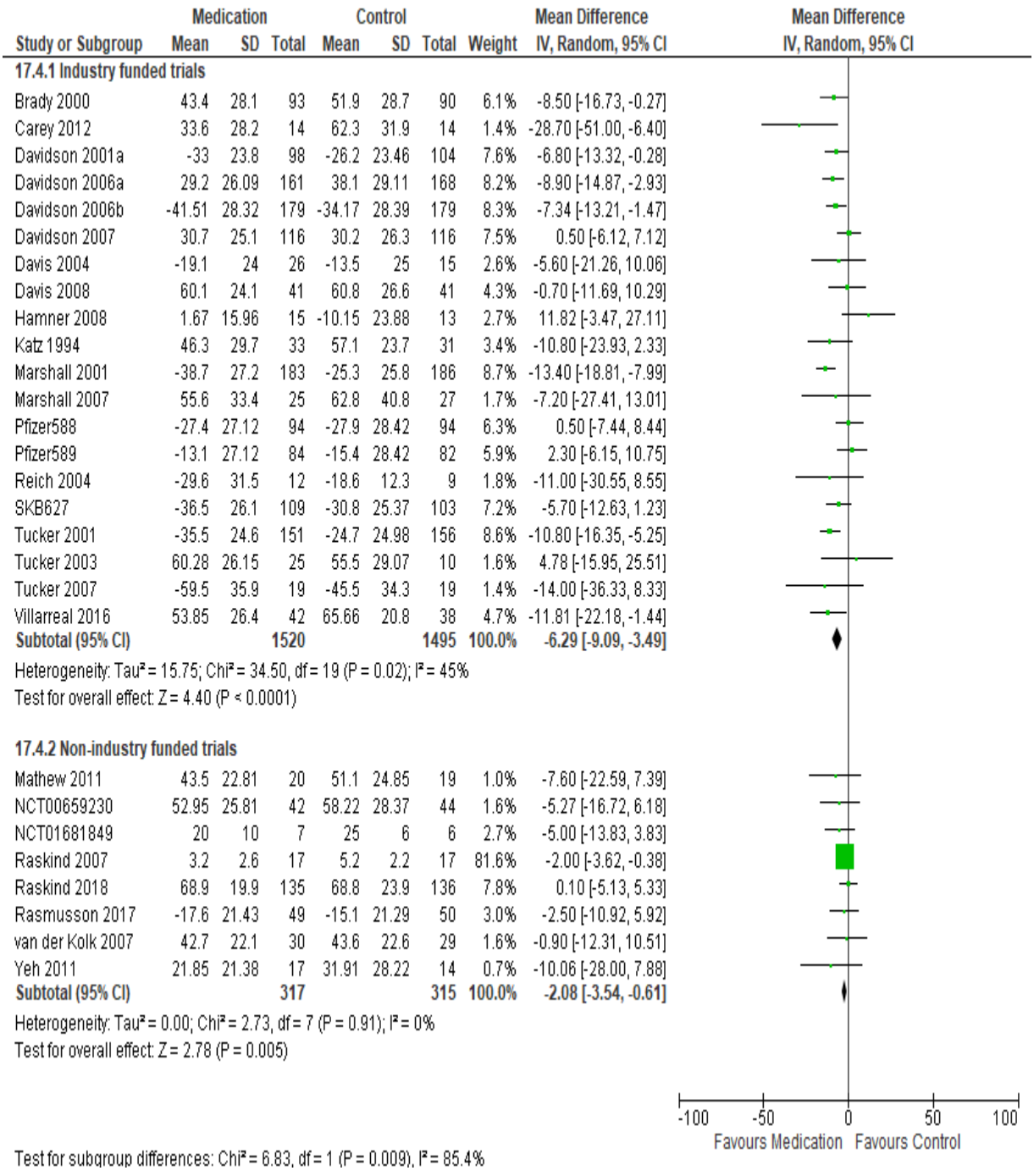
Analysis 17.2. Single versus multi-center trials (The Clinically Administered PTSD Scale: Total score).

There was evidence of a difference in treatment response based on source of funding (k = 20, RR -6.29; 95% CI -9.09 to -3.49, N = 3015; see Analysis 17.3) and to a lesser extent for non-

industry funded trials (k = 8, RR -2.08; 95% CI -3.54 to -0.61, N = 632; see Analysis 17.4) on the CAPS. This was also observed in the analysis of treatment response for industry funded trials versus non-industry funded trials ($Chi^2 = 6.83$, df = 1 (P = 0.009), $I^2 = 85.4\%$; see Analysis 17.3).



Analysis 17.3. Industry versus non-industry funded trials (The Clinical Global Impressions Scale: No. of responders).

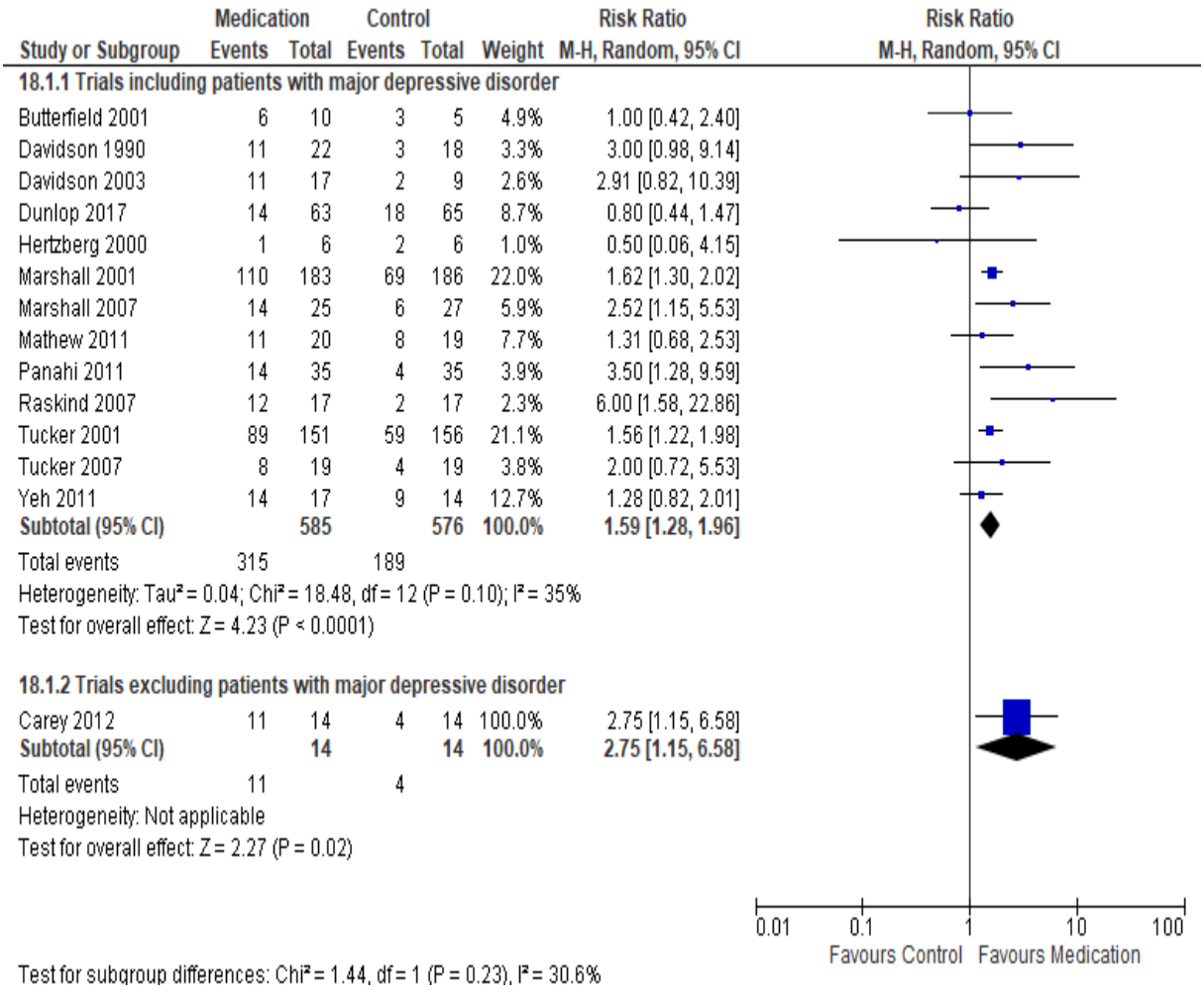


Analysis 17.4. Industry versus non-industry funded trials (The Clinically Administered PTSD Scale: Total score).

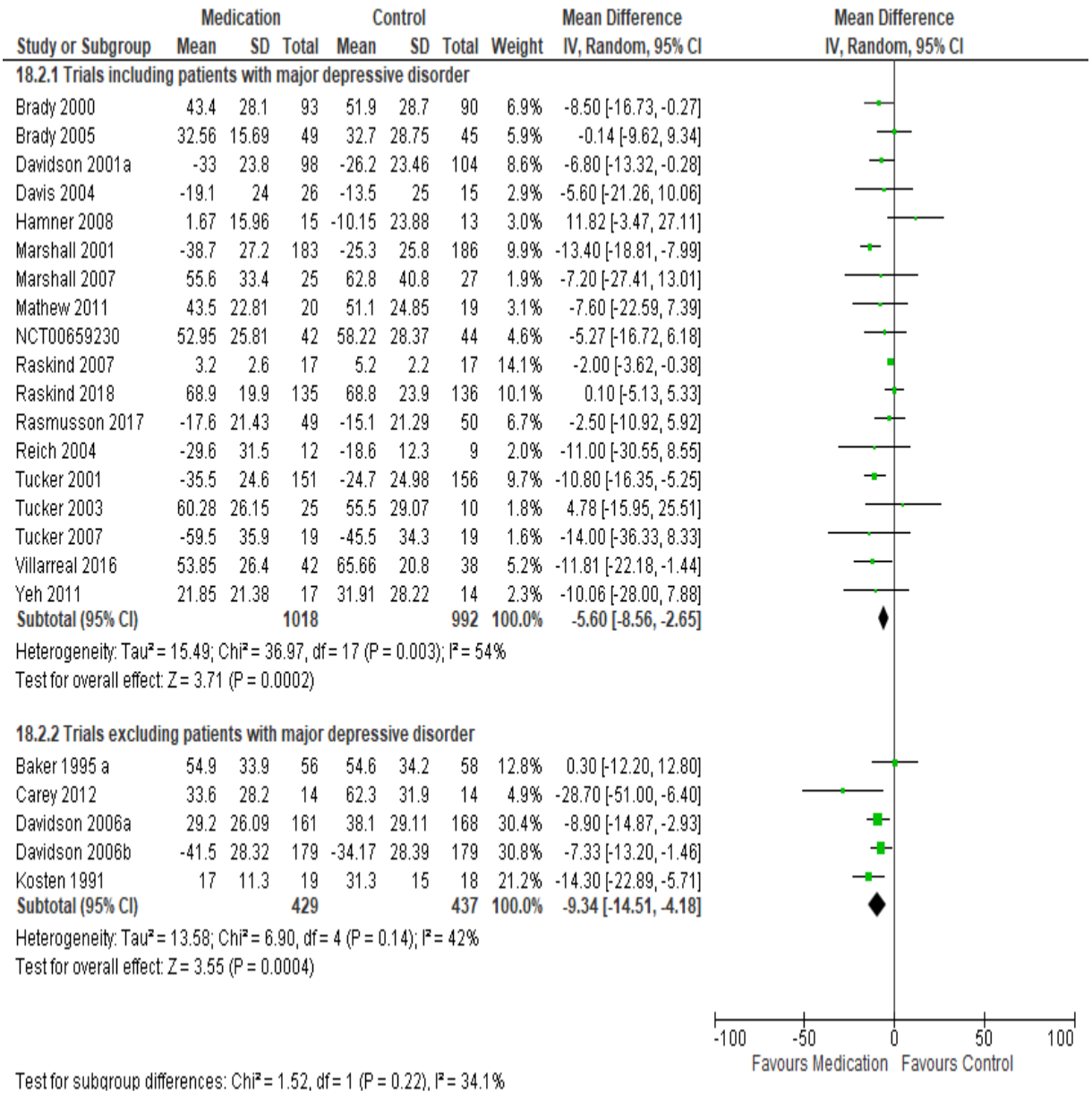
18. Subgroup analyses - Clinical criteria

There was no evidence of an effect of treatment response for trials which included depressed participants compared to those trials which did not ($Chi^2 = 1.44$, df = 1 (P = 0.23), $I^2 = 30.6\%$;

see Analysis 18.1). Symptom severity decreased to an equivalent extent ($Chi^2 = 1.52$, df = 1 (P = 0.22), $I^2 = 34.1\%$; see Analysis 18.2) in trials which included depressed participants (k = 18, MD -5.60 points, 95% CI −8.56 to -2.65, N = 2010; see Analysis 18.2) as in those which did not (k = 5, MD -9.34 points, 95% CI −14.51 to -4.18, N = 866; see Analysis 18.2).



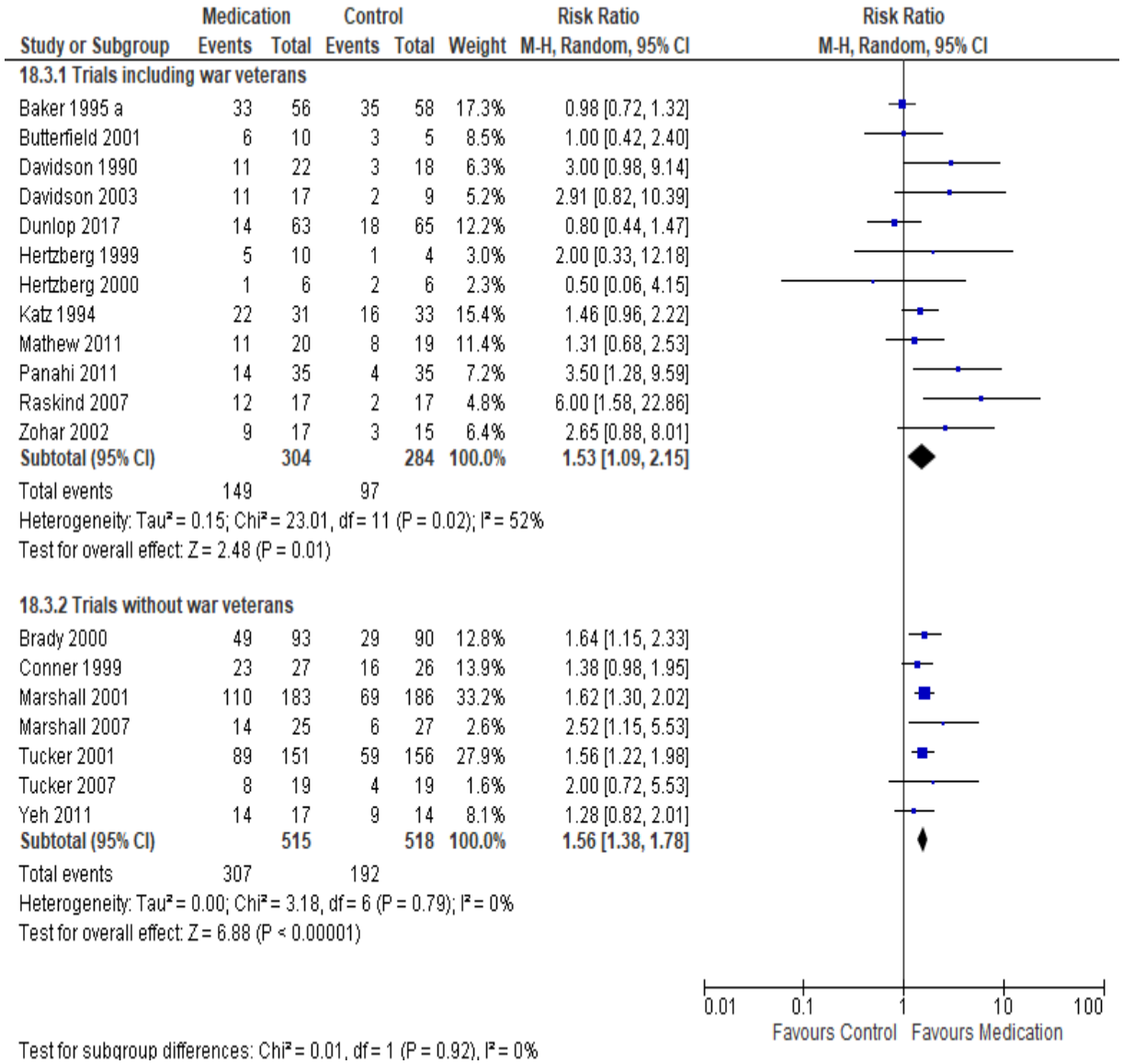
Analysis 18.1. Inclusion of major depression vs. non-inclusion: (The Clinical Global Impression Scale: No. of responders).



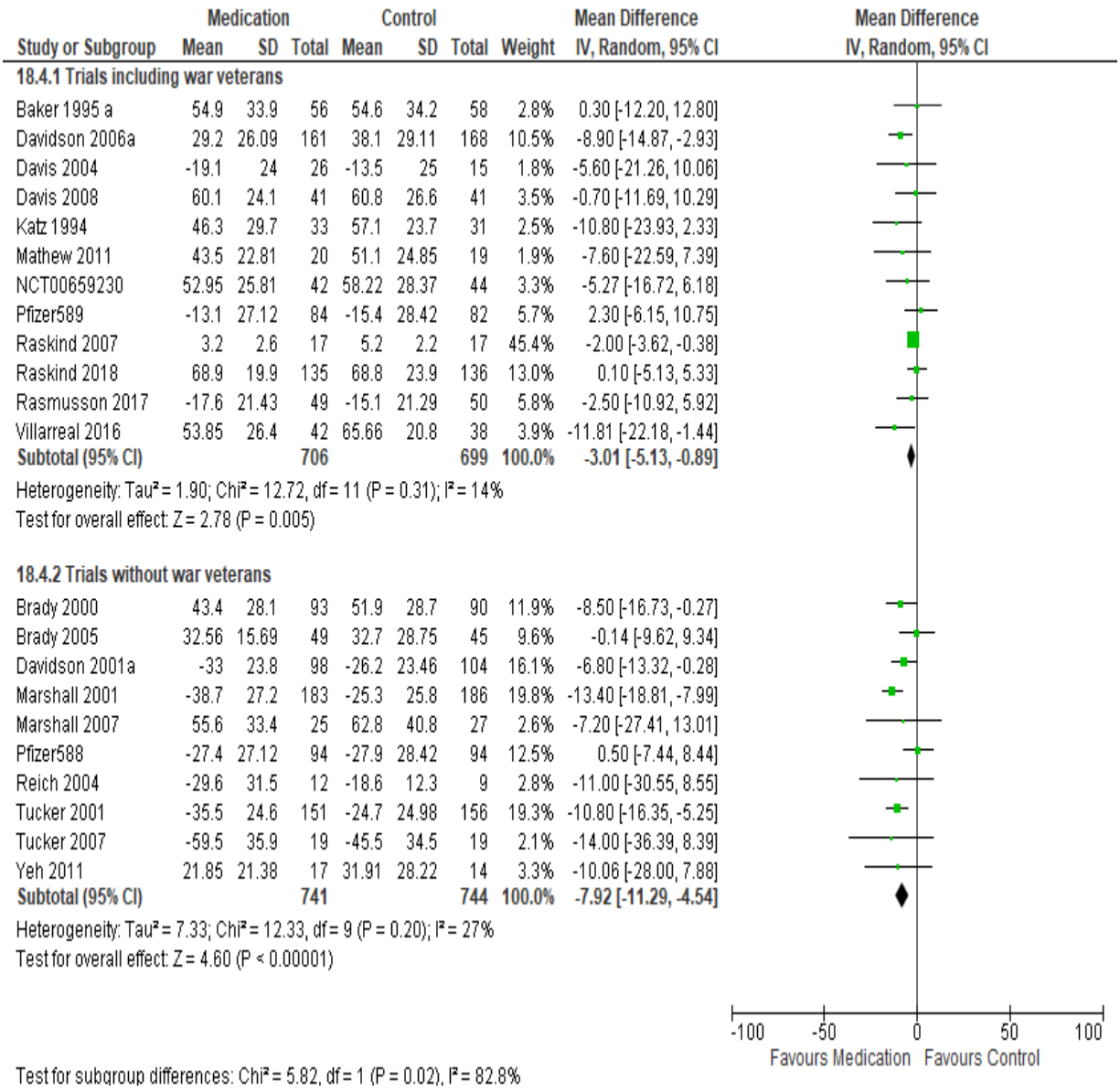
Analysis 18.2. Inclusion of major depression vs. non-inclusion: (The Clinically Administered PTSD Scale: Total score).

The difference between groups were not detected with respect to treatment response (Chi^2 = 0.01, df = 1 (P = 0.92), I^2 = 0%; see Analysis 18.3), however, trials including war trauma provided a greater response (Chi^2 = 23.01, df = 11 (P = 0.02); I^2 = 52%; see Analysis 18.3). RCTs which contained participants without war trauma demonstrated a significantly greater reduction in symptom severity following medication treatment than trials containing

participants with war trauma exposure (Chi² = 5.82, df = 1 (P = 0.02), I² = 82.8%; see Analysis 18.4). This difference was not evident for the individual subgroups, however (see Analysis 18.4). The finding of a difference in the reduction of symptom severity between trials with few war veterans versus those with many was not surprising, given the general characterisation of the war trauma subgroup of PTSD sufferers as more treatment resistant than other subgroups.



Analysis 18.3. Inclusion of war veterans versus non-inclusion: (The Clinical Global Impression Scale: No. of responders).

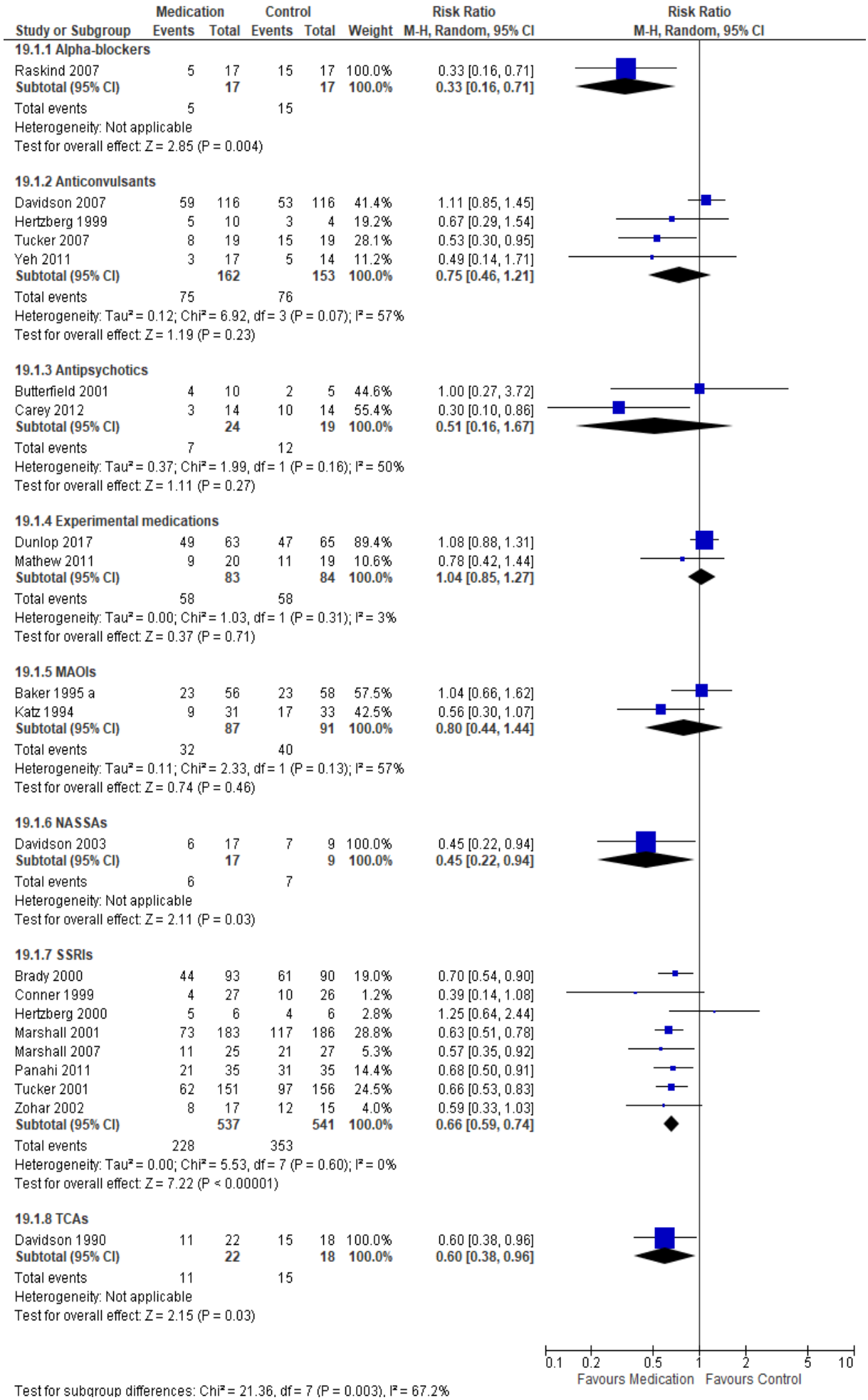


Analysis 18.4. Inclusion of war veterans versus non-inclusion: (The Clinically Administered PTSD Scale: Total score).

19. Sensitivity analyses

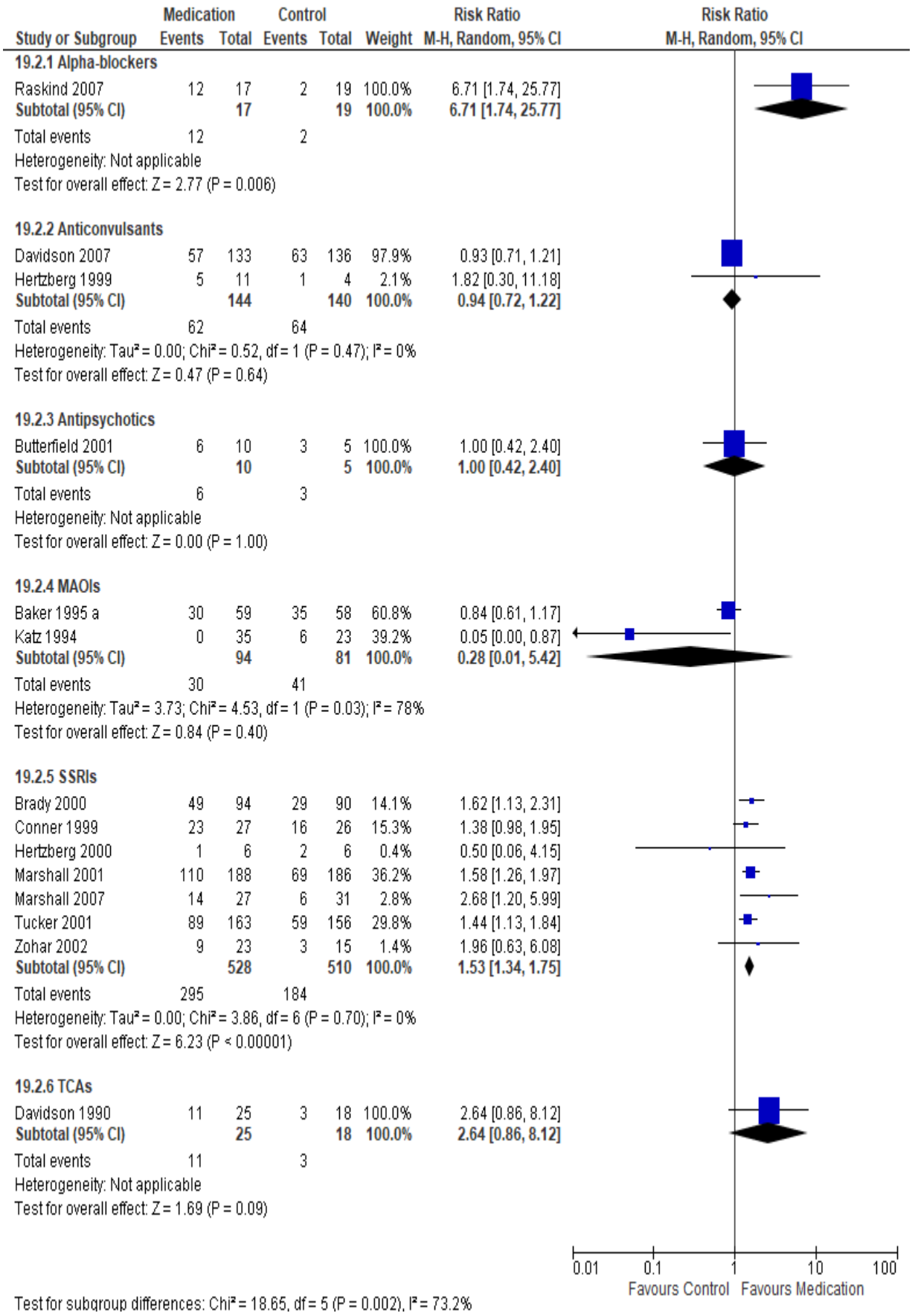
The comparison of the analysis of treatment efficacy in terms of treatment non-response as opposed to response on the CGI-I (or equivalent) revealed similar outcomes for both the overall short-term efficacy of medication (k = 21, RR 0.70; 95% CI 0.60 to 0.81, N = 1881; see Analysis 19.1), as well as for the efficacy of the SSRIs in treating PTSD (k = 8, RR 0.66; 95% CI 0.59 to 0.74, N = 1078; see Analysis 19.1). However, the use of treatment non-response as

a summary statistic indicated that the alpha–blocker prazosin, anticonvulsants, antipsychotics, experimental medications, MAOIs, NaSSAs and the TCA amitriptyline were no more effective than placebo.

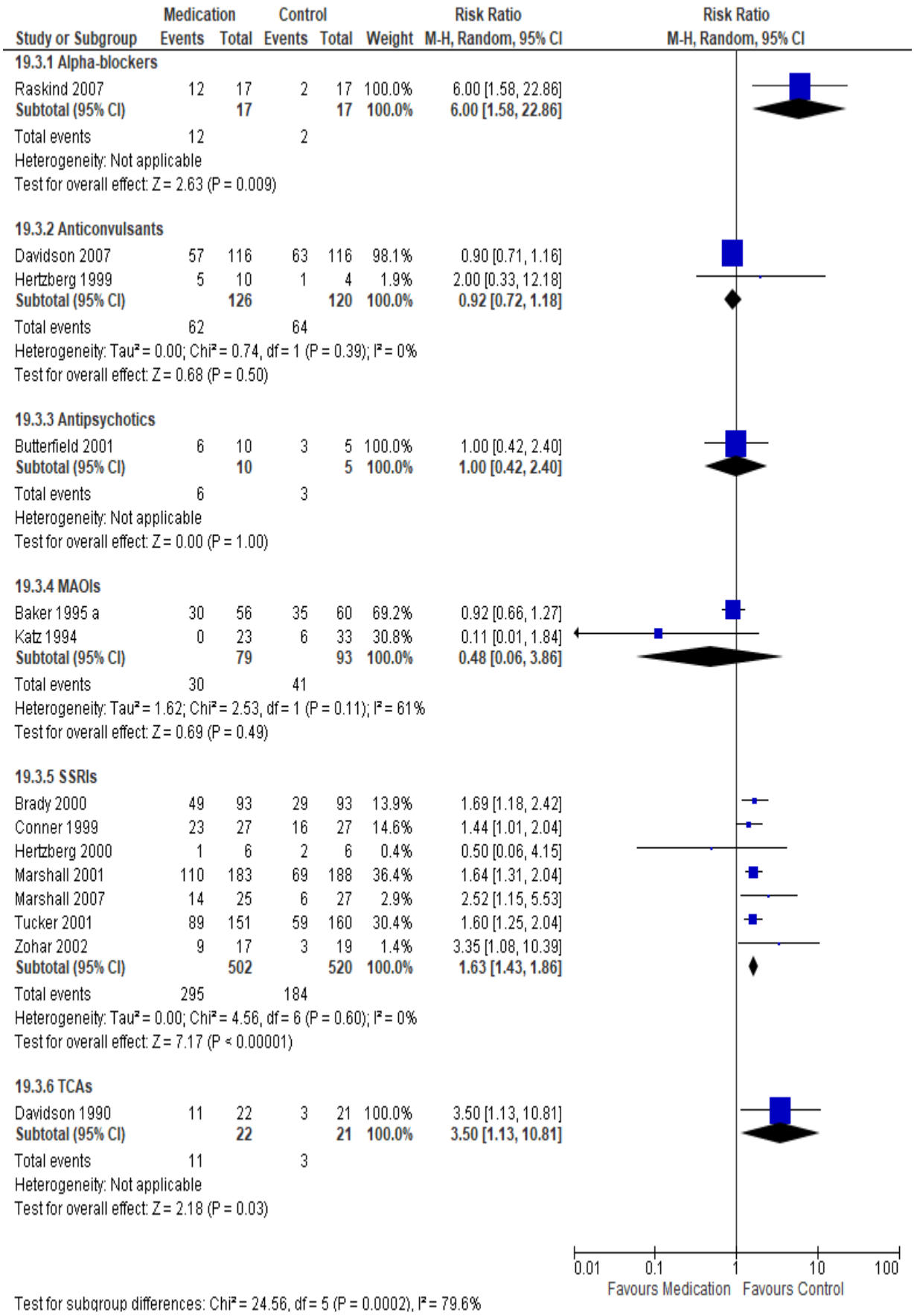

Medication
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
19.1.1 Alpha-blockers
Raskind 2007 5 17 15 17 100.0% 0.33 [0.16, 0.71]
Subtotal (95% CI) 17 17 100.0% 0.33 [0.16, 0.71]
Total events 5 15
Heterogeneity: Not applicable
Test for overall effect: Z = 2.85 (P = 0.004)
19.1.2 Anticonvulsants
Davidson 2007 59 116 53 116 41.4% 1.11 [0.85, 1.45]
Hertzberg 1999 5 10 3 4 19.2% 0.67 [0.29, 1.54]
Tucker 2007 8 19 15 19 28.1% 0.53 [0.30, 0.95]
Yeh 2011 3 17 5 14 11.2% 0.49 [0.14, 1.71]
Subtotal (95% CI) 162 153 100.0% 0.75 [0.46, 1.21]
Total events 75 76
Heterogeneity: Tau² = 0.12; Chi² = 6.92, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 1.19 (P = 0.23)
19.1.3 Antipsychotics
Butterfield 2001 4 10 2 5 44.6% 1.00 [0.27, 3.72]
Carey 2012 3 14 10 14 55.4% 0.30 [0.10, 0.86]
Subtotal (95% CI) 24 19 100.0% 0.51 [0.16, 1.67]
Total events 7 12
Heterogeneity: Tau² = 0.37; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 1.11 (P = 0.27)
19.1.4 Experimental medications
Dunlop 2017 49 63 47 65 89.4% 1.08 [0.88, 1.31]
Mathew 2011 9 20 11 19 10.6% 0.78 [0.42, 1.44]
Subtotal (95% CI) 83 84 100.0% 1.04 [0.85, 1.27]
Total events 58 58
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 0.37 (P = 0.71)
19.1.5 MAOIs
Baker 1995 a 23 56 23 58 57.5% 1.04 [0.66, 1.62]
Katz 1994 9 31 17 33 42.5% 0.56 [0.30, 1.07]
Subtotal (95% CI) 87 91 100.0% 0.80 [0.44, 1.44]
Total events 32 40
Heterogeneity: Tau² = 0.11; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.74 (P = 0.46)
19.1.6 NASSAs
Davidson 2003 6 17 7 9 100.0% 0.45 [0.22, 0.94]
Subtotal (95% CI) 17 9 100.0% 0.45 [0.22, 0.94]
Total events 6 7
Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.03)
19.1.7 SSRIs
Brady 2000 44 93 61 90 19.0% 0.70 [0.54, 0.90]
Conner 1999 4 27 10 26 1.2% 0.39 [0.14, 1.08]
Hertzberg 2000 5 6 4 6 2.8% 1.25 [0.64, 2.44]
Marshall 2001 73 183 117 186 28.8% 0.63 [0.51, 0.78]
Marshall 2007 11 25 21 27 5.3% 0.57 [0.35, 0.92]
Panahi 2011 21 35 31 35 14.4% 0.68 [0.50, 0.91]
Tucker 2001 62 151 97 156 24.5% 0.66 [0.53, 0.83]
Zohar 2002 8 17 12 15 4.0% 0.59 [0.33, 1.03]
Subtotal (95% CI) 537 541 100.0% 0.66 [0.59, 0.74]
Total events 228 353
Heterogeneity: Tau² = 0.00; Chi² = 5.53, df = 7 (P = 0.60); I² = 0%
Test for overall effect: Z = 7.22 (P < 0.00001)
19.1.8 TCAs
Davidson 1990 11 22 15 18 100.0% 0.60 [0.38, 0.96]
Subtotal (95% CI) 22 18 100.0% 0.60 [0.38, 0.96]
Total events 11 15
Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)
0.1 0.2 0.5 1 2 5 10
Favours Medication Favours Control
Test for subgroup differences: Chi² = 21.36, df = 7 (P = 0.003), I² = 67.2%

Analysis 19.1. Clinical Global Impressions scale improvement item (The Clinical Global Impression Scale): non-response.

The number of participants responding to medication was significantly higher relative to the placebo control in both the worst case scenario (k = 14, RR 1.37; 95% CI 1.09 to 1.73, N = 1591; see Analysis 19.2) where those participants from the medication group who were not included in the analysis were regarded as non-responders, and in the best case scenario ((k = 14, RR 1.47; 95% CI 1.61 to 1.87, N = 1532; see Analysis 19.3), in which those participants excluded from the placebo control were regarded as non-responders. The overlap in the confidence intervals for these two outcomes indicates that loss to follow up is unlikely to have influenced assumptions made about the overall efficacy of medication.



Analysis 19.2. "Worst case" loss to follow up analysis.



Analysis 19.3. "Best case" loss to follow up analysis.

19. Publication bias

The distribution of trials on a funnel plot for treatment response (see Figure 4) and symptom severity (see Figure 5) provides no evidence of substantial publication bias.

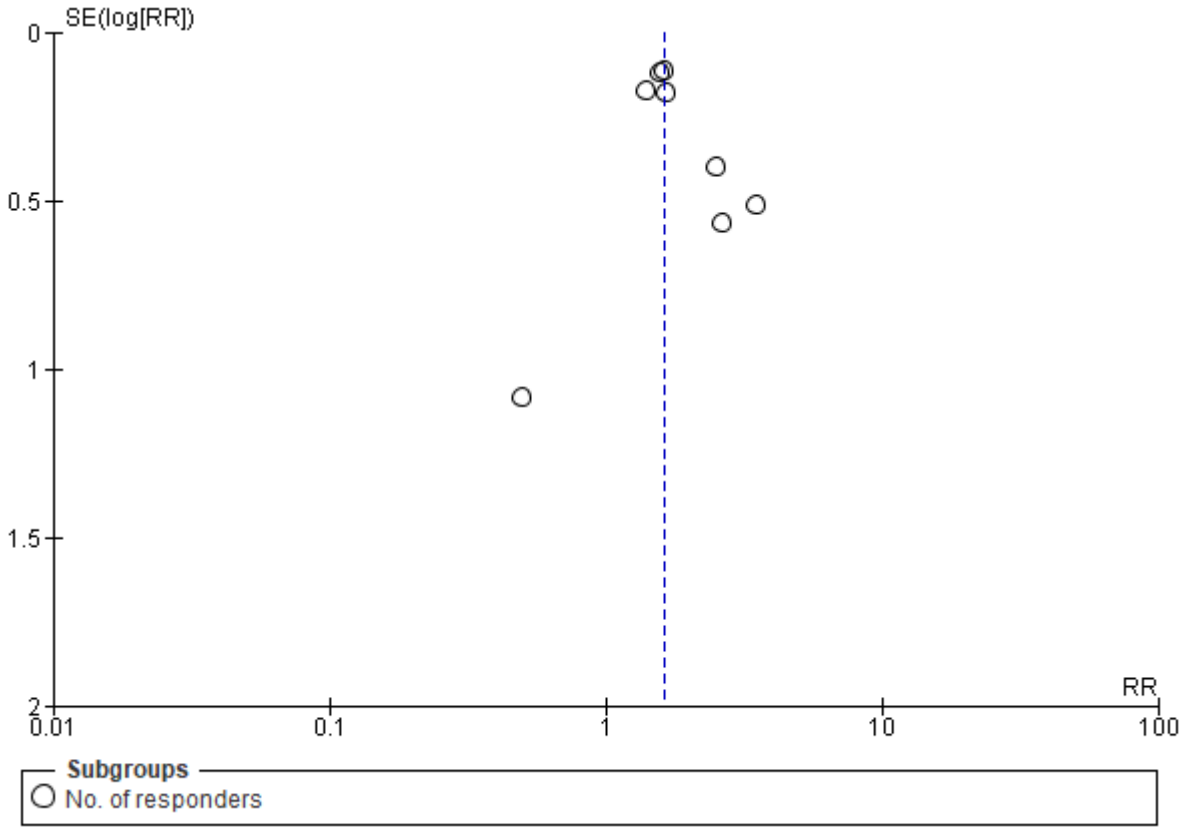


Figure 4. Funnel plot of comparison: 13 Comparison 13: SSRIs versus placebo, outcome: 13.1 Clinical Global Impressions scale improvement item (CGI-I).

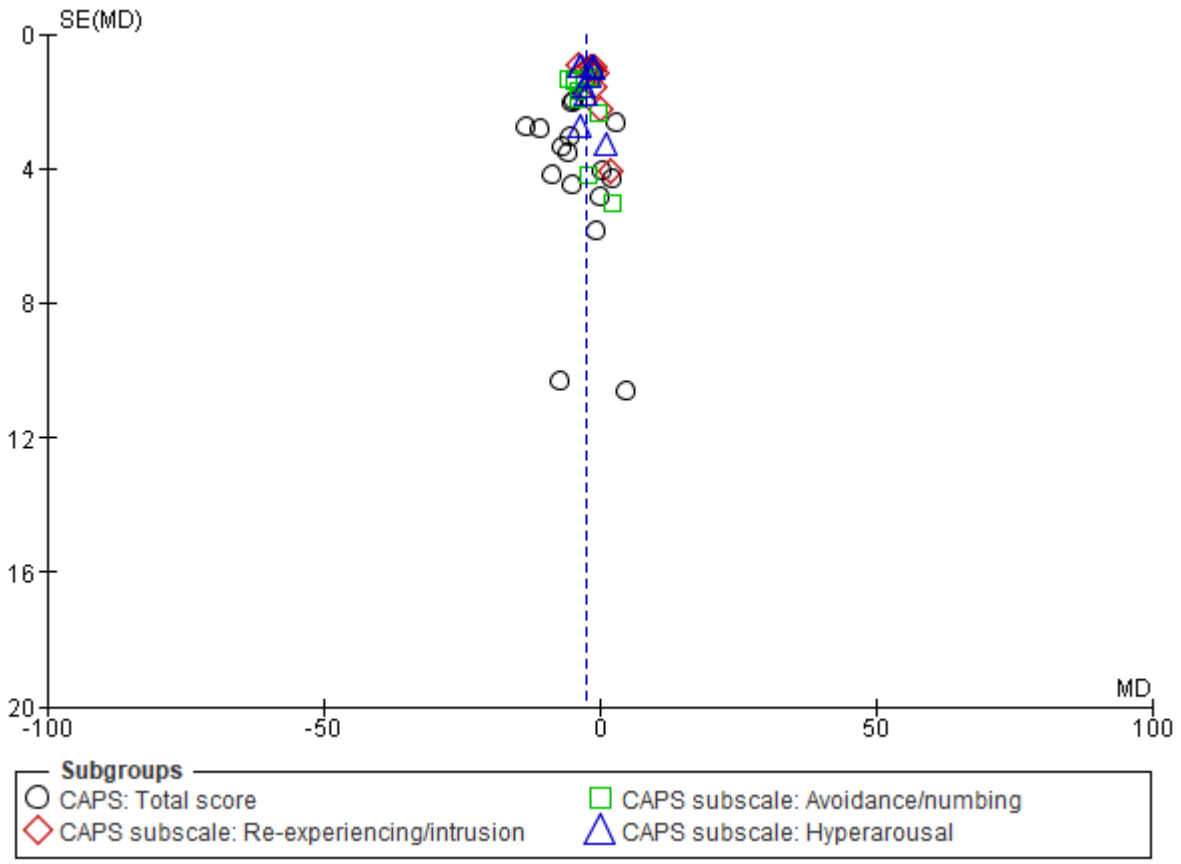


Figure 5. Funnel plot of comparison: 13 Comparison 13: SSRIs versus placebo, outcome: 13.3 Clinically Administered PTSD Scale (CAPS): reduction of PTSD symptoms.

DISCUSSION

Summary of main results

Most evidence was for the SSRIs (i.e. citalopram, fluoxetine, paroxetine, and sertraline) and was moderate in quality. Similarly, low-quality evidence of efficacy was found for the alpha-blocker prazosin and the TCA amitriptyline. The remaining medication classes did not provide evidence of treatment efficacy.

