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Antidepressants versus placebo for generalized anxiety disorder: A systematic review and meta-analysis

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Supervisor: Guaiana, Giuseppe., *The University of Western Ontario* Co-Supervisor: Martin, Janet., *The University of Western Ontario* A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics © Katarina Kopcalic 2023

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Abstract

Objectives: To assess the efficacy and acceptability of antidepressants compared to placebo among adults with a primary diagnosis of generalized anxiety disorder (GAD).

Methods: Five electronic databases and 2 trial registries were searched to identify studies for inclusion. The risk of bias version 1 tool was used to assess the risk of bias. A random-effects meta-analysis was conducted using RevMan web. Results were presented using forest plots.

Results: 38 studies (12,570 participants) were included. Very low-quality evidence showed a benefit for antidepressants over placebo in the rate of treatment response (RR, 1.39: 95% CI: 1.27, 1.52) and no differences in acceptability (RR, 1.02: 95% CI: 0.92, 1.12). These results were consistent across different classes of antidepressants.

Conclusion: Higher quality of evidence is needed. Future studies should be more transparent with their methodology and outcome reporting and future reviews may include patients with comorbidities and explore other sources of heterogeneity.

Keywords

Generalized Anxiety Disorder; Antidepressants; Placebo; Systematic Review; Meta-Analysis; Cochrane Systematic Review

Summary for Lay Audience

Objectives: Generalized anxiety disorder (GAD) is a common mental health condition and is characterized by excessive worry about everyday events. Treatments include various psychological and pharmacological approaches. Antidepressant medications are a common pharmacological treatment for GAD and studies have shown their benefit over placebo (inactive treatment). This review provides an updated summary of all the evidence available on this topic. Specifically, the objectives were: (i) to evaluate the efficacy of antidepressants compared to placebo in reducing the symptoms of GAD; (ii) to assess the acceptability of antidepressants compared to placebo (the total number of people dropping out from each group); and (iii) to investigate adverse effects of antidepressants compared to placebo.

Methods: Online databases and trial registries were searched. Studies were included if they randomly assigned participants into one of two groups that received an antidepressant or placebo. The studies had to be among adults with a primary diagnosis of GAD, and without serious comorbid medical conditions. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidence.

Results: 38 studies with 12,570 participants were included. Antidepressants may be more effective than placebo at reducing symptoms of GAD, and in achieving treatment response and remission. Antidepressants may have similar acceptability to placebo but may be less well tolerated as more people reported experiencing adverse effects and more people taking antidepressant treatment dropped out due to adverse effects. Some specific adverse effects such as sleepiness/drowsiness were more frequently reported among antidepressants and limited evidence suggested a similar number of people experiencing agitation/anxiety and suicide wishes/gestures/attempts between the antidepressants over placebo in improving quality of life.

Conclusion: The findings of this review should be interpreted with caution due to the very-low quality evidence that was found. The applicability of this review was also limited to patients with a primary diagnosis of GAD and without other serious medical conditions. Clinicians and patients should jointly decide on the treatment regime that will most closely meet the needs and values of the patient.

Co-Authorship Statement

This review was published as a Cochrane Protocol in the Cochrane Database for Systematic Reviews (2018; Issue 2; No: CD012942; DOI: 10.1002/14651858.CD012942.). The following authors were responsible for the writing and publication of the protocol: Dr. Giuseppe Guaiana, Corrado Barbui, and Russlan Abouhassan. I was not part of the writing and publication of the protocol.

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I began this process without any background in epidemiology and biostatistics and throughout the last two years, I feel I've gained invaluable knowledge and experience in the field thanks to all of you. I look forward to applying what I've learned to my career and translating this knowledge to benefit the health of populations around the world. I wish you all the best.

Dedication

To my family. Thank you for always being there for me and providing me with endless love and support.

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Chapter 1

1 Introduction

Generalized anxiety disorder (GAD) is a mental health condition characterized by excessive anxiety and ongoing worry about everyday events [1]. People with GAD will also experience a variety of somatic symptoms including feelings of restlessness, fatigue, irritability, and muscle tension [1]. GAD is a common disorder, with a global lifetime prevalence of about 3.7% and generally affecting women twice as often as men [2].

GAD is often comorbid with other medical and psychiatric disorders [3]. This makes GAD particularly challenging to diagnose and treat. Nevertheless, since its establishment as an independent diagnosis in 1980, research on GAD has greatly increased our understanding of it [3]. GAD is a very debilitating disorder for both the individual and society. People with GAD often experience poorer quality of life, impaired functioning, reduced productivity and have higher usage of the healthcare system [4]. These burdens may be exacerbated in those with comorbid GAD and other medical and psychiatric disorders [4, 5].

Current treatments include pharmacological and psychological therapies. Examples of psychotherapies are: cognitive behavioral therapy, mindfulness, and psychodynamic therapy. Many pharmacotherapies also exist, with different mechanisms of action, dosing regimens, and safety profiles. Some of these pharmacotherapies include benzodiazepines, azapirones, antihistamines, anticonvulsants, second generation antipsychotics, and antidepressants. Many studies have investigated the efficacy, tolerability, and safety of pharmacotherapies in the treatment of people with GAD [6]. A number of studies have found pharmacotherapies to be effective in the treatment of people with GAD. However, pharmacological treatments may also cause adverse effects [5]. For example, benzodiazepines may provide benefit, but have been associated with dependency [4].

Studies assessing antidepressants in the treatment of GAD have shown them to be efficacious, well tolerated, and cause less dependency than other treatments such as benzodiazepines [7, 8]. Accordingly, antidepressants have increasingly been used for the

treatment of GAD [9]. Many different types of antidepressants are available including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), selective norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), noradrenergic and dopaminergic reuptake inhibitors (NDRIs), noradrenergic reuptake inhibitors (NDRIs), and others, all with varying mechanisms of action and dosing regimens. Particularly, SSRIs and SNRIs are the two classes of antidepressants that are commonly used as first-line treatments for GAD [10]. This means that SSRIs and SNRIs are often the first medication to be prescribed to people with GAD because they are considered to provide the greatest benefit and improved tolerability compared to other available medications. Nevertheless, the antidepressants are not without drawbacks and the risks of taking them, as with any medication, should be considered. Some adverse effects found to be associated with antidepressants are sexual dysfunction, nausea, diarrhea, and even increased suicidal ideation [11].

The evidence supporting the use of antidepressants comes from a variety of randomized controlled trials (RCTs) comparing antidepressants to placebo. RCTs are important in clinical research as they can reduce bias through randomization and can be used to explore cause-effect relationships, therefore providing valuable information on the efficacy of the treatment [12]. However, reviewing all the individual studies on a topic can be very time consuming and overwhelming. Systematic reviews and meta-analyses provide a more efficient way to access information by systematically identifying, evaluating and synthesizing all the available evidence on a specific issue [13].

Few authors have attempted to summarize all the available evidence on antidepressants compared to placebo through a systematic review and meta-analysis. Schmitt et al., (2005) is the only such review that has been done [14]. The review by Schmitt et al., (2005), however, was conducted almost 20 years ago, though is now outdated given the new studies that have been published. Other reviews on pharmacotherapy for GAD have been conducted but with purposes other than to directly compare all antidepressants to placebo. For example, Baldwin et al., (2011) and Slee et al., (2019) performed network meta-analyses comparing all drug treatments in GAD, while He et al., (2019) (also a

network meta-analysis) restricted their analysis to first-line treatments only [15-17]. Thus, a new and updated review comparing antidepressants to placebo is needed. The aim of this systematic review and meta-analysis is to provide an updated investigation on the efficacy, acceptability, specific adverse effects, and impacts on quality of life of antidepressants compared to placebo in the treatment of adults with GAD. This review will further our understanding of the benefits and drawbacks of antidepressants in the treatment of GAD and will provide insight into the current evidence available on this topic. The findings of this review can provide valuable information to clinicians and policy makers on the treatment of GAD with antidepressants and will serve as a tool to guide future research on pharmacotherapy in GAD.

1.1 Thesis Structure

This thesis was written in monograph format, following the requirements of the Western University School and Graduate and Postdoctoral Studies. It is a systematic review and meta-analysis comparing antidepressants to placebo in the treatment of adults with GAD. Chapter 2 is a literature review on GAD and its treatments. Chapter 2 is meant to provide a background on GAD and to highlight the need for this review. Chapter 3 describes the methods used for this review, including the details regarding the statistical analyses. Chapter 4 is a detailed description of the main results, including subgroup and sensitivity analyses. Chapter 5 is a discussion of the significance of the results, the limitations of the review and how this review can be applied to practice and future research.

Chapter 2

2 Literature Review

This chapter discusses the prior literature on generalized anxiety disorder (GAD) and its treatments. As we will see, GAD is a complex disorder, and many studies have been conducted to better understand it. This chapter begins with an introduction to GAD, including its symptoms, psychological models of worry, and its neurobiology and genetics. This is followed by a discussion of its epidemiology, burden of disease, screening, diagnosis, and the current treatments available for GAD. This chapter concludes with other systematic reviews and meta-analyses that have been done on the topic, gaps in the literature, and justification for why the current systematic review is needed.

2.1 Generalized Anxiety Disorder

GAD is a mental condition characterized by psychological symptoms such as excessive anxiety and worry about everyday events [1, 18]. These feelings of worry and anxiety are often difficult to control and are typically accompanied by somatic symptoms such as feelings of restlessness, fatigue, feeling on edge, insomnia, sleep disturbance, irritability, trouble concentrating, and muscle tension [1, 18]. In contrast to other anxiety disorders, people with GAD will experience worry and anxiety about a broad range of circumstances, instead of having a specific and primary trigger [1].

2.1.1 Psychological Models of Worry

Researchers have attempted to explain the chronic worry that may eventually manifest as GAD through psychological models. On such model is Borkovec's emotional avoidance model. This model suggests an inhibition of emotional processing of fear-inducing stimuli. This emotional response is required for the eventual extinction of an anxiety response, and if it is not activated, a constant state of worry is assumed [19, 20]. Other models, such as the contrast avoidance model, describe worry as a coping strategy used by people with GAD to avoid intense emotions [20, 21]. The model suggests that the degree of emotional 'shock' experienced in response to a negative event is less intense if

a person is already in a state of worry, compared to if the person were in a content state before the negative event. As a result, a state of worry is maintained to reduce drastic changes in emotion. This preference for a constant state of worry despite negative consequences is explained by the emotion dysregulation model. This model suggests that people who develop GAD are highly sensitive to emotions but have trouble regulating them [19]. This heightened sensitivity essentially motivates them to avoid intense negative emotional experiences [19].

Other models of worry include the meta-cognitive model and the information processing model. The meta-cognitive model is described as 'worry about worry' [22]. The model suggests individuals who experience worry also have negative beliefs about it. These negative beliefs ultimately lead to a continuous state of worry [22]. The information processing model suggests that these individuals tend to pay more attention to threatening or worrisome stimuli and because they also have inhibited cognitive processing, they are unable to focus attention on other tasks [20].

This section focused on some psychological models that attempt to explain the development of GAD through worry. Other researchers have also tried to explain its development through biological and social risk factors, which are discussed in the following sections.

2.1.2 Neurobiology, Neuroimaging, and Genetics of GAD

Many studies have been done with various imaging technologies to better understand changes in the brain that are associated with GAD. Although many areas of the brain appear to be affected, the most common finding among studies involves hypoactivation of the prefrontal cortex (PFC) and hyperactivation of the amygdala [5, 23]. The amygdala is the fear center of the brain. Its hyperactivation may explain why people with GAD are more vulnerable and sensitive to negative emotions [5, 21]. The PFC is involved in emotion regulation, which may explain why people with GAD also struggle with managing their emotions [21, 23]. Studies have shown that other areas of the brain are also affected, however more extensive research is still needed to reach a definitive conclusion about their role in GAD [23].