Evidence of efficacy for reducing PTSD symptoms was observed for the alpha-blocker prazosin (based on low quality evidence), antipsychotics (based on low quality evidence) and

the SSRIs (based on very low quality evidence) on the CAPS. Medication was significantly more effective than placebo across the three symptom clusters which characterise PTSD (re-experiencing/intrusion, avoidance/numbing, and hyperarousal) as assessed by the CAPS subscales for the SSRIs. Evidence of a difference was also found for reducing PTSD symptoms on the CGI-S and SIP for the antipsychotics, the SNRI venlafaxine and the SSRIs, as well as for the MAOIs, the SNRI venlafaxine and SSRIs on the self rated IES and DTS. Similarly, direct comparisons of sertraline and nefazodone, and venlafaxine and sertraline demonstrated that these medications were equally effective in reducing PTSD symptom severity.

Individuals diagnosed with PTSD who were treated with SSRIs were more likely to withdraw from treatment due to treatment-related adverse events. Nevertheless, the absolute proportion of individuals dropping out from treatment due to adverse events was low (8%), with the difference in dropouts from the controls group of two percentage points unlikely to be clinically significant. The evidence for this outcome was based on moderate quality evidence. The review also found a difference in dropouts due to any cause for the experimental medications, although dropout rates were low (12%).

Some evidence was found that war veterans are more resistant to pharmacotherapy than other patient groups, at least with regards to the reduction of symptom severity. A difference in the inclusion of major depression versus non-inclusion was also observed on the CGI-I and CAPS, as well as for the remaining sub groups analyses (multi centre versus single centre, and industry funded versus non industry funded).

Overall completeness and applicability of evidence

Completeness of evidence

The current evidence base of RCTs is unable to demonstrate superior efficacy or acceptability for any particular medication class. Although some have suggested that the SSRIs are more effective than older antidepressants (Dow 1997; Penava 1996), class membership did not contribute significantly to the variation observed in symptom severity outcomes between trials, while the confidence intervals for the summary statistic of responder status on the SSRI trials overlapped with that of the alpha-blocker, antipsychotics, RIMA and TCA trials. Similarly, direct comparisons of sertraline and nefazodone, and venlafaxine and sertraline demonstrated that these medications were equally effective in reducing PTSD symptom severity. Although the SSRIs have often been said to have superior tolerability in comparison to older medication classes, this was not readily apparent on analysis of drop-out rates due to treatment emergent side-effects in medication versus placebo groups. However, it should be emphasised that drop-out rates due to adverse events may not always provide an accurate measure of medication tolerability (Loke 2005). In addition, it is important to be aware of the need for careful monitoring after initiation of SSRIs (CSM 2004). Nevertheless, the SSRI trials constitute the bulk of the evidence for the efficacy of medication in treating PTSD, both in terms of the number of studies and their size. The finding of the effectiveness of the SSRIs were also more robust to differences in the particular summary statistic employed than was the case for the rest of the medication trials. It is therefore reasonable to support the expert consensus (NICE 2018; Foa 1999; Ballenger 2000; Ballenger 2004) that SSRIs constitute the first line medication choice in PTSD.

Applicability of evidence

The outcomes of this review may be generalisable to a diverse range of settings. Studies were conducted in both single and multi-centres and included both men and women across a wide age range. Differences in treatment delivery, as well as the background and training of study investigators and outcome assessors, increases the likelihood that the findings of this review are applicable to a range of countries in different income brackets. However, given the high prevalence and enormous personal and societal costs of PTSD, there are still relatively few RCTs of pharmacotherapy for PTSD. No controlled trials were found in paediatric or geriatric subjects. With few exceptions (Baker 1995 a; Reist 1989; Braun 1990; Davidson 1990; Hertzberg 1999; Hertzberg 2000; Brady 2005), trials have excluded patients with comorbid substance use. One such exception to be included in this review was an RCT of sertraline in treating concurrent PTSD and alcoholism (Brady 2005), in which little difference was found in the efficacy of medication versus placebo in reducing symptom severity. Also, although outside the scope of the current review, there seem to be few RCTs of the treatment of traumatised patients prior to their meeting criteria for PTSD (Robert 1999; Pitman 2002; Mellman 2002; Schelling 2004), a potentially important clinical area.

Quality of the evidence

Fifteen RCTs had a high risk of bias related to at least one aspect of study design, with the most commonly observed weakness having to do with attrition bias (Butterfield 2001; Chung 2004; Connor 2006; Davis 2008; Feder 2014; Hertzberg 1999; Kosten 1991; Martenyi 2002b; NCT01681849; Reich 2004; Saygin 2002; Smajkic 2001; Spivak 2006; van der Kolk 1994; Villarreal 2016). Lack of blinding for outcome assessors may also have influenced the detection of treatment effects in three trials (Chung 2004; Saygin 2002; Smajkic 2001). There was also evidence for selective reporting bias in Davis 2008, Feder 2014 and Villarreal 2016.

Even though the SSRIs were the best-represented medication class, most of these trials scored unclear for randomisation procedures.

Judgements of response to treatment with the SSRIs were based on evidence rated as being of moderate quality. Therefore, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (see Summary of findings table 12). Findings of treatment efficacy for the alpha-blocker prazosin and the TCA amitriptyline were based on evidence rated as being of low quality (see Summary of findings table 1; Summary of findings table 13), indicating that additional data from further studies may change the size of the treatment effect estimate for these medication classes, as well as ones confidence in that estimate of effect. For the outcome of symptom severity measured by the CAPS the SSRIs were based on evidence rated as being of very low quality (see Summary of findings table 12). This review is therefore very uncertain about this estimate of effect. Findings of treatment efficacy for the alpha-blocker prazosin and the antipsychotics for this outcome was based on evidence rated as being of low quality (see Summary of findings table 1; Summary of findings table 3). Thus, further research is very likely to have an important impact on ones confidence in the estimate of effect and is likely to change the estimate. The most common reasons for downgrading studies were imprecise effect estimates, low response rates, small sample size, a rating of high or unclear bias for study design (based on 50% attrition rates across groups, detection, and selective reporting bias), and inconsistency between studies (indicated by heterogeneity between the medication and placebo group).

Although a recent guideline noted that, with few exceptions, the overall effect size for medication trials of PTSD failed to exceed the limit of 0.5 defined as indicative of clinical effectiveness (NICE 2018; NICE 2005), I would caution that there is no direct translation

between the effect size statistic and assessments of clinical effectiveness and that future research is needed to establish what constitutes a minimally clinically important difference on these outcomes. The findings here that the CGI-I response rate on medication and on placebo, support the growing clinical consensus that medication does have an important role in the treatment of PTSD.

Neither the potential clinical (presence of combat trauma, comorbid depression) or methodological (single versus multi-centre trials, industry versus non-industry funding) predictors of medication response tested in this review can account for the substantial proportion of patients who do not appear to respond to medication. The finding that symptom severity is reduced to a greater extent in the multi-centre than the single centre trials should be interpreted with caution, due to the marginal significance of this finding. The failure to detect an association between the presence of participants with comorbid major depression and treatment efficacy indicates that medications are unlikely to exert their effects in PTSD indirectly via a reduction in depressive symptoms. This review found some evidence that war veterans are more resistant to pharmacotherapy than other patient groups, with regards to response and the reduction of symptom severity. This was even though several RCTs with war veteran samples were excluded from this review (Hamner 1997; Hamner 2003; Stein 2002; Monnelly 2003; Raskind 2003; Bartzokis 2005) (see Characteristics of excluded studies), and that it was not possible to classify certain large-scale unpublished trials according to trauma type (SKB627; SKB650). Given the heterogeneous phenomenology of PTSD, it remains crucial to determine the factors which do predict response to medication, and to delineate whether certain medications are more effective for particular symptom sets (including symptoms such as psychosis (Hamner 1996), dissociation (Fichtner 1990; Marshall 1998b) and

vulnerability to stress (Connor 1999)). Future RCTs and meta-analyses should attempt to address such questions in greater detail.

Potential biases in the review process

An extensive search was conducted for studies meeting rigorous inclusion criteria and I repeatedly attempted to obtain missing data from the trial investigators. Nevertheless, there were insufficient data available to assess the extent to which selective publication may have introduced bias in the findings for medication classes besides the SSRIs.

Furthermore, meta-analysis has limitations, and these should be considered (Bailar 1997); certainly, this methodology is by no means a substitute for clinical research. This is especially the case when there is evidence of the possibility that smaller trials with negative outcomes are not being published. Furthermore, the context of clinical practice differs from controlled trials in many respects, not the least being the inclusion of more complex patients (including patients with possible "secondary gain" from symptoms, a group that has been specifically excluded from more recent RCTs (Brady 2000)) and the possible need for polypharmacy in a subgroup of PTSD patients (Kolb 1984; Kinzie 1989; Burdon 1991; Hargrave 1993; Leyba 1998). Moreover, methodological shortcomings, such as failure to employ independent outcome assessors in trials which adjust medication dosage based on side-effect severity, and inadequate statistical methods of compensating for patient withdrawals, risk undermining the best efforts to minimise bias in the findings of systematic reviews of health care interventions.

Agreements and disagreements with other studies or reviews

The finding in this review of moderate to substantial variability in the response of participants with PTSD to pharmacotherapy is likely to reflect real differences in efficacy across different

medication and differences brought on by trial methodology and the clinical characteristics of patients. In comparing medication classes in terms of benefit of effect and adverse responses to medication, the data included in this review are consistent with findings from other systematic reviews and meta-analyses in identifying the SSRIs as first line agents for the treatment of PTSD (Ipser 2012; Hoskins 2015), bearing in mind that the finding of efficacy for the SSRIs reported in this review is based on a considerably larger database.

This review classified medications based on their putative mechanisms of action (taken from CCMD antidepressant classification map) (Davies 2015), and they do not necessarily map onto the drug classification schemes employed in other reviews. Nevertheless, the review confirms the efficacy of the SSRIs and TCAs.

The alpha-blocker prazosin was also effective in PTSD, but the finding is based on two trials (Raskind 2007; Raskind 2018). It is therefore reasonable to view this drug as a second-line agent.

Author conclusions

Implications for practice

Medication treatments can be effective in PTSD, acting to reduce its core symptoms, and should be considered as part of the treatment of this disorder. The existing evidence base of RCTs includes a heterogenous sample of participants with a range of different traumas, trauma duration and severity, and comorbidity. The greatest number of trials showing efficacy to date, as well as the largest, have been with the SSRIs. Little or no evidence was observed for the rest of the medication classes. It is also noteworthy that this review included short term trials investigating SSRIs compared to placebo and that treatment duration can increase the incidence

of withdrawal amongst patients (Weller, 2005), in addition to side effects like dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, weight, sexual dysfunction, bleeding, and hyponatremia (Wang, 2018). Discontinuation of these agents is also difficult leading to inappropriate long-term use (Eveleigh, 2018). Although there was only one RCT in which psychotherapy was compared with pharmacotherapy, from a clinical perspective it is as well to remember the possible value of this modality alone or in combination with pharmacotherapy.

Implications for research

Given the prevalence and costs of PTSD, there is a need for further controlled clinical trials in the treatment of this disorder. The differential efficacy and acceptability of different classes of medication, including newer agents potentially useful in this disorder (e.g. escitalopram, tiagabine, tianeptine, topiramate), requires study. Questions for future research also include the precise effects of medication on quality of life measures, appropriate dose and duration of medication, and determining factors which predict response to medication. Further research on the value of medication in PTSD in different trauma groups, in paediatric and geriatric subjects, in patients with comorbid substance use, and in treatment-refractory patients is needed. Clinical trials to determine the possible benefits of early (prophylactic), combined (with psychotherapy), and long-term (maintenance) intervention in PTSD may also be valuable.

In the next chapter I will explore the NMA approach and the available evidence of published NMAs of pharmacotherapy for the treatment of common mental disorders.

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CHAPTER 4.

A systematic review of network meta-analyses for pharmacological treatment of common mental disorders.

Chapter four consists of a comprehensive outlook on the amount of studies within psychology and psychiatry that have been published and have used the new meta-analytic approach (i.e. network meta-analysis, NMA), including the assessment of the quality of these published NMAs. A specific focus was also placed on what the NMA approach entails and on the reporting of rankings and/or probabilities which was lacking throughout the published NMAs included in the review.

BACKGROUND

In previous chapters I conducted a Cochrane systematic review and meta-analysis for the pharmacotherapy of PTSD in adults. In this chapter I conduct a systematic review of published NMAs of common mental disorders and assesses the quality of these NMAs. I also assess the risk of bias of published SAD and PTSD NMAs in particular .

Worldwide, psychiatric disorders have become a priority and are the leading cause of disability (Whiteford, 2013). Globally, depression and anxiety disorders account for the fifth highest burden of disease based on disability-adjusted life years (Whiteford, 2013). According to one recent meta-analysis of the epidemiology of common mental disorders (major depression, generalized anxiety disorder (GAD), panic disorder (PD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD) and specific phobia) these disorders occur globally in 29.2% of people across their lifetime (Steel, 2014). For many disorders, a range of different treatment options are available (Schacht, 2013). Given

their efficacy and tolerability (Baldwin, 2014; Cipriani, 2016; Ipser, 2012) antidepressants are recommended for these conditions by National Institute for Health and Care Excellence guidelines (Kendrick, 2012; McCloud, 2015) and World Health Organization (WHO) guidelines (WHO, 2013).

Standard pairwise meta-analyses have provided clinicians with an overview of medication efficacy and tolerability through the quantitative synthesis of data on treatment effect size estimates from randomised controlled trials (RCTs) (WHO, 2013). Nonetheless, standard pairwise meta-analyses can only be used to draw strong conclusions about interventions that have been directly compared with one another and are not designed to support comparisons between all potential interventions at clinicians' disposal (Efthimiou, 2016; Mavridis, 2015). Network meta-analysis (NMA) methods combine direct head-to-head comparisons with indirect comparisons between all interventions in a network of clinical trials (Chaimani, 2014; Efthimiou, 2016; Higgins, 2014) and may be particularly relevant when competing interventions are available (Mavridis, 2015; Salanti, 2012).

Recognition of the potential utility of NMAs has been signaled by a rapid recent increase in the number of publications using this (Annemans, 2014; Chaimani, 2017; Jansen, 2011; Jonas, 2013; Linde, 2015; Mayo-Wilson, 2014). Caution is advised in interpreting NMAs, however, as their validity depends on methodological assumptions such transitivity (i.e., the distribution between the effect modifiers is similar across treatment comparisons) and consistency (i.e., indirect and direct evidence is in agreement) (Mavridis, 2015). Previous systematic reviews of NMAs across medical conditions have documented that violations of these assumptions are common and may arise for a number of reasons (Mavridis, 2015; Petropoulou, 2017; Salanti, 2014). For instance, although transitivity was mentioned in 33% of the 353 NMAs included in

Petropoulou 2017 overall, this proportion increased over time, such that 77% of the networks published in 2015 discussed transitivity (Petropoulou, 2017).

Failure to consider these factors would, to a large extent, undermine the utility of NMAs in informing comparative efficacy choices (Jansen, 2011). Indeed, NMAs have been criticised for generating false-positive results (Del Re, 2014; Jansen, 2011), and leading to conclusions about the superiority of particular medications that are unwarranted, as current evidence may not support the choice of one second-generation antidepressant over another in terms of differences in efficacy and effectiveness (Del Re, 2014; Gartlehner, 2011).

OBJECTIVE

In light of these considerations, I decided to (A) conduct a systematic review of published NMAs that have assessed the efficacy of pharmacological treatment for common mental disorders, (B) review the quality of the methods of the published NMAs using a quality rating approach that has been designed specifically for NMAs and (C) discuss differences in rankings of the efficacy and tolerability of pharmacological treatment in terms of methodological and clinical characteristics of the NMAs by disorder.

STUDY SELECTION AND ANALYSIS

Eligibility criteria

NMAs were considered eligible for inclusion in this review if they included RCTs of pharmacotherapy in treating adult participants (18–65 years) with common mental disorders (depression, GAD, PD, OCD, PTSD, SAD and specific phobia) diagnosed according to the Diagnostic Statistical Manual for Mental Disorders (DSM-III and later) or the International Classification of Diseases ((ICD-10). NMAs containing RCTs that included participants with

comorbid secondary mental disorders were also included. Participants with substance use disorders were excluded. Studies were not restricted by language, publication date or setting.

Search strategy

NMAs of medication for the treatment of common mental disorders in adults published up until 22 March 2017 were identified by searching Scopus, PubMed Central and the Cochrane Library. Parallel search strategies were employed, including a general strategy using broad search terms incorporating pharmacological classes, as well as a more specific query incorporating generic medication names. Both search queries included the following terms: adults, common mental disorders, pharmacotherapy, network meta-analysis and the abbreviation NMA.

The following search strategies were employed:

Search 1:

"medication*" OR "pharmacotherapy" OR "treatment" AND "antidepressant*" OR "selective serotonin reuptake inhibitors*" OR "SSRIs" OR "Serotonin Uptake Inhibitors" [mh] OR "serotonin and norepinephrine reuptake inhibitors*" OR "SNRIs" OR "norepinephrine and dopamine reuptake inhibitors*" OR "NDRIs" OR "Tricyclic antidepressant*" OR "TCAs" OR "monoamine oxidase inhibitors*" OR "MAOIs" OR "Antidepressive Agents" [mh]) AND (network [tiab] OR mixed-treatment OR "multiple treatment*") AND (meta-analysis)

(“common mental disorders” or “Anxiety disorders” OR "posttraumatic stress disorder*" OR "post-traumatic" OR "posttraumatic" OR "post-traumatic stress disorder" OR "PSTD" OR “stress related disorders” OR "social phobia*" OR "social anxiety" OR "SAD" OR "SP" OR “generalised anxiety disorder” OR “GAD” OR "obsessive-compulsive*" OR "obsessive

compulsive disorder" OR "OCD" OR “Depression” OR “Depressive Disorders” OR “Depressive Symptoms” OR “Unipolar Depression” OR “Bipolar Depression” OR “Moderate Depression” OR “Persistent Depression” OR “Panic Disorder” OR “PD” OR “Panic attacks” OR “Specific Phobias”) AND ("medication*" OR "pharmacotherapy" OR "treatment" AND ("Bayesian network meta-analysis" OR "indirect-treatment comparison" OR "mixed-treatment comparison" OR "multiple treatment network analysis*" OR "NMA" OR "network analysis" OR "network meta-analyses" OR "multiple-treatments meta-analysis" OR "multiple-treatment comparisons meta-analysis" OR "mixed-treatment comparisons meta-analysis" AND "systematic review*") AND ("adult*")

Search 2:

(buspirone OR phenelzine OR atomoxetine OR mirtazapine OR brofaromine OR moclobemide OR nefazodone OR venlafaxine OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline) AND (network [tiab] OR mixed-treatment OR "multiple treatment*") AND (meta-analysis).

Study	No. of RCTS/ Duration of included RCTS (weeks)	Participants	Disorder	Medication Class	Diagnostic Criteria	Outcomes Acceptability (i.e. all cause dropouts) Tolerability (i.e. side effects dropouts)	Funding
Annemans et al. 2014	NR > 12 months	26,872 (approx.)	MDD	NaSSA, SNRIs, SSRIs	NR	**Cost** NIHDI, Societal **Response** NR **Acceptability,** NR **Tolerability,** NR	NR
Baldwin et al. 2011	27 8-12 weeks	7659 (approx.)	GAD	Placebo, SNRIs, SSRIs	DSM-IV	**Cost,** NR **Response** HAM-A **Tolerability** Side effects **Acceptability,** NR	Lundbeck
Cipriani et al. 2009	117 Weeks - NR	25961	MDD	NARI, NaSSA, NDRI, SNRIs, SSRIs	DSM-IV, ICD-10	**Cost,** NR **Response** CGI, HAM-D, MADRS **Tolerability** Side effects **Acceptability** All cause dropouts	None
Coleman et al. 2012	27 8 weeks	7061	MDD	Placebo, SNRIs	DSM defined	**Cost,** NR **Response** HAM-D,17 **Tolerability** Side effects **Acceptability,** NR	NR
Gartlehner et al. 2011	234 6-12 weeks	> 1000	MDD	NaSSA, NDRI, SARIs, SSRIs, SNRIs	NR	**Cost,** NR **Response** HAM-D, MADRS **Tolerability,** NR **Acceptability,** NR	AHRQ
Hansen et al. 2008	18 > 12 weeks	6506	SAD	Placebo, SNRI, SSRIs	DSM defined	**Cost,** NR **Response** CGI-I, LSAS	Cecil G. Sheps Center

						Tolerability Side effects **Acceptability** Loss to follow-up	
Jonas et al. 2013	34 10-12 weeks	4817	PTSD	Placebo, NaSSA, NDRI, SNRI, SSRIs, TCA	DSM defined	**Cost,** NR **Response** NR **Tolerability** Side effects **Acceptability,** NR	NR
Kriston et al. 2014	41 4-12/5-24 weeks	4850	MDD	Placebo, MAOI, NARI, RIMA, SARI, SNRIs, SSRIs, TCAs	Standardised criteria	**Cost,** NR **Response** NR **Acceptability,** NR **Tolerability,** NR	Grant 01KG0923
Linde et al. 2015	66 4-52 weeks	14177	MDD	Placebo, NARI, NaSSA, RIMAs, SARI, SSRE, SSRIs, TCAs	DSM-IV, ICD 10 or older	**Cost,** NR **Response** CGI, HAM-D, MADRS **Tolerability** Side effects **Acceptability** All cause dropouts	Grant 01KG1012
Liu et al. 2013	11 Weeks – NR	801	MDD & Parkinson's Disease	Placebo, Dopamine agonists, SNRIs, SSRIs, TCAs	NR	**Cost,** NR **Response** BDI, CGI, HAM-D, MADRS **Tolerability,** NR **Acceptability** All cause dropouts	None
Mavranezuli et al. 2013	42 8 weeks – 6 months	13508	GAD	Placebo, SNRIs, SSRIs	DSM defined	**Cost** **Response** HAM-A **Tolerability,** NR **Acceptability** All cause dropouts	NICE (Partial)
Mayo-Wilson et al. 2014	42 2-28 weeks	8665 (approx.)	SAD	Placebo, MAOI, NaSSA, RIMA, SNRI, SSRIs	Based on diagnostic criteria	**Cost,** NR **Recovery**	NICE

						ADIS, BAI, BDI, FNE, SIAS, SPAI-SP, SPS **Acceptability,** NR **Tolerability,** NR	
Meister et al. 2016	34 4-24 weeks	4769	MDD	Placebo, 5-HT2 receptor antagonist, Antipsychotics, Benzodiazepine, MAOIs, RIMA, SARI, SNRIs, SSRIs, TCAs	NR	**Cost,** NR **Response,** NR **Tolerability** Side effects, AE checklist, Patient reports, AE scale, Interviews, Clinical manual, Retrospective chart view, Clinical observation **Acceptability,** NR	Grant NWF-14/06
Naudet et al. 2013	31 4-13 weeks	7459	MDD	Placebo, SNRI, SSRI	DSM defined, ICD-10	**Cost,** NR **Response** HAM-D, MADRS **Acceptability,** NR **Tolerability,** NR	INSERM
Nussbaumer et al. 2014	101 6 weeks -12 months	2333	MDD	Placebo, NDRIs, SARIs, SNRIs, SSRIs	NR	**Cost,** NR **Response** HAM-D **Tolerability** Side effects **Acceptability,** NR	AHRQ
Papadimitropoulou et al. 2017	31 2-8 weeks	NR	MDD (TRD)	Anticonvulsants, Antimanic agents, Atypical antipsychotics, NaSSA, SARI, SSRIs, SNRIs, TCAs	DSM-IV, HAM-D, 17, 24, MADRS	**Cost,** NR **Response** MADRS **Tolerability** Side effects **Acceptability,** NR	Janssen
Ramsberg et al. 2012	87 > 6 weeks	19878	MDD	NARI, NaSSA, SNRIs, SSRIs, TCAs, TeCA	NR	**Costs** **Response,** NR **Acceptability,** NR **Tolerability,** NR	None

Reichenpfader et al. 2014	63 6 weeks	> 26000	MDD & Sexual Dysfunction	Placebo, NaSSA, NDRIs, SARIs, SNRIs, SSRIs	DSM defined	**Cost,** NR **Measures** CES-D, CGI-I, CGI-S, CSFQ, HAM-D, MADRS, PGI **Tolerability** Side effects **Acceptability,** NR	None
Skapinakis et al. 2016	64 4-24 weeks	6652 (N=37)	OCD	TCA, SNRI, SSRIs	DSM defined, FRDC, ICD	**Cost,** NR **Response,** NR **Tolerability,** NR **Acceptability** All cause dropouts	NIH
Zhou et al. 2015	48 2-12 weeks	6654	MDD (TRD)	Placebo, Anticonvulsant, Antipsychotics, Antimanic agents, Beta blockers, CNS stimulants, NDRI, Thyroid hormone	DSM defined, RDC	**Cost,** NR **Response** HAM-D ≥ 50, MADRS ≥ 50 **Tolerability** Side effects **Acceptability** All cause dropouts	Chinese NBR

Table 1. Descriptive Characteristics of Included NMAs (N=20). **Legend:** ADIS: Anxiety Disorders Interview Schedule – Severity; AE: Adverse Events; AHRQ: Agency for Healthcare Research and Quality; Approx.: Approximately; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; CGI-I: Clinical Global Impression Improvement; CGI-S: Clinical Global Impression–Severity; CNS: Central Nervous System; CSFQ: Changes in Sexual Functioning Questionnaire; DSM: Diagnostic and Statistical Manual of Mental Disorders; FNE: Fear of Negative Evaluation Scale; FRDC: Fairfax Renaissance Development Corporation; GAD: Generalised anxiety disorder; HAM-A: Hamilton anxiety scale; HAM-D: Hamilton Depression Rating Scale for Depression; ICD-10: International Statistical Classification of Diseases and Related Health Problems; Inc.: incorporated; INSERM: Institut National de la Santé et de la Recherche Médicale; LSAS: The Liebowitz Social Anxiety Scale (LSAS); MADRS: Montgomery-Åsberg Depression Rating Scale; Major depressive disorder; MAOI: Monoamine oxidase inhibitor; MDD: Major Depressive Disorder; NARI: Noradrenaline reuptake inhibitor; NaSSA: Noradrenergic and specific serotonergic Antidepressants; NBR: National Basic Research; NDRI: Norepinephrine and dopamine reuptake inhibitor; NICE: National Institute for Health and Clinical Excellence; NIH: National Institute for Health; NIHDI: National Institute for Health and Disability Insurance; N: Number of studies; No.: Number; NR: Not reported; NWF: Networking & TCP/IP Fundamentals; OCD: Obsessive Compulsive Disorder; PGI: Patient Global Impression of Improvement; PTSD: Posttraumatic stress disorder; RDC: Research Diagnostic Criteria; RIMA: Reversible inhibitors of

monoamine oxidase A; SAD: Social Anxiety Disorder; SARI: Serotonin Antagonist and Reuptake Inhibitor; SIAS: Social Interaction Anxiety Scale; SNRI: Serotonin and norepinephrine reuptake inhibitor; SPAI-SP: Social Phobia Anxiety Inventory – Social Phobia Subscale; SPS: Social Phobia Scale; SSRE: Selective Serotonin Reuptake Enhancers; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressants; TeCA: Tetracyclic antidepressants; TRD: Treatment resistant.

Study selection and data extraction

The review assessed the relevance of each study first by title and abstract, followed by the retrieval of full-text articles that passed the initial screen for further inspection. General descriptive information was extracted (see table 1) with specific emphasis placed on the methodological quality of each published NMA (Chambers, 2015; Petropoulou, 2017; Zarin, 2017) (see table 2).

Data (where provided) was also included from rankograms or cumulative ranking probability plots (the surface under the cumulative ranking curve) (Mavridis, 2015), indicating the best treatment, in terms of both efficacy and proportion of patients who left the study early (as a proxy measure of treatment tolerability and acceptability).

CRITERIA	No. of NMAs (%)
Study method assessment criteria	
Was a Bayesian or a frequentist framework used to assess the probabilistic interpretation of uncertainty and ranking of interventions?	14 (66%)[1] 2 (10%)[2]
Was the risk of bias of included clinical trials assessed to explain variability in either the results or the validity of the included studies?	15 (71%)
Did the analysis include adjustments for model covariates to improve similarity and consistency assumptions to explain heterogeneity?	16 (76%)
Was a fixed or random effects model used to assess the true relative effects across studies?	2 (10%)[3] 16 (76%)[4]
Was an assessment of model fit reported to reduce confounding bias and were stable parameter estimates provided?	16 (76%)
Was a sensitivity analysis performed to improve similarity and reduce inconsistency across studies?	14 (67%)
For studies with at least one closed loop, was the consistency of direct evidence and indirect evidence evaluated?	16 (76%)
Study transparency and reproducibility assessment criteria	
Were the search terms reported for the replication of the study search?	18 (86%)
Was a network diagram of included treatments presented for transparency of all comparisons investigated?	15 (71%)
Was data from the included clinical studies necessary to reproduce the network meta-analysis presented?	21 (100%)
Was a table of key clinical study characteristics presented describing each of the included studies in the NMA?	20 (95%)
Was the model code presented or source cited (i.e. Bayesian framework only) for the replication of the analysis?	3 (14%)
Presentation of study findings	
Were pairwise comparisons of all included treatments presented for the assessment of discrepancy between direct and indirect comparisons?	11 (52%)
Was the probability of each treatment being best reported for the interpretation of uncertainty and ranking of interventions?	7 (33%)
Was a ranking of treatments in terms of effectiveness reported for the interpretation of uncertainty and ranking of interventions?	7 (33%)

Table 2 Explanation of Assessment Criteria based on Chambers et al. (2015) Survey. Legend: Footnote1: Bayesian framework; Footnote2: Frequentist framework; Footnote3: Fixed effects model; Footnote4: Random effects model; NMAs: Network meta-analyses.

Appraisal of reporting standards and methodological quality of included NMAs

The extent to which the included studies complied with recommended standards for reporting NMA methodology was assessed by applying the checklist of good research practices from the International Society for Pharmacoeconomics and Outcomes Research guidance document, an instrument that was specifically designed for the purpose of evaluating the quality of NMAs (Jansen, 2011). In addition, I modelled my approach on that of Chambers et al. (2015) and the updated review by Zarin et al. (2017) and Petropoulou et al. (2017) who assessed the following criteria: study method, study transparency and reproducibility, and the presentation of study findings (Chambers, 2015; Petropoulou, 2017; Zarin, 2017) (see online published supplementary tables 2 and 3).

In addition, risk of bias using the Cochrane "Risk of Bias' tool in RevMan 5.3.5 was assessed for each comparison as well as an overall summary of the evaluation of RoB for each included RCT of SAD and PTSD according to the following categories specified by Furukawa et al. (2016): 1) Low risk of bias: there is no item rated at high risk among the nine items listed above; 2) Moderate risk of bias: there is one item rated at high risk; 3) High risk of bias: there are two or more items rated at high risk. A rating of unclear was common across comparisons.

Assessment criteria (N = 20)							
1. General study characteristics							
	No. of treatments compared Mean (SD)	Total no. of RCTs per NMA Mean (SD)	Total no. of patients Mean (SD)	*HTA region (UK, USA, Europe, Australia, Africa) Mean (SD)	Journal impact factor (2015/2016) Mean (SD)		
	10.85 (5.23)	58.84 (50.83) (N = 19)	10295.89 (8443.1) (N = 19)	10 (50%)	3.11 (1.32) (N = 19)		
2. Study method							
Bayesian or Frequentist framework	Risk of bias Assessment	Adjustment for covariates	Random effects model	Assessment of model fit	Sensitivity Analysis	Consistency reported**	Transitivity ***
15 (75%)	15 (75%)	15 (75%)	15 (75%)	15 (75%)	13 (65%)	15 (75%)	13 (65%)
3. Study transparency and reproducibility							
	Search terms reported	Network diagram	Extracted data from contributing clinical stu0dies	Table of key clinical study characteristics	Model code****		
	16 (80%)	14 (70%)	20 (100%)	19 (95%)	3 (15%)		
4. Presentation of study findings							
	Full matrix of head-to head comparisons	Reported probability of being best	Ranking of included Treatments				
	10 (50%)	9 (45%)	9 (45%)				

Table 3. Assessment of network meta-analysis study characteristics based on the extent to which the included studies complied with recommended standards for reporting NMA methodology (based on ISPOR guidelines for network meta analyses and demonstrated by Chambers et al. 2015, Zarin et al. (2017) and Petropoulou et al.'s (2017) reviews). **Legend:** *HTA: health technology assessment regions; N: Number of studies; No.: Number; RCTs: Randomised control trials; SD: Standard deviation. *HTA refers to the systematic evaluation of properties, effects, and/or impacts

of health technology, for example the evaluation of the social, economic, organizational and ethical issues of a health intervention or health technology to inform policy decision making,[45];**(Closed loops (i.e. any subset of interventions where each of that have been directly compared with one another,[11]); *** Transitivity: which implies that the distribution between the effect modifiers is similar across treatment comparisons; ****The model code refers to the software code for the Bayesian models used to calculate rankings.

FINDINGS

Description of search

Four hundred and thirty-five studies were found across the three databases searched. Of these studies, 135 were duplicates. The abstracts for the remaining 300 studies were scanned for eligibility, of which 259 studies were excluded for a variety of reasons (see the selection flow chart, figure 1). Full-text articles were subsequently retrieved for further assessment of the 41 studies that passed the initial screening phase. After independent reviewing, 21 failed to meet inclusion criteria, leaving 20 eligible for inclusion. Each NMA study included published and/or unpublished RCTs (with the inclusion of cross-over studies, quasi experimental designs and/or open label studies, where study designs were reported) (see figure 1).

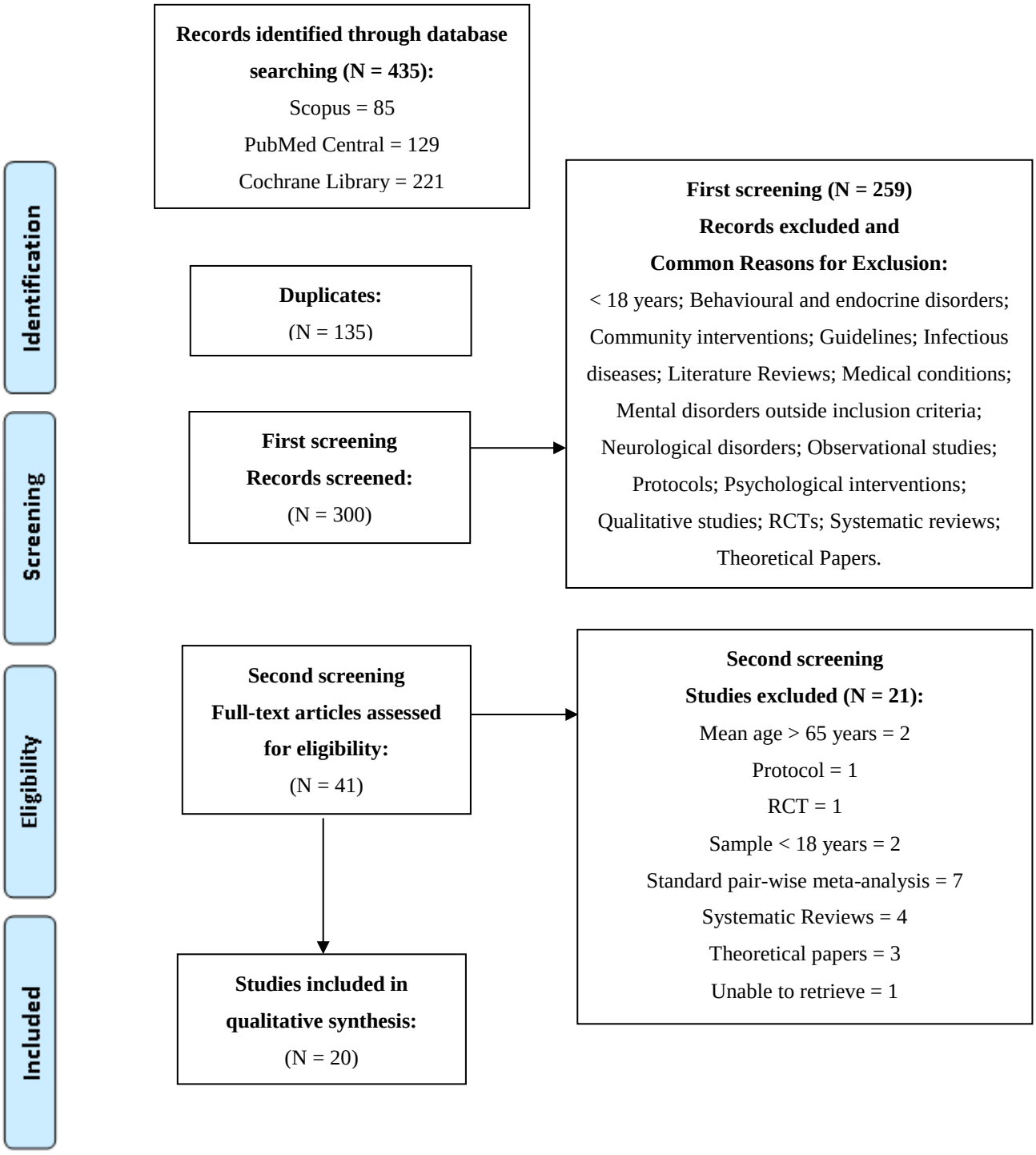

Figure 1. Flow chart of NMAs included in the systematic review. NMA, network meta-analysis; RCT, randomised controlled trial.

Description of the included NMAs

NMAs investigating treatment of depressive disorders (i.e., major depressive disorder) represent 70% (number of studies (N)=14) of the included studies (Annemans, 2014; Chambers, 2015; Cipriani, 2009; Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Kriston, 2014; Linde, 2015; Liu, 2013; Meister, 2016; Nussbaumer, 2014; Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014; Zarin, 2017; Zhou, 2015). Two of the 14 NMAs reported an additional primary diagnosis of Parkinson's disease (Liu, 2013) and sexual dysfunction (Reichenpfader, 2014), and two NMAs included patients with drug-resistant depression (Papadimitropoulou, 2017; Zhou, 2015). Of the remaining six NMAs, two investigated the treatment of GAD (Chaimani, 2017; Mavranezouli, 2013), two SAD (Hansen, 2008; Mayo-Wilson, 2014), one PTSD (Jonas, 2013) and one OCD (Skapinakis, 2016). Diagnostic criteria (DSM defined, n=12; ICD 10, n=4) was based on standardised measures and/or research diagnostic criteria. Recruitment was conducted in inpatient and/or outpatient settings across health technology and WHO regions (n=10, for example, the UK, Australia and Canada) with regards to the clinical effectiveness, safety and cost-effectiveness of interventions employed. The social, ethical and legal aspects of these technologies were also assessed (Luce, 2010).

Across all 20 included NMAs, the number of RCTs per NMA ranged from 1131 to 234 (Gartlehner, 2011), and sample size from 801 (Liu, 2013) to more than 26 000 (Annemans, 2014; Reichenpfader, 2014) participants. Year of publication for the 20 NMAs ranged from 2008 (Hansen, 2008) to 2017 (Papadimitropoulou, 2017) (also see figure 2). Only one of the 20 included NMAs reported funding by industry (Chaimani, 2017). The mean journal impact factor (based on 2015/2016 ResearchGate ratings) across the 19 peer reviewed and published

NMAs was 3.11 (SD: 1.32) (see table 3). The remaining NMA was published as a report (Jonas, 2013).

Studies assessed a range of medications administered according to either fixed or flexible doses. The most common agents were antidepressants (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants, including immediate release and/or extended release) (table 1 and figure 3). The individual RCTs reported by these NMAs were conducted over a period ranging from two weeks (Mayo-Wilson, 2014; Zhou, 2015), to more than 12 months (Annemans, 2014). Fourteen of the included NMAs included a placebo group as a comparator (also see table 1). The remaining 30% of the included NMAs did not include a placebo comparator (Annemans, 2014; Cipriani, 2009; Gartlehner, 2011; Papadimitropoulou, 2017; Ramsberg, 2012; Skapinakis, 2016).

The outcomes assessed across the 20 NMAs varied from the assessment of treatment response in 14 NMAs (i.e., treatment efficacy) (Chaimani, 2017; Cipriani, 2009; Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Hansen, 2008; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Nussbaumer, 2014, Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014) dropouts due to any cause (n=5) and/or dropouts due to side effects (n=12) (Chaimani, 2017; Cipriani, 2009; Coleman, 2012; Jonas, 2013; Linde, 2015; Liu, 2013; Mavranezouli, 2013; Meister, 2016; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). Standardised and self-report measures were used to assess these outcomes and were specific to the different disorders (see table 1). Additional outcomes were symptom severity, remission and relapse. Probability rankings were provided for the outcome of cost-effectiveness for three NMAs (Annemans, 2014; Mavranezouli, 2013; Ramsberg, 2012).

Assessment of standard of reporting of the included NMAs

Study method

Fifteen of the 20 NMAs employed a Bayesian framework (using Markov Chain Monte Carlo estimation methods) (Chaimani, 2017; Cipriani, 2009; Coleman, 2012; Gartlehner, 2011; Jonas, 2013; Kriston, 2014; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Nussbaumer, 2014, Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015), with a Frequentist approach being employed in addition in two of the NMAs (Mayo-Wilson, 2014; Papadimitropoulou, 2017).

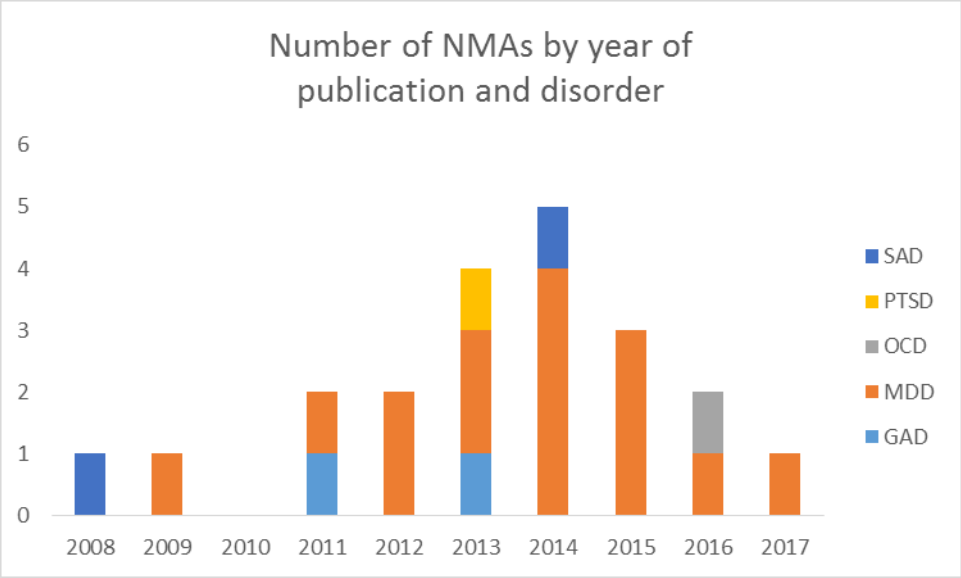

Figure 2. Descriptive characteristics of year of publication by disorder. GAD, generalised anxiety disorder; MDD, major depressive disorder; NMAs, network meta-analysis; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder.

Both direct and indirect estimates were calculated using a random effects model for each of the 15 NMAs, with a fixed effects model also employed by one NMA (Papadimitropoulou, 2017). Risk of bias (RoB) and quality assessment was assessed for 15 NMAs, based on a variety of

instruments, including the Cochrane RoB tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Chaimani, 2017; Chambers, 2015; Cipriani, 2009; Cipriani, 2014; Gartlehner, 2011; Jonas, 2013; Kriston, 2014; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Meister, 2016; Nussbaumer, 2014; Papadimitropoulou, 2017; Reichenpfader, 2014; Skapinakis, 2016; Zarin, 2017; Zhou, 2015). Three of the 15 NMAs did not report the findings for RoB assessment, however (Liu, 2013; Mavranezouli, 2013; Zhou, 2015). Overall the RCTs included were rated unclear or high for RoB. Publication bias was reported by four NMAs (Cipriani, 2014; Hansen, 2008; Meister, 2016; Zhou, 2015).

Fifteen NMAs reported adjusting for covariates (Cipriani, 2009; Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Nussbaumer, 2014; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2015; Zhou, 2015), and provided information about the model used to fit the data (Cipriani, 2009; Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Nussbaumer, 2014; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). Additional sensitivity analyses were reported by 13 NMAs (Annemans, 2014; Cipriani, 2009; Cipriani, 2014; Gartlehner, 2011; Jonas, 2013; Kriston, 2014; Linde, 2015; Mavranezouli, 2013; Nussbaumer, 2014; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). Fifteen NMAs reported that the assessment of consistency would be calculated across comparisons, however, the findings were only reported by 13 of these studies (Chaimani, 2017; Cipriani, 2009; Hansen, 2008; Kriston, 2014; Liu, 2014; Mavranezouli, 2013; Mayo-Wilson, 2014; Meister, 2016; Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). In addition, two of the 13 NMAs by Gartlehner et al. (2011) and Linde et al.

(2015) reported the use and method of node splitting across direct and indirect evidence as a method of assessing inconsistency with a Z-test (Efthimiou, 2016; Gartlehner, 2011; Linde, 2015). An assessment of heterogeneity in the effect sizes reported across studies was obtained in 13 NMAs by calculating the I squared statistic (I^2), the $\chi 2$ statistic ($\chi 2$), the Q statistic and/or the Gelman-Rubin statistic (Chaimani, 2017; Cipriani, 2009; Gartlehner, 2011; Hansen, 2008; Jonas, 2013; Kriston, 2014; Liu, 2013; Mayo-Wilson, 2014; Meister, 2016; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). Four NMAs reported the τ statistic to explain heterogeneity in the effect estimates (Linde, 2015; Mayo-Wilson, 2014; Mavranezouli, 2013; Skapinakis, 2016).

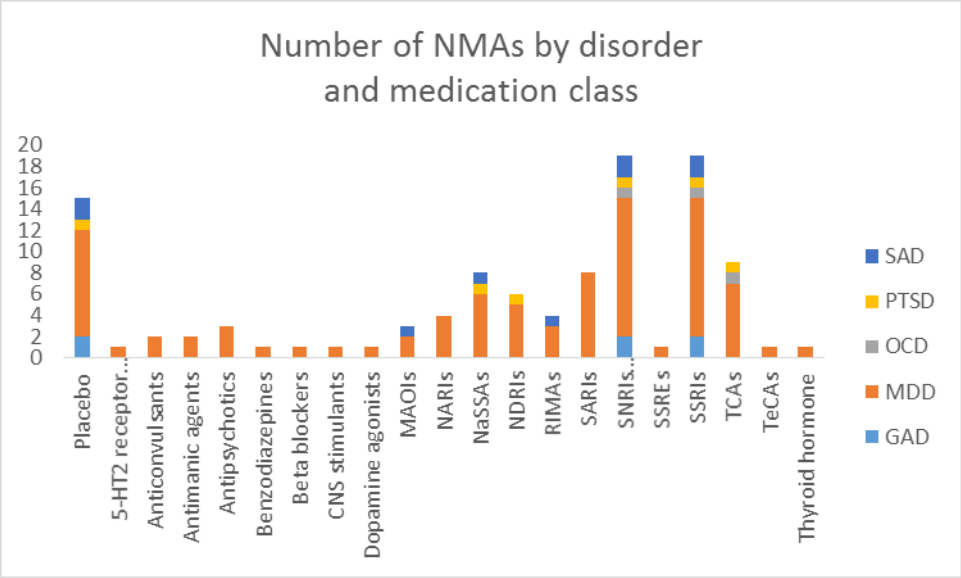

Figure 3. Descriptive characteristics of the number of NMAs by disorder and medication class. 5-HT2, receptor antagonists; CNS, central nervous system; GAD, generalised anxiety disorder; MAOIs, monoamine oxidase inhibitors; MDD, major depressive disorder; NARI, norepinephrine reuptake inhibitor; NASSAs, noradrenergic and specific serotonergic antidepressants; NDRI, norepinephrine and dopamine reuptake inhibitor; NMAs, network meta-analysis; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; RIMAs, reversible inhibitors of monoamine oxidase A; SAD, social anxiety disorder; SARIs,

serotonin and reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRE, selective serotonin reuptake enhancer; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TecA; tetracyclic antidepressant.

Thirteen NMAs reported testing of transitivity assumptions via the comparison of effect modifiers across studies, including dosage (Cipriani, 2009; Coleman, 2012; Liu, 2013; Ramsberg, 2012), treatment duration (Coleman, 2012; Kriston, 2014; Ramsberg, 2012), sample size (Kriston, 2014; Liu, 2013), drug-placebo comparisons (Kriston, 2014; Linde, 2015), recruitment settings (Linde, 2015; Papadimitropoulou, 2017; Ramsberg, 2012), and baseline symptom severity and similarity (Cipriani, 2014; Coleman, 2012; Hansen, 2008).

Transparency and reproducibility

The majority of the NMAs documented which databases were used (95%) (Annemans, 2014; Chaimani, 2017; Cipriani, 2009; Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Hansen, 2008; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Meister, 2016; Mavranezouli, 2013; Nussbaumer, 2014; Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015), as well as the specific search terms that were used to identify trials (80%) (Chaimani, 2017; Cipriani, 2009; Cipriani, 2014; Gartlehner, 2011; Hansen, 2008; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Mavranezouli, 2013; Nussbaumer, 2014; Ramsberg, 2012; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015), and the date of the last search (100%). Twelve NMAs provided additional search strategy queries as supplementary information (Chaimani, 2017; Cipriani, 2009; Gartlehner, 2011; Jonas, 2013; Mavranezouli, 2013; Mayo-Wilson, 2014; Meister, 2016; Nussbaumer, 2014; Papadimitropoulou, 2017; Reichenpfader, 2014; Skapinakis, 2016; Zhou, 2015). All of the NMAs extracted data from contributing clinical studies and 95% of the NMAs provided a study

characteristic table. Only three of the 15 NMAs that used a Bayesian framework to calculate rankings provided the model code that they used to conduct their analysis (Mavranezouli, 2013; Mayo-Wilson, 2014; Skapinakis, 2016). The risk of bias across studies and comparisons was also low for SAD and PTSD NMA studies.

Comparison	Study	N	Risk of Bias							RoB of each study and of comparison
Social Anxiety Disorder										
			Sequence generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessors**	**Incomplete outcome data**	**Selective reporting**	**Sponsorship**	**Low Moderate High**
PLB vs ESC	Kasper 2005	358	Unclear	Low	Unclear	Low	Low	Low	Unclear	Low
PLB vs ESC vs PAR	Lader 2004	856	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs FLU	Davidson 2004b	117	Low	Low	Low	Low	Low	Unclear	Unclear	Low
	Kobak 2002	60	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs FLV	Asakura 2007	271	Low	Low	Low	Low	Low	Unclear	Unclear	Low
	Davidson 2004a	279	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
	Stein 1999	92	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
	van Vliet 1994	30	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
	Westenberg 2004	30	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs GAB	Pande 1999	69	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs GR205171 vs CIT	Furmark 2005	36	Low	Low	Low	Low	Low	Unclear	Unclear	Low
PLB vs LEV	Zhang 2005	19	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Moderate
PLB vs LY686017 vs PAR	Tauscher 2010	189	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Moderate
PLB vs MIR	Schutters 2010	60	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs MOC	Burrows 1997	578	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Low
	Oosterbaan 2001	54	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low
	Schneier 1998	78	Low	Low	Low	Low	Low	Unclear	Unclear	Low
	Stein 2002	390	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
PLB vs MOC vs PLZ	Versiani 1992	78	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
PLB vs PAR	Allgulander 1999	92	Low	Low	Unclear	Unclear	High	Unclear	Unclear	Moderate
	Baldwin 1999	290	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low
	Liebowitz 2002	384	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Lepola 2004	370	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
	GSK2006/NCT00403962	107	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Stein 1998	187	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
	Wagner 2004	322	Low	Unclear	Low	Unclear	Low	High	Unclear	Moderate
PLB vs PAR vs PGB	Pfizer 2007	-	-	-	-	-	-	-	-	-
PLB vs PGB	Feltner 2011	328	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Pande 2004	135	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
PLB vs PLZ	Blanco 2010	84	Low	Unclear	Unclear	Low	Low	Unclear	Low	Low
	Heimberg 1998	64	Low	Low	Low	Low	Low	Unclear	Unclear	Low

PLB vs PLZ vs ALP	Gelerner 1991	65	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
PLB vs PLZ vs ATN	Liebowitz 1990	-	-	-	-	-	-	-	-	-
PLB vs SER	Blomhoff 2001	196	Low	Low	Unclear	High	Low	Unclear	Unclear	Moderate
	Liebowitz 2003	415	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Van Ameringen 2001	204	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs VEN ER	Liebowitz 2005	279	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Rickels 2004	272	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
	Stein 2005	395	Unclear	Low	Low	High	High	Unclear	Unclear	High
PLB vs VEN ER vs PAR	Allgulander 2004	288	Unclear	Low	Unclear	Low	Low	Low	Unclear	Low
	Liebowitz 2005	440	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Posttraumatic Stress Disorder										
PLB vs AMT	Davidson 1990	46	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
PLB vs BROF	Baker 1995	114	Low	Unclear	Low	Unclear	Unclear	High	Unclear	Moderate
	Katz 1994	68	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
PLB vs BUP SR (aug)	Becker 2007	30	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Moderate
PLB vs CIT vs SER	Tucker 2003	58	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs DVP	Davis 2008a	85	Low	Low	Unclear	Low	Low	High	Unclear	Moderate
PLB vs DVP (aug)	Hamner 2009	29	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
PLB vs FLU	Connor 1999	54	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low
	Hertzberg 2000	12	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
	Martenyi 2002	301	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low
	Martenyi 2007	411	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Van Der Kolk 2007	59	Low	Unclear	Unclear	Low	Low	Unclear	Low	Low
PLB vs GFC (aug)	Davis 2008b	36	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
PLB vs GFC (mono)	Neylan 2006	63	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Low
PLB vs LTG	Hertzberg 1999	15	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs MIR	Davidson 2003	29	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs NK-1RA	NCT01000493	129	Low	Low	Low	Unclear	High	Low	Unclear	Moderate
	Matthew 2011	47	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
PAR + NLX vs PAR + PLB vs DES + NLX vs DES + PLB (aug)	Petrakis 2012	88	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
PLB vs NEF	Davis 2004	42	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low
NEF vs SER	McRae 2004	37	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low
PLB vs OLZ	Butterfield 2001	15	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
	Carey 2012	34	Low	Low	Low	Unclear	Unclear	Low	Unclear	Low
PLB vs OLZ (aug)	Stein 2002	19	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low

PLB vs PAR	GSK 29060 627	322	Low	Unclear	Low	Unclear	Low	Low	Unclear	Low
	Marshall 2001	551	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Marshall 2007	563	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
	Tucker 2001	307	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs PLZ + IMI	Kosten 1991	60	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs PRZ	Raskind 2003	10	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Low
	Raskind 2007	40	Low	Unclear	Low	Low	Low	Unclear	Low	Low
PLB vs PRZ (aug)	NCT00532493	304	Low	Low	Low	Unclear	High	Low	Low	Moderate
	Raskind 2013	67	Low	Unclear	Low	Unclear	High	Low	Low	Moderate
REV vs FLV	Spivak 2006	40	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Low
PLB vs RIS (mono)	Padala 2006	19	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs RIS (aug)	Bartzokis 2004	65	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Moderate
	Hamner 2003	37	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Krystal 2011	296	Low	Low	Unclear	Unclear	Low	High	Unclear	Moderate
	Reich 2004	21	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
	Rothbaum 2008	25	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs SER	Brady 2005	94	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low
	Brady 2000	187	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Davidson 2001	208	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Friedman 2007	169	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Panahi 2011	70	Low	Unclear	Low	Unclear	Low	Unclear	Low	Low
	Pfizer 588	190	Low	Low	Low	Unclear	Low	Low	Unclear	Low
	Zohar 2002	42	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
PLB vs TGB	Davidson 2007	232	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
PLB vs TOP	Akuchekian 2004	67	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
	Tucker 2007	40	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
	Yeh 2011	35	Low	Unclear	Low	Low	High	Unclear	Low	Moderate
PLB vs TOP (aug)	Lindley 2007	40	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low
PLB vs VEN ER	Davidson 2006a	329	Low	Low	Unclear	Unclear	Low	Unclear	Unclear	Low
PLB vs VEN ER + SER	Davidson 2006b	531	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low

Appendix 1. Risk of bias assessment across SAD and PTSD studies. **LEGEND**: ALP: Alprazolam; AMT: Amitriptyline; ATN: Atenolol; BROF: Brofaromine; BUP SR: Bupropion Slow Release; CIT: Citalopram; DES: Desipramine; DVP: Divalproex; ESC: Escitalopram; FLU: Fluoxetine; FLV: Fluvoxamine; GAB: Gabapentin; GFC: Guanfacine; IMI: Imipramine; LEV: Levetiracetam; LTG: Lamotrigine; MIR: Mirtazapine; MOC: Moclobemide; NEF: Nefazodone; NK-1RA: Neurokinin 1 antagonists; NLX: Naltrexone; OLZ: Olanzapine; PAR: Paroxetine; PGB: Pregabalin;

PLB: Placebo; PLZ: Phenelzine; PRZ: Prazosin; RIS: Risperidone; SER: Sertraline; TGB: Tiagabine; TOP: Topiramate; VEN ER: Venlafaxine Extended Release.

Presentation of study findings

Half of the NMAs included in this review used standard network graphs and plots to visually represent their data (50%) (Cipriani, 2014; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Meister, 2016; Nussbaumer, 2014; Papadimitropoulou, 2017; Reichenpfader, 2014; Zhou, 2015). The most common figure reported was a flow diagram that provided information regarding the eligibility of the RCTs and number of RCTs included in the network. In addition, 14 NMAs displayed their results with a forest plot indicating effect estimates across comparisons and outcomes (Cipriani, 2014; Coleman, 2012; Gartlehner, 2011; Hansen, 2008; Jonas, 2013; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Meister, 2016; Nussbaumer, 2014; Papadimitropoulou, 2017; Ramsberg, 2012; Reichenpfader, 2014; Zhou, 2015). Ten NMAs provided a full matrix of head-to-head comparisons (for direct and indirect comparisons) (Chaimani, 2017; Cipriani, 2009; Cipriani, 2014; Kriston, 2014; Linde, 2015; Liu, 2013; Mayo-Wilson, 2014; Meister, 2016; Ramsberg, 2012; Zhou, 2015).

Nine NMAs employing a Bayesian (n=7) or Frequentist framework (n=2) reported the probability that particular agents were the most effective treatment and ranked treatments accordingly as best, second best, third best and so on (Annemans, 2014; Chaimani, 2017; Cipriani, 2009; Liu, 2013; Mavranezouli, 2013; Papadimitropoulou, 2017; Ramsberg, 2012; Skapinakis, 2016; Zhou, 2015). Based on the results for rankings (n=9) and statistical significance (n=20) for the included NMAs, antidepressants were often (55%, 11/20 NMAs) rated as the most efficacious and/or tolerable treatment across disorders (see tables 4 and 5).

Reported best ranked treatments (based on probability best) (N=9)				
Disorder	**Efficacy**	**Acceptability: All cause dropouts**	**Tolerability: Dropouts due to side effects**	**Cost effectiveness**
MDD [Annemans, 2014]	--	--	--	Escitalopram (SSRI) 61-100% more cost effective than the SSRI fluoxetine and the SNRI venlafaxine. €30,000 per QALY.
MDD [Cipriani, 2009]	Mirtazapine (NaSSA) (24·4%)	Escitalopram (SSRI) (27·6%)	Escitalopram (SSRI) (27·6%)	--
MDD [Liu, 2013]	--	--	TCAs pramipexole and pergolide, and SNRIs (unable to determine probability).	--
MDD [Ramsberg, 2012]	--	--	--	Escitalopram (SSRI) Societal perspective: €14 755 per QALY (0.6978). Health care perspective: €5 088 per QALY (0.6978).
MDD [Zhou, 2015]	Quetiapine (Antipsychotic) (81.3%)	Thyroid hormone (85.9%)	Buspirone (5HT1A partial agonist) (84.5%)	--
MDD [Papadimitropoulou, 2017]	Quetiapine 800 mg (aug) (17.7%)	--	--	--
GAD [Chaimani, 2017]	Fluoxetine (SSRI) (62.9%)	--	Sertraline (SSRI) (49.3%)	--
GAD [Mavranezouli, 2013]	Duloxetine (SNRI) (38%)	--	Sertraline (SSRI) (75%)	Sertraline (SSRI) 75 %; £20,000 per extra QALY gained.
OCD [Skapinakis, 2016]	SSRIs (unable to determine probability)	SSRIs (unable to determine probability)		

Table 4. Reported best ranked treatments (based on ProbBest) **Legend**: Aug: Augmentation; GAD: Generalised anxiety disorder; MDD: Major depressive disorder; NaSSA: Noradrenergic and specific serotonergic Antidepressants; OCD: Obsessive compulsive disorder; QALY: Quality-

adjusted life year; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TCAs: Tricyclic antidepressants.

Reported treatments based on statistical significance (N=20)				
Disorder	**Efficacy**	**Acceptability: All cause dropouts**	**Tolerability: Dropouts due to side effects**	**Cost effectiveness**
MDD [Annemans, 2014]	--	--	--	The SSRI escitalopram was identified as the optimal strategy: it dominated all other treatments except venlafaxine from the NIHDI and societal perspective.
MDD [Linde, 2015]	No difference was observed however TCAs, SSRIs, the SNRI venlafaxine, and a low-dose of the SARI trazodone was significantly superior.	--	RIMAs were associated with significantly fewer dropouts.	--
MDD [Gartlehner, 2011]	No difference, although the evidence favoured the SSRI escitalopram.	--	No difference in dropouts due to side effects.	--
MDD [Cipriani, 2009]	Mirtazapine (NaSSA), escitalopram (SSRI), venlafaxine (SNRI), and sertraline (SSRI) were significantly more efficacious than duloxetine (SNRI), fluoxetine (SSRI), fluvoxamine (SSRI), paroxetine (SSRI), and reboxetine (NARI). Reboxetine was significantly less efficacious than all the other antidepressants tested.	The SSRIs escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine (SNRI), fluvoxamine (SSRI), paroxetine (SSRI), reboxetine (NARI), and venlafaxine (SNRI).	The SSRIs escitalopram and sertraline showed the best profile of tolerability, leading to significantly fewer discontinuations than did duloxetine (SNRI), fluvoxamine (SSRI), paroxetine (SSRI), reboxetine (NARI), and venlafaxine (SNRI).	--
MDD [Kriston, 2014]	A significant difference was found for the SSRIs fluoxetine, paroxetine and sertraline, the RIMA moclobemide, the TCA imipramine, the antipsychotic amisulpride, the 5HT1A partial	Sertraline (SSRI) and amisulpride (Antipsychotic) showed low dropout rates.	--	--

	agonist ritanserin, and acetyl-l-carnitine.			
MDD [Cipriani, 2014]	Antidepressant agents were significantly more efficacious than the placebos. The SNRI venlafaxine was more efficacious than the SSRI fluoxetine.	--	--	--
MDD [Nussbaumer, 2014]	IR or extended-release formulations (the SNRI venlafaxine, SSRIs: fluoxetine, paroxetine and fluvoxamine, the SARI trazodone and the aminoketone bupropion) did not differ in efficacy.	--	Adverse event rates were comparable for the IR and the extended release formulation of paroxetine and fluoxetine. No difference was found for the SNRI venlafaxine formulations. No evidence was reported for the aminoketone bupropion, the SSRI fluvoxamine, and the SARI trazodone.	--
MDD [Liu, 2013]	With efficacy of TCAs as the standard of comparison, the degree of difference was small in comparison to SSRIs; Pramipexole; Pergolide; SNRIs; and Placebo.	--	With Placebo as the standard of comparison, TCAs, pramipexole, pergolide and SNRIs showed better profile of acceptability, leading to significant fewer discontinuations than that of SSRIs.	--
MDD [Ramsberg, 2002]	--	--	--	Despite its relatively high acquisition cost, the SSRI escitalopram is associated with a lower total cost compared with all other treatment strategies. Furthermore, escitalopram is associated with a larger health gain (QALYs) at one year, and therefore dominates the other treatment strategies as more

				QALYs are achieved at a lower total cost.
MDD [Reichenpfader, 2014]	The norepinephrine-dopamine reuptake inhibitor bupropion had a statistically significantly lower risk of sexual dysfunction than some other SGAD, and both the SSRI escitalopram and paroxetine showed a statistically significantly higher risk of sexual dysfunction than some other SGAD.	--	Inconsistent and insufficient evidence to report this.	--
MDD [Coleman, 2012]	No difference (p=0.43)	--	No difference (p=0.06), findings favour the SNRI desvenlafaxine.	--
MDD [Zhou, 2015]	The antipsychotics quetiapine and aripiprazole, the thyroid hormone, and the antimanic agent lithium were significantly more effective than placebo.	In terms of acceptability, no significant difference was found between active agents and placebo.	In terms of tolerability, compared to placebo, the antipsychotics quetiapine, olanzapine, aripiprazole, and the antimanic agent lithium were significantly less well tolerated.	--
MDD [Papadimitropoulou, 2017]	At 4, 6 and 8 weeks, the antipsychotic quetiapine (aug; 800 mg/day) and risperidone (aug) were found to be the first and second best treatments, respectively.	--	The most tolerable treatment was the anticonvulsant lamotrigine (aug) showing a comparable profile to placebo/sham.	--
MDD [Meister, 2016]	--	--	Medications associated with a high discontinuation rate: TCAs, SSRIs, MAOIs, antipsychotics, and the SARI trazodone. The odds were significantly higher for acetyl-l-carnitine, TCAs and SNRIs.	--
SAD [Mayo-Wilson, 2014]	MAOIs (phenelzine), SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine,	--	--	--

	paroxetine and sertraline) and the SNRI venlafaxine had greater effects.			
SAD [Hansen, 2008]	No difference, the results favour the SSRIs escitalopram, fluvoxamine, paroxetine, sertraline, and the SNRI venlafaxine.	--	No difference except by profile.	--
GAD [Chaimani, 2017]	The SSRI fluoxetine was ranked first for response (probability of 62.9%).	--	The SSRI sertraline was ranked first for tolerability (49.3%).	--
GAD [Mavranezouli, 2013]	In terms of conditional response, all drugs showed a significant effect over placebo. The SNRI duloxetine had the highest probability of resulting in conditional response (mean 0.649), followed by sertraline (SSRI), venlafaxine XL (SNRI), pregabalin (anticonvulsant), escitalopram (SSRI) and paroxetine (SSRI) (mean 0.516). Placebo had the lowest probability of conditional response among the options assessed (mean 0.425).	--	The SSRI sertraline was the best drug in limiting discontinuation due to side effects and the second best drug in achieving response in patients not discontinuing treatment due to side effects.	The SSRI sertraline also resulted in the lowest costs and highest number of QALYs among all treatment options assessed. Its probability of being the most cost-effective drug reached 75% at a willingness-to-pay threshold of £20,000 per extra QALY gained.
PTSD [Jonas, 2013]	No difference, the findings favour the SSRI paroxetine and the anticonvulsant topiramate.	--	--	--
OCD [Skapinakis, 2016]	SSRIs showed reductions in mean YBOCS, and the TCA clomipramine had a larger effect compared with placebo than did SSRIs, but the difference was not significant.	--	--	--

Table 5. Reported treatments based on statistical significance **Legend:** Aug: Augmentation; GAD: Generalised anxiety disorder; IR: Immediate release; MAOIs: Monoamine oxidase inhibitors; MDD: Major depressive disorder; mg: Milligrams; NARI: Noradrenaline reuptake inhibitor; NaSSA: Noradrenergic and specific serotonergic antidepressants; NIHDI: National institute for health and disability insurance; OCD: Obsessive compulsive disorder; PTSD: Posttraumatic stress disorder; QALY: Quality-adjusted life year; RIMAs: Reversible inhibitors of monoamine oxidase A; SAD: Social anxiety disorder; SGAD: Social generalised anxiety disorder; SARIs: Serotonin antagonist and reuptake inhibitor; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRIs: Selective serotonin reuptake inhibitor; TCAs: Tricyclic antidepressants; XL: Long acting; YBOCS: Yale–Brown Obsessive Compulsive Scale.

CONCLUSIONS

Twenty NMAs investigating pharmacological treatment for depression and anxiety disorders, PTSD and/or OCD were included in the review. Antidepressants were rated as the most effective and/or tolerable agents in 11 (55%) of the NMAs, as assessed either by rankings or by overall statistical significance (see tables 4 and 5). The remaining studies reported rankings or overall statistical significance for 5HT1A partial agonists (Kriston, 2014; Reichenpfader, 2014), anticonvulsants (Jonas, 2013; Mavranezouli, 2013), antipsychotics (Kriston, 2014; Papadimitropoulou, 2017; Zhou, 2015), dopamine antagonists (Liu, 2013), acetyl-l-carnitine (Kriston, 2014), the antimanic agent lithium (Zhou, 2015), the noradrenergic and specific serotonergic antidepressant mirtazapine (Cipriani, 2009) and the thyroid hormone (Zhou, 2015).

The potential clinical utility of NMAs for evaluating the relative efficacy and tolerability of different classes of antidepressants is somewhat undermined by evidence for methodological quality across the 20 NMAs in the review. More than a quarter of NMAs did not provide a network diagram, report RoB assessment or conduct sensitivity analyses. Fifteen NMAs reported the results of tests for consistency in effect estimates across trials, and 13 NMAs evaluated transitivity. Only four NMAs assessed and reported publication bias, a bias that may impact the overall estimate of effects and ranking of medications (Trinquart, 2012). Moreover, the sample size and number of RCTs for the NMAs of depression were larger than the remaining NMAs. On a more positive note, more than 70% of the NMAs included in the review accounted for the influence of variability of covariates on effect estimates (e.g., meta-regression or logistic regression), assessed model fit and extracted data from clinical studies where they provided a table of study characteristics.

The fact that only three NMAs provided their model code may reflect convergence on standard software routines for this purpose, or that the model code has become easily accessible and freely available, as previously noted for Bayesian frameworks (Chambers, 2015). The majority of the NMAs did not take full advantage of reporting tools designed to convey design-specific considerations (e.g., inconsistency or ranking plots). Moreover, only 10 NMAs provided a full matrix of effect estimates for head-to-head comparisons (for direct and indirect comparisons), and even fewer (n=9) reported treatment rankings. Lack of presentation and utilisation of visual graphics provided by these NMAs lends weight to the critique that NMAs are complex and mainly used by researchers with strong statistical skills (Chaimani, 2014). Failure to report rankings may partly reflect the concern that positions in these ranks are sensitive to small and clinically non-significant differences in reported treatment effects (Leucht, 2016; Li, 2011).

Nevertheless, the NMAs included in this review performed favourably with respect to seven aspects of quality, compared with other recent, and more inclusive, systematic surveys of published NMAs for medical disorders (Chambers, 2015; Petropoulou, 2017; Zarin, 2017). Compared with Chambers et al. (2015), Zarin et al. (2017) and Petropoulou et al. (2017) the NMAs included in this review more frequently provided a network diagram of both direct and indirect comparisons (70% compared with 61%, 48%, 26%, respectively); assessed consistency (75% compared with 69%, 53%, 30%, respectively) and made use of a random effects model (75% compared with 70%, 49%, 74%, respectively) (Chambers, 2015; Petropoulou, 2017; Zarin, 2017). A higher proportion of NMAs in this review also modelled the data (75% vs 40% and 48%) and adjusted effect estimates for covariates (75% vs 29% and 18%), compared with Chambers et al. (2015) and Petropoulou et al. (2017), respectively (Chambers, 2015; Petropoulou, 2017). The heterogeneity assumption was explored in 65% of the NMAs reported on in this paper, compared with 56% for Zarin et al. (2017) and Petropoulou

et al. (2017) (Petropoulou, 2017; Zarin, 2017). Finally, more than three quarters (77%) of the NMAs included in Petropoulou et al. (2017) did not discuss transitivity, compared with 65% in our review (Petropoulou, 2017).

The relatively good standing of the NMAs in our review may partly reflect their relatively recent publication, consistent with Petropoulou et al's (2017) finding that more recently published NMAs adhere to more rigorous methodological standards (Petropoulou, 2017). For instance, Petropoulou et al (2017) reported an increase in the number of NMAs discussing transitivity and inconsistency from 0% to 86% when comparing NMAs published in 2005 with those published in 2015 (Petropoulou, 2017). In addition, although the NMAs in our review performed favourably compared with those assessed in studies of medical disorders with respect to multiple methodological features, optimal methods were not always employed, with the evaluation of consistency being a particular case in point. Nonetheless, the NMAs included in this review show strong methodological quality (even though low risk of bias across SAD and PTSD NMAs were found) and relatively favourable adherence to reporting for the treatment of common mental disorders, and factors that support their replication across the clinical spectrum.

CLINICAL IMPLICATIONS

The 20 NMAs of depression and anxiety disorders, PTSD and/or OCD included in this review reflect the growing evidence base of trials on the pharmacological treatment for these disorders, support current treatment guidelines and help inform clinical decision-making (Li, 2011). The included NMAs in this review demonstrated superiority with respect to a number of aspects of methodological quality than recent surveys of NMAs published across medical disorders; I have a relatively high level of confidence in the findings of the NMAs included in this review.

Nevertheless, studies employing NMA methods going forward may gain from addressing some of the shortcomings identified in this review.

In the next chapter I will conduct a network meta-analysis for PTSD.

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CHAPTER 5.

Comparative efficacy and acceptability of pharmacological treatments for posttraumatic stress disorder in adults: a network meta-analysis.

This chapter compares direct and indirect comparisons of RCTs for the pharmacotherapy of PTSD, using the network meta-analytic approach (Bayesian) to synthesising data. Trials were assessed for eligibility and inclusion in the study and the quality of each RCT was assessed with the Risk of Bias Tool. Thereafter the data was analysed.

INTRODUCTION

I will now discuss the rationale for this chapter and conduct a network meta-analysis for the pharmacotherapy of PTSD.

Treatments available for PTSD span a variety of psychological and pharmacological interventions (Jonas et al. 2013). Numerous organisations have issued guidance for the treatment of patients with PTSD (APA, 2004; NICE, 2005; PA-CPMH, 2013), supporting trauma-focused psychological interventions as first-line treatments for PTSD. These guidelines have also recognised some benefit of pharmacological interventions; however, they have arrived at different conclusions about the value of such interventions and have limited themselves to recommendations about broad categories of treatments. From a clinical point of view, though, it is very important to know what pharmacological intervention is more efficacious and acceptable than others among the various treatment options available for PTSD. Notwithstanding the recent publication of two systematic reviews (Watts et al. 2013; Hoskins et al. 2015), clinical uncertainty still remains about what pharmacological treatment to select among all available compounds because traditional pair-wise meta-analyses do not allow the

simultaneous integration of direct and indirect evidence (Cipriani et al. 2013). The aim of this chapter is to assess efficacy and acceptability of different pharmacological treatments against one another, and to provide a clinically useful summary of the comparative evidence that can be used to guide decisions about acute treatment of PTSD in adults.

METHODS

The study protocol was drafted and made available on the following website: (http://cebmh.warne.ox.ac.uk/cebmh/research_other_reviews.htm).

Study eligibility criteria

All double-blind randomised controlled trials (RCTs) were identified comparing any psychotropic agent at a therapeutic dose with another psychotropic drug or placebo as oral therapy in the treatment of adults with PTSD, diagnosed according to operationalised criteria. Monotherapy and add-on studies were included, and it was assumed that add-on interventions had an additive effect on the treatments of interest. The dose ranges for the medication included in the network meta-analysis were defined according to the FDA, whenever possible (https://dailymed.nlm.nih.gov/dailymed/ or http://www.accessdata.fda.gov/). If information was not available, the British National Formulary (https://www.bnf.org/) was used. The following pharmacological interventions were considered for inclusion: amitriptyline, clomipramine, desipramine, imipramine, maprotiline, mianserin, tianeptine, trazodone, nefazodone, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, desvenlafaxine, venlafaxine, duloxetine, mirtazapine, reboxetine, brofaromine, moclobemide, phenelzine (among antidepressants); haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine (among antipsychotics); lithium, lamotrigine, valproate, tiagabine, topiramate (among mood stabilisers/anti-epileptic drugs); guanfacine, prazosin and selective

NK1R antagonists (among the new drugs with different mechanisms of action). The synthesis comparator set consists of all the interventions listed above, their combinations and placebo (for all details about Methods, see published protocol).

Identification and selection of studies

The Cochrane Depression, Anxiety and Neurosis Group specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, the National PTSD Center Pilots database and PubMed (last update: 15 February 2016) was searched for relevant trials. Databases of the most important regulatory agencies worldwide and online trial registers for published and unpublished RCTs (see search strategy for the Cochrane PTSD review for my details) were also searched. No language restrictions were applied. All relevant authors and principal manufacturers were contacted to supplement the incomplete report of the original papers.

Data collection and study appraisal

Acute treatment was defined as 8-week treatment in all analyses. Mean change scores on the Clinician-Administered PTSD Scale (CAPS) and dropout rates (treatment discontinuation) were chosen as primary outcomes to represent the most sensible and sensitive estimate of acute treatment efficacy and acceptability, respectively. As secondary analyses, the proportion of patients who responded to treatment (according to original study authors' definition) and the proportion of patients who left the study early due to adverse events (tolerability) was estimated. The risk of bias tool was used to assess study quality (Higgins & Green, 2011). Additionally, I assessed the quality of evidence contributing to each network estimate using the GRADE framework, which characterises the quality of a body of evidence on the basis of

the study limitations, imprecision, inconsistency, indirectness, and publication bias for the primary outcomes (Salanti et al. 2014).

Data synthesis and statistical analysis

For the continuous outcome, where different measures were used to assess the same outcome, standardised mean difference (SMD) (Hedges's adjusted g) were used (Altman & Bland, 1996; Higgins & Green, 2011). Dichotomous outcomes were analysed by calculating the odds ratio (OR).

Assessment of clinical and methodological heterogeneity and transitivity

To evaluate the presence of heterogeneity descriptive statistics were generated for trial and study population characteristics across all eligible trials (Furukawa et al. 2006). If the distributions were balanced across comparisons, the NMA concluded against evidence of intransitivity (Salanti, 2012; Jansen & Naci, 2013).

Data synthesis

Initially, standard pairwise meta-analyses were performed using a random effects model (DerSimonian & Lair, 1986) in STATA (StataCorp, 2015). A network meta-analysis (NMA) was then accrued out to synthesise the available evidence from the entire network of trials by integrating direct and indirect estimates and using the methodology of multivariate meta-analysis (different treatment comparisons were treated as different outcomes, assuming a common heterogeneity parameter) (White et al. 2012). The ranking of probabilities was also estimated using the surface under the cumulative ranking curve (SUCRA) (Salanti et al. 2011) and mean ranks. To perform the NMA the mvmeta command in Stata (White, 2011) was used

while checking the model assumptions and presenting the results suite of previously published Stata commands (Chaimani et al. 2013a).

Statistical heterogeneity and inconsistency

To measure the percentage of variability that cannot be attributed to random error, statistically the presence of heterogeneity was assessed in all pairwise comparisons by calculating the heterogeneity standard deviation parameter (τ) and within each comparison using the I-squared (I^2) statistic (Higgins et al. 2003) and its 95% confidence interval (CI). For all outcomes τ was compared with its empirical distribution (Turner et al. 2012; Rhodes et al. 2015). A total I^2 value for heterogeneity in the network was also estimated (Jackson et al. 2014). The NMA evaluated the presence of inconsistency locally (local tests) using the loop-specific approach (Song et al. 2003; Chaimani et al. 2013b; Veroniki et al. 2013). To check the assumption of consistency in the entire network (global test) the design-by-treatment model (White, 2011; Higgins et al. 2012) was used. To distinguish between inconsistency and heterogeneity, the I^2 for inconsistency was employed and measured the percentage of variability that cannot be attributed to random error or heterogeneity (Turner et al. 2012). In case of important heterogeneity or/and inconsistency, a meta-regression or subgroup analyses were carried out by using the following effect modifiers: (a) variance of the observed relative effects; (b) baseline severity; (c) publication year and (d) sponsorship.

Sensitivity analysis

To check the robustness of study findings, a sensitivity analysis was carried out excluding studies rated as at high or unclear risk of bias (Wood et al. 2008).

RESULTS

Description of the evidence base

The systematic review included overall 51 studies with 6189 patients, randomised to 25 different interventions (Figure 1 Appendix 6). The mean duration of primary studies was 10.3 weeks (S.D. 2.1) and the mean age of trial participants was 42.9 years (S.D. 5.9). The great majority of studies were 2-arm (45 studies), but the search retrieved also six 3-arm studies.

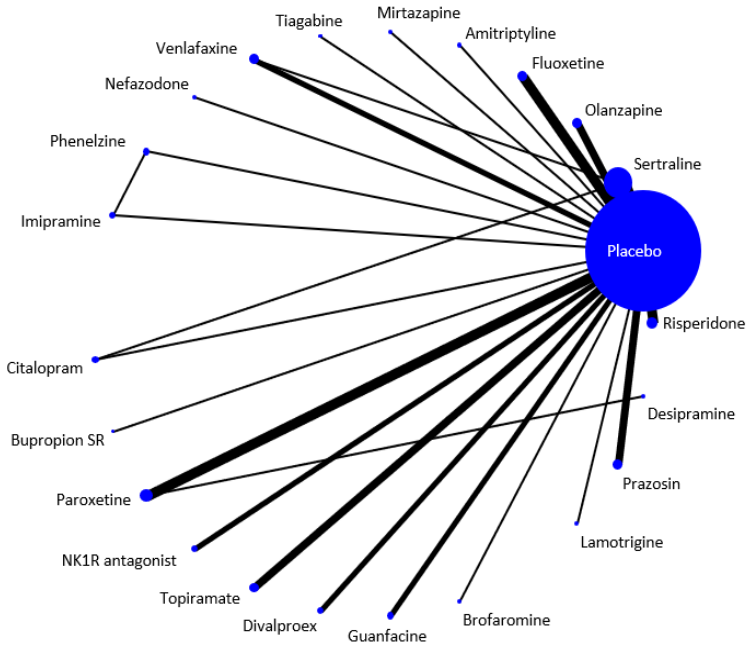
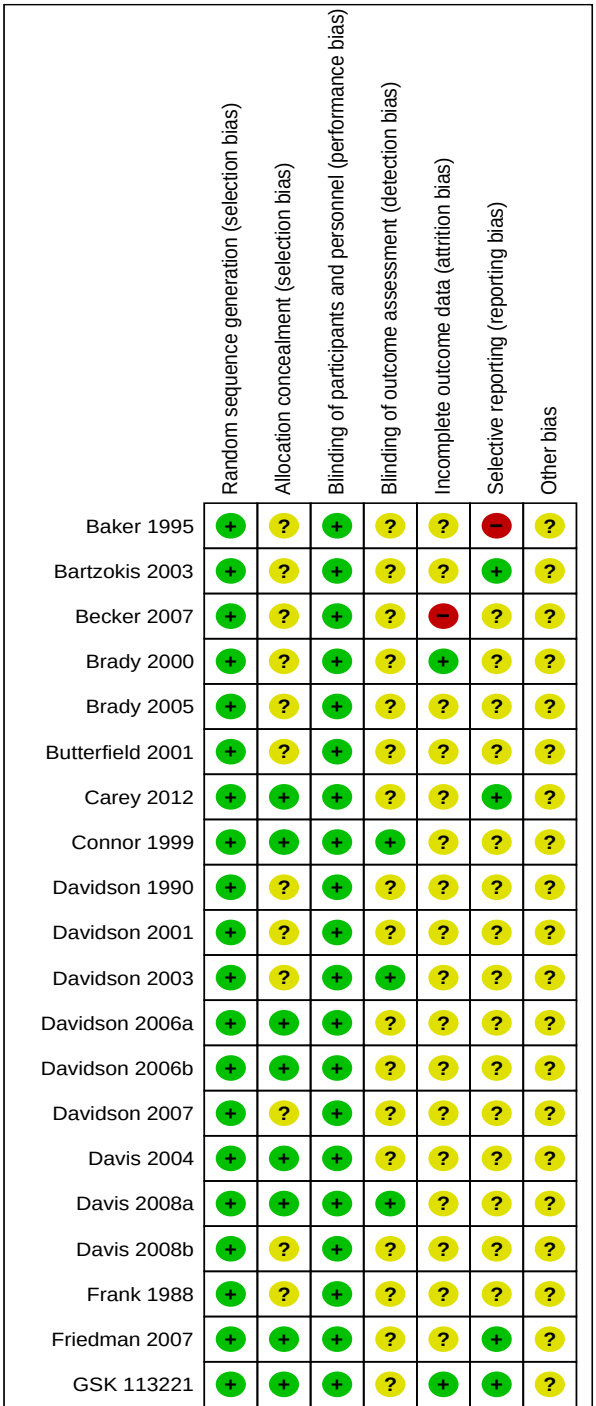
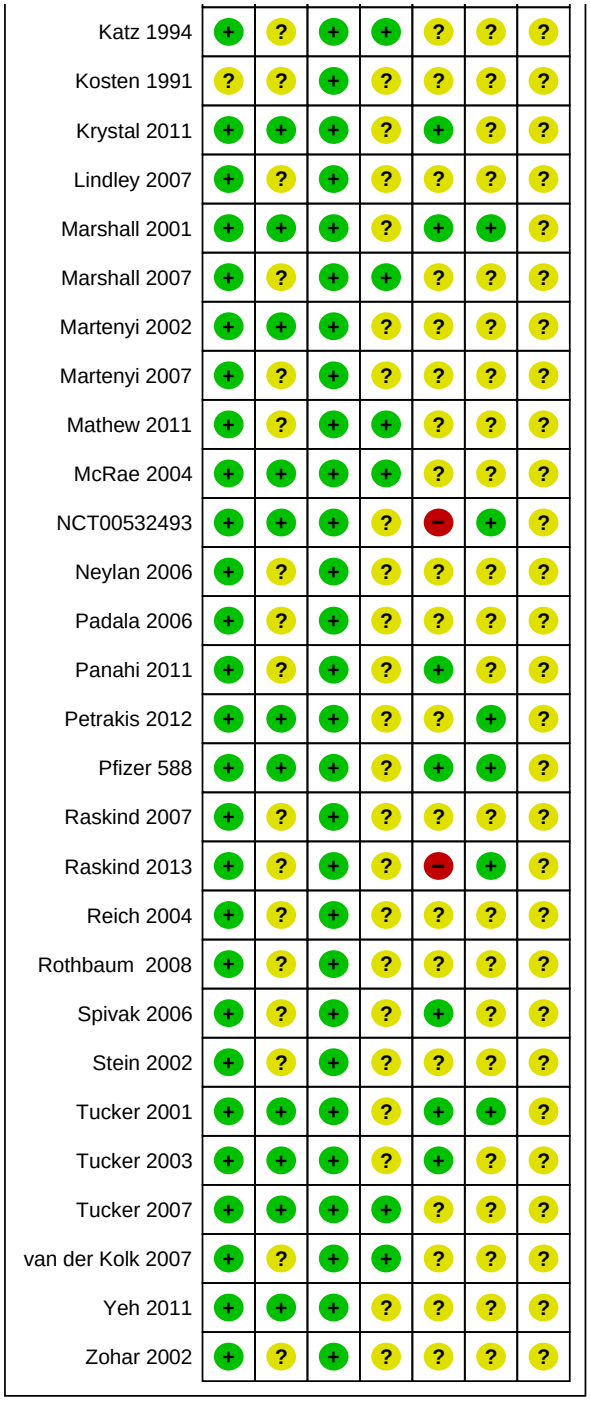


Figure 1 (Appendix 6). Network plot for the outcome 'Any-cause dropouts'. Nodes and edges are weighted according to the number of studies involved in each treatment comparison.

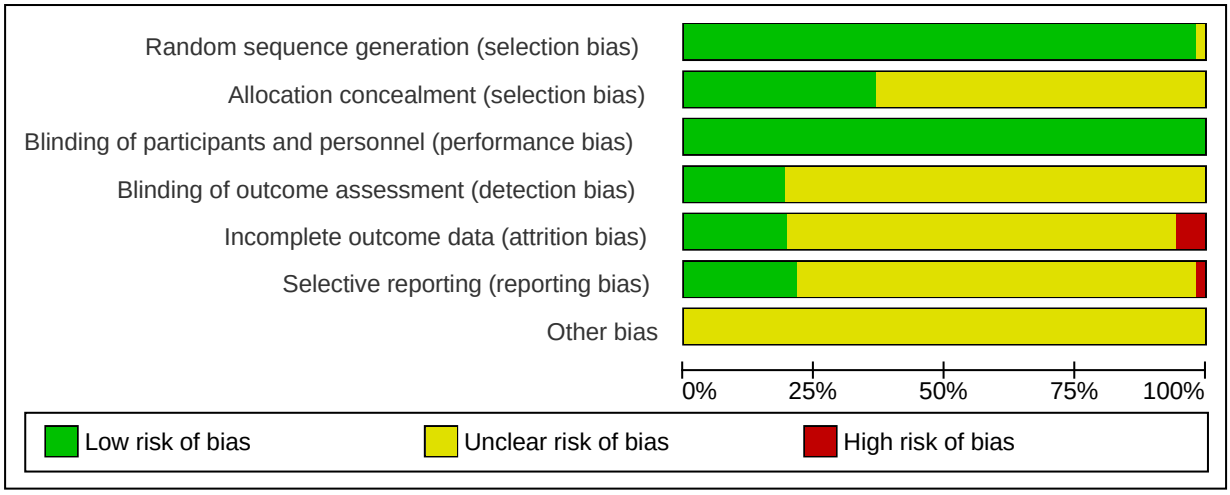
Thirty-six studies (71.0%) used CAPS (or CAPS-2) as the rating scale for assessing efficacy, with a mean baseline severity of 74.1 (S.D. 16.7). Only 11 trials (22.0%) had an add-on design and overall 36 studies (71.0%) were sponsored by pharmaceutical industry. In terms of study quality, the reports often did not provide full details about randomisation sequence procedures

(28 out of 51, 54.9%) but the reporting about allocation concealment was much worse, as only 19 studies out of 51 (37.2%) were judged at low risk of bias (see Appendix 3). The networks of eligible comparisons by outcome are shown in Fig. 2, Appendix 6. The results of the direct pairwise comparisons for all outcomes are reported in Appendix 7. There was considerable variability in the placebo response rates among studies, which varied between 3% and 60% and resulted in a $\tau = 0.1$. However, there was no evidence of a time trend in placebo response (p value 0.93). Heterogeneity was not low only for the dichotomous response rate and results did not materially change when we assumed comparison-specific heterogeneity parameters.