Studies have looked at the extent that genes contribute to the etiology of GAD, and have found that the heritability of GAD is around 25-30%, meaning that a combination of environmental and genetic factors may play a role in its development [18, 24, 25]. However, more research in this area is needed to gain a better understanding of the role genetics plays in the development of GAD.

2.1.3 Epidemiology

A number of studies have attempted to estimate the prevalence of GAD since it first became an independent diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III in 1980. Prevalence estimates across countries are highly variable due to cultural and ethnic differences, and across studies, due to differences in diagnostic criteria, methods of diagnosis, and study design. Comprehensive prevalence estimates are based on a global study using data from the World Health Organization World Mental Health Survey Initiative [2]. This study estimated that the lifetime global prevalence of DSM-5 GAD among adults aged 18-99 years was 3.7% and the 12-month prevalence was 1.8%. This survey also found that prevalence estimates were the lowest among lowincome countries and highest among high income countries [2, 26]. Lifetime prevalence ranged from 0.1% in Nigeria to 8.0% in Australia, and 12-month prevalence ranged from less than 0.1% in Nigeria to 4.3% in Spain [2]. These discrepancies could be due to differences in how various cultures view and describe distress and anxiety [27]. In particular, non-Western countries were found to place more emphasis on somatic symptoms rather than psychological symptoms, which may be missed by the predominantly psychological and worry focused criteria of the DSM-5 [2, 27, 28]. People aged 18-29 years were found to have the highest lifetime prevalence of GAD, whereas those aged 60+ years had the lowest [2].

Although studies have found that the average age of onset of GAD is in the early to midthirties, it is possible for GAD to develop at earlier or later stages in life in response to various unexpected, negative life situations [4, 21, 29, 30]. For example, long term maltreatment and abuse during childhood or increased stress due to chronic illness and social isolation during late life have been found to be associated with increased risk of developing GAD [21, 31]. Women have consistently been found to be at a higher risk of GAD compared to men, with many studies reporting that they are at twice the risk [1, 30, 32]. Other risk factors that have been associated with GAD include having low socioeconomic status, being widowed, separated, or divorced, unemployment, and having an ongoing comorbid psychiatric or medical disorder [1, 30, 32, 33]. Being of White ethnicity was also associated with higher odds of GAD, compared to being of Asian, Black, or Hispanic ethnicity [4, 30].

GAD is known for having high comorbidity with other disorders, with studies estimating that between 50%-95% of people with GAD will also present with another psychiatric disorder, particularly other mood and anxiety disorders [18, 30, 33-36]. It is estimated that 51.7% of people globally have a comorbid anxiety disorder, of which panic disorder, social phobia, and posttraumatic stress disorder have the strongest associations with GAD, with odds ratios (ORs) equal to 9.8, 9.2 and 9.2 respectively [2]. Sixty-three percent of people with GAD had a comorbid mood disorder, with major depressive disorder and bipolar disorder having the strongest associations, with ORs equal to 10.6 and 7.6 respectively [2]. Studies have found that major depressive disorder (MDD) is the most common comorbid condition diagnosed in people with GAD, with around 50% of people having comorbid MDD [2, 35, 37]. Other common comorbidities include disruptive behavioral disorders or substance-related disorders, with a prevalence of up to 10.1% and 22.5% among people with GAD, respectively [2]. The high prevalence of comorbidity among people with GAD can be very debilitating and cause significant personal and economic impairment, as discussed in the next section.

2.1.4 Burden of Disease

GAD has been found to have significant impairment on the people who are affected by it. Seventy to 80% of cases are associated with moderate-severe disability and impairment [38]. Studies have found that people with GAD generally experience lower quality of life, impaired psychological and role functioning, have higher perceived stress and chronic pain, and have lower work productivity compared to those without GAD [1, 4, 32, 39]. Regarding suicidal-related behavior, people with GAD were found to have significantly increased odds of suicidal ideation and suicide attempts compared to people without GAD [40, 41]. Compared to other disorders, people with GAD tend to report greater impairment compared to alcohol and drug use disorders and other anxiety disorders, while they have similar disability compared to major depressive disorder [21, 30, 32, 39]. The presence of psychiatric and medical comorbidities often exacerbates the burden of disease on adult and elder people with GAD, compared to those without comorbidities [4, 31, 39, 42].

People with GAD were also found to have more frequent primary care visits, referrals to specialty care, and higher prescription rates compared to people without GAD or any other anxiety disorder [43]. For example, those with GAD are 1.6 times more likely to see a primary care physician compared to those without GAD [39]. The annual inpatient cost for people with GAD was found to be approximately \$332, and the median healthcare costs were 64% higher compared to those without GAD [39, 44]. Considering the high comorbidity among people with GAD, the healthcare and economic burden increases dramatically. Those with comorbid GAD and MDD were 2.1 times more likely to see a primary care physician, compared to those without GAD or MDD, whereas those with comorbid GAD and MDD were also 23% more likely to be hospitalized, compared to people without comorbidity, potentially because of an increased risk of suicide [1, 39, 45]. In terms of annual inpatient costs in the US, people with comorbid GAD and MDD, as well as people with comorbid GAD alone, respectively [44].

Despite the high human and societal burden of GAD, it remains poorly recognized and treated in primary care settings, with only one third of patients being correctly diagnosed and between 33% and 74% being left untreated [1, 4, 31, 39].

2.1.5 Screening

There are currently no screening guidelines for GAD, and improvements in screening could be a first step in improving outcomes and quality of life for people with GAD. Several tools exist that can be used for GAD screening, some of which include the 2-item Generalized Anxiety Disorder questionnaire, the 7-item Generalized Anxiety Disorder questionnaire, the 7-item Generalized Anxiety Disorder found to have high sensitivity and specificity in detecting GAD [1, 46].

2.1.6 Diagnosis

Diagnosing GAD can be difficult, as it shares many of the same symptoms as other medical conditions, psychiatric conditions, side-effects caused by medications, or substance abuse disorders [1]. Thus, appropriate physical and laboratory tests should be run to rule-out any other serious medical or psychiatric conditions before considering GAD as the diagnosis [1].

Several tools exist that aid in diagnosing GAD, and a brief description and history of each is presented here. The DSM-I contained a general category known as *anxiety reaction* which encompassed all anxious behavior regardless of the circumstance [3]. In the DSM-II, the general category *anxiety reaction* became *anxiety neurosis* which was broadly defined "anxious over-concern extending to panic and frequently associated with somatic symptoms" [3].

GAD was first recognized in 1980 in the DSM-III, when the condition *anxiety neurosis* (from the DSM-II) was split into its two components GAD (or '*anticipatory anxiety*') and panic disorder as it was found that the two conditions responded differently to treatment [3]. For a patient to meet GAD criteria according to the DSM-III, they had to have generalized and persistent anxiety lasting 1 month or more, and meet an unspecified number of symptoms in 3 of the following 4 categories: (i) motor tension, (ii) autonomic hyperactivity, (iii) apprehensive expectation, and (iv) vigilance and scanning [3]. However, over the years there was much debate regarding whether GAD should be considered a separate diagnosis due to its high comorbidity with other psychiatric conditions [3].

Eventually, new research on GAD suggested that it had less autonomic symptoms and a more gradual onset than panic disorder, and that its comorbidity with major depressive disorder decreased the longer GAD lasted [3]. As a result, the DSM-III-R criteria for GAD increased to 6 months, and patients had to meet at least 6 to 18 specified symptoms in the categories (i) motor tension, (ii) autonomic hyperactivity, and (iii) vigilance and scanning to be diagnosed [3].

Between the DSM-III-R and the DSM-IV, the criteria for diagnosis became much more specific and placed more emphasis on the cognitive aspects of the condition [3]. In the DSM-IV, a patient with GAD must experience significant impairment and distress and have excessive and uncontrollable worry about everyday events for at least 6 months, and the presence of at least 3 of 6 specified symptoms from the categories (i) restlessness or feeling keyed up or on edge, (ii) being easily fatigued, (iii) difficulty concentrating or mind going blank, (iv) irritability, (v) muscle tension, or (vi) sleep disturbance [3]. Few changes were made between the DSM-IV and the DSM-5 criteria for GAD, with the DSM-5 explicitly stating that GAD would only be diagnosed if the symptoms were not better explained by any other condition [3].

The World Health Organization's International Classification of Disease (ICD) also recognizes GAD as an independent diagnosis; however, its criteria are broader than the criteria described in the DSM. The ICD-9 first described it as "free-floating, persistent, and excessive worry for at least six months" [47]. A patient being diagnosed with ICD-10 will need to have at least 4 of 22 symptoms, one of which much be from the autonomic arousal category [39, 48]. In the most recent ICD-11, the duration of GAD symptoms is no longer constrained to 6 months, instead symptoms need to last for "several" months in order to separate regular stress from GAD, and more emphasis is placed on the symptom of worry compared to other versions of the ICD [20, 49].

2.2 Current Treatments for GAD

People with GAD are predominantly treated in primary care settings with the main goal of reducing symptoms, preventing future relapse, and achieving response and remission [4, 5, 48, 50]. More severe cases, such as those with comorbidities or those who have suicidal thoughts, may be referred to secondary care with a psychiatrist or other specialist [1]. With a range of pharmacological and psychological therapies available for anxiety disorders, and people with GAD specifically, choosing the correct course of treatment for GAD requires careful consideration of patient preference and motivation, availability and cost of treatment, severity of illness and potential suicide risk, patient's prior response to treatment, and the presence of comorbidities [4, 51]. Furthermore, the age of the person receiving treatment is important to consider, as elderly people are generally more

sensitive to adverse effects or could be taking other medications that could induce drug interactions [4, 51]. A description of the most relevant and studied treatments that currently exist for adults and elders with GAD is summarized below.

2.2.1 Psychotherapies

Non-pharmaceutical options for treating GAD include cognitive behavioral therapy (CBT) and specific CBT-derived approaches that target specified GAD traits, psychodynamic therapy, supportive psychotherapy, mindfulness, and acceptance and commitment therapy [4].

CBT and its subtypes have been the most studied and have all shown efficacy in treating adults with GAD [4, 52, 53]. In particular, two systematic reviews and meta-analyses found that adults being treated with CBT had better rates of treatment response and greater reductions in anxiety and depressive symptoms compared to treatment-as-usual and wait list controls [54, 55]. Effectiveness of CBT in elderly patients is less consistent: some studies showed positive outcomes while others did not [4, 31, 51]. One study showed that relaxation therapy may be more effective than CBT in older patients [31]. Unfortunately, few studies were found comparing psychotherapies to pharmacotherapies in GAD. Two older studies found that CBT had greater effect sizes than benzodiazepines in GAD treatment. However these studies had low statistical power [56]. Other studies have investigated combined pharmacotherapy with psychotherapy versus pharmacotherapy alone in GAD and have found conflicting results [4, 57]. A recent study however, found that combined group CBT plus duloxetine showed faster and superior improvement in people with GAD than duloxetine alone [58]. Due to inconsistent evidence, treatment with combined psycho- and pharmacotherapy is not widely recommended [4].

A few studies have compared different types of psychotherapies in GAD. Studies comparing CBT to applied relaxation have shown that both therapies are beneficial and similar in effectiveness. Two studies showed slightly better endpoint functioning and continued improvement with CBT [59-63]. Trials comparing psychodynamic therapy, anxiety management and CBT in GAD also found similar results between the therapies,

with better outcomes with CBT in anxiety, worry, and depression measures, and in chronically anxious patients [64, 65]. Mindfulness meditation and acceptance and commitment therapies have also been found to be effective in GAD and can be considered if CBT is unavailable or ineffective [1].