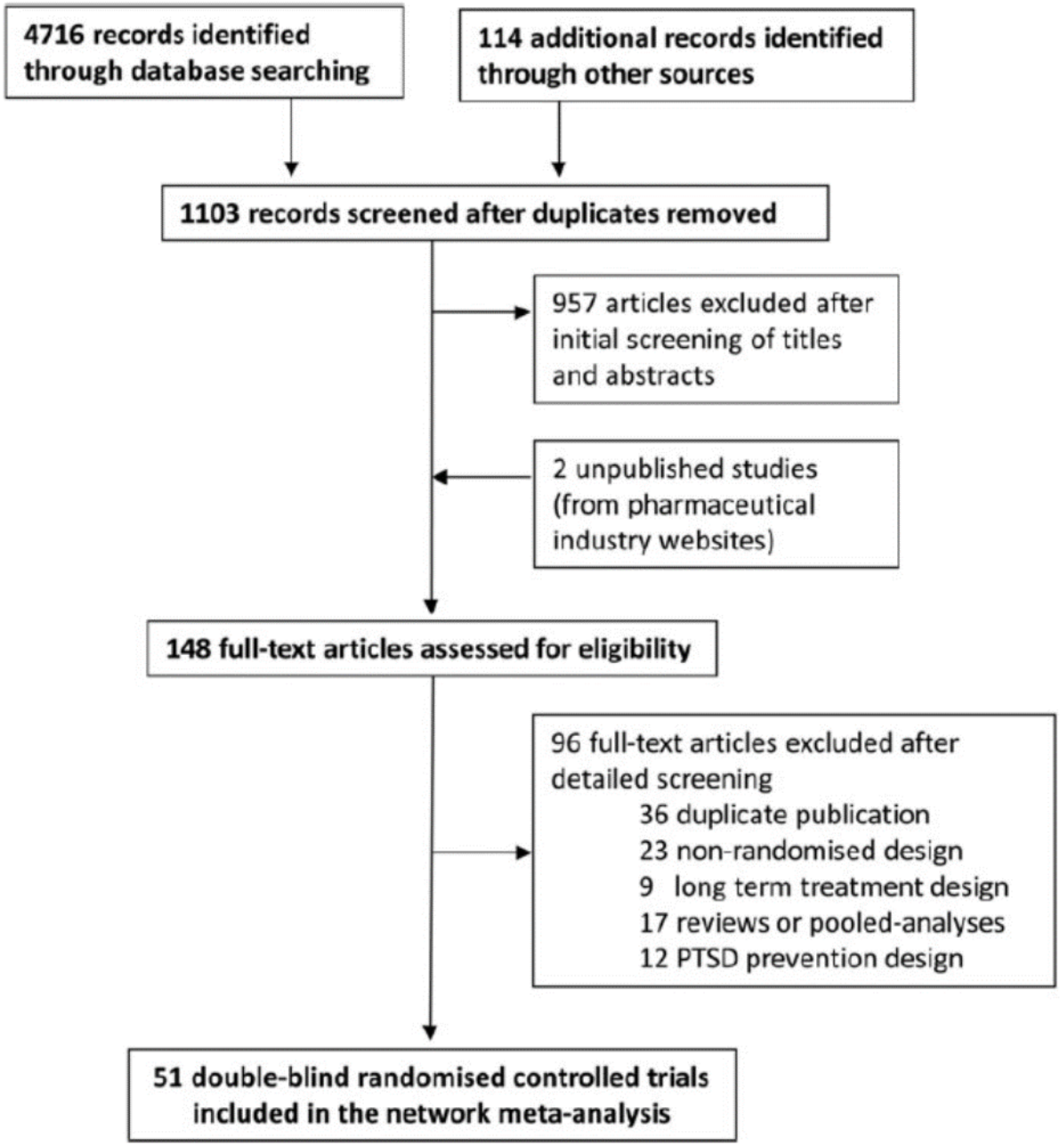




Appendix 3. Risk of bias graph: it is a plot of the distribution of judgments (Yes, Unclear and No) across studies for each risk of bias item.



Appendix 3. Risk of bias summary: it is a summary table of review authors' judgments for each risk of bias item for each study.



Prisma Diagram. Included and Excluded Studies.

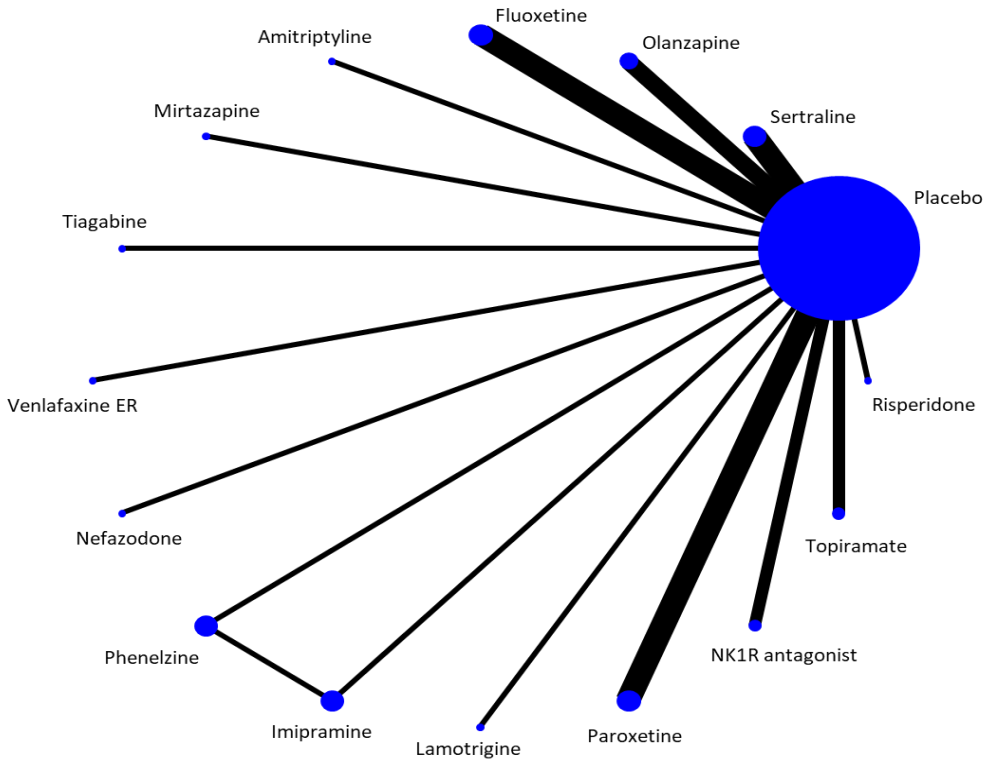


Figure 2 (Appendix 6). Network plot for the outcome 'Response rate'. Nodes and edges are weighted according to the number of studies involved in each treatment comparison.

Comparisons	Primary outcomes		Secondary outcomes	
	Change in symptoms	Any-cause dropouts	Response rate	Dropouts due to adverse events
Placebo vs				
Nefazodone	1	1	1	1
Phenelzine	2	1	2	1
Imipramine	2	1	2	1
Citalopram	1	1	-	-
Bupropion SR	1	1	-	-
Paroxetine	4	4	4	4
NK1R antagonist	2	2	2	1
Topiramate	3	3	2	3
Divalproex	2	2	-	2
Guanfacine	2	2	-	1
Brofaromine	1	1	-	1
Lamotrigine	-	1	1	Excluded
Risperidone	4	4	1	4
Sertraline	8	9	4	5
Olanzapine	3	3	3	3
Fluoxetine	5	4	4	3
Amitriptyline	1	1	1	1
Mirtazapine	1	1	1	1
Tiagabine	1	1	1	1
Venlafaxine ER	2	2	1	2

Prazosin	3	3	-	3
Sertraline vs				
Nefazodone	1	-	-	1
Citalopram	1	1	-	-
Venlafaxine ER	1	1	-	1
Phenelzine vs				
Imipramine	2	1	2	1
Fluvoxamine vs				
Reboxetine	1	1	-	-
Paroxetine vs				
Desipramine	1	1	-	-

Table 1 (Appendix 7). Number of studies per comparison for primary and secondary outcomes. Appendix 7.

Comparisons	Primary outcomes		Secondary outcomes	
	Change in symptoms	Any-cause dropouts	Response rate	Dropouts due to adverse events
Placebo vs				
Nefazodone	41	42	42	42
Phenelzine	59	37	59	37
Imipramine	64	41	64	41
Citalopram	35	35	-	-
Bupropion SR	28	30	-	-
Paroxetine	1101	1260	1260	1260
NK1R antagonist	159	176	176	129
Topiramate	97	115	75	115
Divalproex	110	114	-	114
Guanfacine	87	99	-	63
Brofaromine	52	68	-	114
Lamotrigine	-	15	15	15
Risperidone	343	131	65	131
Sertraline	1236	1346	468	986
Olanzapine	62	70	70	70
Fluoxetine	722	536	778	724
Amitriptyline	40	46	46	46
Mirtazapine	26	29	29	29
Tiagabine	202	232	232	232
Venlafaxine ER	687	687	329	687

Prazosin	358	411	-	411
Sertraline vs				
Nefazodone	26	-	-	37
Citalopram	48	49	-	-
Venlafaxine ER	352	352	-	352
Phenelzine vs				
Imipramine	65	42	65	42
Fluvoxamine vs				
Reboxetine	28	40	-	-
Paroxetine vs				
Desipramine	88	88	-	-

Table 2 (Appendix 7). Number of participants per comparison for primary and secondary outcomes.

Treatments	Primary outcomes				Secondary outcomes			
	Change in symptoms		Any-cause dropouts		Response rate		Dropouts due to adverse events	
	Number of studies	Number of participants	Number of studies	Number of participants	Number of studies	Number of participants	Number of studies	Number of participants
Placebo	45	2256	44	2280	28	1512	36	2115
Nefazodone	2	39	1	27	1	27	2	45
Phenelzine	2	30	1	19	2	30	1	19
Imipramine	2	35	1	23	2	35	1	23
Citalopram	1	25	1	25	-	-	-	-
Bupropion SR	1	18	1	20	-	-	-	-
Paroxetine	5	671	5	765	4	723	4	723
NK1R antagonist	2	84	2	91	2	91	1	69
Topiramate	3	47	3	57	2	37	3	57
Divalproex	2	56	2	60	-	-	2	60
Guanfacine	2	41	2	47	-	-	1	29
Brofaromine	1	26	1	35	-	-	1	56
Lamotrigine	-	-	1	11	1	11	-	-
Risperidone	4	176	4	70	1	33	4	70
Sertraline	9	636	9	679	4	238	6	507
Olanzapine	3	34	3	38	3	38	3	38
Fluoxetine	5	522	4	386	4	582	3	555
Amitriptyline	1	22	1	25	1	25	1	25
Mirtazapine	1	17	1	20	1	20	1	20
Tiagabine	1	105	1	116	1	116	1	116

Venlafaxine ER	2	340	2	340	1	161	2	340
Prazosin	3	179	3	204	-	-	3	204
Fluvoxamine	1	17	1	20	-	-	-	-
Reboxetine	1	11	1	20	-	-	-	-
Desipramine	1	46	1	46	-	-	-	-

Table 3 (Appendix 7). Number of studies and number of participants per treatment for primary and secondary outcomes.

Comparisons Heterogeneity SD	Primary outcomes		Secondary outcomes	
	Change in symptoms (τ=0.1)	**Any-cause dropouts (τ=0)**	**Response rate (τ=0.39)**	**Dropouts due to adverse events (τ=0)**
	SMD (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Placebo vs				
Nefazodone	0.23 (-0.44, 0.90)	0.72 (0.20, 2.58)	1 (0.21, 4.68)	0.11 (0.01, 2.04)
Phenelzine	1.07 (0.50, 1.65)	7.5 (1.72, 32.80)	5.22 (1.50, 18.14)	3.6 (0.34, 38.30)
Imipramine	0.29 (-0.23, 0.81)	1.83 (0.51, 6.57)	5.86 (1.72, 19.97)	0.95 (0.18, 4.91)
Citalopram	-0.17 (-0.94, 0.59)	1.71 (0.32, 9.11)	-	-
Bupropion SR	-0.10 (-0.91, 0.70)	0.75 (0.12, 4.77)	-	-
Paroxetine	0.38 (0.21, 0.55)	1.04 (0.82, 1.32)	2.04 (1.26, 3.30)	0.63 (0.42, 0.94)
NK1R antagonist	0.21 (-0.15, 0.56)	0.83 (0.42, 1.64)	1.51 (0.61, 3.77)	0.55 (0.13, 2.31)
Topiramate	0.29 (-0.13, 0.71)	0.64 (0.28, 1.48)	3.46 (1.06, 11.24)	0.37 (0.11, 1.25)
Divalproex	-0.14 (-0.55, 0.28)	0.91 (0.38, 2.18)	-	0.25 (0.04, 1.57)
Guanfacine	0.12 (-0.33, 0.57)	0.58 (0.20, 1.68)	-	0.26 (0.03, 2.67)
Brofaromine	0.47 (-0.12, 1.06)	0.96 (0.35, 2.62)	-	1.75 (0.72, 4.28)
Lamotrigine	-	8.00 (0.58, 110.27)	2.5 (0.17, 36.04)	Excluded
Risperidone	0.27 (0.01, 0.54)	0.59 (0.25, 1.39)	11.63 (1.20, 112.25)	0.39 (0.11, 1.47)
Sertraline	0.23 (0.09, 0.37)	0.91 (0.71, 1.15)	1.85 (1.03, 3.32)	0.64 (0.40, 1.00)
Olanzapine	0.51 (-0.03, 1.05)	0.83 (0.29, 2.37)	3.35 (0.98, 11.46)	0.26 (0.04, 1.65)
Fluoxetine	0.30 (0.09, 0.51)	1.35 (0.85, 2.14)	1.72 (0.96, 3.07)	0.99 (0.48, 2.03)
Amitriptyline	0.34 (-0.32, 1.01)	0.66 (0.18, 2.46)	1.89 (0.34, 10.48)	0.15 (0.01, 3.07)
Mirtazapine	0.79 (-0.08, 1.66)	1.17 (0.22, 6.28)	4.28 (0.60, 30.32)	0.68 (0.03, 18.43)
Tiagabine	0.02 (-0.33, 0.37)	1.60 (0.94, 2.73)	0.97 (0.38, 2.44)	1 (0.38, 2.62)

Venlafaxine ER	0.31 (0.10, 0.53)	1.23 (0.90, 1.70)	1.93 (0.79, 4.72)	0.85 (0.50, 1.46)
Prazosin	-0.06 (-0.32, 0.20)	0.95 (0.58, 1.57)		0.72 (0.24, 2.14)
Sertraline vs				
Nefazodone	0.01 (-0.79, 0.81)	-	-	0.94 (0.12, 7.50)
Citalopram	-0.65 (-1.27, -0.03)	1.33 (0.35, 5.13)	-	-
Venlafaxine ER	0.07 (-0.23, 0.37)	1.29 (0.83, 2.02)	-	1.39 (0.71, 2.71)
Phenelzine vs				
Imipramine	-0.69 (-1.22, -0.16)	0.24 (0.06, 0.97)	1.12 (0.34, 3.67)	0.26 (0.03, 2.59)
Fluvoxamine vs				
Reboxetine	-0.17 (-0.96, 0.62)	0.22 (0.05, 0.98)	-	-
Paroxetine vs				
Desipramine	0.14 (-0.33, 0.62)	2.27 (0.96, 5.36)	-	-

Table 4 (Appendix 7). Summary estimates for primary and secondary outcomes derived from standard pairwise meta-analysis (using random effects model and assuming a common heterogeneity). Heterogeneity was estimated using the restricted maximum likelihood (REML). SMDs smaller than 0 or ORs smaller than 1 favor the first treatment. Underlined results indicate statistical significance.

Comparisons	Primary outcomes		Secondary outcomes	
	Change in symptoms	Any-cause dropouts	Response rate	Dropouts due to adverse events
	SMD (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Placebo vs				
Nefazodone	0.23 (-0.41, 0.86)	0.72 (0.20, 2.58)	1.00 (0.26, 3.82)	0.11 (0.01, 2.04)
Phenelzine	1.07 (0.52, 1.63)	7.5 (1.72, 32.80)	5.25 (1.72, 15.98)	3.60 (0.34, 38.30)
Imipramine	0.29 (-0.20, 0.79)	1.83 (0.51, 6.57)	5.77 (1.94, 17.15)	0.95 (0.18, 4.91)
Citalopram	-0.17 (-0.91, 0.56)	1.71 (0.32, 9.11)	-	-
Bupropion SR	-0.10 (-0.88, 0.67)	0.75 (0.12, 4.77)	-	-
Paroxetine	0.38 (0.20, 0.56)	1.04 (0.82, 1.32)	1.98 (1.46, 2.69)	0.63 (0.42, 0.95)
NK1R antagonist	0.20 (-0.11, 0.51)	1.31 (0.16, 10.95)	1.53 (0.59, 4.00)	0.55 (0.13, 2.31)
Topiramate	0.29 (-0.12, 0.69)	0.68 (0.20, 2.27)	3.44 (1.21, 9.78)	0.37 (0.11, 1.25)
Divalproex	-0.19 (-0.75, 0.38)	0.91 (0.38, 2.18)	-	0.25 (0.04, 1.57)
Guanfacine	0.12 (-0.30, 0.54)	0.58 (0.20, 1.68)	-	0.26 (0.03, 2.68)
Brofaromine	0.47 (-0.08, 1.02)	0.96 (0.35, 2.62)	-	1.75 (0.72, 4.28)
Lamotrigine	-	8.00 (0.58, 110.27)	2.5 (0.19, 32.19)	Excluded
Risperidone	0.26 (0.04, 0.47)	0.60 (0.22, 1.67)	11.63 (1.38, 98.18)	0.40 (0.11, 1.47)
Sertraline	0.25 (0.07, 0.42)	0.91 (0.71, 1.15)	1.98 (0.89, 4.45)	0.64 (0.40, 1.00)
Olanzapine	0.49 (-0.14, 1.13)	0.83 (0.29, 2.37)	3.46 (1.11, 10.78)	0.26 (0.04, 1.65)
Fluoxetine	0.31 (0.07, 0.55)	1.35 (0.85, 2.14)	1.77 (0.87, 3.62)	0.99 (0.48, 2.03)
Amitriptyline	0.34 (-0.29, 0.97)	0.66 (0.18, 2.46)	1.90 (0.41, 8.74)	0.15 (0.01, 3.07)
Mirtazapine	0.79 (-0.05, 1.63)	1.17 (0.22, 6.28)	4.28 (0.71, 25.92)	0.68 (0.03, 18.43)
Tiagabine	0.02 (-0.26, 0.30)	1.60 (0.94, 2.73)	0.97 (0.58, 1.62)	1.00 (0.38, 2.62)
Venlafaxine ER	0.31 (0.16, 0.46)	1.23 (0.90, 1.70)	1.93 (1.22, 3.06)	0.83 (0.41, 1.67)

Prazosin	-0.07 (-0.46, 0.32)	0.95 (0.58, 1.57)	-	0.71 (0.24, 2.16)
Sertraline vs				
Nefazodone	0.01 (-0.76, 0.78)	-	-	0.94 (0.12, 7.50)
Citalopram	-0.65 (-1.23, -0.07)	1.33 (0.35, 5.13)	-	-
Venlafaxine ER	0.07 (-0.14, 0.28)	1.29 (0.83, 2.02)	-	1.39 (0.71, 2.72)
Phenelzine vs				
Imipramine	-0.69 (-1.20, -0.19)	0.24 (0.06, 0.97)	1.09 (0.38, 3.12)	0.26 (0.03, 2.59)
Fluvoxamine vs				
Reboxetine	-0.17 (-0.93, 0.59)	0.22 (0.05, 0.98)	-	-
Paroxetine vs				
Desipramine	0.14 (-0.28, 0.56)	2.27 (0.96, 5.36)	-	-

Table 5 (Appendix 7). Summary estimates for primary and secondary outcomes derived from standard pairwise meta-analysis (using a random effects model and using different heterogeneity parameters). Heterogeneity was estimated using the method of moments estimator. SMDs smaller than 0 or ORs smaller than 1 favor the first treatment. Underlined results indicate statistical significance.

Network meta-analysis results

Table 1 and Fig. 3 (Appendix 6) show the relative treatment effects from NMA for the two primary outcomes (change in symptom's severity and all-cause dropouts). In terms of efficacy, phenelzine, desipramine, paroxetine, venlafaxine, fluoxetine, risperidone, and sertraline were more effective than placebo (Fig. 3, Appendix 6). Phenelzine appeared to be statistically significantly more effective than nearly half of the other active treatments included in the network (9 out of 21), while both citalopram and divalproex were statistically significantly less efficacious than phenelzine, desipramine, and paroxetine (citalopram was also inferior to mirtazapine, olanzapine, venlafaxine, and fluoxetine) (Table 1). In terms of dropout rate, phenelzine was the only drug which was significantly better than placebo (OR 7.50, 95% CI 1.72–32.80) and most of the other active treatments (Table 1). No other statistically significant differences were found between the rest of the treatments and placebo (Fig. 1). Notwithstanding fewer events, response rate data did match with our efficacy findings using continuous data (Appendix 8); in terms of dropouts due to adverse events, no drug was statistically significantly better tolerated than placebo, but sertraline and paroxetine performed worse than placebo (OR 0.59, 95% CI 0.38–0.91 and 0.63, 95% CI 0.42–0.94, respectively), and brofaromine better than paroxetine (OR 2.78, 95% CI 1.04–7.42), topiramate (OR 4.77, 95% CI 1.04–21.75), and sertraline (OR 2.99, 95% CI 1.10–8.09) (Appendix 8).

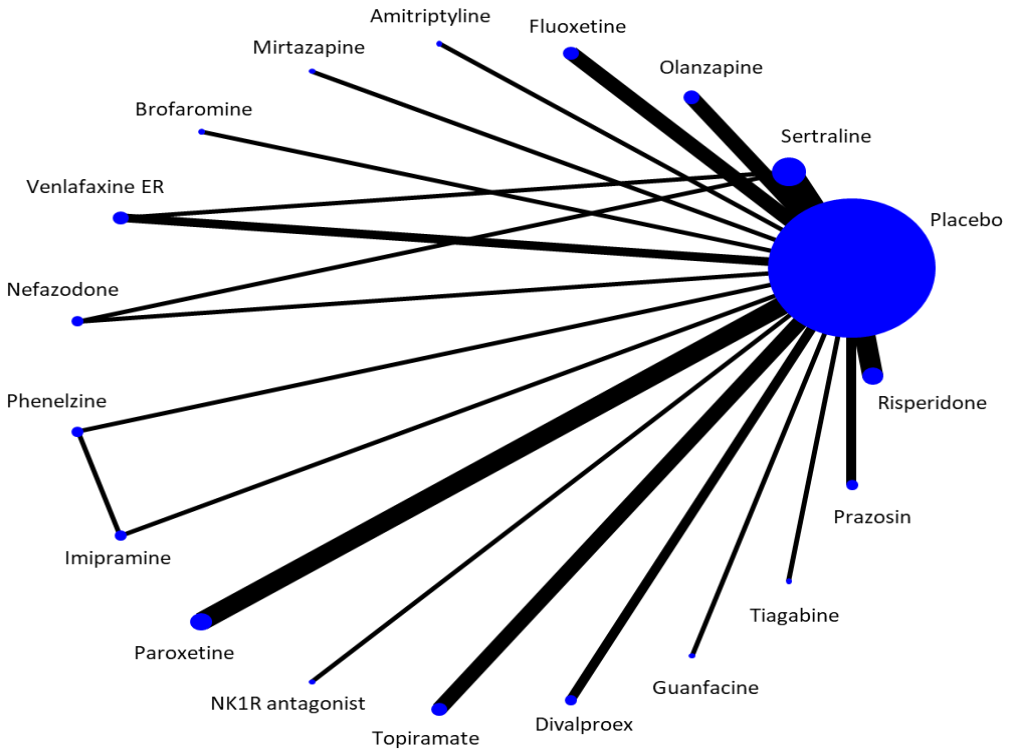


Figure 3 (Appendix 6). Network plot for the outcome 'Dropouts due to adverse events'. Nodes and edges are weighted according to the number of studies involved in each treatment comparison.

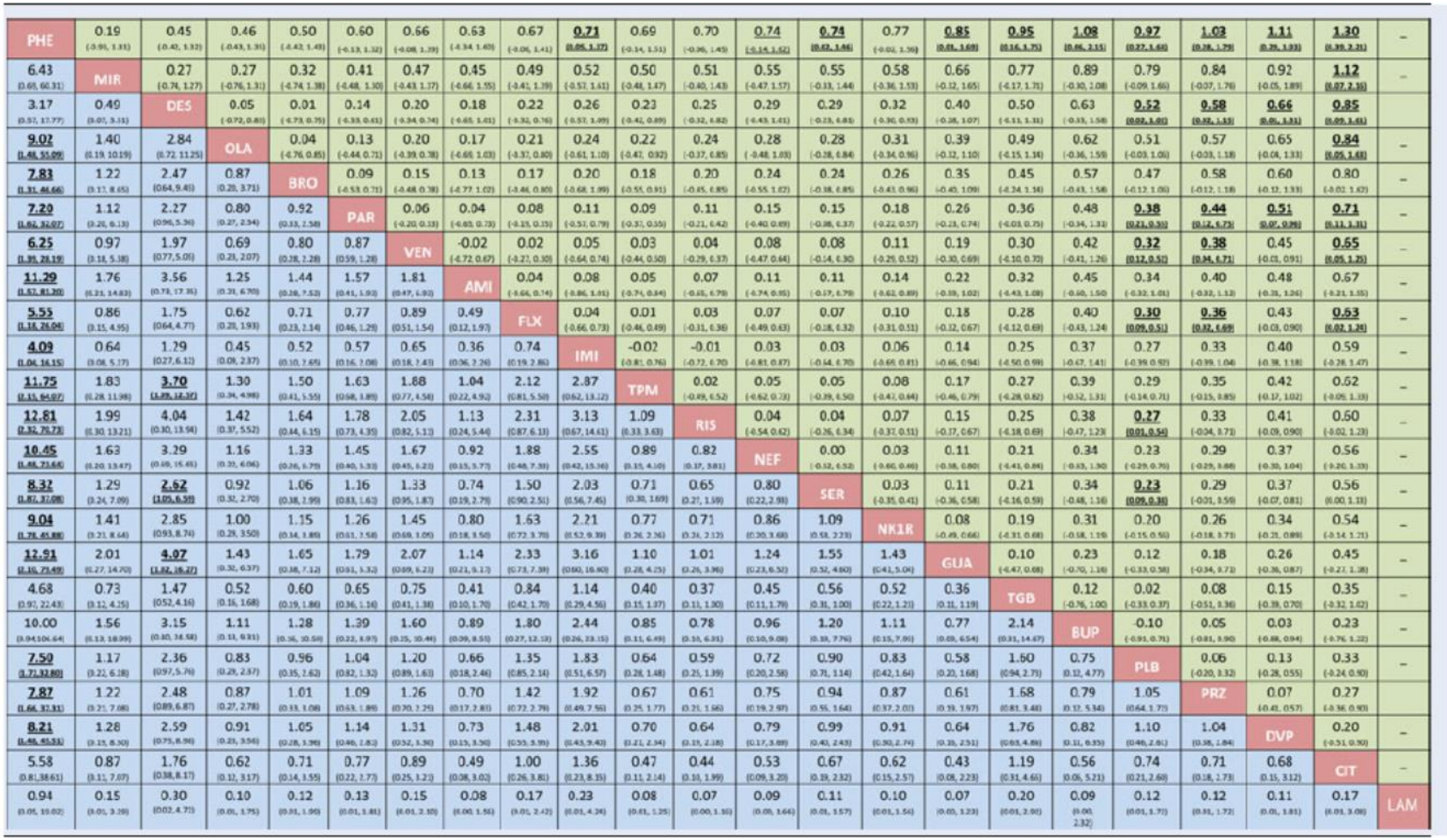


Table 1 (Appendix 8). NMA results for the two primary outcomes. **Legend:** Mean change in symptoms severity (green) and all-cause dropout rate (blue). For efficacy (green), standardized mean difference values greater than 0 indicated that the treatment specified in the row is more

efficacious. For acceptability, odds ratios greater than 1 indicated that the treatment specified in the column is better (fewer dropouts). Bold underlined results indicate statistical significance. The overall heterogeneity (τ) is equal to 0.1 for efficacy and equal to 0 for acceptability. For efficacy, I2 was 22.4% for heterogeneity and 22.5% for inconsistency; for acceptability, I2 was 0% for heterogeneity and 8% for inconsistency. AMI, amitriptyline; BRO, bromipramine; BUP, bupropion; CIT, citalopram; DES, desipramine; DVP, divalproex; FLX, fluoxetine; GUA, guanfacine; IMI, imipramine; LAM, lamotrigine; MIR, mirtazapine; NEF, nefazodone; NK1R, NK1 receptor antagonist; OLA, olanzapine; PAR, paroxetine; PHE, phenelzine; PLB, placebo; PRZ, prazosin; RIS, risperidone; SER, sertraline; TGB, tiagabine; TPM, topiramate; VEN, venlafaxine.

The NMA was not able to assess statistically the transitivity assumption by comparing the distributions of potential effect modifiers across comparisons as most comparisons were informed by a small number of studies. Inconsistency was also evaluated in each loop of available evidence (Appendix 9). Although the NMA did not find any statistical evidence of inconsistency assuming either network-specific or loop-specific heterogeneity, there are a few closed loops per outcome and few studies involved, so one cannot exclude the possibility of potentially important inconsistency to be present. The design × treatment interaction model did not provide evidence that any of the networks present as a whole, statistically significant inconsistency (Appendix 10); again, the small number of closed loops and studies limits the power of these tests. The I^2 for both heterogeneity and inconsistency in NMA were calculated to distinguish between these two sources of variability. For efficacy as a continuous outcome, I^2 was 22.4% for heterogeneity and 22.5% for inconsistency; for acceptability, I^2 was 0% for heterogeneity and 8% for inconsistency. The percentage of variability attributed to heterogeneity was 43.2% for the dichotomous efficacy outcome (the respective measure for inconsistency could not be assessed for this outcome – see above). For dropout rate due to adverse events, I^2 was 0% for heterogeneity and 13% for inconsistency. Overall, all these measures were in general low, but it should be acknowledged that the uncertainty around them might be high (see below).

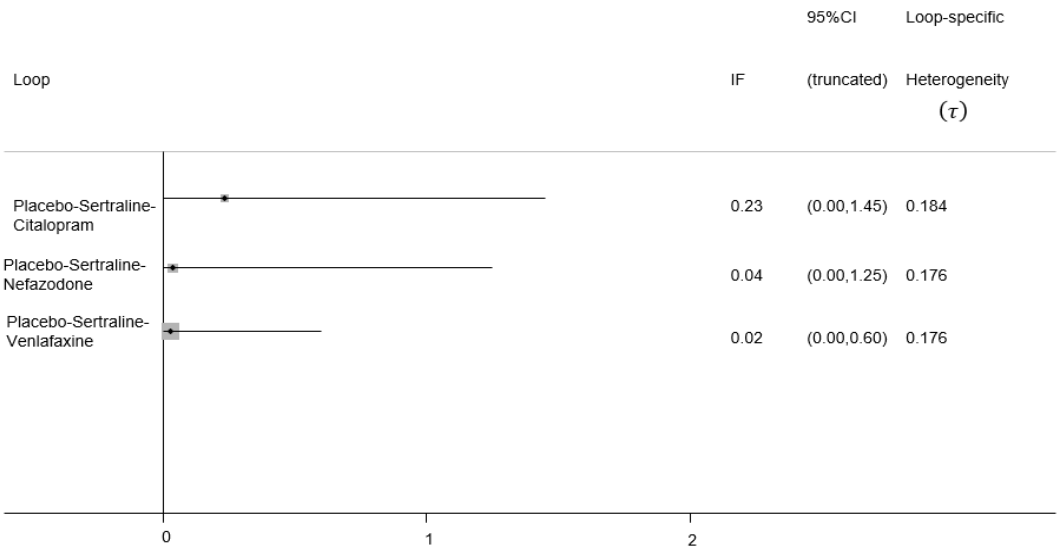


Figure 1 (Appendix 9). Inconsistency plot for the outcome 'Change in symptoms' assuming loop-specific heterogeneity estimates using the method of moments estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the absolute difference between direct and indirect estimates and therefore confidence intervals are truncated to zero. Loops that their lower CI limit does not reach the zero line are considered to present statistically significant inconsistency.

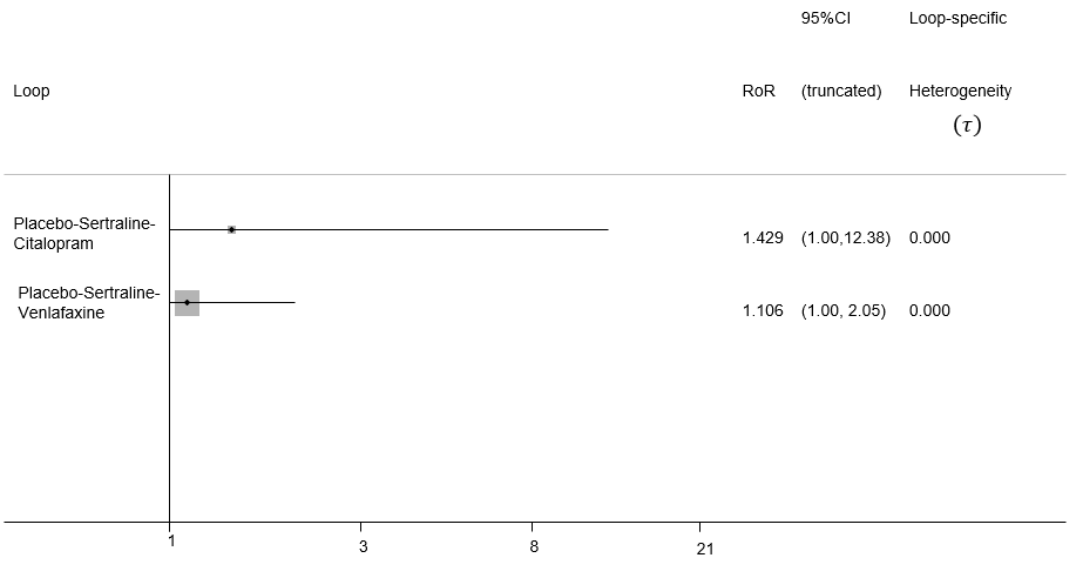


Figure 2 (Appendix 9). Inconsistency plot for the outcome 'Any-cause dropouts' assuming loop-specific heterogeneity estimates using the method of moments estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the ratio of the ORs from direct and indirect evidence in the loop and therefore confidence intervals are truncated to one. Loops that their lower CI limit does not reach the line of 1 are considered to present statistically significant inconsistency.

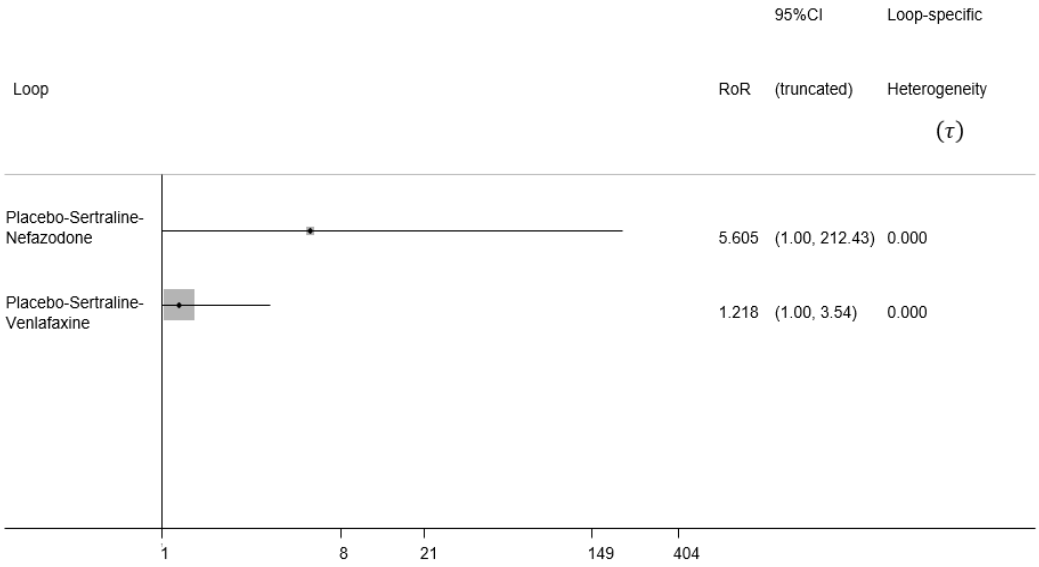


Figure 3 (Appendix 9). Inconsistency plot for the outcome 'Dropouts due to adverse events' assuming loop-specific heterogeneity estimates using the method of moments estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the ratio of the ORs from direct and indirect evidence in the loop and therefore confidence intervals are truncated to one. Loops that their lower CI limit does not reach the line of 1 are considered to present statistically significant inconsistency.

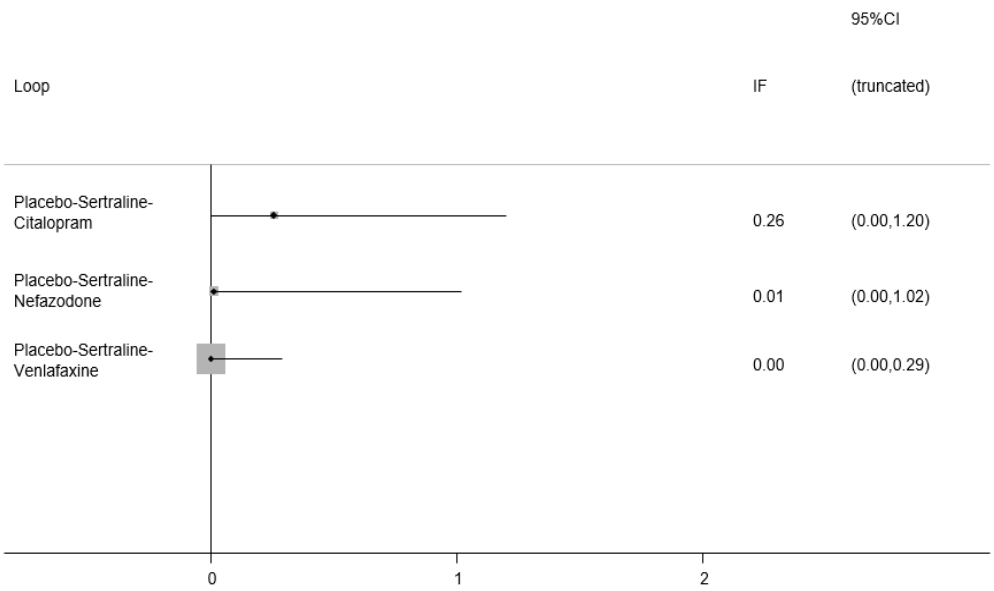


Figure 4 (Appendix 9). Inconsistency plot for the outcome 'Change in symptoms' assuming a network-specific heterogeneity common for all loops estimated using the restricted maximum likelihood estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the absolute difference between direct and indirect estimates and therefore confidence intervals are truncated to zero. Loops that their lower CI limit does not reach the zero line are considered to present statistically significant inconsistency.

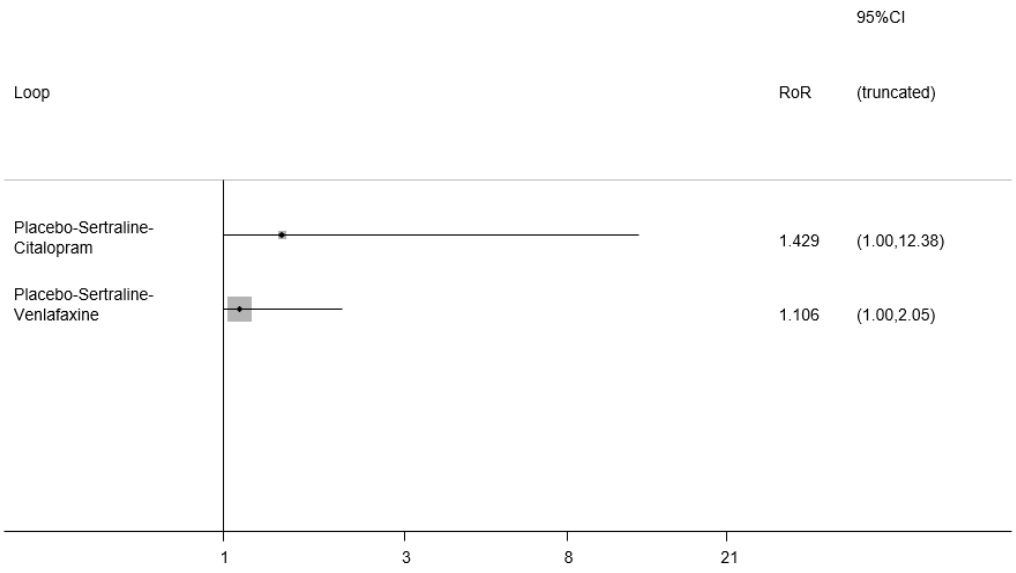


Figure 5 (Appendix 9). Inconsistency plot for the outcome 'Any-cause dropouts' assuming a network-specific heterogeneity common for all loops estimated using the restricted maximum likelihood estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the ratio of the ORs from direct and indirect evidence in the loop and therefore confidence intervals are truncated to one. Loops that their lower CI limit does not reach the line of 1 are considered to present statistically significant inconsistency.

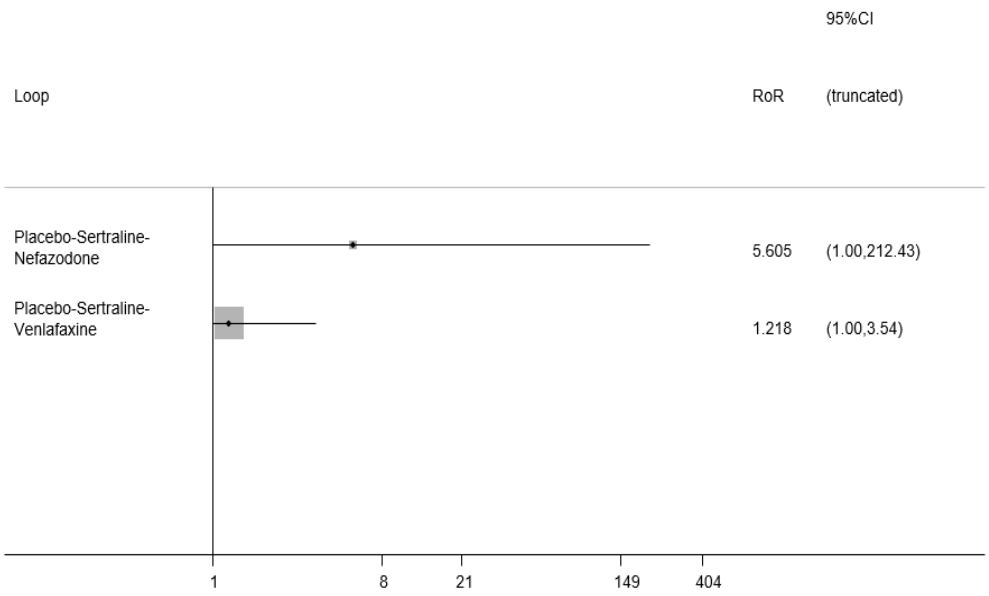


Figure 6 (Appendix 9). Inconsistency plot for the outcome 'Dropouts due to adverse events' assuming a network-specific heterogeneity common for all loops estimated using the restricted maximum likelihood estimator. Inconsistency factors (IF) along with their confidence intervals are displayed. IFs are calculated as the ratio of the ORs from direct and indirect evidence in the loop and therefore confidence intervals are truncated to one. Loops that their lower CI limit does not reach the line of 1 are considered to present statistically significant inconsistency.

Outcome	χ^2 test	Degrees of freedom	p-value	Heterogeneity (τ) under the consistency model	Heterogeneity (τ) under the inconsistency model
Change in symptoms	0.56	4	0.97	0.10	0.14
Any-cause dropouts	0.72	3	0.87	0	0
Response rate	Not implemented (neither loop nor design inconsistency can be assessed)				
Adverse events	3.04	3	0.38	0	0

Table 4 (Appendix 10). Design by treatment inconsistency model for the four outcomes.

For a continuous outcome in a 'drug versus placebo' comparison in mental health the suggested median value for τ is 0.22 and for a 'drug versus drug' comparison it is 0.20. Both values are greater than our estimation of heterogeneity for the efficacy as a continuous outcome using the restricted maximum likelihood (REML) estimator (τ = 0.1). For a binary mental health outcome, the suggested median values for τ are 0.35 and 0.31 for a 'drug versus placebo' and a 'drug versus drug' comparison, respectively. Our estimation of τ for the dichotomous efficacy outcome was 0.4, whereas the values of τ were 0 for all the remaining dichotomous outcomes, dropouts due to any cause and dropouts due to adverse events.

In Fig. 4 the hierarchical cluster analysis was used to group treatments according to their ranking for the two primary outcomes. Different colours represent different groups of treatments by considering jointly their relative ranking for two outcomes (treatments that belong to the same group may be considered as being of comparable performance with respect to both outcomes). According to all possible cluster rankings, phenelzine performed better than the rest of the treatments both in terms of efficacy and dropouts (Appendix 11); this was also supported by considering the actual effect sizes presented in Table 1 and Fig. 3. Although mirtazapine yielded a relatively high rank in the efficacy outcomes, the respective SUCRA value for the dropout outcome was 51.5% (Appendix 12). Brofaromine performed well in terms of change in symptoms and adverse events, whereas divalproex had the worst ranking considering this particular pair of outcomes. Risperidone was the best treatment in terms of response rate whereas it is among the worst for the outcome of adverse events. See Appendix 12 for all details about rankings and SUCRA values. The NMA could not perform the preplanned sensitivity analyses because only five studies were rated as low risk of bias for allocation concealment (see Appendix 3) and because I did not impute any outcome data (all information I needed was retrieved by checking for unpublished data and contacting the

original study authors). According to GRADE, the quality of evidence for primary outcomes was rated as low or very low for most comparisons.

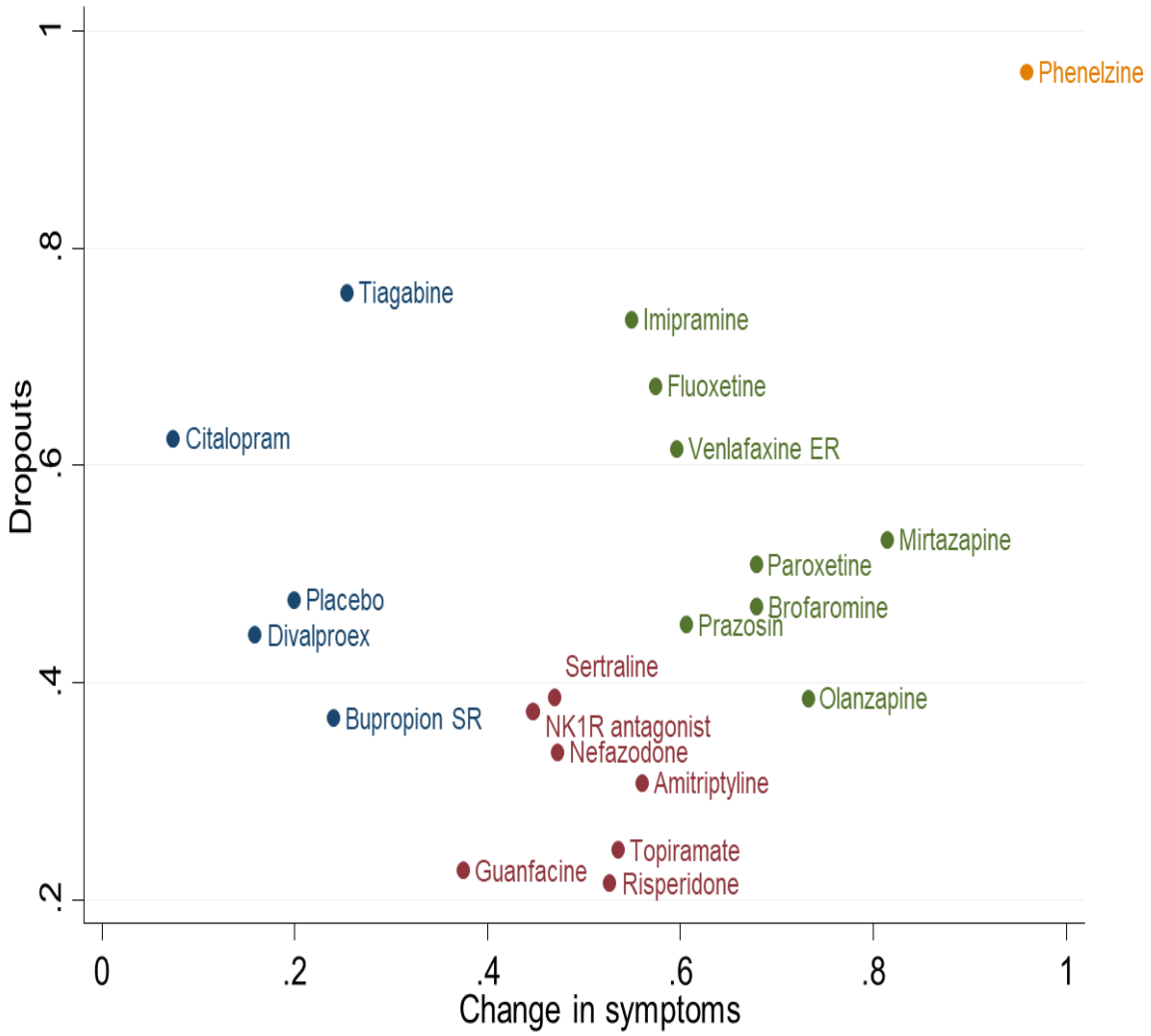


Figure 1 (Appendix 11). Clustered ranking based on SUCRA values for the outcomes 'Change in symptoms' (unadjusted model) and 'Any cause dropouts'. Hierarchical cluster analysis is performed to group the competing treatments. Different colors represent different groups according to treatments' similarity regarding the two outcomes.

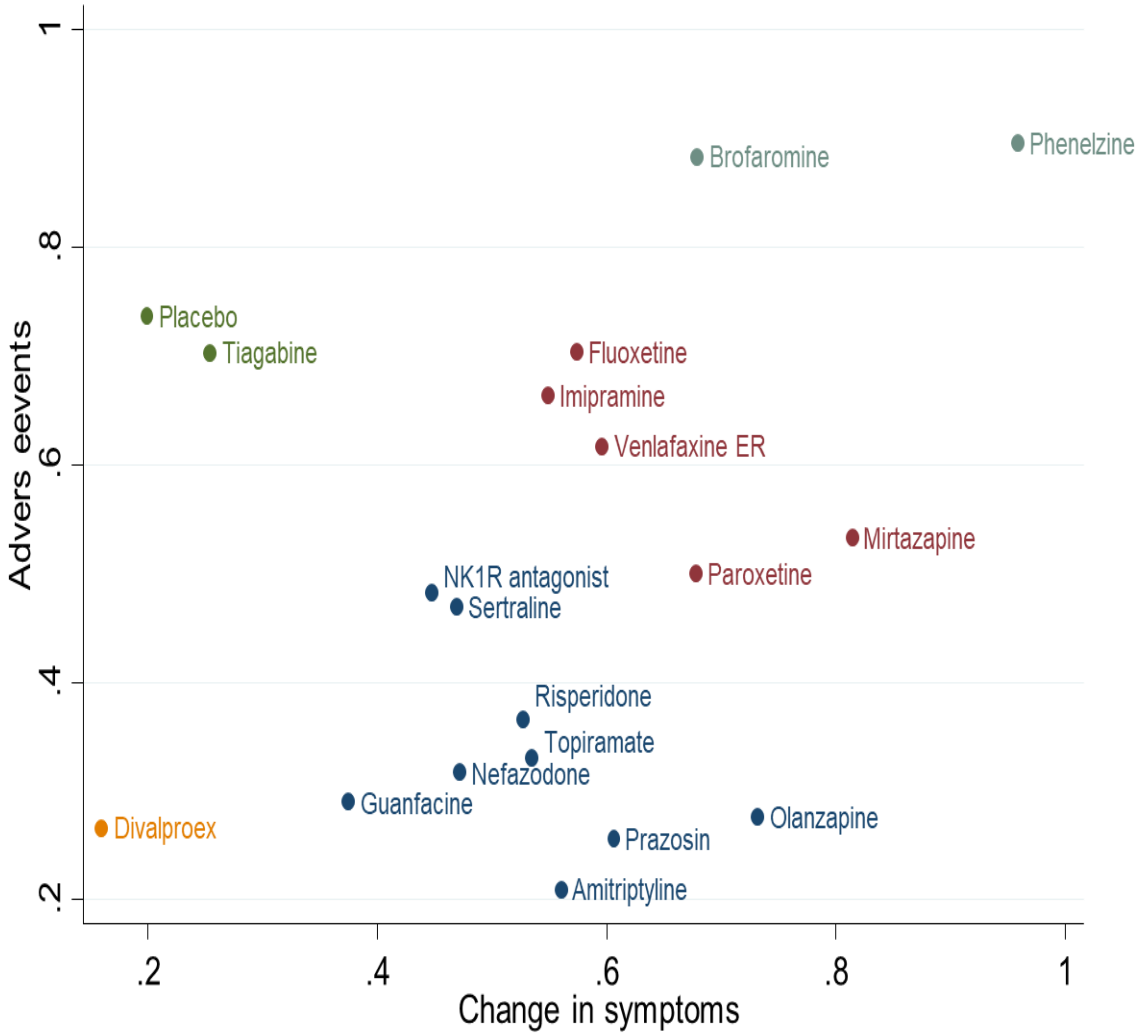


Figure 2 (Appendix 11). Clustered ranking based on SUCRA values for the outcomes 'Change in symptoms' (unadjusted model) and 'Dropouts due to adverse events'. Hierarchical cluster analysis is performed to group the competing treatments. Different colors represent different groups according to treatments' similarity regarding the two outcomes.

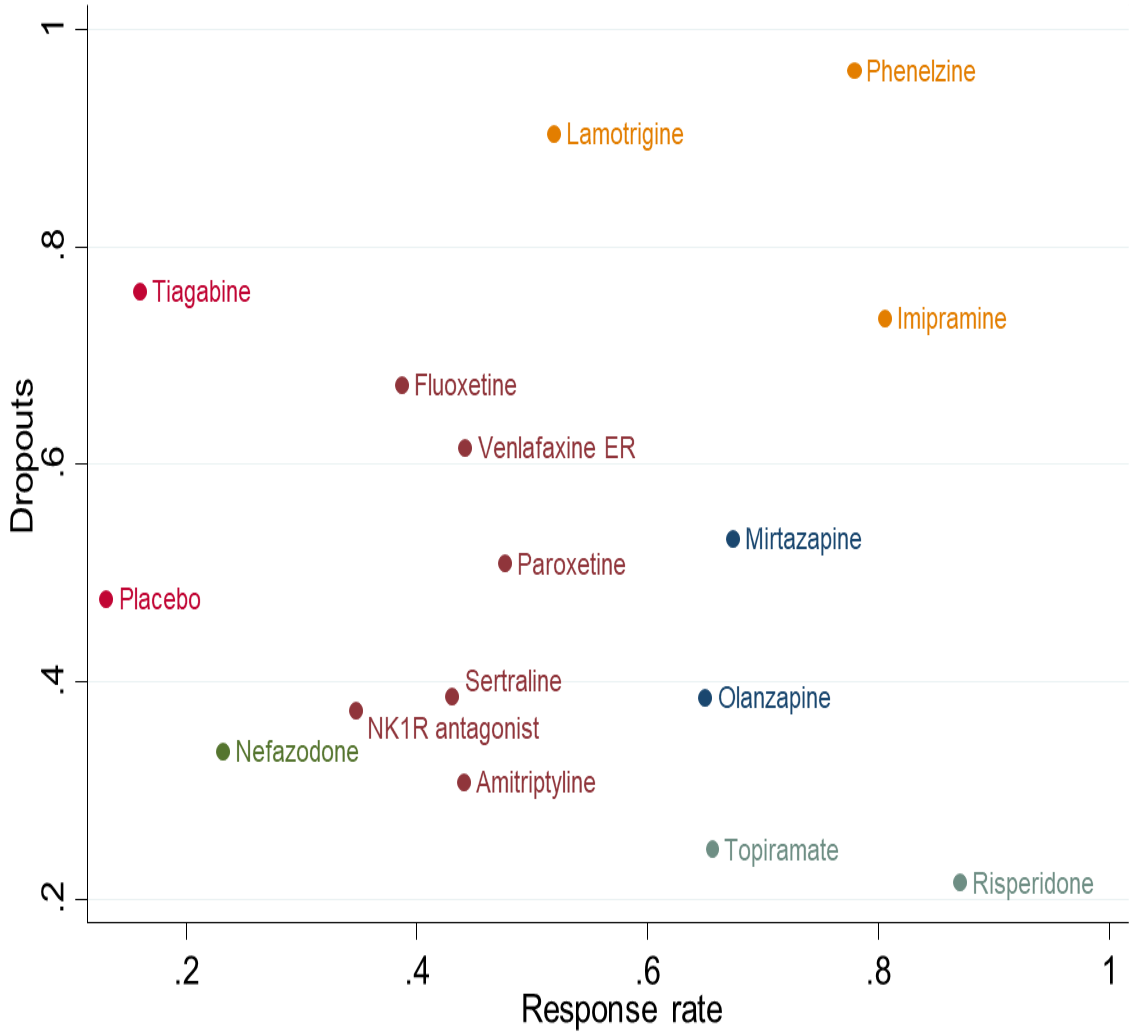


Figure 3 (Appendix 11). Clustered ranking based on SUCRA values for the outcomes 'Response rate' and 'Any cause dropouts'. Hierarchical cluster analysis is performed to group the competing treatments. Different colors represent different groups according to treatments' similarity regarding the two outcomes.

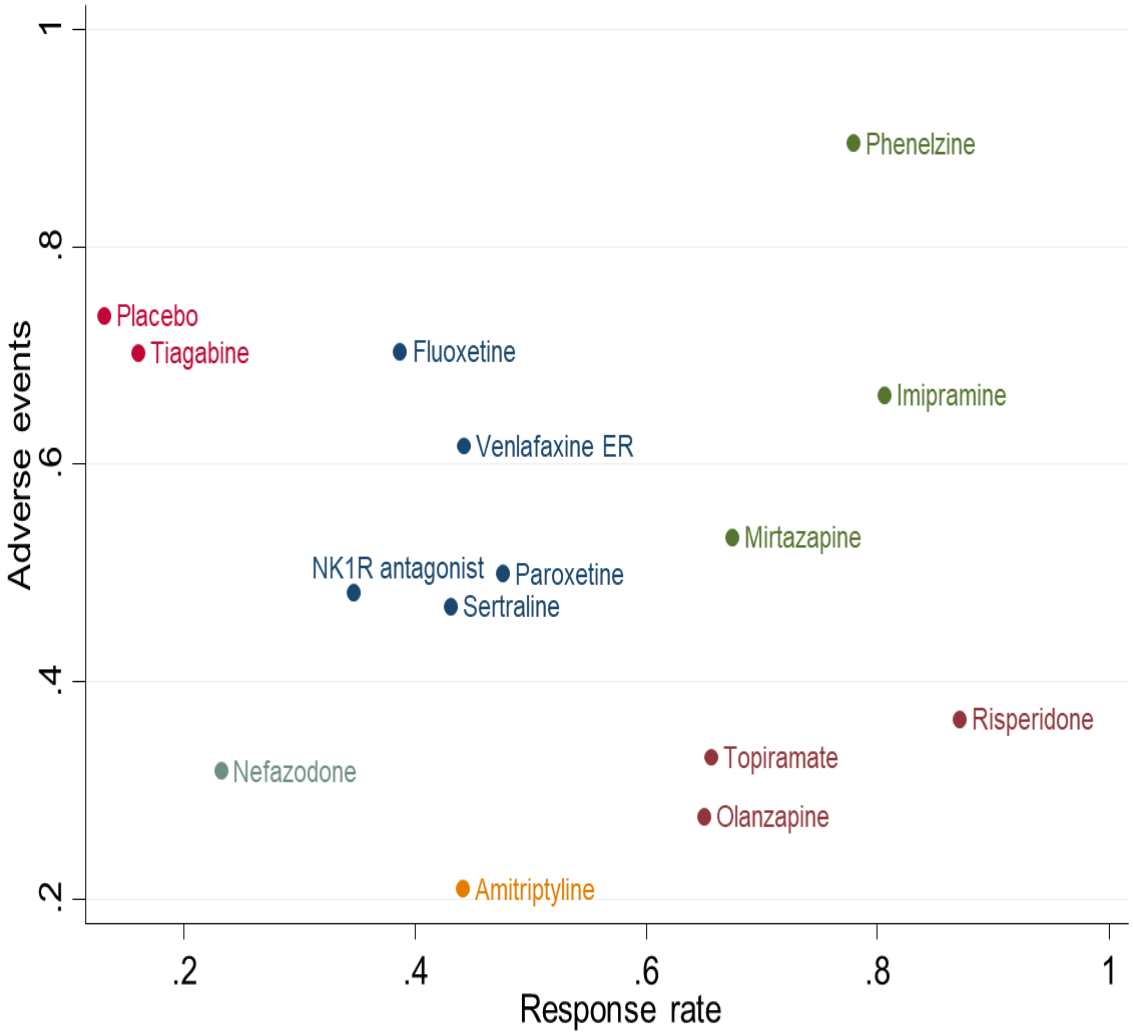


Figure 4 (Appendix 11). Clustered ranking based on SUCRA values for the outcomes 'Response rate' and 'Dropouts due to adverse events'. Hierarchical cluster analysis is performed to group the competing treatments. Different colors represent different groups according to treatments' similarity regarding the two outcomes.

Treatment	Change in symptoms	Any-cause dropouts	Response rate	Adverse events
Phenelzine	**93.8**	96.3	**77.5**	89.1
Mirtazapine	**84.1**	51.5	**70.7**	51.6
Desipramine	**75.6**	83.2	-	-
Olanzapine	**74.2**	36.8	**64.0**	26.5
Brofaromine	**69.3**	44.7	-	87.3
Paroxetine	**67.6**	50.0	**49.4**	47.9
Venlafaxine ER	**59.9**	60.5	**45.5**	60.0
Amitriptyline	**59.1**	29.1	**41.6**	21.1
Fluoxetine	**57.3**	66.3	**40.2**	70.4
Imipramine	**51.4**	71.7	**73.7**	63.5
Topiramate	**54.9**	23.5	**66.0**	32.4
Risperidone	**54.3**	20.1	**86.4**	32.5
Nefazodone	**49.4**	31.2	**22.9**	30.0
Sertraline	**48.8**	37.1	**44.0**	44.7
NK1R antagonist	**45.9**	34.9	**34.5**	43.9
Guanfacine	**38.5**	21.8	-	28.9
Tiagabine	**26.8**	74.1	**17.8**	69.3
Bupropion SR	**25.4**	37.3	-	-
Placebo	**21.7**	46.1	**14.3**	72.6
Prazosin	**18.3**	42.7	-	54.8
Divalproex	**15.4**	42.1	-	23.5
Citalopram	**8.2**	58.5	-	-

Lamotrigine	-	90.6	**51.5**	-

Table 1 (Appendix 12). SUCRA values for the four outcomes.

Treatment	Change in symptoms	Any-cause dropouts	Response rate	Adverse events
Phenelzine	**2.3**	1.8	**4.4**	3.0
Mirtazapine	**4.3**	11.7	**5.4**	9.7
Desipramine	**6.1**	4.7	-	-
Olanzapine	**6.4**	14.9	**6.4**	14.2
Brofaromine	**7.4**	13.2	-	3.3
Paroxetine	**7.8**	12.0	**8.6**	10.4
Venlafaxine ER	**9.4**	9.7	**9.2**	8.2
Amitriptyline	**9.6**	16.6	**9.8**	15.2
Fluoxetine	**10.0**	8.4	**10.0**	6.3
Imipramine	**11.2**	7.2	**4.9**	7.6
Topiramate	**10.5**	17.8	**6.1**	13.2
Risperidone	**10.6**	18.6	**3.0**	13.2
Nefazodone	**11.6**	16.1	**12.6**	13.6
Sertraline	**11.8**	14.8	**9.4**	11.0
NK1R antagonist	**12.4**	15.3	**10.8**	11.1
Guanfacine	**13.9**	18.2	-	13.8
Tiagabine	**16.4**	6.7	**13.3**	6.5
Bupropion SR	**16.7**	14.8	-	-
Placebo	**17.4**	12.9	**13.9**	5.9
Prazosin	**18.2**	13.6	-	9.1
Divalproex	**18.8**	13.7	-	14.8
Citalopram	**20.3**	10.1	-	-

Lamotrigine	-	3.1	**8.3**	-

Table 2 (Appendix 12). Mean ranks for the four outcomes

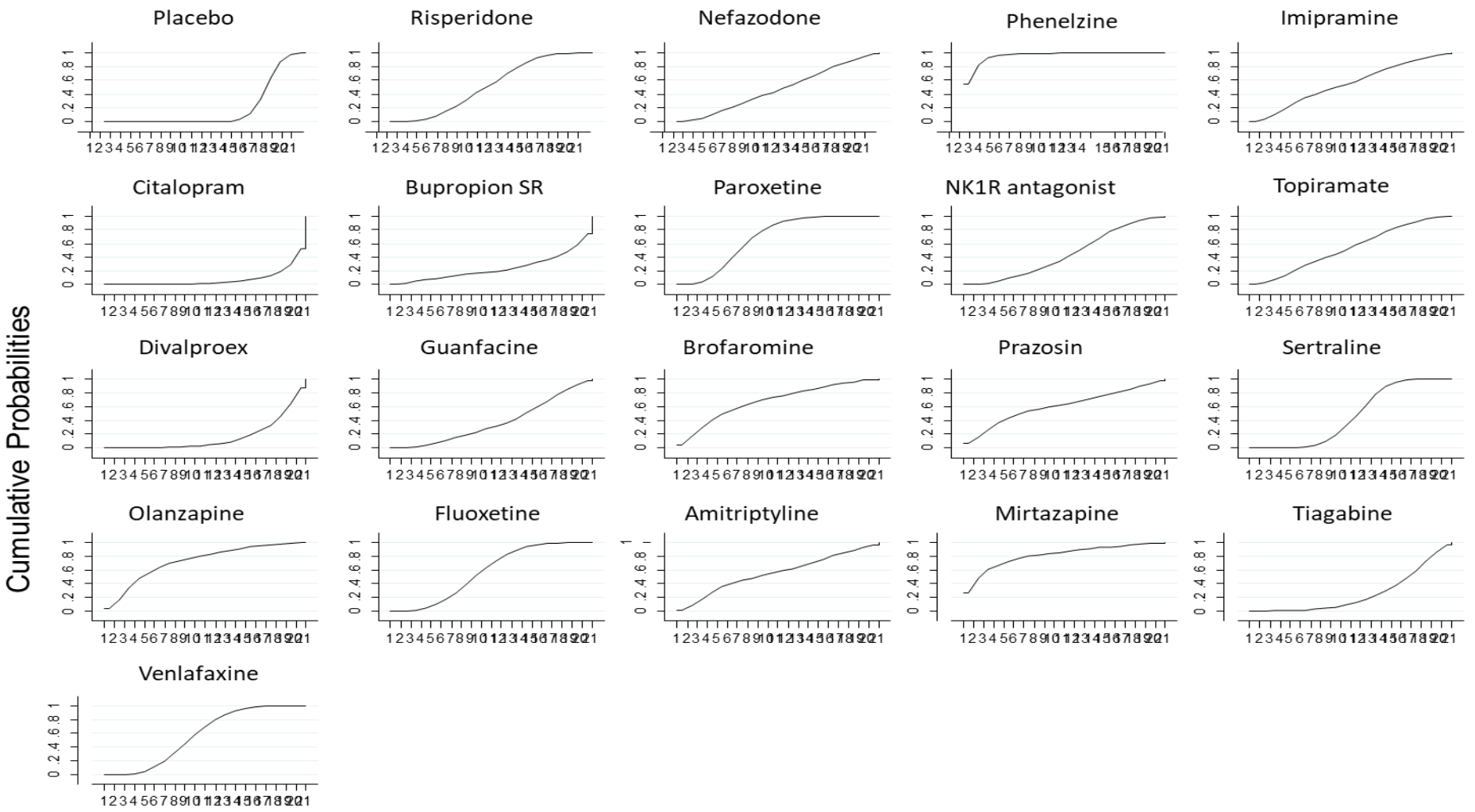


Figure 1 (Appendix 12). Plots of the surface under the cumulative ranking curves (SUCRAs) for all treatments for the 'Change in symptoms' outcome.

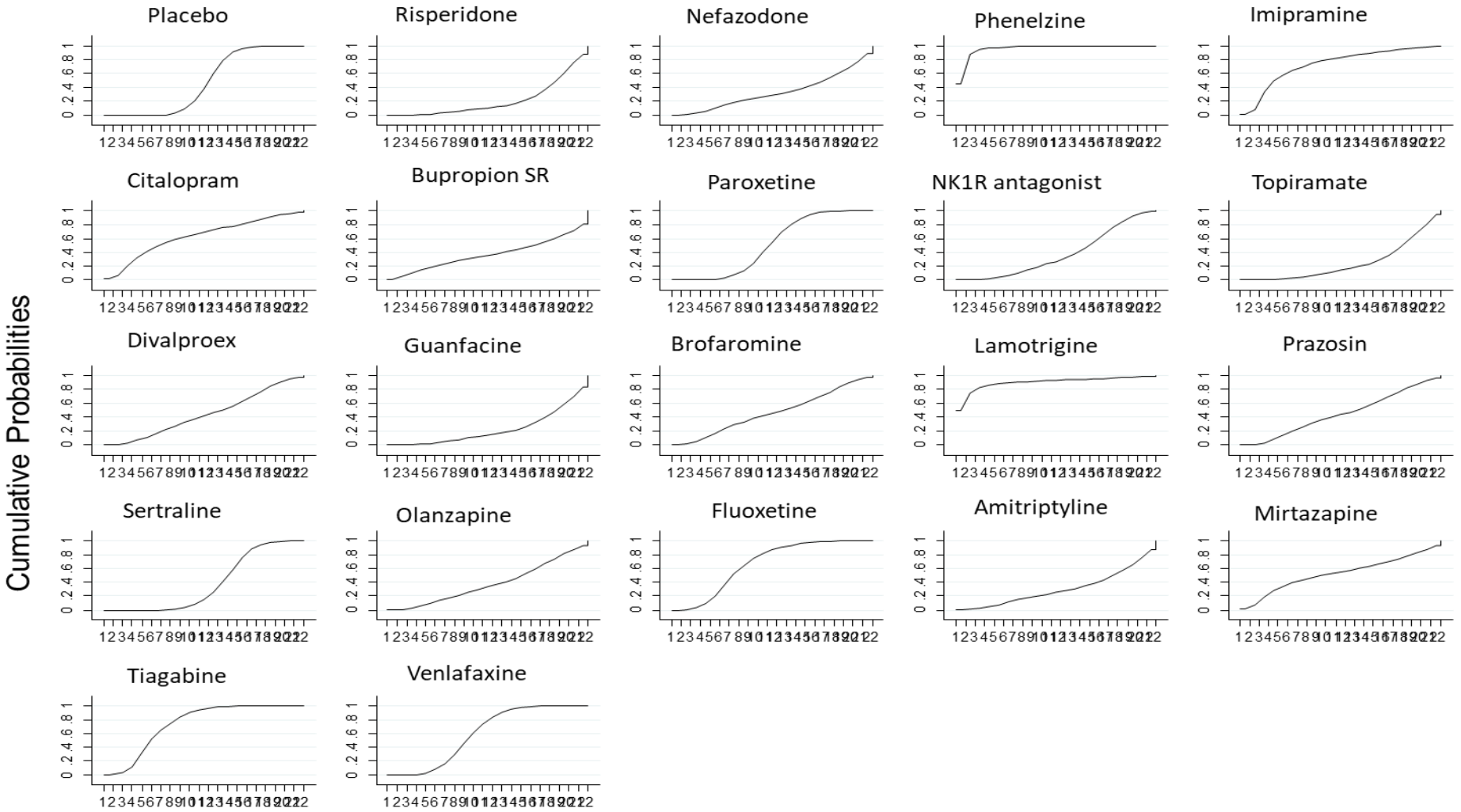


Figure 2 (Appendix 12). Plots of the surface under the cumulative ranking curves (SUCRAs) for all treatments for the 'Any-cause dropouts' outcome.

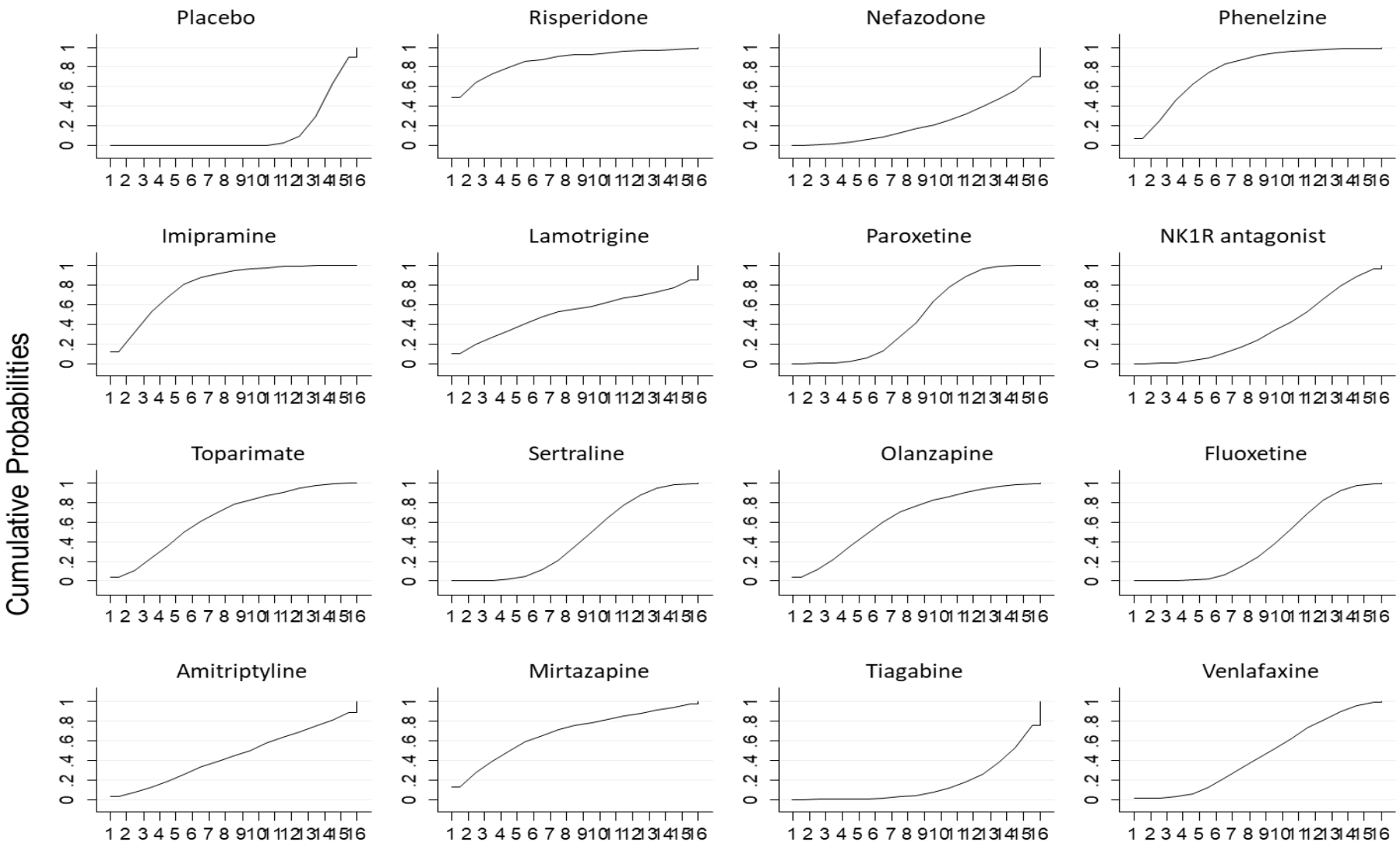


Figure 3 (Appendix 12). Plots of the surface under the cumulative ranking curves (SUCRAs) for all treatments for the 'Response rate' outcome.

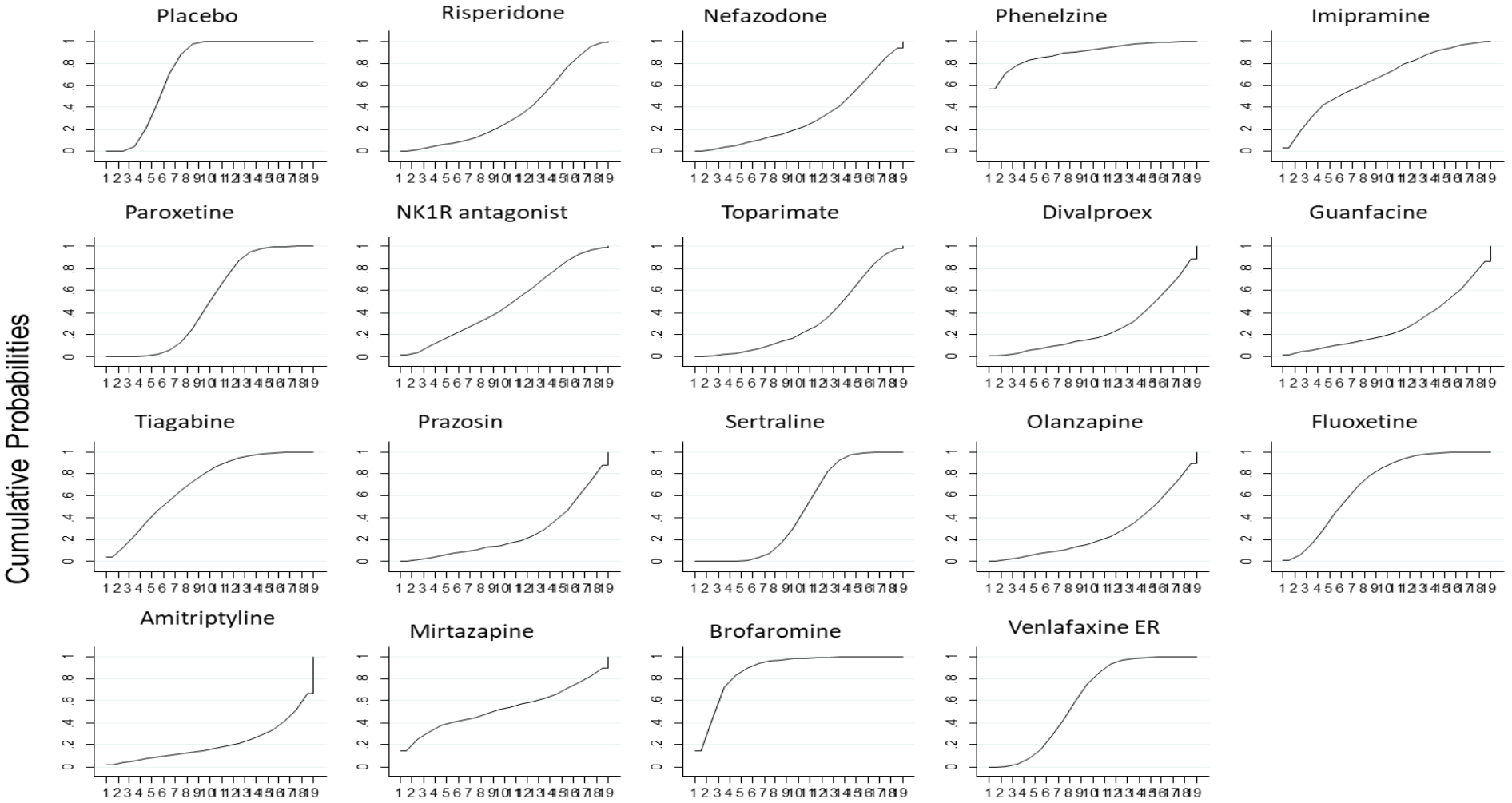


Figure 4 (Appendix 12). Plots of the surface under the cumulative ranking curves (SUCRAs) for all treatments for the 'Dropouts due to adverse events' outcome.

Impact of effect modifiers

Because of concerns about power to detect potentially important heterogeneity and inconsistency, network meta-regression models were applied to explore the impact on effect modifiers on heterogeneity and inconsistency. Pre-specified covariates were included in separate network meta-regression models. All results are presented in Appendix 13. For the primary efficacy outcome, the meta-regression model that accounted for baseline severity resulted in a marginally non-significant coefficient 0.11 (95% CI −0.01 to 0.22) implying that the active treatments tended to be more effective (compared with placebo) in studies with more severe patients. The estimation of heterogeneity (τ) was of 0.1 for both the meta-regression model accounting for baseline severity and the model without covariates, showing that accounting for baseline severity did not explain heterogeneity. Appendix 14 presents the effect sizes and the treatment hierarchy (using SUCRAs) of the standard analysis and those from the meta-regression model at the mean centralised baseline severity. Accounting for differences in baseline severity across studies had a minimal impact on the effect sizes and the treatment ranking.

	Variance of the observed relative effects (positive values indicate that less precise studies tend to show placebo better than more precise studies)	Baseline severity (positive values indicate that studies with greater baseline tend to show active treatment better than studies with lower baseline)	Publication year (positive values indicate that older studies tend to show active treatment better than newer studies)	Sponsorship (positive values indicate that the non-sponsored treatment is favored)
Change in symptoms	-0.35 (95% CI: -2.26, 1.63) ($\tau = 0.1$)	0.11 (95% CI: 0.00, 0.21) ($\tau = 0.1$)	0.13 (95%CI: -0.03, 0.30) ($\tau = 0.1$)	0.13 (95%CI: -0.14, 0.39) ($\tau = 0.1$)
Dropouts due to any cause	0.19 (95% CI : -0.58, 1.03) ($\tau = 0.1$)	0.16 (95% CI : -0.13, 0.46) ($\tau = 0.2$)	0.11 (95% CI : -0.25, 0.48) ($\tau = 0.1$)	0.32 (95% CI : -0.18, 0.85) ($\tau = 0.1$)
Response rate	-0.22 (95% CI: -1.50, 1.20) ($\tau = 0.4$)	0.26 (95% CI: -0.22, 0.74) ($\tau = 0.5$)	0.06 (95% CI: -0.61, 0.89) ($\tau = 0.6$)	0.16 (95% CI: -1.08, 1.18) ($\tau = 0.5$)
Dropouts due to adverse events	0.38 (95% CI 0.13 to 0.93) ($\tau = 0.1$)	0.25 (95% CI: -0.33, 0.87) ($\tau = 0.1$)	0.13 (95% CI: -0.66, 0.94) ($\tau = 0.2$)	-0.99 (95% CI: -1.97, 0.08) ($\tau = 0.3$)

Table 1 (Appendix 13). Network meta-regression coefficients for the covariates variance, baseline severity, publication year and sponsorship.

TREATMENT	EFFECT ESTIMATES		SUCRAs	
	Standard analysis	Model that accounts for baseline severity (95% CI)	Standard analysis	Model that accounts for baseline severity
Phenelzine	**0.97 (0.27, 1.68)**	**1.12 (0.41, 1.81)**	93.8	95.3
Mirtazapine	0.79 (-0.09, 1.66)	0.79 (-0.04, 1.63)	84.1	82.8
Desipramine	**0.52 (0.02, 1.02)**	0.41 (-0.55, 1.39)	75.6	60.3
Olanzapine	0.51 (-0.03, 1.06)	0.53 (-0.01, 1.08)	74.2	72.7
Brofaromine	0.47 (-0.12, 1.06)	0.47 (-0.16, 1.11)	69.3	67.7
Paroxetine	**0.38 (0.21, 0.55)**	0.27 (-0.52, 1.08)	67.6	50.1
Venlafaxine ER	**0.32 (0.12, 0.52)**	0.34 (-0.09, 0.77)	59.9	59.0
Amitriptyline	0.34 (-0.32, 1.01)	-	59.1	-
Fluoxetine	**0.30 (0.09, 0.51)**	**0.30 (0.06, 0.56)**	57.3	56.5
Imipramine	0.27 (-0.39, 0.92)	0.42 (-0.36, 1.15)	51.4	61.2
Topiramate	0.29 (-0.14, 0.71)	0.29 (-0.15, 0.72)	54.9	53.6
Risperidone	**0.27 (0.01, 0.54)**	0.27 (-0.03, 0.59)	54.3	52.1
Nefazodone	0.23 (-0.29, 0.76)	0.27 (-0.27, 0.82)	49.4	51.0
Sertraline	**0.23 (0.09, 0.38)**	**0.27 (0.05, 0.50)**	48.8	51.9
NK1R antagonist	0.20 (-0.15, 0.56)	-	45.9	-
Guanfacine	0.12 (-0.33, 0.58)	0.17 (-0.32, 0.66)	38.5	42.2
Tiagabine	0.02 (-0.33, 0.37)	-0.01 (-0.46, 0.45)	26.8	25.1
Bupropion SR	-0.10 (-0.91, 0.71)	-	25.4	-
Placebo	REFERENCE	REFERENCE	21.7	22.5
Prazosin	-0.06 (-0.32, 0.20)	-0.10 (-0.60, 0.40)	18.3	19.2
Divalproex	-0.13 (-0.55, 0.28)	-0.11 (-0.58, 0.34)	15.4	17.9
Citalopram	-0.33 (-0.90, 0.24)	-0.32 (-0.93, 0.28)	8.2	8.8

Table for Appendix 14. NMA results (effect estimates and SUCRAs) for the primary efficacy outcome (change in symptoms) according to the standard analysis and the model that accounted for baseline severity. Values greater than 0 indicate that the active treatment is more efficacious. Underlined results indicate statistical significance. Lamotrigine is not included in this table because the primary study did not report data for this outcome (see studies included in the review). The effect estimates and the treatment ranking for the model that accounts for baseline severity correspond to the centralized mean of the baseline severity. Studies that do not report on the baseline severity are excluded from this analysis.

The funnel plot analyses suggested a possible association between study precision and dropout due to adverse events (Appendix 15). However, the relative effect estimates derived from the network meta-regression model that accounted for small study effects did not converge and drawing conclusions based on these findings would be invalid. A random-effects pairwise meta-analysis was performed for the comparison active v. placebo which resulted in a summary effect OR of 1.42 (95% CI 1.15–1.75) indicating that placebo is associated with fewer dropouts due to adverse events than active treatments. Accounting for study precision in a meta-regression model resulted in a statistically significant coefficient 2.07 (95% CI 1.10–3.88). This result suggests that less precise studies tended to show placebo to be better tolerated than it would have been in larger studies (Appendix 15).

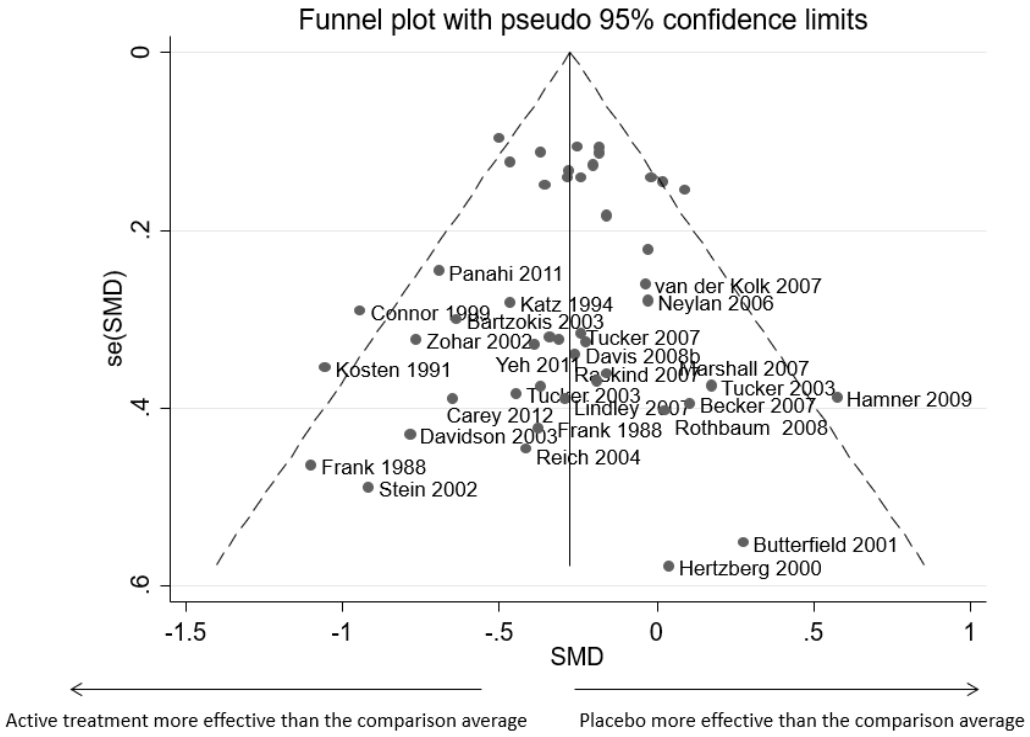


Figure 1 (Appendix 15). Funnel plot including all the comparisons of the form active treatment vs. placebo for the outcome change in symptoms.