The evidence supporting psychotherapy alone, in particular CBT, in treatment of GAD suggests that it could be a viable option for people who do not respond well to pharmacotherapy [4, 51].

2.2.2 Other Non-Pharmaceutical Therapies

Other non-regulated herbal products have been proposed for GAD, including Kava, Silexan (an oil derived from lavender), and chamomile. Kava has been the most studied. A recent systematic review was unable to find consistent evidence supporting Kava as an effective treatment for GAD, with only two studies out of 12 favoring Kava over placebo [66]. Other trials have found that Kava may be effective at reducing anxiety symptoms in the short term [1]. Nevertheless, Kava has been associated with hepatoxicity and is therefore no longer available in many countries [48]. One study comparing Silexan to lorazepam found that Silexan has a comparable efficacy to lorazepam in reducing GAD symptoms, while another study comparing Silexan to paroxetine and placebo found that Silexan has comparable efficacy to paroxetine and superior efficacy compared to placebo [67, 68]. Additionally, both studies showed that Silexan has good tolerability. Chamomile has also been found to reduce anxiety symptoms and has good tolerability [24]. Given the insufficient evidence to date, current guidelines do not specify their use in GAD [4].

2.2.3 Pharmacotherapies for GAD

Many pharmacotherapies for GAD have been investigated, all showing varying degrees of efficacy in the treatment of GAD in adults and elderly people. Several classes of pharmacotherapies exist, as discussed below, each with varying mechanisms of action, dosing regimens, and safety profiles. Pharmacological therapies can sometimes take between 4 - 8 weeks to provide relief of symptoms, and up to 12 weeks for full response [4]. Therefore, guidelines often suggest maintaining therapy for at least 3-6 months and up to 1-2 years to see long-term improvements and reduce the risk of relapse [4, 7].

Furthermore, intense adverse effects can often be experienced when initiating treatment with pharmaceuticals; therefore, it is often recommended that treatment begins at low dosage and is slowly titrated to higher dosages [24, 69].

Although agency approvals for these drugs vary slightly between countries, many studies have shown successful outcomes in people with GAD with off-label pharmacotherapies (i.e., medications that have not been nationally approved for use in GAD in a specific country), often making them promising alternative treatments if these first-line treatments are not successful [69].

The following section is a discussion of some important pharmacotherapies that have been studied in the treatment of GAD, along with a brief overview of their mechanism of action, comparisons to other therapies, and general guidelines that have been provided by experts for their use.

2.2.3.1 Benzodiazepines

Benzodiazepines are a widely prescribed medication class for psychiatric disorders, and they work by indirectly increasing the effects of the neurotransmitter GABA [7]. Many benzodiazepines are approved by the Food and Drug Administration (FDA) for anxiety, and some have been approved for GAD by the European Medicines Agency (EMA) [7, 24, 69]. Treatment guidelines for the use of benzodiazepines vary between the different types. Benzodiazepines have been shown to have quicker onset of therapeutic effects compared to antidepressants, and a recent meta-analysis even found that benzodiazepines were more effective at reducing GAD symptoms in adults compared to selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) regardless of treatment duration [10]. However, benzodiazepines have also been largely associated with falls in elderly populations, cognitive impairment, misuse, and dependence which has been one of the main arguments against their longterm use [7, 50, 69]. Due to their quick onset and risk of developing dependence, it has been suggested that benzodiazepines only be used for short-term treatment, such as for quick relief of symptoms while waiting for the response to SSRIs or SNRIs. Their use may be safe among those with low risk for substance abuse [1, 4, 7, 48, 50, 69, 70]

2.2.3.2 Azapirones

Buspirone is an FDA-approved anxiolytic for the treatment of anxiety, and it is often used to treat GAD. It is approved for use in GAD by Health Canada and by the EMA [4, 7, 24, 71]. Buspirone works as a partial agonist of a serotonin receptor [69]. Studies on buspirone have found that it is generally effective but not well tolerated in the treatment of GAD in adults although they are often used to ease the sexual adverse effects experienced when taking antidepressants [1, 7, 71]. A Cochrane review showed that buspirone was more effective than placebo at treating GAD but not as effective as benzodiazepines and antidepressants [7, 50]. Nevertheless, buspirone can be used for GAD if patients are hesitant to use antidepressants, or it can be used alongside antidepressants if patients are not fully responding to treatment [7, 69]. Canadian guidelines have recommended it as a second-line therapy [4]. The anxiolytic effects of buspirone generally take about up to 4 weeks to begin, and current guidelines suggest starting with a range of 10-15 mg/day and slowly increasing to a therapeutic dose of 10-60mg/day [4, 7, 69].

2.2.3.3 Antihistamines

Hydroxyzine is an antihistamine with mild anticholinergic effects allowing for short-term treatment of anxiety symptoms [1]. Hydroxyzine is not FDA-approved for GAD, but it is approved for GAD by the EMA [7, 24]. A Cochrane systematic review found that hydroxyzine had similar efficacy to benzodiazepines and buspirone in treating GAD however, the quality of the studies in the review was low and its prominent sedative effects were of concern [72]. Nevertheless, hydroxyzine may be a viable option for treatment when other first- and second-line treatments are ineffective [1, 50]. The current treatment guidelines for hydroxyzine a therapeutic dose between 25-100 mg/day [4, 7, 69].

2.2.3.4 GABA-Related Interventions/Anticonvulsants

GABA-related medications include Pregabalin, Tiagabine, and Gabapentin. These drugs are commonly used for reducing seizures in epileptic patients as they ultimately reduce neuronal activity in the central nervous system [50, 69]. The Canadian guidelines consider pregabalin as first-line treatment, however other guidelines sometimes consider it second-line [4, 69]. It is considered off-label use for GAD by the FDA but is approved by the EMA [1, 7, 69]. Current guidelines for pregabalin vary slightly with studies suggesting a range between 75-600mg/day [4, 7, 69]. Studies looking at pregabalin have found it to be effective for GAD in adults, and some have found it to have similar efficacy to benzodiazepines, but with lower discontinuation rates [7, 50]. Studies comparing pregabalin to venlafaxine and sertraline found effects of pregabalin to begin earlier than venlafaxine and sertraline, with lower discontinuation rates compared venlafaxine [1, 50]. As a result, pregabalin can be used alongside antidepressants during the first stages of treatment to provide more rapid symptom relief [10]. Studies suggest that pregabalin is generally well-tolerated; however, has common adverse effects such as dizziness, weight gain, somnolence, diarrhea, and has potential for abuse which is why some guidelines do not recommend it as a first-line therapy [1, 7, 50, 51]. Strong evidence from an RCT also suggests that pregabalin is effective and well-tolerated in elderly patients, and other studies suggest that it could be used as adjunctive therapy for those with comorbid depression [4]. Studies have shown mixed results for the efficacy of tiagabine, and Canadian guidelines do not recommend it as treatment for GAD [4, 50]. Gabapentin is sometimes used as off-label treatment for anxiety disorders, but no studies were found for gabapentin in GAD, therefore there are no current guidelines for their use in GAD [73, 74].

2.2.3.5 Second Generation Antipsychotics

Second generation antipsychotics include olanzapine, ziprasidone, risperidone, aripiprazole, and quetiapine, with quetiapine being the most studied in GAD. No antipsychotics are FDA- or EMA- or Health Canada approved for GAD however, they can sometimes be used as off-label treatments [7, 69]. Specifically, olanzapine, aripiprazole and risperidone have been recommended by Canadian guidelines to be used in addition to other treatments to further improve patient outcomes [7]. Studies looking at quetiapine have found it to have similar efficacy to escitalopram and paroxetine and have also found it to be efficacious in patients over 65 [4, 7, 69]. However, due to adverse

effects associated with these drugs such as weight gain and sedation, it is recommended they are used only when first and second-line treatments are inefficacious [1, 4, 69].

2.2.3.6 Antidepressants

Antidepressants are considered mainstream treatment for GAD, as they have been shown to have good efficacy and tolerability. They also have other benefits including lower risk of dependence and the ability to simultaneously treat depression [4, 50]. Despite these benefits, antidepressants can have challenging adverse effects, often precluding their use as first-line treatments. Antidepressants that are used in GAD are discussed below.

2.2.3.6.1 Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants were one of the first classes of antidepressant used for treatment of GAD. TCAs work by blocking serotonergic, norepinephrine, cholinergic, muscarinic, and histaminergic receptors to varying degrees [75]. Canadian guidelines consider imipramine to be second-line treatment, and TCAs are not approved by the FDA, but some TCAs can still be used as effective off-label substitutes when other treatments are ineffective [4]. However, caution should be taken when prescribing TCAs as they have a broad range of adverse effects, including weight gain, dry mouth, sedation, and death from overdose [4, 7, 50, 69]. Studies comparing imipramine to benzodiazepines found that imipramine had better long-term treatment outcomes and was also more effective at treating psychic symptoms (but not somatic symptoms) compared to benzodiazepines [50]. Another study comparing imipramine to paroxetine also found they had similar efficacy, but paroxetine was better tolerated [69]. There is some weak evidence supporting the use of clomipramine and nortriptyline in GAD therefore clomipramine is sometimes used as off-label treatment for GAD [24]. The current dosing recommendations for those being treated with TCAs begin with a 10 mg/day dosage with therapeutic ranges between 50-300 mg/day [4, 7, 69].

2.2.3.6.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are a class of antidepressants that work by inhibiting the reuptake of serotonin and, to a lesser extent, dopamine and norepinephrine [50]. SSRIs include paroxetine,

citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline. Due to differences in their affinities for these reuptake transporters, SSRI medications differ in their efficacy and adverse effects [50]. Compared to other classes of antidepressants such as TCAs and MAOIs, SSRIs have fewer adverse effects due to selectivity for serotonin with limited effect on other neurotransmitters [76]. In particular, SSRIs can cause jitteriness when first taken, insomnia, and sexual dysfunction, among others, and have been associated with increased risk of suicidality among young adults [7, 24, 76]. A brief discussion of the SSRIs used in GAD is found below.

Paroxetine is approved for treatment of GAD in adults by the FDA, EMA, and by Health Canada [4, 24, 50]. Studies comparing paroxetine to sertraline, escitalopram, and benzodiazepines found that paroxetine had similar efficacy to sertraline and escitalopram but better improvement than diazepam, however, it has worse tolerability than escitalopram [50]. Paroxetine has also been associated with stronger withdrawal effects compared to other SSRIs; however, Canadian guidelines still recommend it as a first-line treatment option due to strong evidence of its benefits from RCTs [4, 50]. Studies suggest a starting dose of 10 mg/day with titration up to range between 10-60 mg/day [4, 7, 69].

Citalopram and escitalopram are the most recent SSRIs to have been released in the US, with escitalopram being FDA, EMA, and Health Canada approved [4, 7, 24, 50]. Citalopram and escitalopram have the strongest selectivity for the serotonin transporter compared to other SSRIs; citalopram also has antihistaminergic effects [50]. Canadian guidelines consider escitalopram to be first-line treatment due to positive evidence from RCTs as well as good tolerability in adults with GAD. On the other hand, citalopram is considered third-line treatment in GAD due to a lack of evidence from RCTs [4, 69]. Escitalopram was also found to have low drug interaction which may be beneficial, for example, in older adults who are taking other medications [4]. Studies suggest a starting dose between 5-10 mg/day, with titration ranging between 10-30 mg/day with escitalopram or 10-40 mg/day with citalopram [4, 7, 69].

Fluoxetine is not approved for GAD in either the USA or Canada due to only open-label studies; however, it is sometimes used as an off-label treatment, and Canadian guidelines

consider it third-line treatment due to a lack of data [4, 7]. Guidelines for its use vary slightly, however studies have suggested therapeutic doses can range between 10-80 mg/day [4, 7, 69]. No data for fluvoxamine in GAD was found.