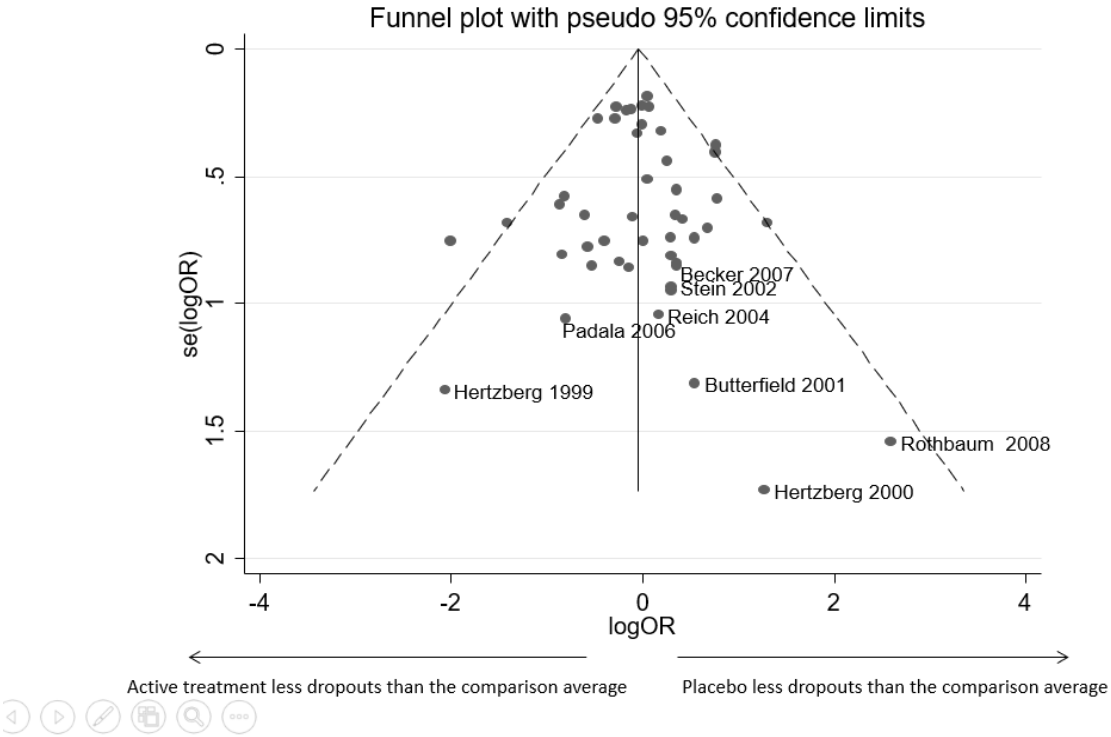


Figure 2 (Appendix 15). Funnel plot including all the comparisons of the form active treatment vs. placebo for the outcome any cause dropouts.

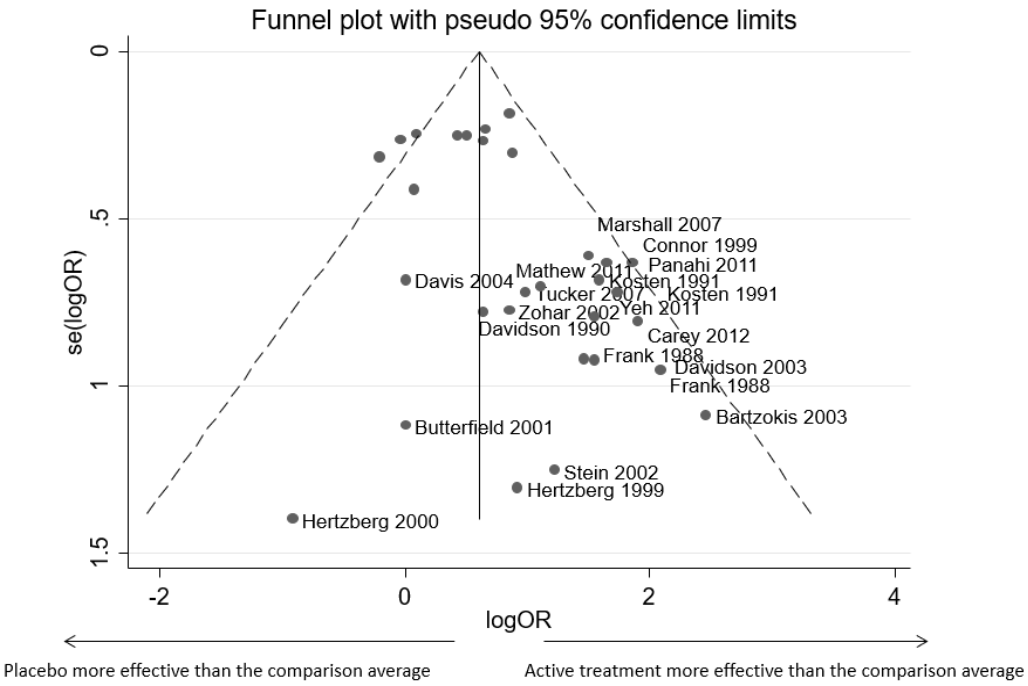


Figure 3 (Appendix 15). Funnel plot including all the comparisons of the form active treatment vs. placebo for the outcome response

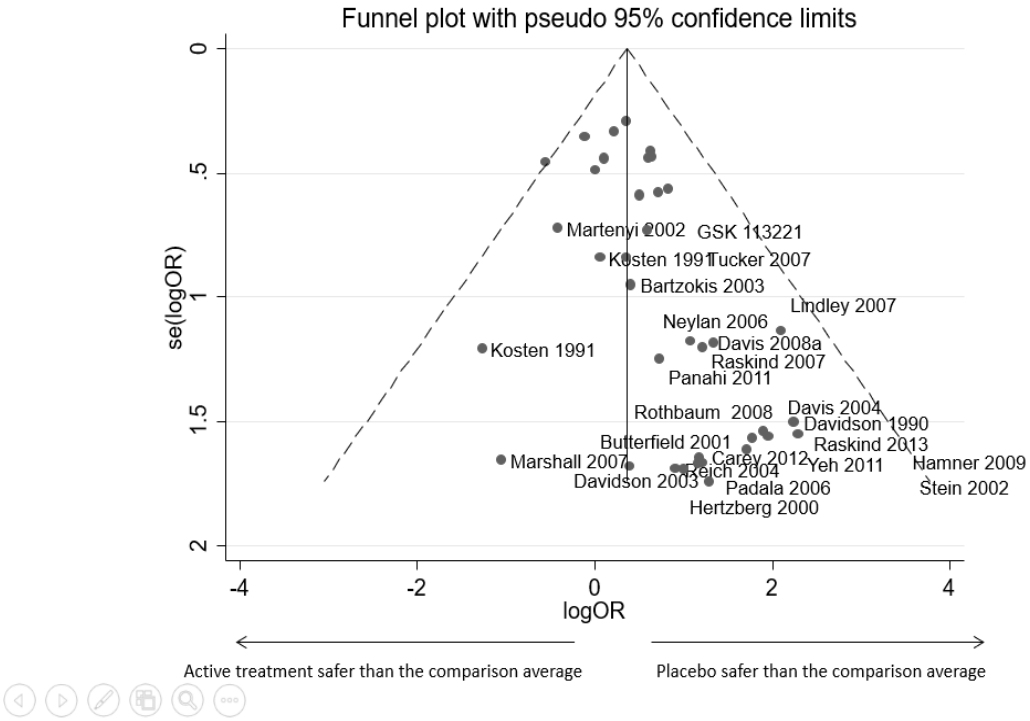


Figure 4 (Appendix 15). Funnel plot including all the comparisons of the form active treatment vs. placebo for the outcome adverse events. Missing points on the left suggest that small studies favoring the active treatment are missing.

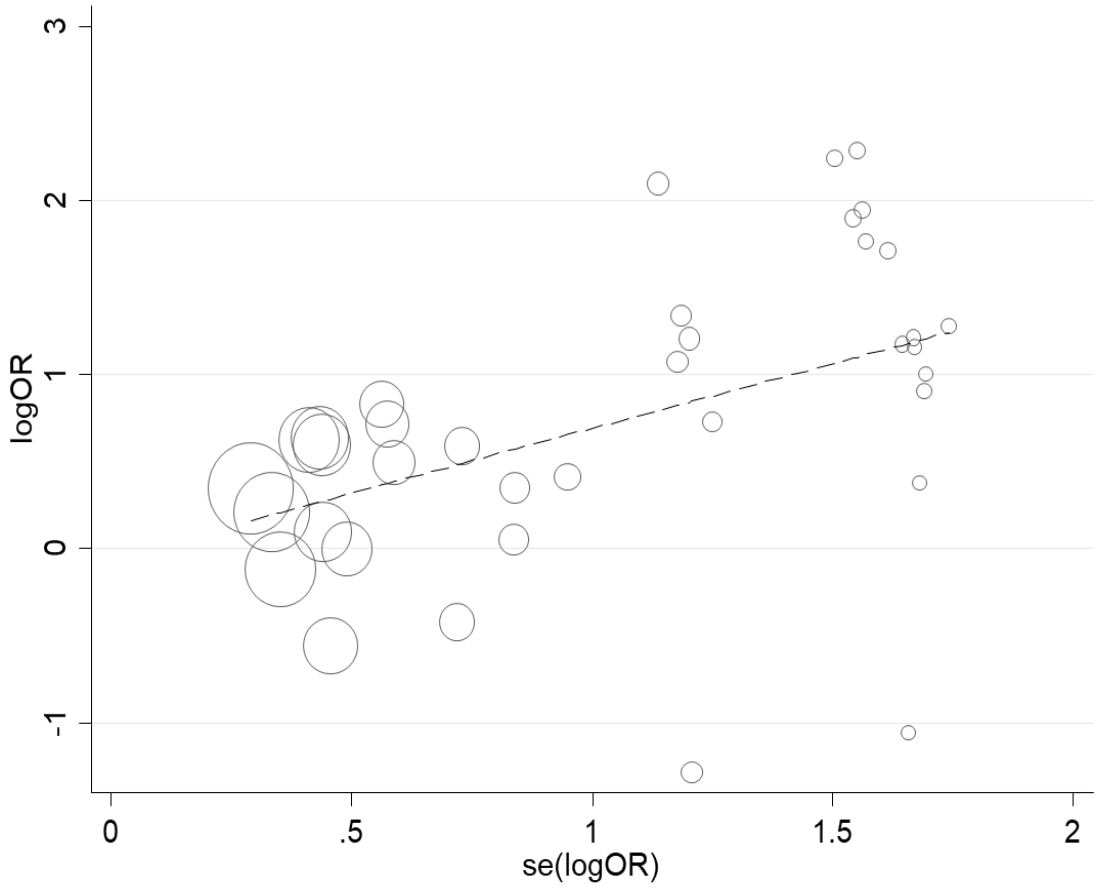


Figure 5 (Appendix 15). Random-effects meta-regression including all the comparisons of the form active treatment vs. placebo for the outcome adverse events. The slope of the regression line indicates that less precise studies tend to show placebo safer compared to more precise studies.

DISCUSSION

This network meta-analysis provides an evidence-based hierarchy for the efficacy and acceptability of pharmacological treatments for PTSD, using all available comparative data and thus overcoming the major limitation of previous pairwise meta-analyses (NICE, 2005; Watts et al. 2013; Hoskins et al. 2015). Interestingly, results from this study challenge the previous dogma that the efficacy of psychopharmacological agents within the same drug class is the same. Similarly, clinically important differences in efficacy were found among antipsychotics

for schizophrenia (Leucht et al. 2013) and also among antidepressants, where differences were reported not only in major depression (Cipriani et al. 2009), but also for anxiety disorders, like generalized anxiety disorder (NICE, 2011) and social anxiety disorder (NICE, 2013). The efficacy and acceptability hierarchies generated by our study were robust against many sources of bias, as various supplementary analyses related to severity at baseline, year of publication, small study effect, and sponsorship did not change the final ranking to an important extent.

It can be emphasised that the statistically significant differences in efficacy between drugs and placebo were small, with the only exception of phenelzine (according to Cohen, 1988, an effect size of 0.2 is small, 0.5 is medium, and 0.8 is large (Cohen, 1988)). It is probably misleading clinically to dismiss the effects of desipramine, fluoxetine, paroxetine, risperidone, sertraline, and venlafaxine as being small. Their point estimates of SMD were around 0.3, which is the same as antidepressants for depression, and indeed for many standard treatments in psychiatry and medicine (Leucht et al. 2012). Phenelzine had a standardized mean difference of 0.97 when compared with placebo and ranged between 0.19 and 1.30 with other active drugs. These differences in efficacy between active treatments were possibly substantial enough to be clinically important and pose the question whether phenelzine should be used as a first line drug treatment for PTSD. However, the overall evidence about this drug is based only on one trial with 60 participants. The contribution of this single study to all 'phenelzine versus other' network estimates was assessed for the primary outcome 'change in symptoms' (Appendix 16 - Fig. 1). The only study comparing phenelzine contributes more than 35% to the relative effects of all treatments against this specific intervention. Given that the contribution of this study to the relative effects of the rest of the treatment comparisons is very low (results not shown but available from the authors), it is therefore unlikely that the retrieved evidence can currently be considered robust enough to suggest phenelzine as a drug of choice, particularly

in view of the need for concomitant dietary restrictions and the risk of drug interactions. This is in line with the interpretation of recent clinical practice guidelines (Katzman et al. 2014), however, the analysis had higher statistical power than previous analyses, because of the comprehensive search of published and unpublished data and because the review used the network meta-analytical method.

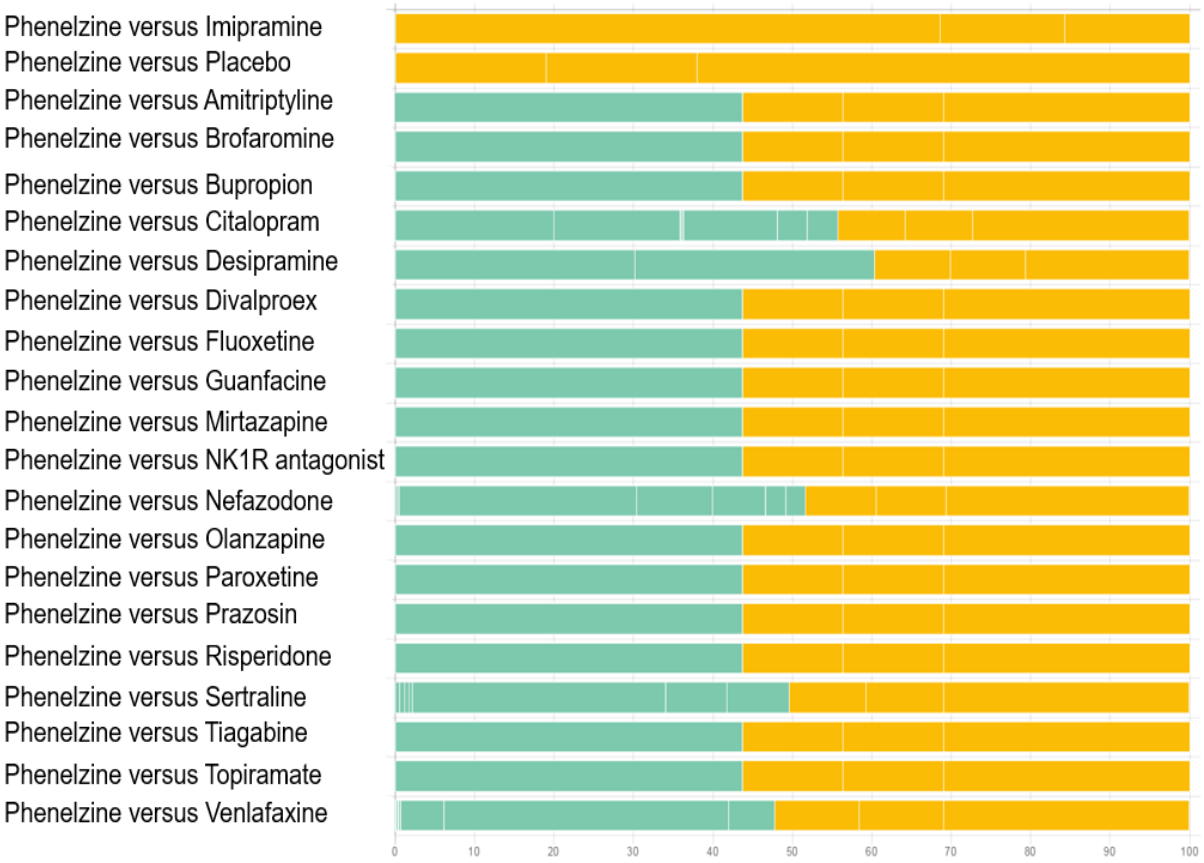


Figure 1 (Appendix 16). Percentage contributions of the Kosten 1991 study in all the 'phenelzine versus other' network estimates for the primary outcome 'change in symptoms'. Analysis is performed using the random effects model and the outcome is measured as the Cohen standarised mean difference. Yellow indicates the percentage contributions of Kosten 1991 and blue the contribution of the rest of the studies.

Phenelzine is a potent inhibitor of monoamine oxidase (MAOI), licensed in the USA and UK for depressed patients clinically characterised as 'atypical,' 'non-endogenous,' or 'neurotic', who often have mixed anxiety and depression and phobic or hypochondriacal features (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/011909s038lbl.pdf). Even though approved for depression only, phenelzine is also effective in the treatment of anxiety disorders such as panic disorder and social phobia (Sheehan et al. 1980; Johnson et al. 1994). Of course, phenelzine may owe its apparently striking efficacy in PTSD to the expected increases in brain levels of biogenic amines (serotonin, noradrenaline, and dopamine) produced by MAO inhibition. However, the reversible MAOI-A inhibitor, brofaromine, was of only modest efficacy in the current analysis. It may, therefore, be relevant that unlike other MAOIs, phenelzine also possesses the ability (at least in animal studies) to increase brain levels of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), through blocking the GABA metabolising enzyme, GABA transaminase. Studies with magnetic resonance spectroscopy (MRS) indicate that cortical GABA levels may be lower in patients with PTSD (Rosso et al. 2014). Hence the efficacy of phenelzine in PTSD might result from a combination of monoamine and GABA potentiation. However, it is also possible that GABA transaminase inhibition by itself, for example with the anticonvulsant drug vigabatrin, could be a viable therapeutic strategy in PTSD.

Interestingly, treatment with phenelzine reduces dream recall frequency (Landolt et al. 2001) and induces almost total REM sleep suppression in anxious-depressed patients (Wyatt et al. 1971). Although objective sleep findings in PTSD are mixed, there is some evidence that REM sleep fragmentation and REM sleep autonomic imbalance are associated with an increased risk for the development and persistence of PTSD (Mellman et al. 2007). Sleep disturbances are an indicator of heightened risk for poor psychiatric outcomes following trauma exposure

(Germain, 2013). To date, prazosin (an alpha-1 antagonist) is the recommended pharmacological treatment options for PTSD-related nightmares, as it is associated with improvements in nightmares and insomnia (Aurora et al. 2010). In our analysis prazosin was not among the most efficacious treatments for relieving acute symptoms of PTSD, so the fact that phenelzine may reduce the REM sleep disturbances associated with PTSD could also give it additional benefit over drugs like SSRIs and SNRIs which also lower REM sleep, but to a lesser extent than phenelzine (Sharpley & Cowen, 1995).

This study has several limitations. The validity of the above findings might be limited due to the lack of sufficient data to properly evaluate the required assumptions. Results from network meta-analysis may be unreliable when there is a high risk of intransitivity in the network (Salanti, 2012; Cipriani et al. 2013). Statistical assessment of the transitivity assumption (i.e. one can learn indirectly for a pairwise comparison via one or more anchor treatments) considers whether the distribution of the potential effect modifiers is balanced across the available direct comparisons. In the network, this study was unable to judge the plausibility of transitivity since most comparisons included very few studies. Thus, the study could only rely on clinical understanding of the studied condition and outcomes to assume that transitivity was likely to hold in the identified data. Important intransitivity might be reflected in the data in the form of statistical inconsistency. The network included only a few closed loops of evidence, for which inconsistency could be assessed (three loops for efficacy as a continuous outcome, two for all-cause dropout, none for response rate and two for dropouts due to adverse events). Using the loop specific approach and the design-by-treatment interaction model this study did not find any statistically significant inconsistency (Song et al. 2003; Higgins et al. 2012). However, the tests for inconsistency very often have low power and may fail to detect inconsistency as statistically significant even when it is present (Veroniki et al. 2013). Inconsistency is closely

related with heterogeneity and the two notions should be considered jointly. The small number of studies in the majority of the available direct comparisons renders the assessment of comparison-specific heterogeneities impractical (when it is estimable). The common heterogeneity across all comparisons from the network meta-analysis was estimated close to zero and the I^2 measure for heterogeneity suggested that heterogeneity was low in the network. This finding slightly mitigates concerns for the reliability of study results. However, all statements comparing the drugs in the network must be tempered by the potential limitations of the methodology, the complexity of patients with PTSD and the uncertainties that may result from the choice of dose or treatment setting.

The association of several characteristics and their impact on the relative effects using network meta-regression models were explored. The model accounting for baseline severity for the efficacy primary outcome resulted in a marginally non-statistically significant regression coefficient suggesting that the active treatments have a tendency to appear more effective (when compared with placebo) in studies with more severe populations. The meta-regression model that accounted for small-study effects on the outcome of adverse events suggested that small studies showed the placebo safer than did larger studies. This finding might be due to publication bias or selective reporting bias or might be the manifestation of other characteristics such as study quality (Chaimani & Salanti, 2012; Chaimani et al. 2013b). Despite this finding, this study was unable to use the results from this model for drawing conclusions with respect to the relative safety of the treatments due to the lack of convergence for the estimated relative effect.

Most trials included in the analysis did not report adequate information about randomisation and allocation concealment, and this might undermine the validity of overall findings.

However, all the studies were double-blind and the scant information in terms of quality assessment could be more an issue of reporting in the text than real defects in study design, as it has been commonly found in other systematic reviews (Huwiler-Müntener et al. 2002). Finally, findings from this analysis apply only to acute-phase treatment of PTSD. Clinically, the assessment of efficacy after four weeks of treatment or after 16 weeks or more might lead to wide differences in treatment outcome, and this may limit the ability to provide valid estimates of treatment effect if different durations of follow-up are combined. To overcome this problem, a common definition of acute response was included which comprised of a pre-defined follow-up duration (eight weeks). Moreover, because network meta-analysis requires reasonably homogeneous studies, in this project I had to restrict studies to short-term trials (Cipriani et al. 2011; Miura et al. 2014).

All-cause discontinuation has been used in other NMAs as a measure of the acceptability of treatments because it encompasses at the same time efficacy and tolerability. Response rate and dropout rate were chosen as primary outcomes to have the best estimate of acute treatment effectiveness (Cipriani et al. 2009; Leucht et al. 2013). In the analysis, the results paralleled the efficacy findings in that phenelzine, the most effective drug also had the lowest discontinuation rates. The neutral term all-cause discontinuation was used because clinicians might intuitively associate the word acceptability more with tolerability than with efficacy. However, it is worth noting that phenelzine, even though not statistically significant, showed a trend of better tolerability in terms of dropout rate due to adverse events when compared with placebo. Even if in clinical practice MAOIs are used much less frequently than other antidepressant agents because of the dangers of dietary and drug interactions (http://www.bnf.org/bnf/index.htm), findings from this review reinforce the idea that phenelzine should be prioritised in future trials in PTSD, particularly in the significant

proportion of patients who remain symptomatic despite first line psychological and pharmacological treatments. It would also be of interest to use magnetic resonance spectroscopy to assess the effect of phenelzine treatment on GABA levels in the human brain and to relate symptomatic improvement in PTSD symptomatology to changes in GABA concentration.

In the next chapter I will conduct a network meta-analysis of pharmacotherapy for SAD.

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CHAPTER 6.

Comparative Efficacy and Acceptability of Pharmacological Treatments for Social Anxiety Disorder in Adults: A Systematic Review and Network Meta-Analysis.

Chapter six compares direct and indirect comparisons of RCTs of pharmacotherapy for PTSD, using the network meta-analytic approach (Frequentist) to synthesising data. Trials were assessed for eligibility and inclusion in the study and the quality of each RCT was assessed with the Risk of Bias Tool. Thereafter the data was analysed.

INTRODUCTION

In the previous chapter a network meta-analysis was conducted for the pharmacotherapy of PTSD. In this chapter I now focus of SAD and conduct a network meta-analysis of pharmacotherapy for this disorder.

There is a growing body of literature on the treatment of SAD, including work on a few psychological and pharmacological interventions (Cuijpers *et al*. 2013; Mayo-Wilson et al. 2014). Current guidelines and systematic reviews suggest selective serotonin reuptake inhibitors (SSRIs) (escitalopram and sertraline) and serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine) as first line medication agents for the treatment of social anxiety (De Menezes *et al*. 2011; NICE, 2011; Blanco *et al*. 2013; WHO, 2013). Standard pairwise meta-analyses, which pool data from studies and compare estimates directly, have traditionally provided clinicians with an overview of the efficacy and acceptability of medication for the treatment of SAD (Curtiss *et al*. 2017; Williams *et al*. 2017). Nevertheless, this approach only provides conclusions about interventions that have directly been compared with one another, and do not provide clinicians with comparisons between all potential

interventions at their disposal in treating a specific disorder (Mavridis *et al*. 2015; Efthimiou *et al*. 2016).

Network meta-analysis (NMA) is a quantitative data synthesis approach that allows investigators to combine direct and indirect head-to-head comparisons of clinical trials and is therefore particularly informative within clinical settings where competing interventions are available (Salanti, 2012; Mavridis *et al*. 2015). Two NMAs of the efficacy of pharmacotherapy for SAD have been published (Hansen *et al*. 2008; Mayo-Wilson et al. 2014). These require updating and would benefit from additional focus on acceptability of interventions (dropouts due to sides effects and dropouts due to any cause), the use of SUCRA values (Salanti *et al*. 2011) to rank interventions for SAD, and the grading direct and indirect pairwise statistics by quality of evidence and best treatment. Here I provide an updated NMA to compare the efficacy and acceptability of different pharmacological interventions in the treatment of SAD in adults.

OBJECTIVES

The aim of this paper is to compare the efficacy and acceptability of different pharmacological interventions against one another in the treatment of SAD in adults; to identify which factors (methodological or clinical) predict response to treatment; and to provide a clinically useful summary of the comparative evidence that can be used to guide decisions about acute treatment of SAD in adults.

METHODS

The study protocol is available from the PROSPERO International prospective register of systematic reviews website (https://www.crd.york.ac.uk/prospero; ID: CRD42015017493).

Search strategy

This NMA incorporates the results of a systematic search of a range of databases conducted as part of our previous SAD Cochrane review (see Williams *et al.* 2017 for more details) by the Cochrane Common Mental Disorders Group who searched their controlled trials register (CCMDCTR-Studies) (17 August, 2015; 2 August, 2017). The CCMDCTR includes generic searches of Medline, Embase, and PsychINFO, including the Cochrane Central Register of Controlled Trials (CENTRAL). Individual updated searches were also conducted by me of Medline (via PubMed), PsychINFO (via EbscoHost) (to August 2012 and repeated 17 August, 2015, 24 May, 2017 and 13 November, 2018), clinical.trial.gov, and the Clinical Trials Search Portal **(**ICTRP) (apps.who.int/trialsearch) (to August 2012 and repeated 15 March, 2017 and 13 November, 2018) using terms 'social phobia' OR 'social anxiety disorder' and 'medication' OR 'pharmacotherapy' OR 'treatment'. All clinical trials registers were updated with a search conducted on 13 November, 2018.

Google Scholar was also hand searched on multiple occasions for additional trials, with the last search conducted on 13 November, 2018. In addition, the bibliographies of all identified trial reports were scanned for additional studies. Published and unpublished trials from key researchers were also obtained. No restriction was placed on the language or publication status of included trials. Trials for eligibility and inclusion were independently assessed by my main supervisor and I. Disagreements were resolved via discussion with a third party (DS).

The following search queries were employed:

CCMDCTR core MEDLINE search

Core Ovid MEDLINE search used to inform the Cochrane Common Mental Disorders Specialised Register (CCMD-CTR). A weekly search alert based on Condition + RCT filter

only.

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or

bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.

Similar weekly search alerts were also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

A quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted c/o the Cochrane Register of Studies Online (CRSO).

CCMD searches to 2015

#1 (social* NEAR2 (anxious or anxiety or phobi*)) or "phobic avoidance" or "social avoidance" or "interpersonal anxiety"

#2 "social* inhib*" or "social* stress*" or heterosocial* or "taijin kyofusho"

#3 (#1 or #2)

CCMD update search 2017

In August 2017 the CCMD Group's information specialist ran an update search to identify new studies published or registered since the date of the last search. Records were de-duplicated, screened and new studies were placed in awaiting classification. These will be incorporated in the next version of this review.

As the CCMD Group's specialised register was out of date at this point, the information specialist ran searches on the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (c/o Cochrane Register of Studies Online (CRSO))

Search All Fields [condition only]: (“social anxiety” or “social phobia”) AND 31/01/2015 to

31/08/2017:DL

2. CCMDCTR (studies and references)

("social anxiety" or "social phobia") 18/08/2015 to 14/06/2016

3. OVID Cross-search

Databases: PsycINFO <1806 to July Week 4 2017>, Embase <1974 to 2017 Week 31>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to 2-Aug-2017>

Search Strategy:

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1 (social* adj2 (phobi* or anxi*)).ab,kf,id,hw.

2 trial.ti.

3 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf,kw,id.

4 (RCT or at random or (random* adj3 (assign* or allocat* or control* or crossover or cross-over or design* or divide* or division or number))).ti,ab,kf,kw,id.

5 placebo.hw,ti,ab,kf,kw,id.

6 (control* adj2 (trial or group?)).ab.

7 Randomized Controlled Trial.sh,pt.

8 Double Blind Procedure/

9 Double Blind Method/

10 Controlled Clinical Trial and placebo.af.

11 (clinical trial or empirical study).md.

12 ((single or double or triple) adj2 (blind* or mask* or dummy)).ti,ab,kf,kw,id.

13 or/2-12

14 placebo.af.

15 drug therapy.fs.

16 exp Central Nervous System Agents/

17 drug literature index.ec.

18 drug activity/ or drug effect/ or drug efficacy/

19 "Clinical Psychopharmacology ".cc.

20 drug therapy/

21 exp drugs/

22 or/15-21

23 (2015* or 2016* or 2017*).yr.

24 (2015* or 2016* or 2017*).dd.

25 (2015* or 2016* or 2017*).dc,ed. and (medline* or pubmed* or in-data-review or in-process or publisher).st.

26 (2015* or 2016* or 2017*).an. and PsycINFO database record.ab.

27 or/23-26

28 (1 and 13 and 14 and 27)

29 (1 and 13 and 22 and 27)

30 (28 or 29)

31 remove duplicates from 30

4. International Trial Registers

ClinicalTrials.gov

Advanced Search: Interventional Studies | social phobia OR social anxiety | Studies received

from 01/01/2015 to 02/08/2017

WHO ICTRP

Advanced Search: All Studies social phobia OR social anxiety | Studies received from 01/01/2015 to 02/08/2017

5. PubMed (not MEDLINE) 2-Aug-2017

#1 Search ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))

#2 Search (social anxiety[Title] OR social phobia[Title])

#3 Search RCT OR random* OR placebo

#4 Search (#1 AND #2 AND #3) Sort by: PublicationDate Filters: Publication date from 2015/01/01 to 2017/12/31

Selection criteria, study characteristics and intervention type

Randomised, double-blind, controlled trials comparing any pharmacological intervention with placebo or another pharmacological intervention in the treatment of SAD were included, as well as trials studying multimodal treatments (including cognitive behavioural therapy), if an active drug and placebo group was a comparator. Both monotherapy and drug augmentation studies were included. Quasi-randomised controlled trials and open-label randomised control trials (RCTs) were excluded. Adult participants diagnosed with SAD according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR) or the International Classification of Diseases (ICD-9+) were included. RCTs investigating specific social anxiety (performance anxiety) were excluded. No restrictions were placed on psychiatric comorbidity and setting of the trials (in-and-or-out patients). Trials that only included a subset of participants that met the review inclusion criteria in the analysis were

excluded. No restriction was placed on the dose of medication interventions, and both fixed-dose and flexible-dose designs were allowed.

RCTs that evaluated one or more of the following pharmacological interventions were included: 5HT1A partial agonists (e.g. buspirone and vilazodone), anticonvulsants (e.g. gabapentin, levetiracetam and pregabalin), antipsychotics (e.g. olanzapine), benzodiazepines (e.g. clonazepam and bromazepam), beta-blockers (e.g. atenolol), mono-amine oxidase inhibitors (MAOIs, e.g. phenelzine), noradrenaline reuptake inhibitors (NARIs, e.g. atomoxetine and mirtazapine), noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g. mirtazapine), reversible inhibitors of monoamine oxidase A (RIMAs, e.g. brofaromine and moclobemide), serotonin antagonist and reuptake inhibitors (SARIs, e.g. nefazodone), serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine), and selective serotonin reuptake inhibitors (SSRIs, e.g. paroxetine, fluvoxamine, sertraline, fluoxetine and citalopram). RCTs of other medications not included in the list above, as well as experimental drugs (e.g. GW876008, GR205171, LY686017) were also eligible for inclusion in the NMA.

Outcome measures

Acute treatment was defined as an 8-week treatment in all analyses. If studies did not provide information at 8 weeks, data at 6, 7, 8, 10, 11 and/or 12 weeks of treatment (with preference given to timepoints closest to week 8) was included.

Primary outcome measures

The primary continuous outcome of treatment efficacy was measured using the total score on the Liebowitz Social Anxiety Scale (LSAS). The LSAS scale was chosen given that this is a

validated, commonly used, and psychometrically sound instrument for measuring SAD (Liebowitz, 1987). Acceptability of treatment was defined as the proportion of patients who left the study early by any cause during the first eight weeks of treatment (range six to 12 weeks).

Secondary outcome measures

The secondary, dichotomous outcome of treatment efficacy was the total number of patients who responded to treatment, as assessed using the Clinical Global Impressions Improvement Scale (CGI-I). Responders were defined as having a change item score of 1 ('very much') or 2 ('much') improved (Guy, 1976) on the CGI-I, or a similar scale. Tolerability of treatment was defined as the proportion of patients who left the study early due to side effects during the first eight weeks of treatment (range six to 12 weeks).

Data extraction

The titles and abstracts of RCTs identified from an updated search of the literature was independently assessed by TW and JI . Subsequently full-text articles agreed upon as potentially eligible were scanned. Any disagreements in the trial assessment and data collation procedures was resolved by discussion with my co-supervisor (DS). Information was extracted using a previously piloted data extraction form, and included study characteristics (such as lead author, publication year, study setting, and sponsorship), participant characteristics (such as diagnostic criteria, sample size, mean baseline score, mean age and/range, and psychiatric comorbidity), intervention details (such as medication, dose ranges, and duration of trials) and outcome measures (i.e. rating scales).

Furthermore, the Cochrane 'Risk of Bias' tool was used to assess the risk of bias of individual studies (Higgins & Green, 2011). Similarly, the certainty of evidence contributing to each network estimate was assessed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework, which characterises the quality of a body of evidence based on the study limitations, imprecision, inconsistency, indirectness, and publication bias for the primary and secondary outcomes (Puhan *et al*. 2014; Salanti et al., 2014).

Statistical analysis

For continuous outcomes, where the same measure was used to assess an outcome, the weighted mean difference (WMD) was extracted (Higgins & Green, 2011). Dichotomous outcomes were analysed by calculating the odds ratio (OR). Missing dichotomous outcome data was managed according to the intention to treat (ITT) principle, or the last observation carried forward (LOCF) when inadequate data on interventions missing were provided. When SD values were not reported in articles and attempts to obtain them by contacting trial authors was unsuccessful, they were derived from p-values, t-values, confidence intervals or standard errors, where available (Higgins & Green, 2011).

To evaluate the presence of clinical and methodological heterogeneity within treatment comparisons descriptive statistics were generated for trial and study population characteristics across all eligible trials (Altman & Bland, 1996). Where heterogeneity was found (based on I^2 values) reasons for heterogeneity were explored in terms of the PICO (population, intervention, comparison and outcomes) (Schardt *et al*. 2014) standard. In order to be valid, NMAs should not violate the assumption of transitivity, which implies that the available treatment comparisons do not differ with respect to the distribution of effect modifiers. (Chaimani *et al.*

2014). Accordingly, transitivity was assessed by means of performing a series of meta-regressions of outcomes on the following variables: year of publication, baseline severity, sponsorship and mean age at onset across the different pairwise comparisons. If the distributions were balanced across comparisons, the NMA concluded against evidence of intransitivity (Wood *et al*. 2008). This was done by comparing the covariates (effect modifiers) log estimate of treatment effect size and standard error of treatment effect size for each outcome in STATA version 15.

Initially, a standard pairwise meta-analysis was performed using a random effects model (Higgins & Green, 2011) and inverse variance method using R package meta (Schwarzer, 2007) for every treatment comparison with at least two studies. A frequentist random effects network meta-analysis was also performed to synthesise the available evidence from the entire network of trials by pooling direct and indirect treatment using R package netmeta (Rücker *et al.*2018). A constant heterogeneity variance was assumed which was added to each comparison of the network and was estimated via a generalised method of moments estimate (Jackson *et al.* 2012). Results from the NMA were presented as summary relative effect sizes (WMD or OR) for each possible pair of treatments. Furthermore, the P-score was calculated, as a frequentist analogue to SUCRA (Rücker & Schwarzer, 2015), to rank the treatments with respect to efficacy.

Finally, the robustness of study findings was assessed in a sensitivity analysis excluding studies with 'high' or 'unclear' risk of bias (Wood *et al.* 2008).

RESULTS

Description of included studies

A total of 3581 records were found through electronic database searching (k = 3078) and from a clinical trials registry (k = 503). Two thousand eight hundred and seven records were excluded after initial screening of titles and abstracts. After independent review of the remaining 774 full-text studies, 707 studies did not meet study inclusion and were excluded from the search (see Figure 1 and search query). The systematic review included 67 studies (published from 1993 to 2016) with 12122 patients, randomised to 27 different interventions. The mean duration of studies was 15.5 weeks (SD = 10.2; k = 67) and the mean age of the patients was 36.2 years (SD = 3.5; k = 63). Most of the studies were 2-arm (k=49) with one 6-arm study, and over 50% of the studies were industry funded (k = 40). Only 6% (k = 4) of the studies had an add-on design (augmentation design). Fifty-six (84%) studies used the LSAS (the remaining using LSAS-SR, LSAS-J, or LSPS) as a rating scale for assessing the reduction of anxiety symptoms, with a mean baseline severity of 80.1 (SD = 15.9; k = 52), where reported. Over half of the studies included patients with coexisting psychiatric conditions (N = 37) and the RCTs were mainly conducted in outpatient settings (N = 45) (see Appendix B for details regarding comorbidity and clinical setting).

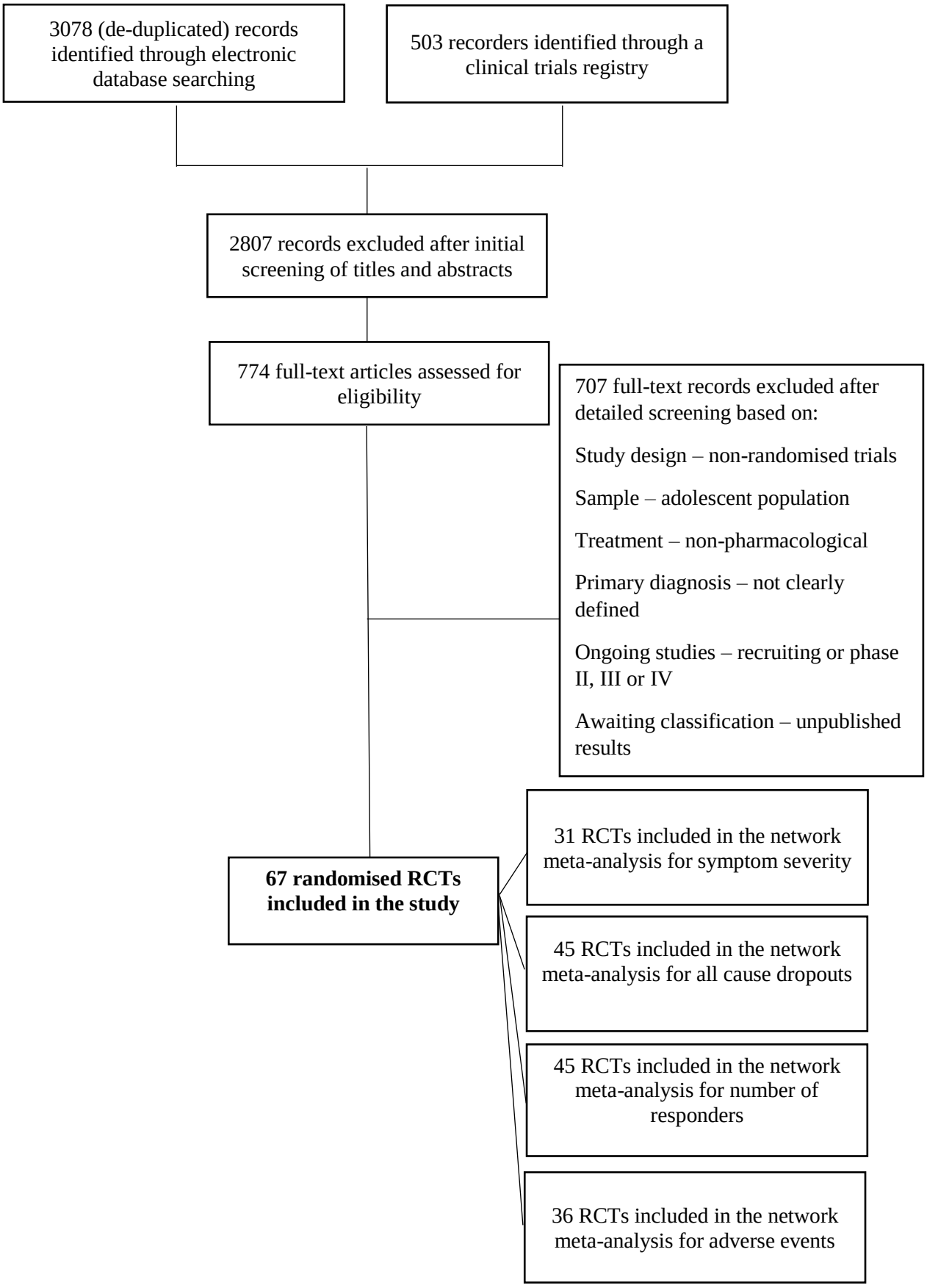


Figure 1. Study selection process. PRISMA Diagram of included and excluded studies.

Study	Drug						Add on	F-up [wks]	Setting	Diagnosis Rating Scales	Psych comorb.	Sample (n)						Dose (mg)					Sponsor
	A	B	C	D	E	F*						A	B	C	D	E	F	A	B	C	D	E	
Allgulander 1999	PAR		-	-	-	PBO	n	12 (12)	n/s	DSM-IV CGI-I, LSAS	Y	44	-	-	-	-	48	20-50	-	-	-	-	Novo Nordisk
Allgulander 2004	VEN	PAR	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	144	144	-	-	-	146	75–225	20–50	-	-	-	Wyeth Research
Asakura 2016	ESC	ESC	-	-	-	PBO	N	12 (12)	n/s	DSM-IV-TR CGI-I, LSAS-J	Y	198	193	-	-	-	196	10	20	-	-	-	Mochida
Asakura 2007	FLV	-	-	-	-	PBO	N	10 (10)	n/s	DSM-IV CGI-I, LSAS-J	n/s	182	-	-	-	-	89	50-300	-	-	-	-	Solvay Seiyaku K.K. Meiji Seika Kaisha, Ltd
Baldwin 1999	PAR	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	139	-	-	-	-	151	20-50	-	-	-	-	Smith Kline Beecharn
Barnett 2002	OLZ	-	-	-	-	PBO	N	8 (8)	n/s	DSM-IV CGI-I, LSAS	n/s	7	-	-	-	-	5	5-20	-	-	-	-	Eli Lilly
Blanco 2010	PHEN+	-	-	-	-	PBO	N	24 (12)	out	DSM-IV CGI-I, LSAS	Y	45	-	-	-	-	39	15-75	-	-	-	-	Grants
Blomhoff 2001	SER	-	-	-	-	PBO	Y	24 (24)	n/s	DSM-IV CGI-I, SPS	Y	98	-	-	-	-	98	50-150	-	-	-	-	Pfizer Inc.
Book 2008	PAR	-	-	-	-	PBO	N	16 (16)	n/s	DSM-IV (SCID) CGI-I, LSAS	Y	20	-	-	-	-	22	10-60	-	-	-	-	Grants

Careri 2015	VIL	-	-	-	-	PBO	N	12 (12)	n/s	DSM-IV-TR CGI-I, LSAS	Y	22	-	-	-	-	22	10-40	-	-	-	-	Grant
Connor 1998	CLZ	-	-	-	-	PBO	N	20 (20)	n/s	DSM-III-R CGI-S	n/s	17	-	-	-	-	19	0.25-2.5	-	-	-	-	Grant
Davidson 1993	CLZ	-	-	-	-	PBO	N	10 (10)	out	DSM-III-R LSAS	Y	39	-	-	-	-	36	0.25-1	-	-	-	-	None
Davidson 2004a	FLV	-	-	-	-	PBO	N	12 (12)	n/s	DSM-IV CGI-I, LSAS	Y	139	-	-	-	-	140	100-300	-	-	-	-	Solvay
Davidson 2004b	FLU	-	-	-	-	PBO	Y	14 (14)	out	DSM-IV CGI-I, BSPS	n/s	57	-	-	-	-	60	10-40	-	-	-	-	Grant
Fahlen 1995	BROF	-	-	-	-	PBO	N	52 (12)	out	DSM-III-R CGI-I, LSAS	Y	37	-	-	-	-	40	25-150	-	-	-	-	Ciba
Feltner 2011	PGB	PGB	PGB	-	-	PBO	N	11 (11)	out	DSM-IV CGI-I, LSAS	Y	78	86	82	-	-	82	300	450	600	-	-	Pfizer Inc.
Furmark 2005	NK-1RA	CIT	-	-	-	PBO	N	6 (6)	n/s	DSM-IV CGI-I, LSAS	Y	12	12	-	-	-	12	5	20-40	-	-	-	GlaxoSmithKline, the Swedish Research Council, the Bank of Sweden Tercentenary Foundation, and the Swedish Brain Foundation
Heimberg 1998	PHEN+	-	-	-	-	PBO	N	24 (12)	n/s	DSM-III-R CGI-I, LSAS	n/s	31	-	-	-	-	33	15-90	-	-	-	-	Grants
Kasper 2005	ESC	-	-	-	-	PBO	N	16 (12)	out	DSM-IV CGI-I, LSAS	Y	181	-	-	-	-	177	10-20	-	-	-	-	H. Lundbeck A/S
Katschnig 1997	MOC	MOC	-	-	-	PBO	N	12 (12)	out	SCID-Ro CIC-SP, LSPS	Y	191	193	-	-	-	194	300	600	-	-	-	None

Katzelnick 1995	SER	-	-	-	-	PBO	N	16 (10)	out	DSM-III-R LSAS	Y	6	-	-	-	-	6	50-200	-	-		-	Pfizer
Kobak 2002	FLU	-	-	-	-	PBO	N	16 (14)	n/s	DSM-IV CGI-I, LSAS	Y	30	-	-	-	-	30	20-60	-	-	-	-	Eli Lilly & Co
Lader 2004	ESC	ESC	ESC	PAR	-	PBO	N	24 (12)	out	DSM-IV CGI-I, LSAS	Y	167	167	170	169	-	166	5	10	20	20	-	H. Lundbeck A/S
Lepola 2004	PAR	-	-	-	-	PBO	N	12 (12)	out	MINI CGI-I, LSAS	Y	186	-	-	-	-	184	12.5-37.5	-	-	-	-	GlaxoSmithKline
Liebowitz 1992	PHEN+	ATN		-	-	PBO	N	8 (8)	n/s	DSM-III CGI-I, LSPS	Y	29	28	-	-	-	28	50-100	15-90	-	-	-	Grant
Liebowitz 2002	PAR	PAR	PAR	-	-	PBO	N	12 (12)	out	SCID CGI-I, LSAS	Y	97	95	97	-	-	95	20	40	60	-	-	SmithKline Beecham
Liebowitz 2003	SER	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	Y	211	-	-	-	-	204	25-200	-	-	-	-	Pfizer Inc.
Liebowitz 2005a	VEN#	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	139	-	-	-	-	140	75-225	-	-	-	-	Wyeth research
Liebowitz 2005b	VEN#	PAR	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	Y	133	136	-	-	-	144	75-225	20-50	-	-	-	Wyeth research
Lott 1997	BROF	-	-	-	-	PBO	N	10 (10)	out	DSM-III-R CGI-I, LSAS	n/s	52	-	-	-	-	54	50-150	-	-	-	-	Ciba-Geigy Corporation
Muehlbacher 2005	MIR	-	-	-	-	PBO	N	10 (10)	out	DSM-IV LSAS	Y	33	-	-	-	-	33	30	-	-	-	-	None
NCT00273039 2006	PAR	**NCE**	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	36	-	-	-	-	71	20-30	-	-	-	-	n/s
NCT00318669 2006	PAR	PAR	-	-	-	PBO	N	12 (12)	n/s	DSM-IV-TR	n/s	132	135	-	-	-	133	20	40	-	-	-	n/s

NCT00397722 2008	GW8 76008	GW8 76008	PAR	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	81	83	42	-	-	88	25-50	100-125	20-30	-	-	n/s
NCT00403962 2006	PAR	**NCE+ PAR**	-	-	-	PBO	Y	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	68	-	-	-	-	65	7.5	-	-	-	-	n/s
NCT00470483 2009	PAR	-	-	-	-	PBO	N	8 (8)	n/s	DSM-IV CGI-I, LSAS	n/s	17	-	-	-	-	16	20	-	-	-	-	n/s
Nordahl 2016	PAR	-	-	-	-	PBO	Y	24 (12)	out	DSM-IV LSAS	Y	26	-	-	-	-	26	20–60	-	-	-	-	Dept. of Psychology and Neuroscience (NTNU)
Noyes 1997	MOC	MOC	MOC	MOC	MOC	PBO	N	12 (12)	n/s	DSM-III-R CGI-I, LSAS	Y	84	86	86	82	83	85	75	150	300	600	900	Hoffmann-La Roche
Oosterbaan 2001	MOC	-	-	-	-	PBO	N	75 (15)	out	DSM-III-R CIC, LSAS	Y	27	-	-	-	-	27	150-450	-	-	-	-	Hoffmann-La Roche
Pande 1999	GAB	-	-	-	-	PBO	N	14 (14)	out	DSM-IV CGIC, LSAS	Y	34	-	-	-	-	35	300-3.600	-	-	-	-	Parke-Davis
Pande 2004	PGB	PGB	-	-	-	PBO	N	10 (10)	out	DSM-IV CGI-I, LSAS	Y	42	47	-	-	-	46	150	600	-	-	-	Parke-Davis
Randall 2001	PAR	-	-	-	-	PBO	N	8 (8)	out	DSM-IV CGI-I, LSAS	Y	6	-	-	-	-	9	20-60	-	-	-	-	SmithKline Beecham
Ravindran 2009	ATM	-	-	-	-	PBO	N	10 (10)	out	DSM-IV CGI-C, LSAS	Y	14	-	-	-	-	14	20-100	-	-	-	-	Eli Lilly/Grant
Rickels 2004	VEN#	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	126	-	-	-	-	135	75-225	-	-	-	-	None

Schneier 1998	MOC	-	-	-	-	PBO	N	12 (8)	out	DSM-III-R CGI-I, LSAS	Y	40	-	-	-	-	37	100-400	-	-	-	-	Grant
Schutters 2010	MIR	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	30	-	-	-	-	30	30-45	-	-	-	-	Organon/Grant
Stein 1996	PAR	-	-	-	-	PBO	N	12 (12)	n/s	DSM-IV CGI-I, LSAS	Y	8	-	-	-	-	8	10-50	-	-	-	-	None
Stein 1998	PAR	-	-	-	-	PBO	N	12 (12)	n/s	DSM-IV CGI-I, LSAS	Y	94	-	-	-	-	93	20-50	-	-	-	-	SmithKline Beecham
Stein 1999	FLV	-	-	-	-	PBO	N	12 (12)	n/s	DSM-IV CGI-I, LSAS	n/s	48	-	-	-	-	44	50-300	-	-	-	-	Solvay
Stein 2002a	MOC	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CIC-SP, LSAS	Y	191	-	-	-	-	193	300-750	-	-	-	-	None
Stein 2002b	PAR	-	-	-	-	PBO	N	24 (12)	out	DSM-IV CGI-I, LSAS	n/s	162	-	-	-	-	161	20-50	-	-	-	-	SmithKline Beecham
Stein 2003	FLV*	-	-	-	-	PBO	N	24 (12)	out	DSM-IV CGI-I, LSAS	Y	57	-	-	-	-	55	100-300	-	-	-	-	Solvay
Stein 2005	VEN#	VEN#	-	-	-	PBO	N	24 (12)	out	DSM-IV CGI-I, LSAS	n/s	128	129	-	-	-	129	75	150-225	-	-	-	Wyeth/Grant
Stein 2010	LEV	-	-	-	-	PBO	N	24 (12)	out	DSM-IV CGI-C, LSAS	Y	111	-	-	-	-	106	250-3.000	-	-	-	-	UCB Pharma
Tauscher 2010	LY68-6017	PAR	-	-	-	PBO	N	14 (12)	out	DSM IV-TR CGI-I, LSAS	n/s	77	38	-	-	-	74	50	10-20	-	-	-	Eli Lilly & Co

Turner 1994	ATN	-	-	-	-	PBO	N	24 (12)	n/s	DSM IV-TR SPAI	n/s	25	-	-	-	-	21	25-100	-	-	-	-	Stuart
Vaishnavi 2007	QTP	-	-	-	-	PBO	N	8 (8)	out	DSM-IV CGI-I, BSPS	n/s	10	-	-	-	-	5	25-200	-	-	-	-	AstraZeneca
Van Ameringen 2001	SER	-	-	-	-	PBO	N	20 (20)	out	DSM-IV CGI-I, BSPS	Y	135	-	-	-	-	69	50-200	-	-	-	-	Pfizer
Van Ameringen 2007	NEF	-	-	-	-	PBO	N	14 (14)	out	DSM-IV CGI-I, LSAS	n/s	51	-	-	-	-	51	300-600	-	-	-	-	Bristol-Myers Squibb/Grant
Van Vliet 1992	BROF	-	-	-	-	PBO	N	24 (12)	out	DSM-III-R SPS	n/s	15	-	-	-	-	15	50-150	-	-	-	-	None
Van Vliet 1994	FLV	-	-	-	-	PBO	N	12 (12)	out	DSM-III-R SPS	n/s	15	-	-	-	-	15	50-150	-	-	-	-	None
Van Vliet 1997	BUS	-	-	-	-	PBO	N	12 (12)	out	DSM-IV SPS	n/s	15	-	-	-	-	15	15-30	-	-	-	-	None
Versiani 1992	PHEN+	MOC		-	-	PBO	N	8 (8)	n/s	DSM-III-R CGI-I, SPS	n/s	26	26	-	-	-	26	100-600	15-90	-	-	-	None
Versiani 1997	BZO	-	-	-	-	PBO	N	12 (12)	n/s	DSM-III-R CGI-I, LSAS	N	30	-	-	-	-	30	3-9	-	-	-	-	None
Walker 2000	SER	-	-	-	-	PBO	N	24 (24)	out	DSM-IV CGI-I, BSPS	n/s	25	-	-	-	-	25	50-200	-	-	-	-	Pfizer
Westenberg 2004	FLV*	-	-	-	-	PBO	N	12 (12)	out	DSM-IV CGI-I, LSAS	n/s	149	-	-	-	-	151	100-300	-	-	-	-	Solvay

Zhang 2005	LEV	-	-	-	-	PBO	N	7 (7)	out	DSM-IV CGI-I, LSAS	Y	11	-	-	-	-	7	50-3000	-	-	-	-	UCB Pharma/Grant

Appendix B. Characteristics of studies included in the network meta-analysis.

Assessment of the quality of evidence

In terms of quality of reporting, 28% of studies reported randomisation procedures, 25% described allocation of treatment for each group, 21% mentioned how participants and personnel were blinded, and 19% of the studies how the outcomes assessors were blinded. Eight RCTs provided study protocols to fully determine bias caused by selective reporting. Although over half of the studies provided data on the number of participants who dropped out of the study, it was not possible to assess the degree to which missing data might introduce attrition bias in the remaining studies due to insufficient information provided by trials (see Appendix C).

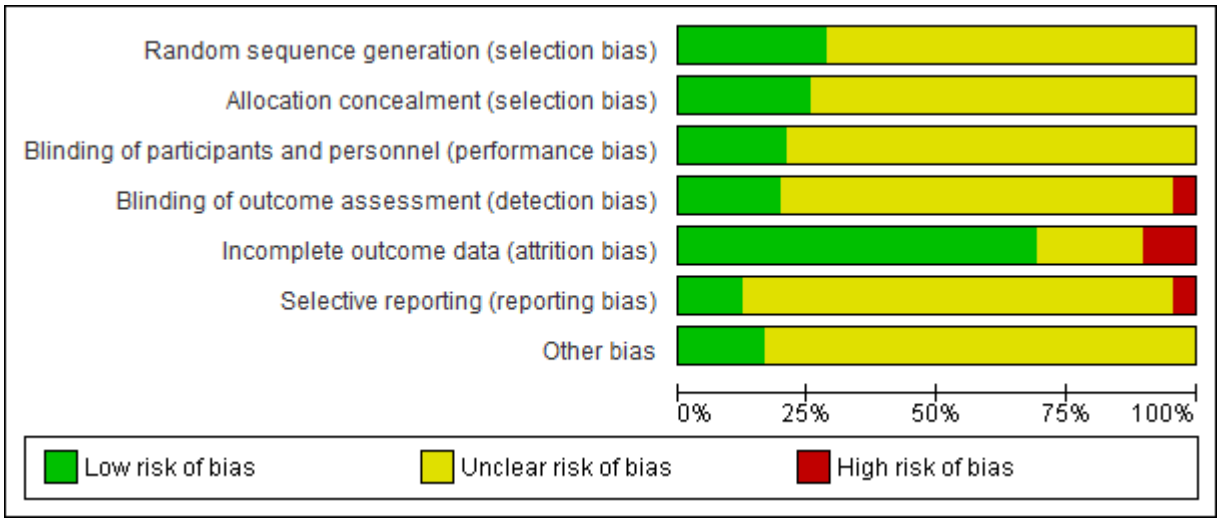


Figure 1 (Appendix C). Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

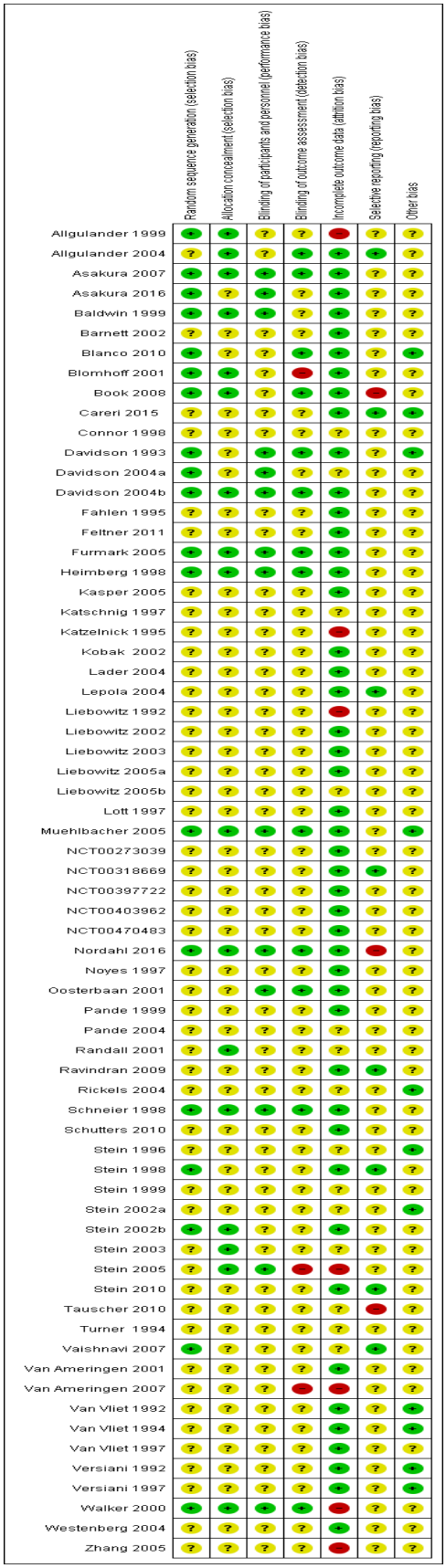


Figure 2 (Appendix C). Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

GRADE Quality Ratings

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**Mean Difference (95% CIs)**	**Quality of Evidence**	**Mean Difference (95% CIs)**	**Quality of evidence**	**Mean Difference (95% CIs)**	**Quality of evidence**
Atomoxetine: Placebo	2.60 [-35.38; 40.58]	Very low*‡‡	No estimate††	--	2.60 [-35.38; 40.58]	Very low*‡‡
Brofaromine: Placebo	-8.10 [-43.29; 27.09]	Low*‡	No estimate††	--	-8.10 [-43.29; 27.09]	Low*‡
Bromazepam: Placebo	-31.60 [-66.64; 3.44]	Low*‡	No estimate††	--	-31.60 [-66.64; 3.44]	Low*‡
Clonazepam: Placebo	-23.60 [-58.87; 11.67]	Moderate‡	No estimate††	--	-23.60 [-58.87; 11.67]	Moderate‡
Escitalopram: Placebo	-8.05 [-41.81; 25.71]	Low*‡	No estimate††	--	-8.05 [-41.81; 25.71]	Low*‡
Fluvoxamine: Placebo	-2.12 [-21.88; 17.64]	Low*‡	No estimate††	--	-2.12 [-21.88; 17.64]	Low*‡
Gabapentin: Placebo	-11.50 [-47.62; 24.62]	Low*‡	No estimate††	--	-11.50 [-47.62; 24.62]	Low*‡
Levetiracetam: Placebo	-3.82 [-31.80; 24.15]	Low*‡	No estimate††	--	-3.82 [-31.80; 24.15]	Low*‡
Mirtazapine: Placebo	-14. 53 [-38.87; 9.82]	Low*‡	No estimate††	--	-14. 53 [-38.87; 9.82]	Low*‡
Moclobemide: Placebo	-8.51 [-25.87; 8.86]	Low*‡	No estimate††	--	-8.51 [-25.87; 8.86]	Low*‡
Olanzapine: Placebo	-37.80 [-87.24; 11.64]	Very low*‡‡	No estimate††	--	-37.80 [-87.24; 11.64]	Very low*‡‡
Paroxetine: Placebo	-12.75 [-26.97; 1.48]	Low*‡	-143.03 [-233.52; -52.54]	Very low*‡§	-15.89 [-29.94; -1.84]	Low*‡
Paroxetine: Venlafaxine	-74.20 [-108.40; -40.00]	Very low*‡§	-16.94 [-52.09; 18.22]	Low*‡	-46.36 [-70.87; -21.85]	Low*‡
Phenelzine: Placebo	-8.65 [-28.65; 11.36]	Low*‡	No estimate††	--	-8.65 [-28.65; 11.36]	Low*‡
Sertraline: Placebo	-17.45 [-43.76; 8.86]	Low*‡	No estimate††	--	-17.45 [-43.76; 8.86]	Low*‡
Venlafaxine: Placebo	25.68 [1.55; 49.82]	Low*‡	67.52 [0.36; 134.67]	Very Low*‡§	30.47 [7.76; 53.18]	Low*‡
Vilazodone: Placebo	15.60 [-22.05; 53.25]	Very Low*‡‡	No estimate††	--	15.60 [-22.05; 53.25]	Very Low*‡‡

Table 1. (Appendix C). Estimates of effects and quality ratings for comparison of pharmacotherapy for the treatment of social anxiety disorder in adults for the outcome of reduction in symptom severity. **Legend.** *Limitations (risk of bias). ‡Imprecision. §Severe imprecision. ††Cannot be estimated because the drug was not connected in a loop in the evidence network.

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**Odds Ratio (95% CIs)**	**Quality of Evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**
Atenolol: Phenelzine	1.36 [0.32; 5.81]	Low*‡	2.37 [0.28; 20.39]	Very low*‡‡	1.62 [0.49; 5.39]	Low*‡
Atenolol: Placebo	3.16 [0.79; 12.68]	Low*‡	1.88 [0.18; 19.90]	Very low*‡‡	2.76 [0.83; 9.15]	Low*‡
Atomoxetine: Placebo	0.91 [0.15; 5.68]	Low*‡	No estimate††	--	0.91 [0.15; 5.68]	Low*‡
Brofaromine: Placebo	0.95 [0.45; 1.98]	Low*‡	No estimate††	--	0.95 [0.45; 1.98]	Low*‡
Bromazepam: Placebo	0.48 [0.04; 5.70]	Low*‡	No estimate††	--	0.48 [0.04; 5.70]	Low*‡
Buspirone: Placebo	0.12 [0.01; 2.47]	Low*‡	No estimate††	--	0.12 [0.01; 2.47]	Low*‡
Clonazepam: Placebo	1.03 [0.35; 3.02]	Low*‡	No estimate††	--	1.03 [0.35; 3.02]	Low*‡
Escitalopram: Paroxetine	1.05 [0.65; 1.71]	Moderate*	1.05 [0.68; 1.61]	Moderate*	1.05 [0.76; 1.45]	Moderate*
Escitalopram: Placebo	0.98 [0.71; 1.34	Moderate*	1.06 [0.51; 2.20]	Low*‡	0.99 [0.74; 1.32]	Moderate*
Fluoxetine: Placebo	0.59 [0.25; 1.39]	Moderate‡	No estimate††	--	0.59 [0.25; 1.39]	Moderate‡
Fluvoxamine: Placebo	1.51 [1.06; 2.14]	Moderate*	No estimate††	--	1.51 [1.06; 2.14]	Moderate*
GW876008: Paroxetine	0.63 [0.28; 1.38]	Low*‡	0.82 [0.34; 1.96]	Low*‡	0.71 [0.39; 1.27]	Low*‡
GW876008: Placebo	0.71 [0.37; 1.35]	Low*‡	0.51 [0.14; 1.89]	Low*‡	0.67 [0.37; 1.18]	Low*‡
Levetiracetam: Placebo	0.98 [0.53; 1.80]	Low*‡	No estimate††	--	0.98 [0.53; 1.80]	Low*‡
Mirtazapine: Placebo	2.07 [0.18; 24.45]	Low*‡	No estimate††	--	2.07 [0.18; 24.45]	Low*‡
Moclobemide: Placebo	0.90 [0.32; 2.57]	Moderate‡	No estimate††	--	0.90 [0.32; 2.57]	Moderate‡
Olanzapine: Placebo	1.12 [0.11; 11.75]	Very low*‡‡	No estimate††	--	1.12 [0.11; 11.75]	Very low*‡‡
Paroxetine: Placebo	0.93 [0.76; 1.14]	Moderate*	1.39 [0.46; 4.20]	Low*‡	0.94 [0.77; 1.16]	Moderate*
Paroxetine: Venlafaxine	0.85 [0.27; 2.67]	Low*‡	1.21 [0.69; 2.13]	Low*‡	1.13 [0.68; 1.87]	Low*‡
Phenelzine: Placebo	1.66 [0.75; 3.71]	Low*‡	3.30 [0.06; 193.66]	Very low*‡§	1.71 [0.78; 3.75]	Low*‡
Pregabalin: Placebo	1.55 [0.94; 2.57]	Low*‡	No estimate††	--	1.55 [0.94; 2.57]	Low*‡
Sertraline: Placebo	0.87 [0.54; 1.41]	Moderate*	No estimate††	--	0.87 [0.54; 1.41]	Moderate*
Venlafaxine: Placebo	0.79 [0.49; 1.27]	Moderate*	4.30 [0.30; 61.84]	Very low*‡§	0.83 [0.52; 1.33]	Moderate*
Vilazodone: Placebo	0.78 [0.20; 3.15]	Low*‡	No estimate††	--	0.78 [0.20; 3.15]	Low*‡

Table 2 (Appendix C). Social anxiety disorder in adults for the outcome of dropouts due to any cause. **Legend.** *Limitations (risk of bias). ‡Imprecision. §Severe imprecision. ††Cannot be estimated because the drug was not connected in a loop in the evidence network.

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**Odds Ratio (95% CIs)**	**Quality of Evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**
Atenolol: Phenelzine	0.27 [0.07; 1.07]	Low*‡	0.40 [0.07; 2.19]	Low*‡	0.32 [0.11; 0.92]	Low*‡
Atenolol: Placebo	1.16 [0.41; 3.29]	Low*‡	0.54 [0.03; 9.62]	Low*‡	1.07 [0.40; 2.83]	Low*‡
Atomoxetine: Placebo	0.61 [0.09; 4.14]	Low*‡	No estimate††	--	0.61 [0.09; 4.14]	Low*‡
Brofaromine: Placebo	8.10 [3.57; 18.39]	Low*‡	No estimate††	--	8.10 [3.57; 18.39]	Low*‡
Bromazepam: Placebo	20.00 [4.31; 92.71]	Very low*‡§	No estimate††	--	20.00 [4.31; 92.71]	Very low*‡§
Buspirone: Placebo	1.00 [0.05; 19.63]	Very low*‡‡	No estimate††	--	1.00 [0.05; 19.63]	Very low*‡‡
Citalopram: GR205171	1.40 [0.23; 8.44]	Low‡‡	No estimate††	--	1.40 [0.23; 8.44]	Low‡‡
Citalopram: Placebo	2.00 [0.32; 12.48]	Low‡‡	No estimate††	--	2.00 [0.32; 12.48]	Low‡‡
Clonazepam: Placebo	14.50 [3.62; 58.14]	Very low*‡§	No estimate††	--	14.50 [3.62; 58.14]	Very low*‡§
Escitalopram: Paroxetine	0.84 [0.35; 2.04]	Low*‡	0.69 [0.35; 1.34]	Low*‡	0.74 [0.43; 1.26]	Low*‡
Escitalopram: Placebo	1.92 [1.16; 3.19]	Low*‡	2.30 [0.48; 11.11]	Low*‡	1.96 [1.21; 3.17]	Moderate*
Fluoxetine: Placebo	2.39 [0.70; 8.23]	Low*‡	No estimate††	--	2.39 [0.70; 8.23]	Low*‡
Fluvoxamine: Placebo	1.89 [1.14; 3.12]	Low*‡	No estimate††	--	1.89 [1.14; 3.12]	Low*‡
GR205171: Placebo	1.43 [0.23; 9.00]	Low‡‡	No estimate††	--	1.43 [0.23; 9.00]	Low‡‡
GW876008: Paroxetine	0.33 [0.11; 0.94]	Low*‡	0.26 [0.06; 1.18]	Low*‡	0.30 [0.13; 0.72]	Low*‡
GW876008: Placebo	0.76 [0.29; 1.99]	Low*‡	0.97 [0.15; 6.22]	Low*‡	0.80 [0.34; 1.88]	Low*‡
Levetiracetam: Placebo	1.01 [0.41; 2.53]	Low*‡	No estimate††	--	1.01 [0.41; 2.53]	Low*‡
Mirtazapine: Placebo	1.00 [0.19; 5.40]	Low*‡	No estimate††	--	1.00 [0.19; 5.40]	Low*‡
Moclobemide: Placebo	1.82 [0.99; 3.36]	Low*‡	No estimate††	--	1.82 [0.99; 3.36]	Low*‡
Olanzapine: Placebo	15.40 [0.51; 467.28]	Very low*‡‡§	No estimate††	--	15.40 [0.51; 467.28]	Very low*‡‡§
Paroxetine: Placebo	2.76 [2.05; 3.72]	Moderate*	0.93 [0.22; 3.97]	Low*‡	2.64 [1.97; 3.54]	Moderate*
Paroxetine: Venlafaxine	1.25 [0.49; 3.18]	Low*‡	2.43 [1.20; 4.92]	Low*‡	1.91 [1.09; 3.35]	Low*‡
Phenelzine: Placebo	3.35 [1.55; 7.24]	Low*‡	3.82 [0.13; 109.78]	Very low*‡§	3.37 [1.59; 7.15]	Low*‡
Pregabalin: Placebo	1.79 [0.85; 3.76]	Low*‡	No estimate††	--	1.79 [0.85; 3.76]	Low*‡
Sertraline: Placebo	2.50 [1.02; 6.15]	Low*‡	No estimate††	--	2.50 [1.02; 6.15]	Low*‡

Venlafaxine: Placebo	1.35 [0.78; 2.31]	Low*‡	1.84 [0.32; 10.54]	Low*‡	1.38 [0.83; 2.32]	Low*‡
Vilazodone: Placebo	3.42 [0.72; 16.36]	Low*‡	No estimate††	--	3.42 [0.72; 16.36]	Low*‡

Table 3 (Appendix C). Estimates of effects and quality ratings for comparison of pharmacotherapy for the treatment of social anxiety disorder in adults for the outcome of treatment response. **Legend**. *Limitations (risk of bias). ‡Imprecision. §Severe imprecision. ††Cannot be estimated because the drug was not connected in a loop in the evidence network.

	Direct evidence		Indirect evidence		Network meta-analysis	
Comparison	**Odds Ratio (95% CIs)**	**Quality of Evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**	**Odds Ratio (95% CIs)**	**Quality of evidence**
Atomoxetine: Placebo	3.00 [0.11; 80.66]	Very low*‡§	No estimate††	--	3.00 [0.11; 80.66]	Very low*‡§
Brofaromine: Placebo	3.98 [1.28; 12.36]	Low*‡	No estimate††	--	3.98 [1.28; 12.36]	Low*‡
Bromazepam: Placebo	1.00 [0.06; 16.83]	Very low*‡§	No estimate††	--	1.00 [0.06; 16.83]	Very low*‡§
Buspirone: Placebo	3.21 [0.12; 85.49]	Very low*‡§	No estimate††	--	3.21 [0.12; 85.49]	Very low*‡§
Escitalopram: Placebo	2.02 [1.09; 3.75]	Low*‡	No estimate††	--	2.02 [1.09; 3.75]	Low*‡
Fluoxetine: Placebo	2.79 [0.52; 15.09]	Low‡§	No estimate††	--	2.79 [0.52; 15.09]	Low‡§
Fluvoxamine: Placebo	6.51 [3.56; 11.93]	Very low*‡‡	No estimate††	--	6.51 [3.56; 11.93]	Very low*‡‡
GW876008: Paroxetine	0.68 [0.20; 2.28]	Low*‡	1.50 [0.18; 12.13]	Very low*‡§	0.83 [0.29; 2.36]	Low*‡
GW876008: Placebo	3.09 [0.66; 14.37]	Very low*‡§	1.55 [0.36; 6.71]	Low*‡	2.15 [0.75; 6.22]	Low*‡
Levetiracetam: Placebo	2.16 [0.80; 5.79]	Low*‡	No estimate††	--	2.16 [0.80; 5.79]	Low*‡
Mirtazapine: Placebo	5.35 [0.25; 116.72]	Very low*‡§	No estimate††	--	5.35 [0.25; 116.72]	Very low*‡§
Moclobemide: Placebo	1.76 [0.71; 4.34]	Moderate‡	No estimate††	--	1.76 [0.71; 4.34]	Moderate‡
Olanzapine: Placebo	0.67 [0.03; 14.08]	Very low*‡§	No estimate††	--	0.67 [0.03; 14.08]	Very low*‡§
Paroxetine: Placebo	2.47 [1.76; 3.46]	Low*‡	4.67 [1.46; 14.91]	Very low*‡‡§	2.59 [1.87; 3.58]	Low*‡
Paroxetine: Venlafaxine	1.08 [0.64; 1.82]	Very low*‡‡	0.63 [0.30; 1.33]	Very low*‡‡	0.90 [0.59; 1.38]	Low*‡
Pregabalin: Placebo	3.60 [1.31; 9.93]	Very low*‡‡	No estimate††	--	3.60 [1.31; 9.93]	Very low*‡‡
Sertraline: Placebo	2.76 [1.09; 7.02]	Low*‡	No estimate††	--	2.76 [1.09; 7.02]	Low*‡
Venlafaxine: Placebo	3.09 [1.93; 4.94]	Low*‡	2.18 [0.88; 5.41]	Very low*‡‡	2.87 [1.89; 4.36]	Low*‡
Vilazodone: Placebo	1.00 [0.13; 7.85]	Very low*‡‡	No estimate††	--	1.00 [0.13; 7.85]	Very low*‡‡

Table 4 (Appendix C). Estimates of effects and quality ratings for comparison of pharmacotherapy for the treatment of social anxiety disorder in adults for the outcome dropouts due to adverse events. **Legend.** *Limitations (risk of bias). ‡Imprecision. §Severe imprecision. ††Cannot be estimated because the drug was not connected in a loop in the evidence network.

For the primary outcome of symptom severity most evidence was associated with low to very low-quality evidence and for the outcome of acceptability (dropouts due to any cause) the corresponding evidence was rated as being of low to moderate quality. Low to very low quality was reported for the secondary outcome of treatment response, with low to moderate quality evidence for dropouts due to adverse events (see Appendix B).

Network meta-analysis results

Twenty one studies with 18 different interventions were included in the network meta-analysis for the continuous outcome of symptom reduction. For the binary outcome of treatment response 45 studies describing 23 interventions were included in the network. For the binary outcomes of acceptability, 36 (adverse events) and 45 (all cause dropouts) studies describing 18 and 21 different interventions were included in the network, respectively. All studies had at least one placebo-controlled arm. Figure 1 (Appendix D) represents the network structure of eligible comparisons for the primary outcome, symptom severity, for the network meta-analysis (the networks for acceptability and treatment response were similar). The experimental 'LY686017' mediation arm was excluded from the analysis given the lack of FDA approval for this medication. Results of direct pairwise comparisons for all outcomes are reported in Appendix D.

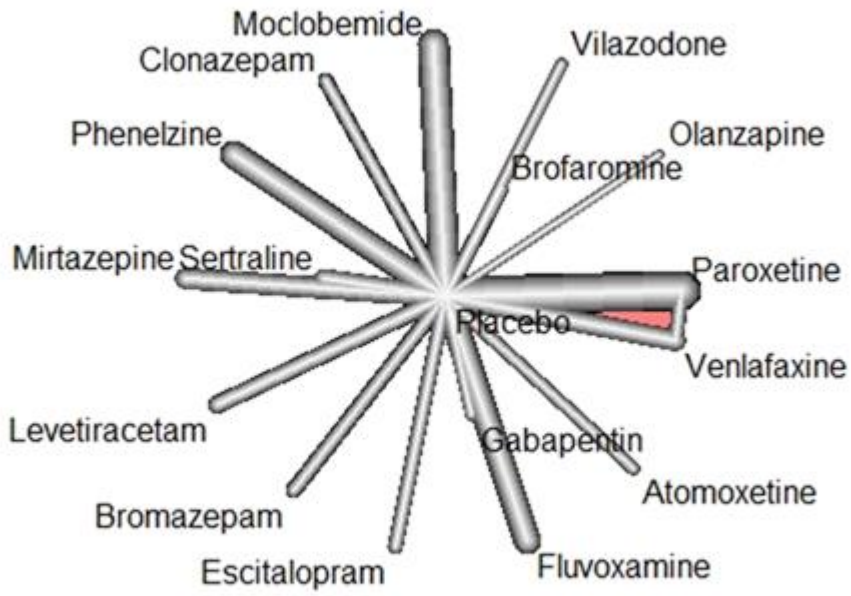


Figure 1 (Appendix D). Network graph of eligible comparisons for the network meta-analysis of the outcome symptom severity.

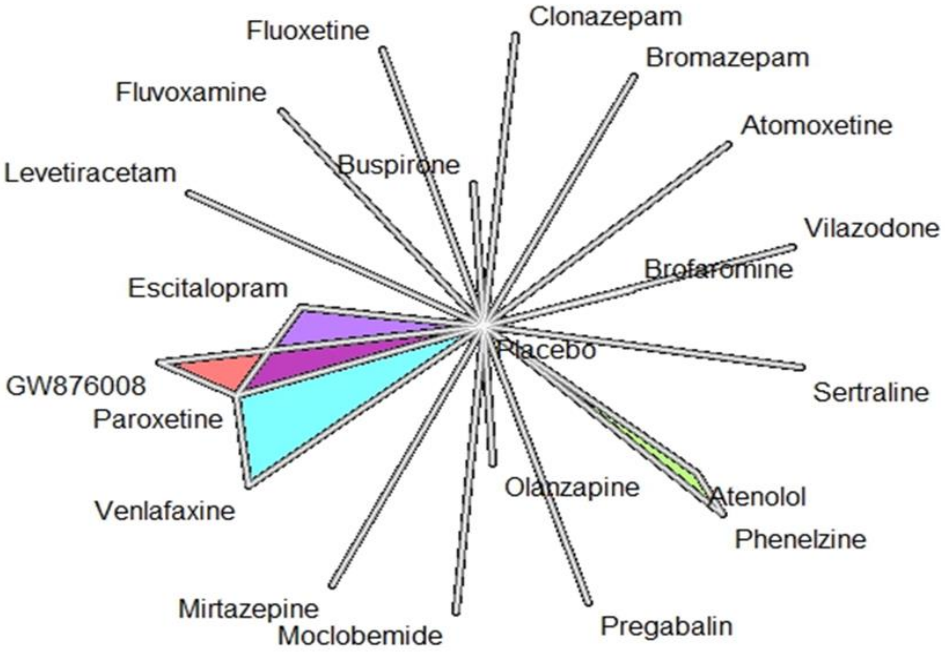


Figure 2 (Appendix D). Network graph of eligible comparisons for the network meta-analysis of the outcome dropouts due to any cause. The width of the lines is proportional to the number of trials and sample sizes comparing every pair of treatments.

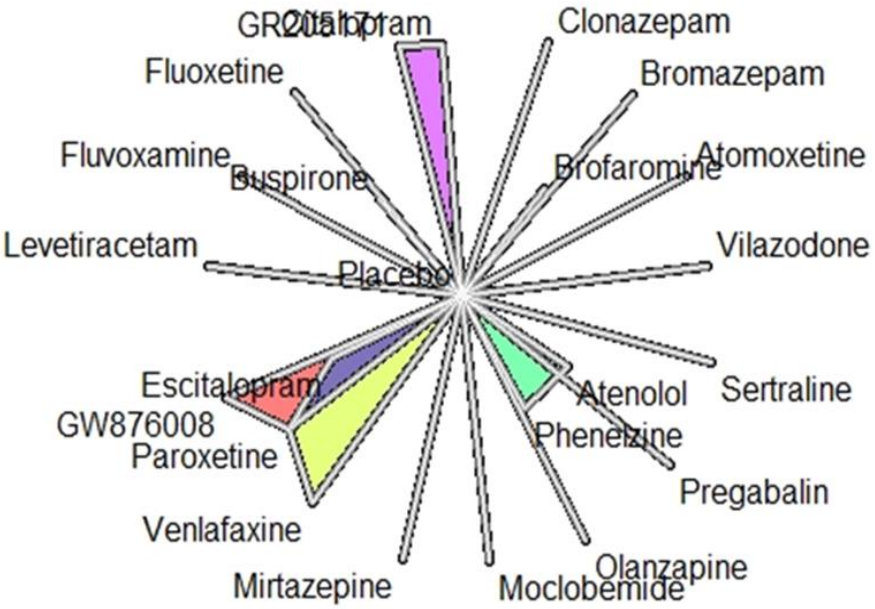


Figure 3 (Appendix D). Network graph of eligible comparisons for the network meta-analysis of the outcome response rate. The width of the lines is proportional to the number of trials and sample sizes comparing every pair of treatments.

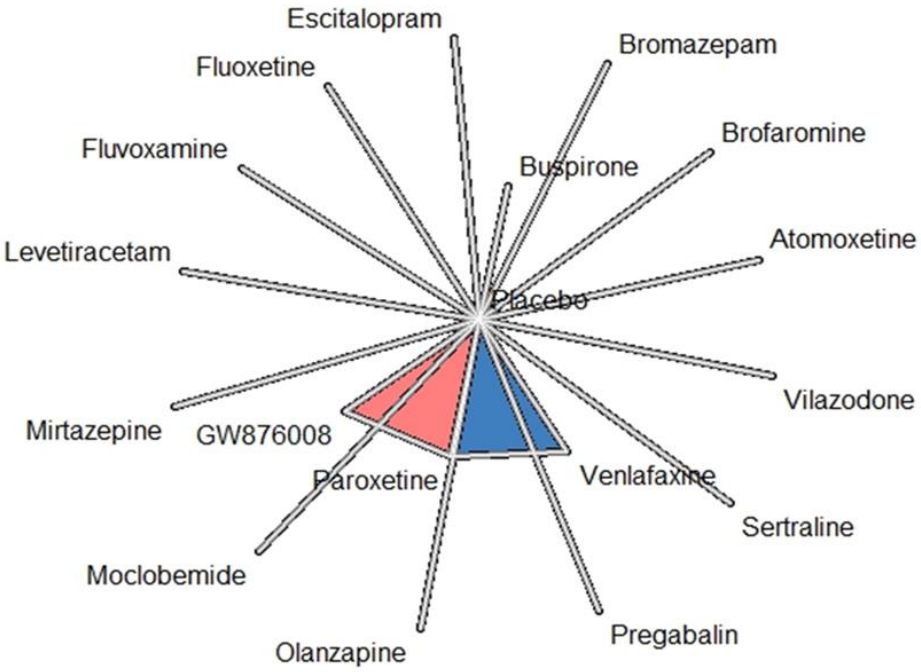
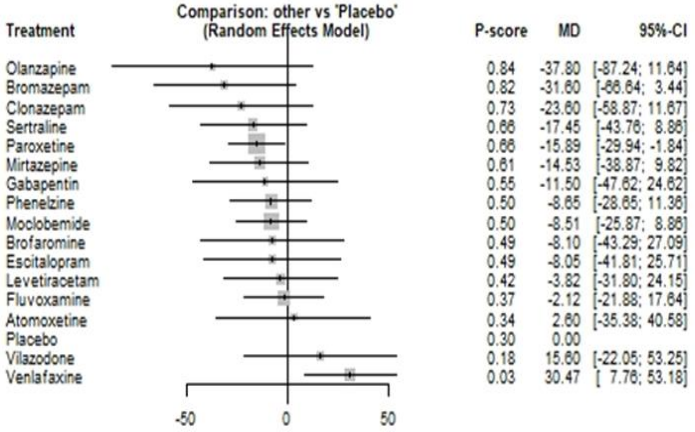


Figure 4 (Appendix D). Network graph of eligible comparisons for the network meta-analysis of the outcome dropouts due to adverse events. The width of the lines is proportional to the number of trials and sample sizes comparing every pair of treatments.

Table 1 shows the relative treatment effects for the two primary outcomes (change in symptom's severity and all-cause dropouts). In terms of efficacy, paroxetine (MD -15.89; CI -29.94 to -1.84) was significantly more effective than placebo in reducing anxiety symptoms. Although a significant difference in symptom severity was observed following treatment with venlafaxine compared to placebo, this effect favoured the placebo intervention (MD 30.47; CI 7.76 to 53.18). No other statistically significant differences were found between the rest of the treatments and placebo. In terms of dropout rate, most of the medications (12 out of 19 comparisons) reported a decrease in dropout rates due to any cause, but no statistically significant difference was found. Fluvoxamine was the only medication for which a significant increase in dropout rates was found, relative to placebo (OR 1.51; CI 1.06 to 2.14) (also see Table 1 and figures for Appendix D).

Symptom Severity



All-cause Dropouts

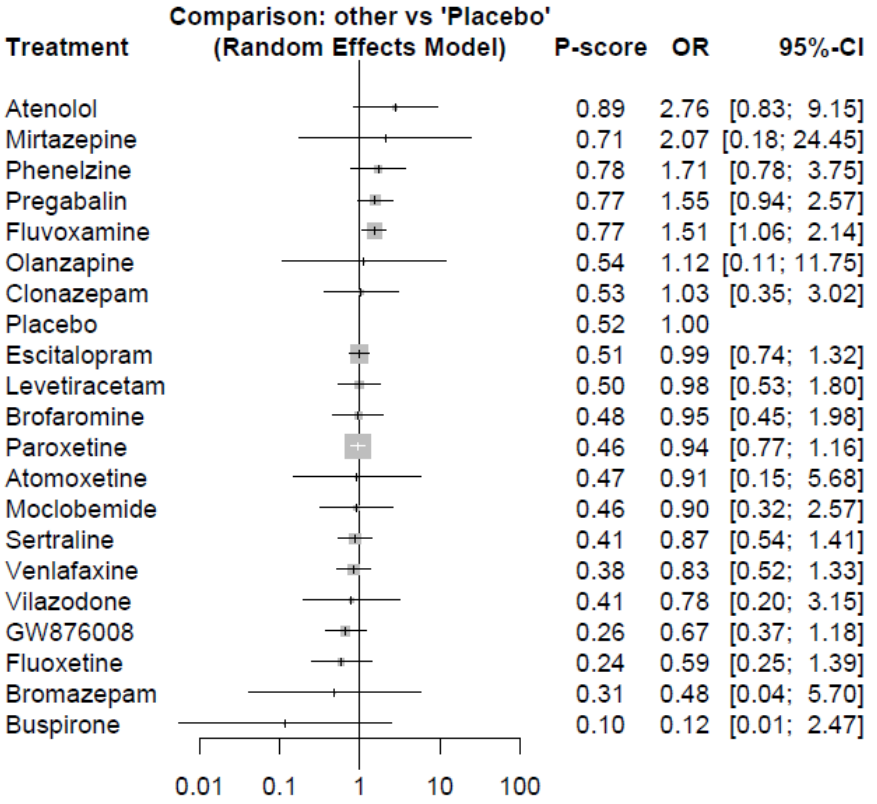


Table 1. Network meta-analysis results and P-scores for the comparisons of active treatments versus placebo for the primary outcomes (a) change in symptoms and (b) all-cause dropouts). **Legend.** MD: mean difference; OR: odds ratio; CI: confidence interval.

Response rate outcomes were consistent with findings for symptom severity reduction. Greater response to treatment compared to placebo was observed for paroxetine (OR 2.64; CI 1.97 to 3.54) once again, as well as for brofaromine (OR 8.10; CI 3.57 to 18.39), bromazepam (OR 20.00; CI 4.31 to 92.71), clonazepam (OR 14.50; 3.62 to 58.14), escitalopram (OR 1.96; CI 1.21 to 3.17), fluvoxamine (OR 1.89; CI 1.14 to3.12), phenelzine (OR 3.37; CI 1.59 to 7.15), and sertraline (OR 2.50; CI 1.02 to 6.15) (see Appendix E). In terms of dropouts due to adverse events, brofaromine (OR 3.98; CI 1.28 to 12.36), escitalopram (OR 2.02; CI 1.09 to 3.75), fluvoxamine (OR 6.51; CI 3.56 to 11.93), paroxetine (OR 2.59; CI 1.87 to 3.58), pregabalin (OR 3.60; CI 1.31 to 9.93), sertraline (OR 2.76; CI 1.09 to 7.02), and venlafaxine (OR 2.87; CI 1.89 to 4.36) performed worse in comparison to placebo (see Appendix E).