Sertraline is not an FDA-approved drug for GAD but can be used as off-label treatment. It is considered first-line treatment by Canadian guidelines, and many RCTs have shown its effectiveness and good tolerability in GAD in adults and in the elderly [4, 7]. Studies have shown that combined CBT and sertraline treatment had better outcomes than sertraline only, CBT alone, and placebo in adults [50]. Other studies in elderly patients found that sertraline was more effective than CBT at one-year follow up [4]. Currently, studies have recommended a starting dose of 25 mg/day with titration up to 50-200 mg/day [4, 7, 69].

2.2.3.6.3 Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs generally increase the concentration of serotonin and norepinephrine in the synapse by inhibiting the activity of their reuptake transporters [69]. Venlafaxine and duloxetine are the commonly studied SNRIs, and RCTs have shown them both to be effective and generally well-tolerated in treating GAD in adults and in elderly patients [4, 51]. Network meta-analyses have shown that SSRIs and SNRIs have similar efficacy for treating GAD [10]. Both SNRIs drugs are approved by the FDA and by Health Canada, and guidelines often recommend them as first-line treatments [4]. Duloxetine is also used for treatment of medical conditions such as fibromyalgia and chronic pain, therefore it can be used as adjunctive therapy in people with GAD and such comorbid conditions [69]. Like SSRIs, SNRIs can also cause sexual dysfunction, nausea, diarrhea, and sleep problems [7, 77, 78]. A more serious adverse effect of venlafaxine is that it has been associated with increased risk of suicidality [77]. Currently, guidelines for use of venlafaxine and duloxetine are a starting dose of 37.5 mg/day with titration up to 75-300 mg/day and 20 mg/day with therapeutic doses ranging between 30-120mg/day, respectively [4, 7, 69].

2.2.3.6.4 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors work by indirectly increasing concentrations of dopamine, serotonin, and norepinephrine in the brain by inhibiting the enzymes that metabolizes them [50]. Tranylcypromine, phenelzine, and selegiline are examples of MAOIs however, phenelzine is most commonly used as off-label treatment for GAD in the US [7]. There is not strong evidence for their use in GAD, therefore MAOIs are typically used only when first- and second-line treatments are not effective due to their common adverse effects including sexual dysfunction, sedation, constipation and their drug interactions, and dietary restrictions [4, 7, 50, 69].

2.2.3.6.5 Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)

The main NaSSA is Mirtazapine. It works through antagonism of adrenergic and histamine receptors, and blockage of serotonin receptors [79]. Despite the lack of studies on mirtazapine in GAD, some studies have found it to have generally good tolerability in both adults and in the elderly, less frequent sexual adverse effects compared to SSRIs and SNRIs, and less drug interactions which makes it a feasible third-line and off-label treatment for GAD [4, 7, 69]. Some unfavorable adverse effects include dry mouth, weight gain, and sedation [7, 79]. Current guidelines for use of mirtazapine recommend a starting dose of 7.5-15 mg/day with therapeutic dosage ranging between up to 15-60 mg/day [4, 7, 69].

2.2.3.6.6 Noradrenergic and Dopaminergic Reuptake Inhibitors (NDRIs)

Bupropion is a dopamine and norepinephrine reuptake inhibitor and has been found to have comparable efficacy to escitalopram in one RCT [7, 69]. Some common adverse effects include insomnia, weight loss, and constipation [80]. Although it is not FDA approved for GAD, is sometimes used alongside SSRIs to reduce their sexual adverse effects [7, 69]. Current guidelines for use of bupropion have therapeutic ranges between 150-300 mg/day [4, 69].

2.2.3.6.7 Noradrenergic Reuptake Inhibitors (NRIs)

No studies investigated noradrenergic reuptake inhibitors, in particular reboxetine, in the treatment of adults with GAD.

2.2.3.6.8 Others

Agomelatine works by agonizing melatonin receptors and antagonizing serotonin receptor derivatives [50]. One RCT has shown that agomelatine has comparable efficacy to escitalopram and also has overall better tolerability in people with GAD [81]. Studies have found common adverse effects of agomelatine to be gastrointestinal symptoms, abnormality in liver function tests, dizziness, and headaches [82]. Canadian guidelines consider it first-line treatment and suggest a therapeutic dose of agomelatine to be between 25-50 mg/day [4].

Vilazodone is another antidepressant that falls under the category of atypical antidepressants as it is both an antagonist and an agonist of serotonin receptors and its subtypes, respectively [50]. Vilazodone is a relatively new drug of interest for GAD, introduced in January 2011, and is thought to have stronger affinity for its serotonin transporter compared to other SSRIs, ultimately quickening anxiolytic onset and reducing sexual dysfunction and suicidal ideation [17, 24]. A network meta-analysis in GAD showed that vilazodone had significantly worse acceptability compared to escitalopram and vortioxetine and another study among people with GAD found it had substantial adverse effects, such as nausea and diarrhea [17, 83]. Consequentially, vilazodone is not recommended as a first line treatment in GAD. However, when used, some guidelines recommend treatment begin with 10 mg/day with titration up to 20-40 mg/day [7, 69].

Vortioxetine is a multimodal antidepressant as it inhibits and modulates the serotonin transporter and its receptors [50]. Vortioxetine is also a relatively new antidepressant only introduced as a potential treatment for GAD in September 2013 [17]. One study found that a 5mg dose maybe be more effective at treating GAD than placebo, whereas other studies did not find significant differences between the two; however, there evidence that vortioxetine is better tolerated than placebo [4, 7, 17]. Head-to-head comparisons from a network meta-analysis showed that vortioxetine was significantly

less effective at treating GAD symptoms compared to venlafaxine, escitalopram, and duloxetine [17]. Currently, Canadian guidelines recommend it as a second-line treatment and dosing regimens recommend a starting dose of 5 mg/day with titration up to 5-20 mg/day [4, 69].

Trazodone is another type of antidepressant that inhibits serotonin reuptake and blocks histamine receptors [84]. One RCT in adults with GAD found that trazodone had similar efficacy to imipramine and diazepam; however, those taking trazodone were given a very high dose of 225 mg, therefore these results should be taken with caution [4, 50, 69]. Due to the lack of evidence supporting trazodone, Canadian guidelines consider it a third-line treatment while other guidelines scarcely mention it [4]. Current guidelines for use of trazodone in GAD are a starting dose of 50 mg before bed with titration up to 200-400 mg divided doses twice per day [69].

This section described some of the common pharmacological treatments for GAD that have been studied in the literature. The diversity of these agents can make it possible for clinicians to treat a variety of patients and help them find the right treatments that meet their unique needs. However, due to their side-effects, careful monitoring of the patient is always recommended.

2.3 Other Systematic Reviews and Meta-Analyses

Several systematic reviews and meta-analyses comparing antidepressants to placebo in GAD have been conducted. One of the first systematic reviews and meta-analysis on the efficacy of antidepressants for generalized anxiety disorder was done by Schmitt et al., (2005) [14]. This review included randomized trials only, excluded people with comorbidities, and was not restricted to adults. Moreover, studies were included if they compared antidepressant to placebo or another active treatment. Only 8 studies were included in this review; 4 comparing venlafaxine to placebo; one comparing sertraline to placebo; one comparing paroxetine to placebo; one comparing placebo, imipramine, trazodone, and diazepam; and one comparing imipramine, paroxetine, and chlordesmethyldiazepam. Random effects analysis showed that risk of response in the placebo group was significantly lower compared to the antidepressant group [Number

needed to treat (NTT) = 5.5, 95% CI: 4.1 to 8.4)]. There was no difference in dropouts between the placebo and antidepressant group. However, more people in the antidepressant group experienced adverse effects compared to the placebo group. As this review was one of the first to systematically review the topic, it provided valuable insight into the literature available, and a summary of what treatments may have been more effective and tolerable at the time. The only limitation specified by the authors is that they included only people with GAD without comorbidities, which may have affected the applicability of the results.

Another systematic review and network meta-analysis by Baldwin et al., (2011) compared all pharmaceutical treatments in generalized anxiety disorder [15]. This review was conducted among adults, included randomized trials of any duration, excluded patients with comorbidities and included studies that had placebo or another active drug as the comparison group. In addition to a mixed-treatment meta-analysis, the authors used Bayesian methods to rank the treatments according to the probability of effectiveness in the three outcomes of interest: treatment response measured as a reduction of at least 50% on the HAM-A, remission measured as a score of 7 or less on the HAM-A; and the proportion of people withdrawing from the trial due to adverse effects. This review included 27 studies evaluating duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine. Results from the Bayesian analysis showed that fluoxetine had the highest probability of response (63%) and remission (61%) compared to all other treatments, while the mixed-treatment metaanalyses showed that there was higher odds of response and remission for all of the treatments compared to placebo. The Bayesian analysis showed that sertraline had the lowest percentage of dropouts due to adverse effects and had the highest probably of being the most tolerable compared to all other treatments (49.3%). The mixed-treatment meta-analysis showed that placebo was associated with lower odds of dropping out due to adverse effects compared to other treatments. The review by Baldwin et al., (2011) was more comprehensive than the one by Schmitt et al., (2005) and performed a more advanced analysis of which drugs are most likely to perform the best. This review also conducted a mixed-treatment meta-analysis, allowing for direct and indirect comparisons to be made between treatments. Considering there is generally a lack of studies that

compare active treatments to each other, these mixed-treatment meta-analyses can provide further insight into how active treatments compare to each other. Some limitations specified by the authors were that they did not search unpublished data; there was a risk of bias in the studies as they were all sponsored by a pharmaceutical company; the exclusion of people with GAD with comorbidities could limit the applicability of the results; and high rates of placebo response and limited data available for some treatments could have affected the strength and validity of the results.

The most recent network meta-analysis on pharmacological treatments in GAD, similar to the one by Baldwin et al., 2011, was done by Slee et al., (2019) [16]. This review included randomized trials with placebo or active treatment, as the comparator among adults with GAD or comorbid GAD and MDD. Eighty-nine trials comparing pharmacotherapies from various drug classes were included in this review. The main outcomes were change in symptom levels measured with the HAM-A scale and acceptability measured as a discontinuation for any reason. All treatments generally showed greater reduction in symptoms compared to placebo, while acceptability was variable. Among studies with large sample sizes, quetiapine showed the largest reduction in symptoms in the HAM-A but had poor tolerability, whereas duloxetine, venlafaxine, and escitalopram showed favorable outcomes and had comparable acceptability to placebo. Paroxetine, benzodiazepines, and vilazodone also had poor discontinuation rates compared to placebo. Significant results between the active treatments were between quetiapine, duloxetine, and bupropion all showing better efficacy than tiagabine. Quetiapine showed better efficacy compared to vortioxetine. The authors also conducted subgroup analyses on studies above and below median age, median proportion of women that were included, median baseline anxiety scores, median baseline depression scores, and all non - Chinese trials. A subgroup analysis of non - Chinese trials was conducted because they tended to be of lower quality. No differences were found between the subgroups. The authors specify that network meta-analyses are limited by their assumption that all trials are similar and considering the included studies were conducted across a wide range of treatment settings and the inclusion of several trials conducted in China, this assumption may not have been fully met.

Other meta-analyses have been done evaluating pharmacological treatments in GAD but have not focused exclusively on comparing all antidepressants to placebo. For example, Gomez et al., (2018) performed a meta-analysis on randomized, placebo-controlled trials comparing benzodiazepines to serotonergic antidepressants [10]. They found that benzodiazepines were more effective than both SSRIs and SNRIs at reducing GAD symptoms, whereas SSRIs and SNRIs had similar efficacy. Analyses evaluating different treatment durations suggested that benzodiazepines maintained their efficacy over antidepressants in long-term treatment. This review was limited in that the authors did not do subgroup analysis to explore whether patient characteristics may be associated with effect sizes.

Another review by He et al., (2019) performed a network meta-analysis on first-line drugs, most of which were SSRIs and SNRIs only [17]. Their results included 56 unique trials evaluating fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, duloxetine, venlafaxine, vilazodone, levomilnacipran, and vortioxetine. Pairwise meta-analyses showed that all drugs had better efficacy than placebo except for vortioxetine; and the drugs were not significantly different than placebo in acceptability, except vilazodone and paroxetine which had worse acceptability than placebo. The network meta-analysis showed that the treatments were more effective at reducing symptoms and had better treatment response compared to placebo except for fluoxetine and vortioxetine. There were also no significant differences in acceptability, except with vilazodone which had worse acceptability compared to placebo. All drugs except for vortioxetine, sertraline and fluoxetine had higher dropouts due to adverse effects compared to placebo. The main findings from head-to-head comparisons in this review were discussed in previous sections.

The review by He et al., (2019) did not exclude patients with other psychiatric comorbidities, making the results more applicable. However, it was limited in that it did not include unpublished or new data, possibly had some small-sample effects, and no subgroup or sensitivity analyses.

Although several reviews have been done comparing different classes of drugs using various methodologies, only the review by Schmitt et al., (2005) compared all antidepressants to placebo exclusively. This review, however, was conducted almost 20 years ago and since then, new trials have been conducted, providing additional data with new insights into the benefits and drawbacks of antidepressants. New antidepressants have also been approved and introduced for GAD, including duloxetine in 2006, vilazodone in 2011, and vortioxetine in 2013, all of which require further investigation [17, 24]. In addition, new diagnostic criteria such as the DSM-5 and more recently, the ICD-11, have become available which need to be taken into account.

Furthermore, the systematic reviews mentioned above only consider a small number of outcomes, most of which include change in symptom levels, rate of treatment response, and acceptability. They did not consider the various tolerability and safety profiles unique to different antidepressants nor did they consider impact on quality of life. In addition to the outcomes reported by the reviews above, the current review will also evaluate the frequency of some clinically important adverse effects and the frequency of dropouts due to adverse effects and lack of efficacy compared to placebo. This will provide a more comprehensive understanding of the safety and tolerability profiles of various antidepressants. The current review will also include quality of life as an outcome, allowing us to determine whether antidepressants can improve a person's life satisfaction and overall well-being.

2.4 Conclusions

In conclusion, an updated and more comprehensive systematic review and meta-analysis comparing all available antidepressants to placebo in adults diagnosed with GAD is needed to provide a stronger understanding of the efficacy, acceptability, tolerability, and impact on quality of life of the various types of antidepressants.

Chapter 3

3 Methods

The protocol for this review was previously registered with the Cochrane Database for Systematic Reviews (2018; Issue 2; No: CD012942; DOI: 10.1002/14651858.CD012942.) [85]. As the review was being conducted and new information arose, certain adjustments had to be made that deviated from the protocol. These deviations are noted in section *3.13 Differences Between Protocol and Review*. The following sections outline the methodology of the review including which databases were searched, the search strategy that was used, detailed descriptions of the inclusion and exclusion criteria, the screening process, data extraction, the risk of bias assessment, statistical analyses, how missing data were addressed, and how publication bias was evaluated.

3.1 PICO

Population: Adults diagnosed with generalized anxiety disorder

Intervention: Antidepressants

Comparator: Placebo

Outcomes: Rate of treatment response, measured as a reduction of at least 50% on the Hamilton Anxiety Scale (HAM-A), acceptability, rate of treatment response (defined by study authors), remission rate, change in symptom levels, total number of participants reporting adverse effects, specific adverse effects (sleepiness/drowsiness, falls, hypotension, agitation/anxiety, suicide wishes/gestures/attempts, death by suicide, subjective memory impairment), average score/change in quality of life/satisfaction, death, total number of patients experiencing withdrawal symptoms, dropouts due to a lack of efficacy, dropouts due to adverse effects.

3.2 Literature Search

A comprehensive search was conducted by a Cochrane librarian in October 2022. The librarian uploaded the results of the search onto Covidence for screening. Details of the screening process are described below. Appendix 1 outlines the complete search strategy used for the electronic databases that were searched.

3.2.1 Databases

Electronic databases that were searched included the following:

- Cochrane Common Mental Disorders (CCMD) register;
- Ovid MEDLINE, Ovid MEDLINE In-Process and other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid OLDMEDLINE (1946 to October 20, 2022);
- Ovid Embase (1974 to October 20, 2022);
- Ovid APA PsycINFO (1806 to Week 3 October 2022);
- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 10 of 12, October 2022).

The national and international trials registers that were searched for unpublished or ongoing trials included the following:

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP);
- ClinicalTrials.gov.

3.3 Inclusion and Exclusion Criteria

The following section describes the inclusion and exclusion criteria that were used to assess the eligibility of each study for our review and were outlined in the protocol. In this review, there were no restrictions on setting, country, or language.

3.3.1 Types of Studies

This review included randomized controlled trials, including cluster-randomized trials. Cross-over RCTs and relapse prevention studies were excluded to avoid carry-over effects.

3.3.2 Types of Participants

Adults, regardless of how they were defined by the authors, of any sex or gender, were included. Studies were included if they investigated a population with a primary diagnosis of GAD, without any other serious medical conditions as described by the authors. Participants with secondary concurrent psychiatric disorders were allowed as long as the primary diagnosis was GAD. There were no restrictions on the type of diagnostic criteria that were used to diagnose GAD.

3.3.3 Types of Interventions

Studies were included if they compared antidepressants as monotherapy with placebo in the treatment of GAD. The following antidepressants were eligible for inclusion without any restrictions on dose, frequency, intensity, or duration of treatment:

• Tricyclic antidepressants (TCAs): amitriptyline, amoxapine, clomipramine, desipramine, dosulepin/dothiepin, doxepin, impiramine, lofepramine, maprotiline, nortriptyline, proptriptyline, trimipramine;

• Selective serotonin reuptake inhibitors (SSRIs): fluoxetine, fluvoxamine, sertraline, citalopram, paroxetine, escitalopram;

• Monoamine oxidase inhibitors (MAOIs): phenelzine, isocarboxazide, tranylcypromine, moclobemide, brofaromine;

• Serotonin and norepinephrine reuptake inhibitors (SNRIs): venlafaxine, desvenlafaxine, duloxetine, milnacipran;

• Noradrenergic and specific serotonergic antidepressants (NaSSAs): mirtazapine;

- Noradrenergic and dopaminergic reuptake inhibitors (NDRIs): bupropion;
- Noradrenergic reuptake inhibitors (NRIs): reboxetine;

• Others: agomelatine, vilazodone, vortioxetine, trazodone, nefazodone, mianserin, maprotiline, non-conventional herbal products (e.g. hypericum).

Irregular (i.e., not daily) use of benzodiazepines was allowed, however studies in which regular use of benzodiazepines at a constant dosage, for a long time, or as part of study medication were excluded. We additionally excluded studies that used psychosocial therapies to treat GAD.

3.3.4 Types of Outcomes Measures

3.3.4.1 Primary Outcomes

The primary outcome measures for this systematic review were specified in the protocol as: (1) rate of treatment response, measured as a reduction of at least 50% on the Hamilton Anxiety Scale (HAM-A), and (2) acceptability, defined as the total number of participants who dropped out during the trial as a proportion of the total number of randomized participants (total dropouts). These outcomes were all measured at the end of the double-blind period of each study.

3.3.4.2 Secondary Outcomes

The following secondary outcomes were prespecified in the protocol:

- Rate of treatment response (with response defined by authors);
- Remission, as measured by the number of participants showing 17 or less on the 14-item HAM-A; any other similar cut-off value on an anxiety scale, depending on the study authors' definition; 'not ill or borderline mentally ill' (a score of 1 or 2) on the Clinical Global Impression (CGI) severity scale; or according to the authors' definition of remitters at follow up;

- Change in symptom levels: Group mean scores at the end of the trial or changes from baseline on: Hamilton Anxiety Scale (HAM-A); any other scale (example COVI scale); or CGI-severity scale (using standardized mean difference);
- Total number of patients reporting adverse effects;
- Specific adverse effects (sleepiness/drowsiness, falls, hypotension, agitation/anxiety, suicide wishes/gestures/attempts, death by suicide, subjective memory impairment);
- Average score/change in quality of life/satisfaction;
- Death;
- Total number of patients experiencing withdrawal symptoms;
- Dropouts due to lack of efficacy;
- Dropouts due to adverse effects.

3.4 Screening (abstracts/titles, full text)

All studies collected from the search process were uploaded into Covidence for screening and data extraction. Two independent review authors (Giuseppe Guaiana (GG) and Chiara Curatoli (CC)) conducted level 1 screening (title and abstract screening). Studies moved on to level 2 screening (full-text screening) if they met a set of preliminary criteria which included: study was a randomized controlled trial, study compared antidepressants against placebo, and the study was conducted in adults with GAD regardless of the diagnostic criteria. Studies that were eligible for level 2 screening were evaluated based on the inclusion and exclusion criteria mentioned in section 3.3. Level 2 screening was conducted by two independent reviewers (Katarina Kopcalic (KK) and CC). Final decisions regarding inclusion of a study were made by the senior investigator (GG).

3.5 Data Extraction

Data were extracted using Covidence via a specialized form which included all the primary and secondary outcomes listed above. Appendix 2 provides an example of the data extraction template. Data extraction was completed by two independent reviewers, (KK and CC) and any disagreements were resolved by a third reviewer (GG). Only data at the end of the double-blind treatment period were extracted. Any data from screening or open-label (single-blind) lead-in periods, or taper periods in which treatments were withdrawn after double-blind treatment periods, were not extracted. Where available, intention-to-treat (ITT) analyses were used. For continuous outcome variables (change in symptom levels and average change/score in quality of life/satisfaction) change from baseline and post-intervention scores were extracted as they can be combined in the same analysis [86]. Where available, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was used to extract average score/change in quality of life/satisfaction and where somnolence was defined, this was used to extract data on sleepiness/drowsiness. Suicidal ideation was also recorded under suicidal wishes/gestures/attempts. In studies that were comparing placebo to different dosages of the same antidepressant, the groups treated with different dosages of the antidepressant were combined. The formula used to combine groups is outlined in the Cochrane Handbook and can be found in Appendix 3 (see formula 3) [86].

Additional information collected from each study included: the method of diagnosis, comorbidities, location, treatment setting, intervention(s), age (mean and standard deviation (SD) for each treatment arm), sex (percent males and females in each treatment arm), dose, and duration of treatment. These study characteristics were used to populate the *Characteristics of Included Studies* table and to determine which studies were similar enough to be combined into a meta-analysis. Studies for which there was not enough information to determine whether they should be included or excluded were placed under 'studies awaiting classification' [86].

3.6 Missing Data

When authors of the primary studies used the last observation carried forward (LOCF) or multiple imputations approach for missing data, we extracted this over endpoint data. Our first approach for handling all missing data was to contact the study authors. When the SD for continuous outcomes were missing and authors did not reply to our requests for additional information, we calculated the SD from standard errors (SE) or 95% confidence intervals (CI) (when available) using methods specified in the Cochrane Handbook for Systematic Reviews (see formulas 1 and 2 in Appendix 3) [86]. When dichotomous outcomes were reported as percentages, they were converted into numerical values [86]. When data were not stated explicitly in the text, but were provided in a graph or figure, GetData Graph Digitizer (Version 2.26.0.20) was used to extract the data when possible [86]. In the case where the missing SDs could not be calculated from the information provided in the study, the missing SD was borrowed from another study within the review under the condition that the two studies were similar in terms of measurement scale, degree of measurement error, treatment duration and dosage, and population (imputation method) [86]. If multiple studies were eligible, then the largest SD out of the eligible studies was imputed [86].