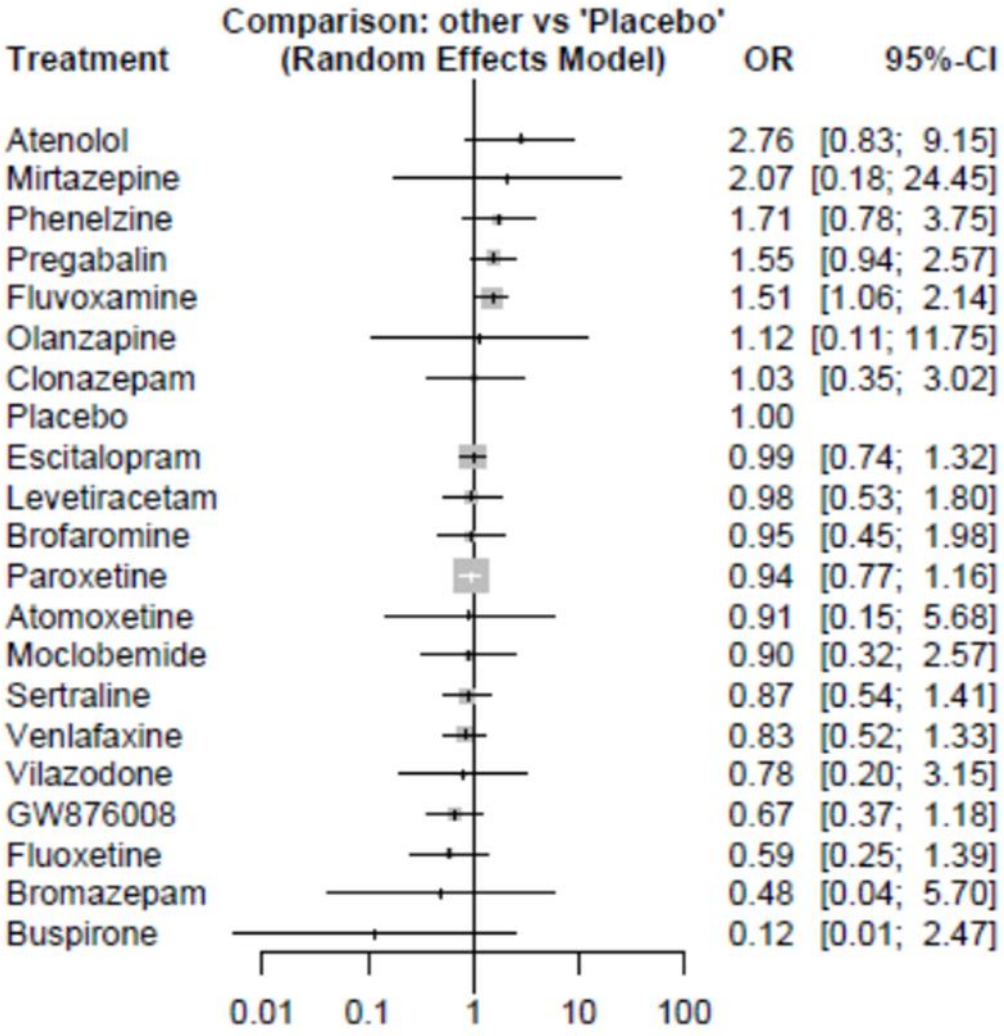


Figure 1 (Appendix E). Forest plot for the outcome ‘Dropouts due to any cause’.

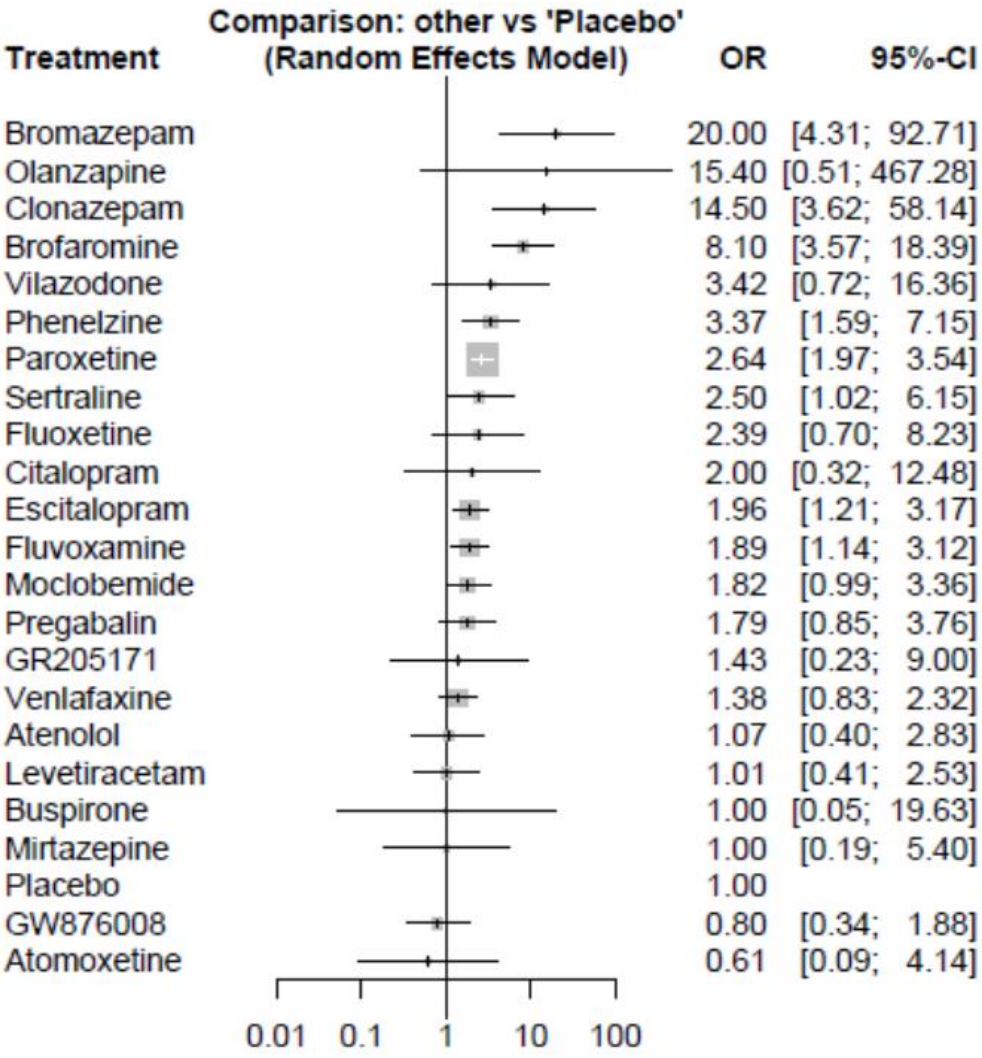


Figure 2 (Appendix E). Forest plot for the outcome ‘Response rate’.

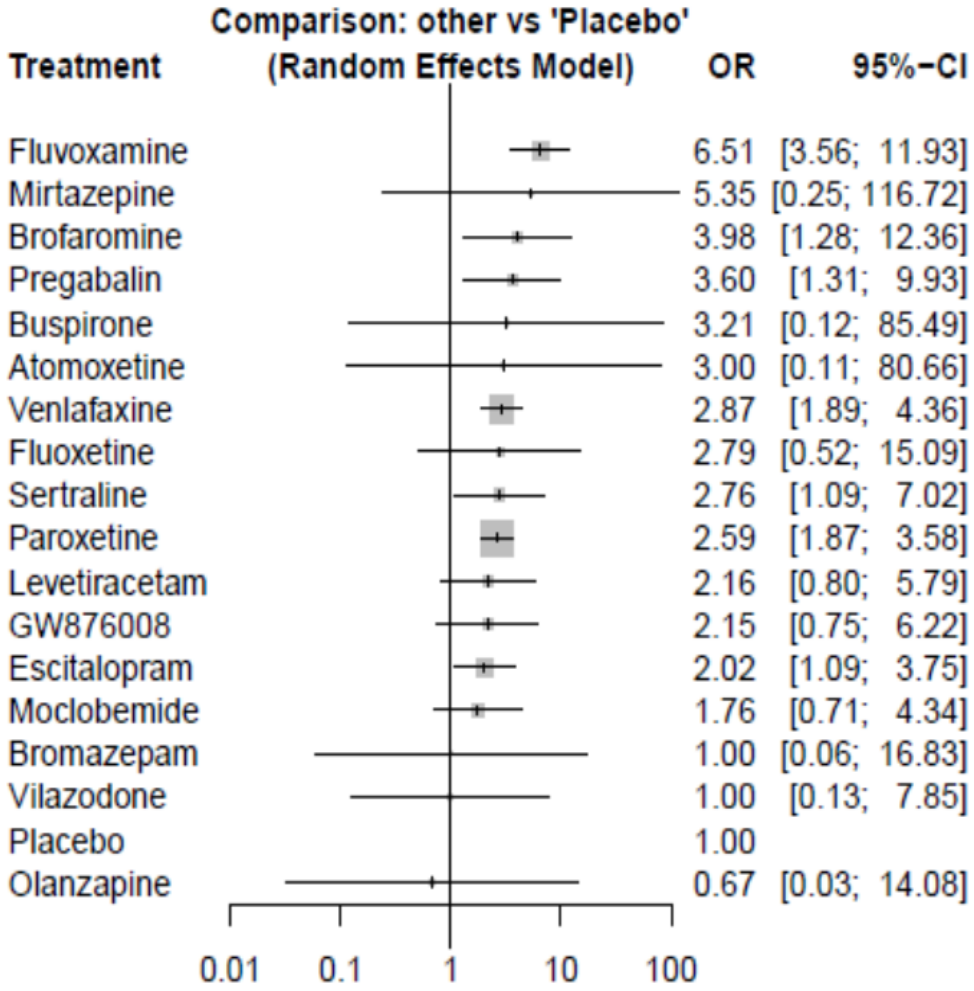


Figure 3 (Appendix E). Network plot for the outcome 'Dropouts due to adverse events'

Heterogeneity was substantial for the binary outcome response rate (i.e. $tau^2 = 0.1640$; $I^2 = 62.1\%$) and the continuous outcome of symptom severity (i.e. $tau^2 = 290.8$; $I^2 = 93.8\%$); in both NMAs the test of overall heterogeneity and inconsistency was highly statistically significant (i.e. $p < 0.0001$). For the binary outcome of acceptability, I^2 was 8.7% for dropouts due to any cause and 1.6% for dropouts due to adverse events.

Treatment rankings for the primary outcomes were reported. According to the ranking's olanzapine performed better than the rest of the treatments in terms of the reduction in social

anxiety symptoms and buspirone worse for dropouts due to any cause. These findings are supported by the actual effect sizes presented in Table 1. Bromazepam performed well in treating the number of responders and placebo groups worse in dropouts due to adverse events based on ranking and P-scores. See Appendix F for all details about rankings and P-scores.

Medication	P-score (random)
Olanzapine	0.84
Bromazepam	0.82
Clonazepam	0.73
Sertraline	0.66
Paroxetine	0.66
Mirtazapine	0.61
Gabapentin	0.55
Phenelzine	0.50
Moclobemide	0.50
Brofaromine	0.49
Escitalopram	0.49
Levetiracetam	0.42
Fluvoxamine	0.37
Atomoxetine	0.34
Vilazodone	0.18

Venlafaxine	0.03

Table 1 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores for the outcome 'Symptom Severity'.

Medication	P-score (random)
Buspirone	0.89
Fluoxetine	0.75
GW876008	0.73
Bromazepam	0.68
Venlafaxine	0.61
Vilazodone	0.59
Sertraline	0.58
Moclobemide	0.54
Paroxetine	0.53
Atomoxetine	0.52
Brofaromine	0.52
Levetiracetam	0.50
Escitalopram	0.49
Placebo	0.47
Clonazepam	0.47

Olanzapine	0.45
Mirtazapine	0.29
Fluvoxamine	0.22
Pregabalin	0.25
Phenelzine	0.21
Atenolol	0.11

Table 2 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores for the outcome ‘Dropout due to any cause’.

Medication	P-score (random)
Bromazepam	0.94
Clonazepam	0.92
Brofaromine	0.87
Olanzapine	0.83
Phenelzine	0.70
Vilazodone	0.65
Paroxetine	0.64
Sertraline	0.59
Fluoxetine	0.56
Escitalopram	0.50
Citalopram	0.49
Fluvoxamine	0.48
Moclobemide	0.46
Pregabalin	0.45
GR205171	0.38

Venlafaxine	0.34
Buspirone	0.33
Mirtazapine	0.27
Atenolol	0.25
Levetiracetam	0.23
Placebo	0.19
Atomoxetine	0.17
GW876008	0.15

Table 3 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores for the outcome 'Response Rate'.

Medication	P-score (random)
Placebo	0.84
Olanzapine	0.76
Vilazodone	0.73
Bromazepam	0.69
Moclobemide	0.62
Escitalopram	0.57
Levetiracetam	0.53
GW876008	0.53
Paroxetine	0.46
Atomoxetine	0.44
Fluoxetine	0.44
Sertraline	0.43
Buspirone	0.43
Venlafaxine	0.40
Pregabalin	0.32

Mirtazapine	0.31
Brofaromine	0.29
Fluvoxamine	0.12

Table 4 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores for the outcome ‘Dropouts due to adverse events.

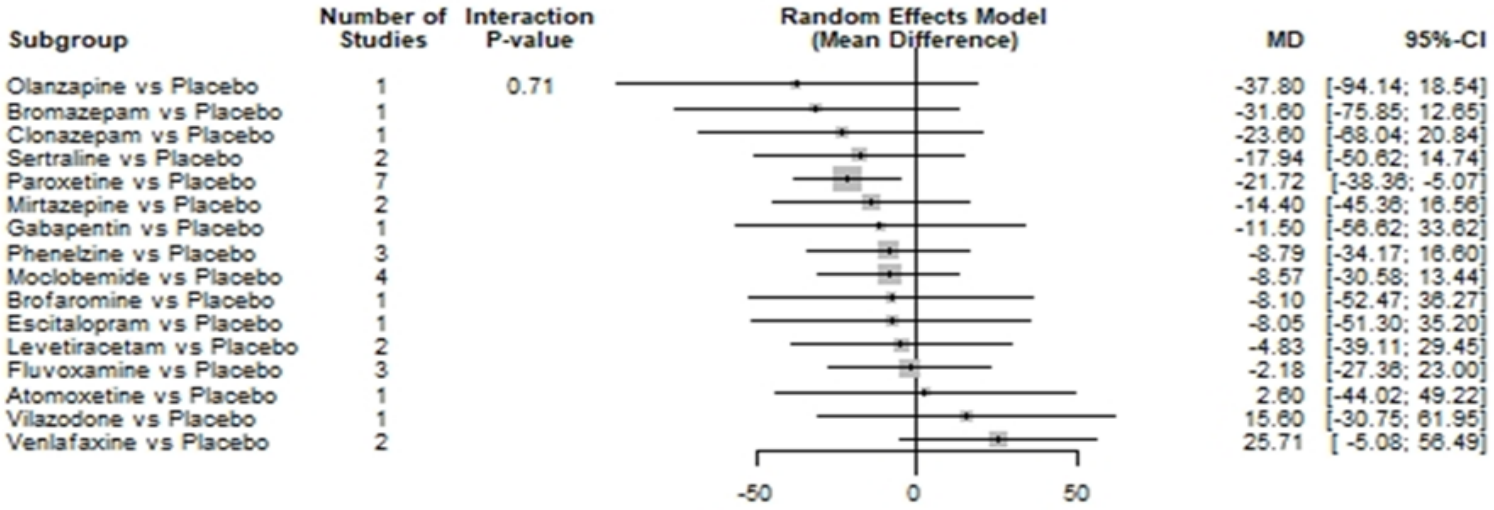


Figure 1 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores and the outcome 'Symptom Severity'

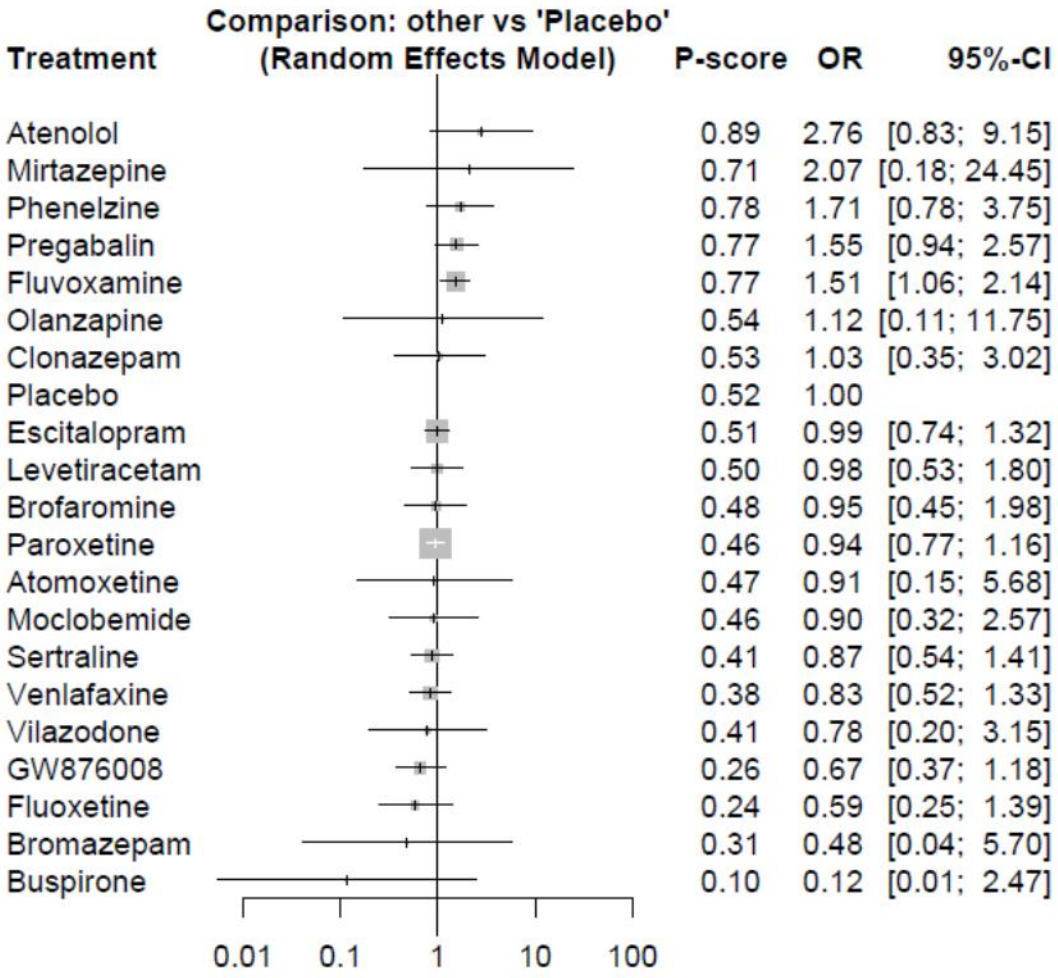


Figure 2 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores and the outcome 'Symptom Dropouts due to any cause'

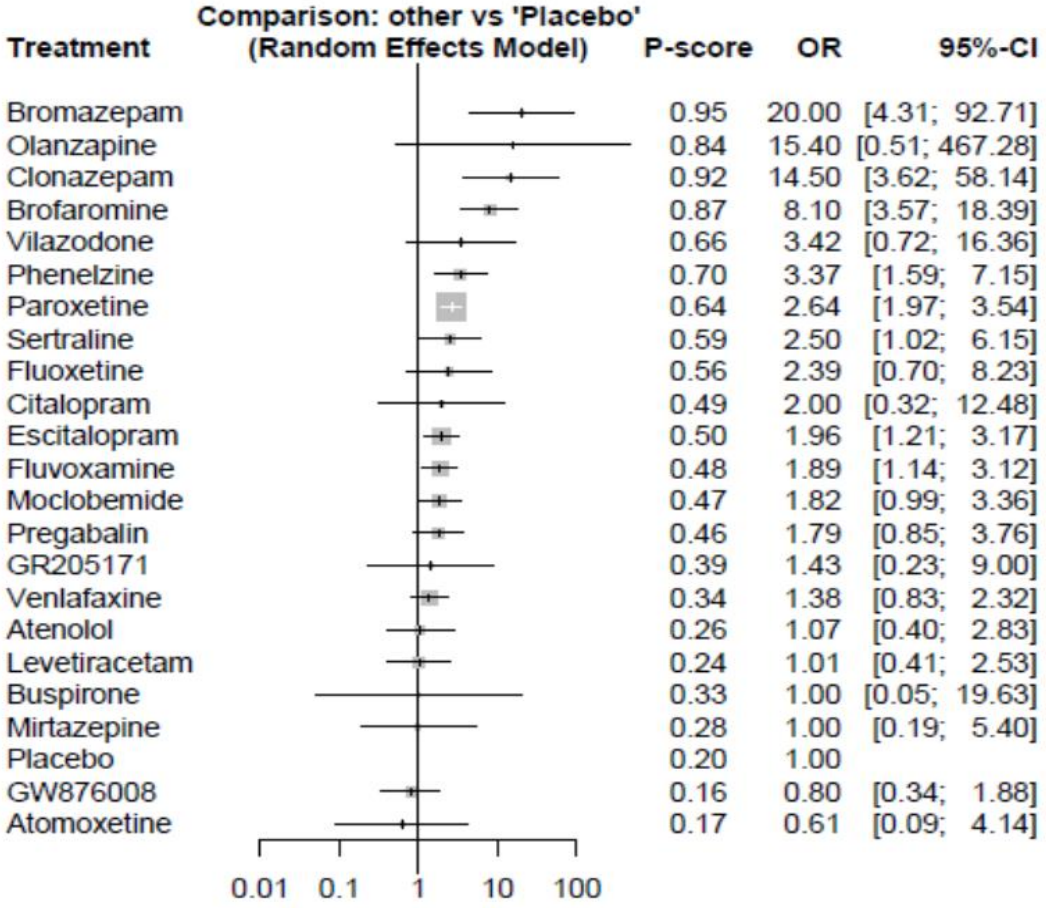


Figure 3 (Appendix F). Network meta-analysis results listed based on rankings and p-scores for random effects scores and the outcome 'Response rate'

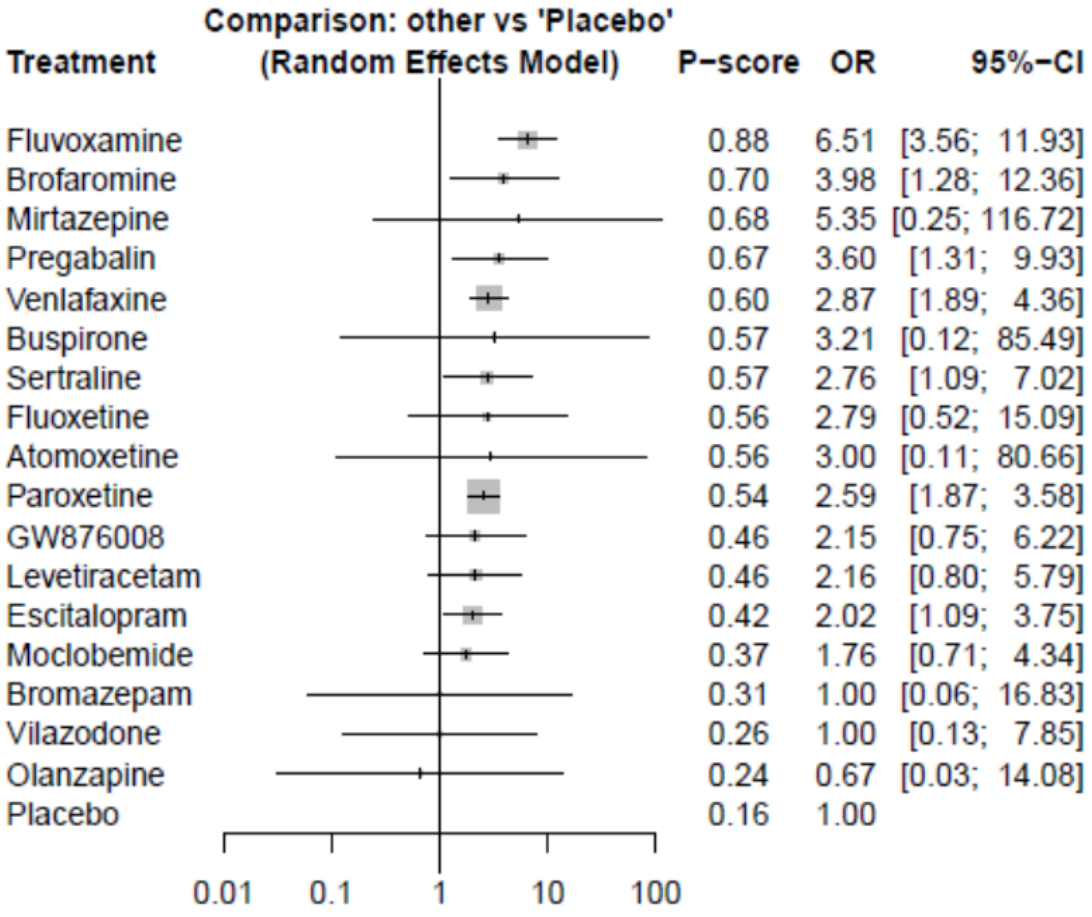


Figure 4 (Appendix F). Network meta-analysis results listed based on SUCRA rankings and p-scores for random effects scores and the outcome 'Symptom Dropouts due to adverse events'

Effect modifiers

For the primary outcomes of symptom severity and tolerability (dropouts due to any cause) mean age, mean age of onset, mean baseline severity, sponsorship and year of publication did not contribute to any heterogeneity in the NMA. For the secondary outcome of treatment effectiveness (number of responders), 14.5% of the variation in the effect size was explained by mean age and 23% by year of publication. This meant that number of responders differed by age as well as with time (i.e. as time progresses treatment response decreases), significantly. For mean age of onset, mean baseline severity and sponsorship the adjusted R^2 was reported by the meta regression as zero for the outcome of dropouts due to any cause and did not contribute to heterogeneity in the model. Mean age, mean age of onset, mean baseline severity, sponsorship and year of publication did not contribute to any heterogeneity in the NMA for the outcome of dropouts due to adverse events.

Sensitivity analysis

Sensitivity analyses could not be conducted due to the lack of information provided by included RCTs.

DISCUSSION

Our network meta-analysis included 45 studies with 23 different interventions compared to at least one placebo-controlled group, for the efficacy and acceptability of pharmacological treatments for SAD. The network revealed that paroxetine was significantly more effective than placebo in reducing anxiety symptoms, with no clear evidence of a beneficial effect for the other medications. Venlafaxine, however, provided evidence of an increase in anxiety symptoms, although based on two RCTs with large sample sizes (Liebowitz *et al*. 2005; Rickels e*t al*. 2004). A greater response to treatment, relative to placebo, was observed for brofaromine,

bromazepam, clonazepam, escitalopram, fluvoxamine, paroxetine, phenelzine, and sertraline. For dropouts due to adverse events, brofaromine, escitalopram, fluvoxamine, paroxetine, pregabalin, sertraline, and venlafaxine performed worse than the rest of the individual medications. Olanzapine yielded a relative high rank for treatment efficacy and buspirone the worse for dropouts due to any cause. A relatively high rank was observed for bromazepam in treating the number of patients who responded to treatment, and placebo groups for dropouts due to adverse events.

The strong evidence supporting the effects of paroxetine in treatment reduction of SAD symptoms (including response) in this review contributes to 33% (15/45) of the evidence in the network. Despite indications that paroxetine may be efficacious in treating SAD, its use was also associated with more dropouts due to adverse effects. The NMA did not observe any evidence of heterogeneity for the outcome dropouts due to adverse effects, nor did mean age, mean age of onset, mean baseline severity, sponsorship and year of publication contribute to any heterogeneity in the NMA. The cause of heterogeneity could be attributed to the response observed by treatment with venlafaxine in the network and the potential limitations of the methodology (risk of bias and quality of evidence), the complexity of patients with SAD and the uncertainties that may result from the choice of dose or treatment setting. Moreover, the validity of the findings of venlafaxine might be limited due to the lack of enough data to properly evaluate the required assumptions, that our network was star-shaped, and that we could not check for inconsistency.

The evidence provided by this NMA for clinical response to treatment with brofaromine, bromazepam, clonazepam, escitalopram, fluvoxamine, paroxetine, phenelzine, and sertraline supports clinical guidelines. This is particularly the case for the SSRI medications, regarded by

many of these guidelines as first line treatments (De Menezes, 2011; NICE, 2011; Blanco, 2013; WHO, 2013). Mean age (14.5%) and year of publication (23%) accounted for up to 50% of the heterogeneity in the model, however. This meant that number of responders differed by age as well as with time (i.e. as time progresses treatment response decreases), significantly. It is also noteworthy that fluvoxamine was the only medication that reported a significant increase in dropout rates due to any cause, and brofaromine, escitalopram, fluvoxamine, paroxetine, pregabalin, sertraline, and venlafaxine a significant increase in dropout rates to adverse events in comparison to the rest of the individual medications. Given that current evidence does not support the choice of one second-generation antidepressant over another in terms of differences inefficacy and effectiveness, clinical decisions should be informed primarily, and on a case by case basis, with regards to patient symptoms and their response to treatment (Del Re, 2014).

Furthermore, olanzapine performed better than the rest of the treatments in terms of treatment response and buspirone worse for dropouts due to any cause. In the network meta-analysis only one study investigating olanzapine and one study investigating buspirone was included in the analysis, with a sample size of 10 and 30, respectively. Bromazepam performed well in terms of number of responders and placebo groups worse for dropouts due to adverse events. This observation was also based on one study investigating bromazepam with a sample size of 60 participants. Given that these medications are not first line treatments, more trials with each of these agents in the future may allow better comparisons between these classes of medication. Moreover, the small samples could account for the high variability associated with the effect estimates for these agents.

This study has several limitations. Most trials included in the analysis did not report adequate information about randomisation and allocation concealment, and this might undermine the

quality of the overall findings. Judgements of response to treatment with the SSRIs were based on evidence rated as being of very low quality, which increases the uncertainty of the reported estimates. This is also confirmed by the total heterogeneity score and inconsistency for between and within group differences ($p < 0.0001$), based on the large number of small studies included in the network meta-analysis. The findings from this analysis apply only to acute-phase treatment of SAD. Future studies considering the maintenance phase of these studies could add additional value in our understanding of the efficacy of these medications in treating SAD over the long term. Moreover, although an extensive and rigorous search of the literature for both published and unpublished pharmacotherapy RCTs of SAD was employed, certain sources, such as conference proceedings, were not systematically searched, which might have biased the results. However, due to the strict inclusion criteria, all the primary studies were sufficiently similar with respect to population, intervention and outcome so that no concerns about indirectness or intransitivity emerged. To address this concern, the study did however follow the PICO standard set out for network meta-analyses throughout the study (Schardt, 2014) which increases the reliance of study results.

The finding that paroxetine was the only medication which demonstrated efficacy in treating SAD symptoms may be due to the relatively large evidence base for this agent, lending greater power to analyses of treatment effect estimates. The data included in this review are consistent with findings from other systematic reviews and meta-analyses in identifying that SSRIs like paroxetine are first line agents for the treatment of SAD (Ballenger *et al*. 1998; Van der Linden *et al.* 2000; Bandelow *et al.*2002; Blanco *et al.* 2003; Bandelow *et al.*2012; Bandelow & Michaelis 2015). Moreover, findings are consistent with the conclusion in an earlier review that, aside from documented differences in the incidence of specific adverse events, existing

evidence for a network meta-analysis does not suggest differences in the effectiveness of this drug(s) (Hansen *et al.*2008).

Nevertheless, the outcomes of this review are generalisable to a diverse range of settings and the interventions targeted both men and women across a wide age range. In this review a cost-effectiveness analysis was not included, therefore future studies should consider the specific contexts (in-and-outpatient hospitals and clinics, research settings) in which the trials took place, given the lack of evidence on the availability and cost-effectiveness of individual medications. Additional work is needed to determine the best approach for people who fail to respond to pharmacotherapy; there are relatively few studies of treatment augmentation (Pecknold *et al.* 1982; Van Ameringen *et al.* 1996; Stein *et al.* 2001; Aarre, 2003; Ipser *et al.*2009) or pharmacotherapy switching (Kelsey, 1995). Another research priority revolves around the combined use of pharmacotherapy with psychotherapy and when and if these treatments should be combined or sequenced (Williams *et al*. 2017).

Finally, the investigation of discontinuing medication and medication side effects are of importance. Although this review and network meta-analysis used short term trials to investigate the treatment of SAD, SSRIs are known for side effects such as dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, weight, sexual dysfunction, bleeding, and hyponatremia (Wang, 2018); MAOIs, in the form of phenelzine, as well as certain benzodiazepines, require dietary and medication restrictions and place individuals at risk to substance abuse (Licata 2008); RIMAs are not available in clinical practice; and atypical antipsychotics increase ones risk of weight gain, sedation, prolactin levels and extrapyramidal side effects (Olsten & Bloch, 2018). Thus, further research is needed to address these concerns.

In the next chapter I provide a summary and conclusion for each chapter included in my dissertation.

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CHAPTER 7.

Summary and Conclusions

In this chapter I provide a summary of the main findings throughout the dissertation, limitations of the data and limitations of the dissertation itself, as well as future research and recommendations.

SUMMARY AND CONCLUSIONS

Main findings

The main findings of this dissertation were 1) that, based on Cochrane review methods, there is a substantial amount of evidence supporting the efficacy of pharmacotherapy for SAD and PTSD, and particularly for the efficacy of the SSRIs in these conditions; 2) across published NMAs of common mental disorders, antidepressants are the most effective and/or tolerable agents, as assessed either by rankings or by overall statistical significance of RCTs included in these NMAs; 3) the results for both standard pair-wise meta-analyses and network meta-analyses were consistent with respect to the efficacy of paroxetine and sertraline; 4) based on Cochrane reviews other medications such as the SNRI venlafaxine, MAOIs, benzodiazepines, the antipsychotic olanzapine, and the NaSSA atomoxetine are effective in reducing SAD symptoms, with evidence of a treatment response for anticonvulsants with gamma-amino butyric acid (GABA) analogues and the benzodiazepines; other medications for treatment of PTSD include the alpha-blocker prazosin and antipsychotics for symptom severity, while the alpha-blocker prazosin and the tricyclic antidepressant amitriptyline improved number of response; 5) for the NMA reviews efficacy was also observed for the individual medications phenelzine, desipramine and risperidone, with a relatively high rank for mirtazapine for treating PTSD symptoms; this was also observed for venlafaxine and olanzapine in treating SAD

symptoms; 6) pharmacotherapy is well tolerated; individuals diagnosed with SAD and PTSD who were treated with SSRIs were more likely to withdraw from treatment due to treatment-related adverse events, but that the absolute proportion of individuals dropping out from treatment due to adverse events was low for both disorders with no difference in withdrawal rates due to any cause, in both standard and in network meta-analyses; 7) that evidence for these conclusions was heterogenous in quality, ranging from moderate (where further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) to very low quality (where further research is needed to confirm the uncertainty of the estimate of effect), for both standard pairwise meta-analyses and NMAs; although previous published NMAs in psychology and psychiatry rank high in quality of reporting.

A number of additional findings, addressing the question of predictors of response, are noteworthy 1) there was evidence that treatment response was influenced by whether RCTs took place at single compared to multiple centres in SAD, 2) that the size of the effect observed was dependent on participant characteristics, with a smaller response to treatment observed in studies that restricted inclusion to participants diagnosed with generalized SAD, and in veterans with PTSD, 3) there was some evidence that treatment response across all medication classes varied as a function of whether trials were funded by industry in standard pairwise analyses of SAD and PTSD, 4) there were inconsistent findings with regards to depression, in SAD trials no difference was observed in comparison to PTSD trials where a difference was found for patients included with MDD versus those that were excluded from analyses; 5) for the NMA reviews effect modifiers such as mean age, mean age of onset, mean baseline severity, sponsorship and year of publication did not contribute to any heterogeneity in the PTSD NMA for treatment efficacy, symptom severity and tolerability; while for the SAD NMA, and the outcome of treatment efficacy, variation in the effect size was partly explained by mean age

and year of publication; 6) there is evidence of possible funnel plot asymmetry providing data on response to short-term medication treatment, for the SSRIs for the standard pairwise analysis of SAD.

The finding here that pharmacotherapy is effective in SAD and PTSD is consistent with growing evidence of psychobiological alterations in these conditions (Furmark, Tillfors, Marteinsdottir et al., 2002; Charney, 2004), and with prior meta-analyses that point to the value of pharmacotherapy in these disorders (Cuijpers, Sijbrandij, Koole et al., 2013; Watts, Schnurr, Mayo et al., 2013). Clinicians should therefore include psychiatric medications when considering the treatment of these conditions. The greatest number of trials showing efficacy to date, as well as the largest, have been with the SSRIs in treating SAD and PTSD. The finding of the effectiveness of the SSRIs were also more robust to differences in the summary statistic employed than was the case for the rest of the medication trials. The current dissertation therefore supports the efficacy of SSRIs for short-term treatment of SAD and PTSD and is in line with current treatment guidelines and systematic reviews (Baldwin, Anderson, Nutt et al., 2014; Hoskins, Pearce, Bethell et al., 2015; NICE, 2011; NICE, 2018) published on these disorders. At the same time, other medications which have been found efficacious can also be considered, although given that they not first line treatments, caution is advised on their use in treating these disorders. These findings also apply to the tolerability of these medications as well as for the SSRIs for treatment emergent side effects.

The RCTs included in the Cochrane reviews and NMAs of SAD and PTSD have a range of randomisation procedure concerns, although the NMAs included in the qualitative review report quality well. The latter finding indicates that more recently published reports adhere to more rigorous methodological standards (Petropoulou, Nikolakopoulou, Veroniki et al. 2015;

Chambers, Naci, Wouters et al. 2015; Zarin, Veroniki, Nincic et al. 2017). Cochrane methodologists may want to review these standards and apply more rigorous gradings against the individual RCTs and their quality of evidence. It appears that Cochrane reviews complement NMAs (and vice versa). NMAs act as an extension to addressing unit of bias errors in Cochrane reviews and allow for the assessment of treatment efficacy through the combination of both direct and indirect comparisons of all interventions on a specific outcome. It is, therefore, not surprising that Cochrane has recently (within the past year) adopted the NMA methodology to address these concerns about the relative efficacy of different agents from trials with different participants, as these findings require confirmation in head-to-head comparisons (Higgins & Greens, 2011).

Neither the potential clinical (presence of combat trauma, comorbid depression) or methodological (single versus multi-centre trials, industry versus non-industry funding) predictors of medication response tested in this dissertation can account for the substantial proportion of patients who do not appear to respond to medication. The finding that symptom severity is reduced to a greater extent in the multi-centre than the single centre trials should be interpreted with caution, due to the marginal significance of this finding in both Cochrane reviews and NMAs of SAD and PTSD.

Most published trials of pharmacotherapy for SAD and PTSD exclude individuals with concurrent psychopathology. Given that SAD and PTSD are highly comorbid, it is notable that most published RCTs on SAD exclude patients with MDD, but PTSD trials often include patients with MDD. Future research on patients with comorbidity is needed.

Limitations of the data

There are several limitations of the existing database of trials. The generalisability of included RCTs was low. Although the outcomes of this dissertation may be generalisable to a diverse range of settings, and that studies were conducted in both single and multi-centers and include both men and women across a wide age range, careful consideration should be given to the specific contexts in which the trials took place, given the lack of evidence on the availability and cost-effectiveness of individual medications across reviews. This is especially the case when there is evidence that smaller trials with negative outcomes may not have been published. The findings of this dissertation do not apply equally to the full range of individuals presenting at clinics for the treatment of SAD and PTSD. The context of clinical practice differs from controlled trials in many respects, not the least being the inclusion of more complex patients. RCTs included in this dissertation were also restricted to those assessing the effectiveness of pharmacotherapy for SAD and PTSD in adults. Clinicians should therefore consider that the findings presented in this dissertation do not apply to the treatment of SAD and PTSD in children. As the database of trials grows, it may be possible to include specific contexts (in-and-outpatient hospitals and clinics, research settings) in which the trials took place, in sub-analyses.

Furthermore, failure to employ independent outcome assessors in trials which adjust medication dosage on the basis of side-effect severity, and inadequate statistical methods of compensating for patient withdrawals, risk undermining the best efforts to minimise bias in the findings of systematic reviews of health care interventions. Many of the RCTs included in the dissertation also failed to report randomisation procedures (random sequence generation, allocation concealment, and blinding). However, all the studies included in the reviews reported that they employed double-blind procedure, and the low quality ratings may be due

more to scant information in the reporting of trial methodology than real defects in study design, as it has been commonly found in other systematic reviews (Huwiler-Müntener, Jüni, Junker et al., 2002). The low quality trials also raise questions around the certainty of treatment estimates and therefore readers should take this into account when assessing which treatment is best in clinical decision making. There was insufficient data available to assess the extent to which selective publication may have introduced bias in the findings for medication classes besides the SSRIs for both PTSD and SAD. These shortcomings increase the uncertainty of the reported estimates and are confirmed by the total heterogeneity score and inconsistency for between and within group differences ($p < 0.0001$), based on the large number of small studies included in the reviews and network meta-analyses for SAD and PTSD.

The findings from this dissertation only apply to acute-phase treatment of SAD and PTSD. Clinically, the assessment of efficacy after four weeks of treatment or after 16 weeks or more might lead to wide differences in treatment outcome, and this may limit the ability to provide valid estimates of treatment effect if different durations of follow-up are combined. To overcome this problem, a common definition of acute response that included a pre-defined follow-up duration (eight weeks) was explored. Moreover, because network meta-analyses require reasonably homogeneous studies, in this dissertation I had to restrict inclusion criteria to short-term trials.

Limitations of the dissertation

Several limitations of the methodology used here should be emphasised. First, tolerability was assessed in terms of drop-out rates due to adverse events, but this may not always provide an accurate measure of medication tolerability (Loke, Price & Herxheimer, 2005 as cited in Higgins & Greens, 2005). Second, failure to report rankings in published NMAs may also

partly reflect the concern that positions in these ranks are sensitive to small and clinically non-significant differences in reported treatment effects (Li, Puhan, Vedula et al., 2011; Leucht, Chaimani, Cipriani et al., 2016). Given that the medications ranked highest for both the SAD and PTSD NMA are not consistent with first-line agents recommended by current guidelines, the findings from these rankings should be treated with caution, particularly since the overall evidence about these drugs are based on one to two studies with small participant sizes. Third, the use of relative risk instead of odds ratios in the Cochrane reviews can be considered a limitation of the review methodology employed in this dissertation. However, according to Deeks, Altman and Bradburn (2011) odd ratios tend to underestimate the size of the treatment effect when the occurrence of the adverse outcome of interest is common (as was the case in this review, with an anticipated non-response greater than 20%), and can be more easily interpreted. Moreover, the results for both disorders were similar when using relative risk and/or odds ratios, however.

Fourth, this review also classified medications based on their putative mechanisms of action (taken from CCMD antidepressant classification map) (Davies, Champion, Dawson et al., 2015), and they do not necessarily map onto the drug classification schemes employed in other reviews. Nevertheless, the efficacy of the SSRIs in the treatment of SAD and PTSD is confirmed.

Fifth, the validity of the NMA(s) findings might be limited due to the lack of enough data to properly evaluate the required assumptions. Results from network meta-analysis may be unreliable when there is a high risk of intransitivity in the network (Salanti, 2012; Cipriani, Higgins, Geddes et al., 2013). In each network, I was unable to judge the plausibility of transitivity since most comparisons included very few studies. Thus, I could only rely on

clinical understanding of the studied condition and outcomes to assume that transitivity was likely to hold in the identified data.

Future research and recommendations

This dissertation points to several gaps in the literature that deserve to be addressed in future studies. First, additional work is needed to determine the best approach for people who fail to respond to pharmacotherapy; there are relatively few studies of treatment augmentation or pharmacotherapy switching. Second, the efficacy of different medications deserves more attention; there are few studies directly comparing modern agents with one another. Third, another research priority revolves around the combined use of pharmacotherapy with psychotherapy and when and if these treatments should be combined or sequenced. Fourth, in terms of efficacy given the heterogeneous phenomenology of SAD and PTSD, it remains crucial to determine the factors which do predict response to medication, and to delineate whether certain medications are more effective for particular symptom sets. Future RCTs, systematic reviews and meta-analyses should attempt to address such questions in greater detail. In addition, future studies considering the maintenance phase of these studies could add additional value in understanding of the efficacy of medications in treating SAD and PTSD over the long term, especially given that discontinuation of various agents over the long-term is problematic and often leads to inappropriate long-term use (Eveleigh, 2018). However, it is also noteworthy that long-term use of medication increases the incidence of withdrawals given the side effects experienced by those treated with the agents. For instance, SSRIs and SNRIs include side effects like dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, weight, sexual dysfunction, bleeding, and hyponatremia (Wang, 2018), MAOIs and benzodiazepines require dietary and medication restrictions and place individuals at risk to substance abuse (Licata 2008), RIMAs are not available in clinical practice, and atypical antipsychotics increase

ones risk of weight gain, sedation, prolactin levels and extrapyramidal side effects (Olten & Bloch, 2018). Thus, further research is needed to address these concerns.

In conclusion, this dissertation explores the utility of a standard pairwise approach and the multiple treatment meta-analytic approach in comparing the efficacy of all medications tested within pharmacotherapy RCTs for SAD and PTSD separately. I found that SSRIs are first line agents for treating SAD and PTSD and that these findings are consistent with past literature and support recent guidelines. The findings also provide insight into the extent to which systematic reviews and network meta analyses inform clinical decision-making based on the totality of evidence for pharmacological treatment for SAD and contributes towards informing future medical research and public policy. Caution is however needed with regards to recommending second line medications, as more evidence in this field is needed to direct clinical decisions.

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