If none of the above methods were appropriate, a 'pooled SD' was calculated using the average SD from all the studies with available SDs [87]. This was done separately for each treatment arm with missing SD. This method has been used in previous systematic reviews and meta-analyses [88, 89].

3.7 Risk of Bias Assessment

Bias is systematic error that can lead to overestimation or underestimation of study findings [90]. There are many potential sources of bias that can arise in studies, such as selection bias, performance bias, detection bias, attrition bias, and reporting bias, among others [90]. In a systematic review and meta-analysis, it is important to evaluate the risk of bias in each of the studies that are included, as the results of the review can be largely impacted if there are many studies with a high risk of bias. In the current review, the Risk of Bias version 1 tool, which is the default risk of bias template used in Covidence, was

used. This template is divided into seven domains used to assess the potential sources of bias listed above [90]. These domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Briefly, to assess selection bias, the domains random sequence generation and allocation concealment were assessed based on whether the authors successfully implemented a randomization sequence to produce comparable groups, and whether the allocation sequence was concealed well enough to prevent participants from predicting which group they were a part of before and during recruitment, respectively [90]. To assess performance bias, the domain *blinding of participants and personnel* was judged based on whether blinding methods were implemented well enough to prevent participants from ascertaining which intervention they received, which could potentially allow them to alter their behavior accordingly, or prevent personnel from ascertaining which intervention participants received, potentially allowing them to treat participants differently accordingly [90]. Detection bias was assessed through *blinding of outcome assessment* which was judged based on whether blinding methods were implemented well enough to prevent outcome assessors from ascertaining which intervention any participant may have received. A lack of blinding of outcomes assessors could potentially lead to biased ascertainment of outcomes [91]. This could occur especially if the outcomes are subjective and if the outcome assessor has strong beliefs about the interventions and wants to make it look more or less favorable [91]. Attrition bias was evaluated through incomplete outcome data. Incomplete outcome data could lead to biased estimates of the results if the rates of dropouts are imbalanced between the treatment groups, if the reasons for dropouts are related to the study treatment and/or if inappropriate analysis methods are used [90]. We evaluated reporting bias through *selective outcome reporting*, where we assessed whether certain results may have been (or not have been) reported based on their direction, magnitude or significance [86, 90]. Any other outstanding sources of bias were recorded under other sources of bias. All domains were judged as having either 'high', 'low', or 'unclear' risk of bias, following the guidelines outlined in Table 8.5d of the Cochrane Handbook [90]. The risk of bias assessment of the included studies, with documented

reasons for each judgement, was performed independently by two authors (KK and CC). Any disagreements between the authors were resolved by a third author (GG).

3.8 Grading the Quality of Evidence

A Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality of evidence assessment was done using GRADEpro software. GRADE is a tool that is used to evaluate the quality of evidence for each outcome of interest based on 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication (or sponsorship) bias. Risk of bias evaluates the extent to which there are concerns with the study design or execution [92]. For example, if study participants are aware of which treatment they are receiving, this may alter their behavior and bias the study results. Inconsistency refers to the degree to which there is unexplained heterogeneity between the included studies which can lead to large differences in treatment effect [92]. Indirectness is the extent to which the evidence aligns with the research question [92]. For example, if the included studies investigated different interventions and outcomes, and were conducted among populations that weren't directly of interest, this would affect the applicability of the results and reduce the directness of the evidence. Imprecision refers to the precision of the effect estimates [92]. Studies are also evaluated based on sponsorship bias. Positive results are more likely to be published if the study is commercially sponsored which may lead to an overestimation of the effect estimates [93, 94].

In this review, a GRADE assessment was done for the two primary outcomes, rate of treatment response, measured as a reduction of at least 50% on the Hamilton Anxiety Scale (HAM-A) and acceptability, as well as for dropouts due to a lack of efficacy and dropouts due to adverse effects for the analyses comparing all antidepressants to placebo. These outcomes were chosen as they were considered the most clinically relevant. For each outcome, the domains were subsequently downgraded by 1 or 2 levels depending on the level of concern. The decision was made based on the steps and guidelines outlined for each domain in the GRADE Handbook and by following the GRADE downgrading table outlined in Appendix 4 [92, 95]. The GRADEpro software then provided an overall certainty of evidence rating of 'very low', 'low', 'moderate', or 'high' for the outcome

depending on how each domain was assessed. The overall quality of evidence rating is a reflection of how confident we were that the effect estimate we found is close to the true effect [92].

3.9 Statistical Analyses

All statistical analyses were done using RevMan Web Version: 5.3.1. Results of all metaanalyses were described in the results and visually represented using forest plots.

3.9.1 Meta-Analysis

Meta-analyses are useful tools that allow researchers to combine results from multiple studies to obtain an overall summary effect estimate with confidence intervals. Generally, the combined summary effects produced by a meta-analysis are a weighted average of the effects found in each individual study included in the meta-analysis [86]. Studies are weighed based on the inverse of the variance of the effect estimate [86]. This means that larger studies that generally have smaller standard errors are given more weight than smaller studies [86]. There are several advantages and disadvantages of meta-analyses. When small studies are limited in their statistical power due to small sample sizes, a meta-analysis allows for increased power and better precision of an effect estimate by combing several studies together and increasing sample size [86]. Meta-analyses also allow researchers to investigate reasons why effect estimates may be similar or different across studies and help resolve conflicting results between individual studies [86, 96]. They also allow researchers to investigate a broader range of research questions as they can quantify effect estimates across various study characteristics such as different populations or settings [86]. Some disadvantages of meta-analyses are that their results depend largely on the quality of the studies that are included because including studies with bias may lead to incorrect or inaccurate results [86]. Another caveat is that in order to be able to combine the effect estimates of individuals studies, the individual studies need to be sufficiently homogenous, otherwise the generalizability of the results may be threatened [86]. Nevertheless, a well-conducted meta-analysis can provide highly valuable information to clinicians, policy makers, and patients. It is always crucial to

investigate potential sources of heterogeneity in meta-analyses and specify strict inclusion and exclusion criteria in advance to avoid reaching erroneous conclusions.

3.9.2 Main Comparisons

The main prespecified comparisons of interest were between placebo and the following comparators (where available) for all outcomes:

- All antidepressants (pooled);
- Tricyclic/heterocyclic antidepressants (TCAs);
- Selective serotonin reuptake inhibitors (SSRIs) (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline);
- Serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g. duloxetine, milnacipran, venlafaxine);
- MAOIs (e.g. moclobemide, phenelzine, tranylcypromine);
- Bupropion;
- Others (e.g. agomelatine, vortioxetine, vilazodone, trazodone, nefazodone, mianserin, maprotiline, non-conventional herbal products).

3.9.2.1 Measures of Treatment Effect

The risk ratio (RR) was the chosen measure of effect for dichotomous outcomes in this review. The Cochrane Handbook generally recommends that RRs be used when performing meta-analyses, because other measures of effect such as the odds ratio are more difficult to interpret, the risk difference does not give consistent estimates of intervention effect, and the number-needed-to-treat cannot reliably be estimated in a meta-analysis [86].

The mean difference was used for all continuous outcomes as all the studies that measured continuous outcomes (*change in symptom levels* and *average change/score in*

quality of life/satisfaction) used the HAM-A total score and the Q-LES-Q to measure these outcomes, respectively. Because the measurement tool did not differ between studies, there was no need to use the standardized mean difference.

3.9.2.2 Unit-of-Analysis Issues

Studies that have multiple intervention groups can cause problems in meta-analyses. This can occur if there are multiple intervention groups and only one shared comparator group (or vice versa). If these situations are not dealt with properly in a meta-analysis, this can lead to a unit-of-analysis issue. Unit-of-analysis issues occur when there are correlations between the effect estimates of a group that is entered multiple times in the same meta-analysis (i.e., the group is 'double-counted') [86]. Depending on the analysis, the multi-arm studies were handled accordingly following the instructions outlined in the Cochrane Handbook [86].

Briefly, for analyses comparing all antidepressants to placebo, if a study contained multiple treatment arms from the same antidepressant class, for example paroxetine and escitalopram (both SSRIs) versus placebo, the data from the antidepressants would be combined and entered into RevMan Web as one group, while the data from the placebo group would remain unchanged. If the treatment arms were not from the same class, the data from the placebo group would be divided in half and each treatment arm versus placebo comparison would be entered into RevMan Web separately.

For analyses comparing classes of antidepressants (SSRI, SNRIs etc.) to placebo, if the treatment arms in the study were from the same class, the same approach described above was used. However, if the treatment arms were from different classes, each treatment versus placebo comparison would be entered into separate meta-analyses, resulting in no unit-of-analysis concerns, thus requiring no adjustments to the data.

3.9.2.3 Random-Effects and Fixed-Effect Models

Fixed effect models assume that all the studies included in the meta-analysis are homogenous and that the true intervention effect is the same across all the studies. Fixed effect models therefore estimate a common underlying effect [86]. Random effects models can account for differences (heterogeneity) between studies by assuming that the underlying effect varies between the studies. The effect estimate produced by a random effects model can be considered as the average intervention effect across the studies [86].

The inverse-variance random-effects model in RevMan Web was used for all metaanalyses in this review due to its ability to account for some heterogeneity between studies. However, the inverse-variance, random-effects model is unsuitable when events are 'rare' and thus a Mantel-Haenszel fixed-effect model was conducted as a sensitivity analysis for those outcomes that were found to have few events and zero cells (specifically *agitation/anxiety* and *suicide wishes/gestures/attempts*) [86].

3.9.2.4 Heterogeneity

Heterogeneity occurs when there is variability between the studies that are included in a meta-analysis [86]. Heterogeneity can be caused by clinical or methodological differences between studies. For this review, heterogeneity was assessed by visual inspection of the forest plot and quantification of the I² value [85]. We used the following parameters to estimate the degree of heterogeneity from the I² value:

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

P-values and Chi^2 statistics were also considered for the forest plots, with p-values < 0.05 for the test of heterogeneity suggesting that heterogeneity may be present.

3.10 Subgroup Analyses

The following subgroup analyses were pre-specified in the protocol. Once data were extracted, some subgroup analyses could not be performed due to a lack of data. Subgroup analyses were performed on the analyses comparing all antidepressants to

placebo for the two primary outcomes only. If details regarding the subgroup were not specified in an individual study, that study was not included in the analysis.

3.10.1 Diagnosis Criteria

We planned to investigate the effect of the diagnostic criteria on the study findings. Studies were to be divided into those using pre-DSM-III, those using DSM-III or DSM III-TR, and those using DSM-IV and later versions. It was found that only one included study used DSM-III-R and all other studies used either the DSM-IV or DSM-IV-TR. Due to a lack of studies in the DSM-III-R group, this subgroup analysis was not performed.

3.10.2 Treatment Setting

We investigated the effect of treatment setting on the primary outcomes. Specifically, subgroups were divided into studies conducted on psychiatric inpatients, studies conducted on psychiatric outpatients, and studies conducted on primary care patients. Once data were extracted, the subgroup analyses that were performed were for outpatients, primary care patients, and primary care and psychiatric outpatients.

3.10.3 Elderly Participants

We had planned to compare patients over 65 years of age to other adult participants. However, no studies looked specifically at patients over 65 years of age therefore this subgroup analysis was not performed.

3.10.4 Studies with Patients that have Psychiatric Comorbidities

Studies where there were no patients with psychiatric comorbidities were to be compared to studies allowing participants with psychiatric comorbidities. Two studies included patients with psychiatric comorbidities, which were included in subgroup analyses.

3.10.5 Duration of Treatment

We investigated the effect of treatment in studies where the double-blind treatment period lasted over 12 weeks versus studies in which the double-blind treatment period lasted 12 weeks or less, as specified in the protocol.

3.11 Sensitivity Analyses

The following sensitivity analyses were performed on the analyses comparing all antidepressants to placebo only. The outcomes for which each sensitivity analyses were done are noted in each section.

3.11.1 High/Unclear Risk of Bias in Random Allocation or Blinding

Studies that were judged to have either an unclear or high risk of bias in either or both the domains *random sequence generation* and *blinding of participants and personnel* were removed from the analysis. This was done for the two primary outcomes only.

3.11.2 Dropout Rate >20%

A sensitivity analysis was done to examine whether removing studies with >20% total dropouts had an effect on the review findings. This was done for the two primary outcomes only.

3.11.3 Missing Standard Deviations

Studies in which the SD had to be imputed by either borrowing from other studies or using a pooled SD from all the included studies were removed. This was done for the outcome *change in symptom levels* only.

3.11.4 Fixed-Effect Models

A fixed effect model was applied to investigate whether results were affected when smaller studies were weighed differently. This was done for the two primary outcomes. Furthermore, a Mantel-Haenszel fixed-effect model was applied for dichotomous outcomes that were found to be 'rare' and included studies with zero events in the analysis (specifically *agitation/anxiety* and *suicide wishes/gestures/attempts*).

3.12 Publication Bias

Funnel plots were produced to investigate small study biases. Funnel plots were only produced if more than 10 trials contributed to the meta-analysis, as suggested in the Cochrane Handbook [86].

3.13 Differences Between Protocol and Review

- Bibliographies were not searched and experts in the field were not contacted because authors were satisfied with the results of the search;
- Relapse prevention studies were excluded to avoid carry-over effects;
- The mean difference was used as the effect measure for continuous outcomes instead of the standardized mean difference because the measurement tool was consistent across the studies;
- Change from baseline and endpoint data were extracted for continuous outcomes instead of just endpoint data because they can be combined into a meta-analysis;
- Vortioxetine and vilazodone were not specified in the protocol but were included because they are antidepressants and studies relevant to our review were found;
- GetDataGraph Digitizer was used to extract data from figures where needed;
- RevMan Web was used for data analysis instead of RevMan 5 as Cochrane has fully upgraded to RevMan Web;
- The comparison *other antidepressants versus placebo* was added for all outcomes as this comparison was deemed clinically important;
- Meta-regression was not performed due to a lack of studies within subgroups;
- A sensitivity analysis was added for *change in symptom levels* where studies with imputed SDs were removed to investigate whether this affected the review findings;
- A Mantel Haenszel fixed effect model was applied to outcomes that had few studies and 'zero' cells to investigate whether this affected the review findings.

Chapter 4

4 Results

4.1 Study Selection

The PRISMA flow diagram [97] (Figure 1) shows the flow of studies for inclusion in the review and meta-analysis. A total of 1191 references were retrieved from the search. After 89 duplicates were removed, a total of 1102 studies eligible for level 1 (title/abstract) screening. A total of 944 studies were removed after level 1 screening and the remaining 158 studies were assessed for eligibility though level 2 (full text) screening. Of those, 60 studies were removed with reasons listed in the PRISMA flow diagram. Additionally, 24 studies were marked as 'awaiting classification' and one study was marked as ongoing. The remaining 38 studies were included in the systematic review and the meta-analysis.

Of the included studies, the authors of 19 studies were contacted for additional information. Study IDs for which authors were contacted are as follows: Bose 2008, Allgulander 2001, Allgulander 2004, Hackett 2003, Pollack 2001, Davidson 2004, Nimatoudis 2004, Feltner 2009, Kasper 2009, Gelenberg 2000, Rothschild 2012, Nicolini 2009, Brawman-Mintzer 2006, Koponen 2007, Lenox-Smith 2003, Rickels 2000, Montgomery 2006, Stein 2008, and Mahableshwarkar 2014. Out of all the authors that were contacted, two authors replied (study ID: Rickels 2000, Stein 2008). The contact for Rickels 2000 could not provide further information. The contact for Stein 2008 referred us to the synopsis of the clinical study results, which we were already aware of and had included in the review.

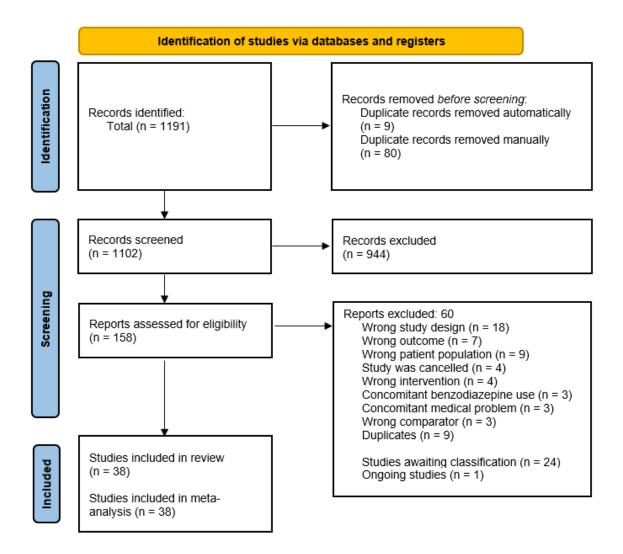


Figure 1. PRISMA flow diagram

4.2 Study Characteristics

A total of 38 studies (12,570 participants) were included in this systematic review and meta-analysis, and the characteristics of the included studies are presented in Table 1. All 38 studies were randomized controlled trials. One study was conducted in China, 16 in the USA, 1 in the UK, 1 in Greece, 1 in Japan, 14 were multinational, and 4 did not specify the location. In terms of treatment setting, 28 of the studies enrolled outpatients, 2 studies enrolled primary care and psychiatric outpatients, 2 studies enrolled primary care

patients, 1 study enrolled volunteers, and 5 studies did not specify the treatment setting. The total sample sizes ranged from 28 [98] to 781 [99]. All included studies were published in English therefore no translations were required.

4.2.1 Population

The primary diagnosis in all the patients was moderate-severe GAD, diagnosed using the DSM-IV, DSM-IV-TR, or DSM-III-R. The majority of the studies were among adults (aged 18 years and older) and only one study [100] was among elder veterans (aged 60 years and older). No studies included patients with serious medical comorbidities. Two studies [101, 102] included patients with secondary psychiatric comorbidities, but with a primary diagnosis of GAD (see Table 1).

4.2.2 Interventions and Comparators

Table 1 displays the interventions used in each study, along with the dosage and length of the double-blind treatment period. The antidepressants that were included among eligible studies were TCAs (n=1) (imipramine), SSRIs (n=19) (escitalopram, paroxetine, sertraline), SNRIs (n=18) (duloxetine, venlafaxine), and other antidepressants (n=6) (agomelatine, vilazodone, vortioxetine). Placebo was the comparator in all studies.

In total, there were 16 multi-armed studies, which are described in Table 1. Of these, 6 compared two antidepressants to placebo [81, 99, 102-105]. Three of these studies compared different classes of antidepressants to placebo, whereas the other 3 compared the same class of antidepressants to placebo. Of the remaining 32 studies, one compared a TCA to placebo [98], 15 compared an SSRI to placebo [100, 106-119], and 12 studies compared an SNRI to placebo [120-131]. Four studies compared an antidepressant from the 'Others' category to placebo [101, 132-134] and there were no studies comparing MAOIs, NaSSAs, NDRIs, or NRIs to placebo.

The minimum double-blind duration ranged from 4 weeks to 28 weeks. Both fixed and flexible dosing protocols were used in the studies. Eleven studies [99, 100, 103, 105, 106, 125-128, 130, 133] compared multiple fixed dosages of the same antidepressant as separate groups which were combined into one group during data extraction.

Table 1. Characteristics of Included Studies^a

Study ID	Diagnostic Criteria	Comorb- idities	Location	Treatment setting	Intervention(s), n	Age (mean (SD)); Sex (F%, M%) ^b	Dose, Duration
Allguland	DOMIN	None	Belgium, Finland,	Primary care and	Placebo, 130	46.1 (NA); 58%, 42%	37.5, 75 or 150 mg/day, 24 weeks
er 2001 [128]	DSM-IV	stated	France, Sweden, UK	psychiatric outpatients	Venlafaxine, 411	44.8 (NA); 61.3%, 38.7%	37.5, 75 or 150 mg/day, 24 weeks
Allguland		Nono	Australia, Canada,		Placebo, 190	42.4 (11.5); 51%, 49%	50-150 mg/day, 12 weeks
er 2004 [118]	DSM-IV	None stated	Denmark, Outpatients Norway, Sweden	Sertraline, 188	40.3 (11.1); 59%, 41%	50-150 mg/day, 12 weeks	
Aventis-	DSM-IV- TR	None stated	NA	Outpatients	Placebo, 122	Total: 40.8 (12.3); Total: 66.9%, 31.1%	20 mg/day, 8 weeks
Sanofi 2007a					Paroxetine, 124		20 mg/day, 8 weeks
[108]					Amibegron, 120		700 mg/day, 8 weeks
Aventis-			United States	Outpatients	Placebo, 119	Total: 40.3 (13.9); Total: 61.9%, 38.1%	10 mg/day, 8 weeks
Sanofi 2007b [115]	DSM-IV- TR				Escitalopram, 122		10 mg/day, 8 weeks
					Amibegron, 118		700 mg/day, 8 weeks

Aventis-		None stated	Belgium, Canada, Finland, France, Italy,	NA	Placebo, 124	Total: 41.6 (NA); Total: 66.0%, 34%	10 mg/day, 8 weeks
Sanofi 2008	DSM-IV- TR				Escitalopram, 113		10 mg/day, 8 weeks
[114]			Sweden, Turkey		Saredutant, 124		100 mg/day, 8 weeks
					Placebo, 139	41.8 (11.6);	5, 10 or 20
Baldwin					,	67%, 33%	mg/day, 12 weeks
2006	DSM-IV-	None	NA	Outpatients	Escitalopram, 403	41.2 (12.3);	5, 10 or 20
[105]	TR	stated		Outputients	Lisentalopranii, 105	64.8%, 35.2%	mg/day, 12 weeks
[105]					Paroxetine, 139	41.7 (12.0);	20 mg/day, 12
						60%, 40%	weeks
					Placebo, 140 37.6 (12.3); 62.5%, 37.5% hts Escitalopram, 131 38.2 (11.5); 64.6%, 35.4%	37.6 (12.3);	10-20 or 75-225
		C:-1				62.5%, 37.5%	mg/day, 8 weeks
Bose 2008	DSM-IV	Social	Linited States	Outractionta		10-20 mg/day, 8	
[102]	DSIVI-IV	phobia and	United States	Outpatients		weeks	
		depression			V 1 C ' 100	37.1 (10.8);	75-225 mg/day, 8
					Escitalopram, 131 64.6%, 35.4% Venlafaxine, 133 37.1 (10.8); 59.7%, 41.3%		weeks
Brawman-					DI 1 170	40.8 (12.3);	50-200 mg/day,
Mintzer	Data	None			Placebo, 170	56.8%, 43.2%	10 weeks
2006	DSM-IV	stated	United States	Outpatients	a 11 1 4 40	40.1 (13.2);	50-200 mg/day,
[119]					Sertraline, 168	59.8%, 40.2%	10 weeks
Brawman-					DI 1 14	NA	50 or 100 mg/day,
Mintzer	DOM	None		Primary care	Placebo, 14	0%, 100%	11 weeks
2009	DSM-IV	stated	United States			NA	50 or 100 mg/day,
[100]					Sertraline, 28	3.6%, 96.4%	11 weeks

		IV None stated	United States	Outpatients	Placebo, 98	39.0 (11.0); 62.2%, 37.8%	75 or 150 mg/day, 8 weeks
Davidson 1999 [127]	DSM-IV				Venlafaxine, 174	37.5 (10.5); 64.4%, 35.6%	75 or 150 mg/day, 8 weeks
					Buspirone, 93	37.0 (10.0); 51%, 42%	30 mg/day, 8 weeks
Davidson	DSM-IV	None stated	United States	Outpatianta	Placebo, 157	39.5 (13.1); 52.9%, 47.1%	10-20 mg/day, 8 weeks
2004 [113]	D3IVI-I V	None stated	United States	Outpatients	Escitalopram, 158	39.5 (12.1); 52.5%, 47.5%	10-20 mg/day, 8 weeks
	DSM-IV	DSM-IV None stated	United States	NA	Placebo, 57	35.0 (10.4); 54.4%, 45.6%	20 mg/day, 4 weeks
Feltner 2009 [107]					Paroxetine, 56	35.0 (12.7); 55.4%, 44.6%	20 mg/day, 4 weeks
					Lorazepam, 56	38.3 (12.0); 64.3%, 35.7%	4.5 mg/day, 4 weeks
Gelenberg		1-IV None stated	United States	Outpatients	Placebo, 127	38.0 (11.0); 59%, 41%	75-225 mg/day, 28 weeks
2000 [120]	DSIVI-IV				Venlafaxine, 124	41.0 (12.0); 59%, 41%	75-225 mg/day, 28 weeks
GlaxoSmit	DSM-IV	None stated	Japan	Outpatients	Placebo, 170	40.6 (12.7); 59.1%, 40.9%	20 mg/day, 8 weeks
hKline 2006 [110]	DSIVI-IV	None stated			Paroxetine, 170	39.5 (12.2); 60.5%, 39.5%	20 mg/day, 8 weeks
Gommoll	DSM-IV-		United States	Outractions	Placebo, 201	40.1 (13.0); 66.2%, 33.8%	20-40 mg/day, 8 weeks
2015 [101]	TR			Outpatients	Vilazodone, 201	40.5 (13.2); 72.5%, 27.5%	20-40 mg/day, 8 weeks

Goodman				Ortestiste	Placebo, 128	40.9 (14.0); 62.5%, 37.5%	10-20 mg/day, 8 weeks
2001 [117]	DSM-IV	None stated	United Stated	Outpatients	Escitalopram, 129	39.6 (13.4); 59.5%, 40.5%	10-20 mg/day, 8 weeks
Goodman	DSM-IV	None stated	United States	Outpatients	Placebo, 145	38.6 (12.5); 48.6%, 51.4%	10-20 mg/day, 8 weeks
2002 [116]	DSIVI-I V	None stated	Officed States	Outpatients	Escitalopram, 149	36.8 (12.2); 61.4%, 38.6%	10-20 mg/day, 8 weeks
	DSM-IV				Placebo, 97	43 (NA); 64%, 36%	75 or 150 mg/day, 8 weeks
Hackett 2003 [125]		None stated	NA	Outpatients	Venlafaxine, 370	44.5 (NA); 66.5%, 33.5%	75 or 150 mg/day, 8 weeks
					Diazepam, 89	44 (NA); 64%, 36%	15 mg/day, 8 weeks
Houtfoud					Placebo, 161	41.9 (14.2); 61.5%, 38.5%	60-120 mg/day or 75-225 mg/day, 10 weeks
Hartford 2007 [104]	DSM-IV	None stated	United States	Outpatients	tpatients Duloxetine, 162 40.4 (13.6); 64.2%, 35.8%	60-120 mg/day, 10 weeks	
					Venlafaxine, 164	40.1 (13.2); 62.2%, 37.8%	75-225 mg/day, 10 weeks
Hewett 2001 [112]	DSM-IV	OSM-IV None stated	ted France, Ireland, Outpatients Germany,	Outpatients	Placebo, 188	45.4 (15.0); 66.5%, 33.5%	20-50 mg/day, 8 weeks
				Paroxetine, 186	46.5 (14.9); 74.3%, 25.7%	20-50 mg/day, 8 weeks	

		None stated	Belgium, Canada, France, Ireland, Italy,	Outpatients	Placebo, 128	40.2 (12.1); 61%, 39%	75-225 mg/day, 8 weeks
Kasper 2009 [124]	DSM- IV-TR				Venlafaxine, 125	42.6 (11.8); 58%, 42%	75-225 mg/day, 8 weeks
			Netherlands, Spain, Sweden		Pregabalin, 121	39.5 (11.9); 64%, 36%	150-600 mg/day, 8 weeks
Koponen			Finland, France, Germany, South		Placebo, 175	44.1 (13.4); 66.9%, 33.1%	60 or 120 mg/day, 9 weeks
2007 [130]	DSM-IV	None stated	Africa, Spain, Sweden, United States	Outpatients	Duloxetine, 338	43.6 (12.7); 68.3%, 31.7%	60 or 120 mg/day, 9 weeks
Lenox-	DCM IV	V None stated	d United Kingdom	Primary care	Placebo, 122	46 (NA); 56.6%, 43.4%	75-150 mg/day, 24 weeks
Smith 2003 [121]	DSM-IV				Venlafaxine, 122	48 (NA); 61.5%, 38.5%	75-150 mg/day, 24 weeks
Mahablesh		SM- Y-TR None stated NA		NA	Placebo, 157	36.8 (12.1); 65.0%, 35.0%	2.5, 5, or 10 mg/day or 60 mg/day, 8 weeks
warkar 2014 [99]	IV-TR		,		Duloxetine, 156	39.5 (12.3); 72.4%, 27.6%	60 mg/day, 8 weeks
					Vortioxetine, 468	38.9 (12.1); 67.1%, 32.9%	2.5, 5 or 10 mg/day, 8 weeks
		None stated			Placebo, 14	40.3 (7.9); 64%, 35.7%	25-200 mg/day, 6 weeks
McLeod 1992 [98]	DSM- III-R		NA	Volunteers	Imipramine, 14	41.8 (8.2); 64%, 35.7%	25-200 mg/day, 6 weeks
					Alprazolam, 14	41.4 (9.8); 64%, 35.7%	0.5-5.5 mg/day, 6 weeks

Mantaan		None stated	Austria, Belgium, Germany, Netherlands,	Primary care and psychiatric	Placebo, 101	43.0 (12.0); 58%, 42%	75 mg/day, 6 weeks
Montgome ry 2006 [123]	DSM-IV				Venlafaxine, 113	46.0 (12.0); 65%, 35%	75 mg/day, 6 weeks
[123]			United Kingdom	outpatients	Pregabalin, 207	43.4 (12.1); 62.1%, 37.9%	400 or 600 mg/day, 6 weeks
NT' 1' '	DSM-IV	None stated	Australia, Argentina, Belgium, Canada, Mexico, Russia, Taiwan, UK	Outpatients	Placebo, 170	Total: 42.8 (NA); Total: 57.1%, 42.9%	20 or 60-120 or 75-225 mg/day, 10 weeks
Nicolini 2009 [103]					Duloxetine, 242		20 or 60-120 mg/day, 10 weeks
					Venlafaxine, 169		75-225 mg/day, 10 weeks
Nimatoudis	DSM-IV	SM-IV None stated	Greece	Outpatients	Placebo, 22	44.0 (12.0); 68.2%, 31.8%	75-150mg/day, 8 weeks
2004 [122]					Venlafaxine, 24	41.0 (14.0); 66.7%, 33.3%	75-150mg/day, 8 weeks
		SM-IV None stated	Hungary, Italy, Korea, United States	NA	Placebo, 101	42.1 (12.5); 65%, 35%	20 mg/day, 8 weeks
Pfizer 2009 [109]	DSM-IV				Paroxetine, 97	43.5 (13.5); 63.9%, 36.1%	20 mg/day, 8 weeks
					Imagabalin, 295	40.9 (12.8); 61.2%, 38.8%	150, 350, or 450 mg/day, 8 weeks

Pollack	DOM IV	None stated	United States and Canada	Outpatianta	Placebo, 163	41.3 (Range 19-80); 66.3%, 33.7%	20-50 mg/day, 8 weeks
2001[111]	DSM-IV	None stated		Outpatients	Paroxetine, 161	39.7 (Range 19-69); 60.9%, 39.1%	20-50 mg/day, 8 weeks
Rickels	DOMIN		TT '4 104 4		Placebo, 96	40.9 (11.3); 57%, 43%	75, 150 or 225 mg/day, 8 weeks
2000 [126]	DSM-IV	None stated	United States	Outpatients	Venlafaxine, 253	40.8 (12.4); 55.3%, 44.7%	75, 150 or 225 mg/day, 8 weeks
Rickels	DOMENT	None stated	United States, Canada	Outpatients	Placebo, 188	40.8 (12.6); 56%, 44%	20 or 40 mg/day, 8 weeks
2003 [106]	DSM-IV				Paroxetine, 385	40.4 (12.7); 55%, 45%	20 or 40 mg/day, 8 weeks
Rothschild	DSM-	Noncorrected		NT A	Placebo, 152	41.4 (12.8); 87.2%, 12.8%	5 mg/day, 8 weeks
2012 [134]	IV-TR	None stated	United States	NA	Vortioxetine, 152	41.0 (14.1); 67.8%, 32.2%	5 mg/day, 8 weeks
Rynn 2008	DOMIN	No		Ontractions	Placebo, 159	41.0 (14.2); 62.3%, 37.7%	60-120 mg/day, 10 weeks
[131]	DSM-IV	None stated	United States	Outpatients	Duloxetine, 168	42.2 (13.9); 61.3%, 38.7%	60-120 mg/day, 10 weeks
Stein 2008	DSM-	None stated	Finland,	Outrationta	Placebo, 58	Total: 41.7 (12.2);	25-50 mg/day, 12 weeks
[132]	IV-TR	None stated	South Africa	Outpatients	Agomelatine, 63	Total: 68.6%, 31.4%	25-50 mg/day, 12 weeks

			Finland, Russia, Poland, Czech Republic, Slovakia, Argentina, South Korea	Outpatients	Placebo, 131	43.0 (12.2); 71.8%, 28.2%	10-20 or 25-50 mg/day, 12 weeks
Stein 2014 [81]	DSM- IV-TR	None stated			Agomelatine, 139	43.6 (12.5); 74.8%, 25.2%	10-20 mg/day, 12 weeks
[01]	11-11				Escitalopram, 142	41.2 (12.5); 68.3%, 31.7%	25-50 mg/day, 12 weeks
Stein 2017	DSM- IV-TR	None stated	Finland, Russia, Poland, Slovakia, Ukraine	Outpatients	Placebo, 142	44.1 (13.1); 63.4%, 36.6%	10 or 25 mg/day, 12 weeks
[133]					Agomelatine, 270	43.9 (14.3); 70%, 30%	10 or 25 mg/day, 12 weeks
Wen-Yuan 2011 [129]	DSM-	None stated	China	Outpatients	Placebo, 102	38.0 (12.0); 54.9%, 45.1%	60-120 mg/day, 15 weeks
	IV				Duloxetine, 108	37.3 (11.9); 46.3%, 53.7%	60-120 mg/day, 15 weeks

^a Abbreviations: NA, Not available; RCT, randomized controlled trial; GAD, generalized anxiety disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV-TR, Diagnostic and Statistical Manually of Mental Disorders 4th edition text revision; DSM-III-R, Diagnostic and Statistical Manually of Mental Disorders 3th edition revised.

^b Age data are presented as mean (SD) or mean (range) where available. Sex data are presented as % females, % males.

4.2.3 Outcomes

Not all the outcomes planned for this review were investigated in each study. Twenty-one studies reported data on rate of treatment response measured as a reduction of at least 50% on the HAM-A, 34 studies reported data on acceptability, 18 studies reported data on rate of treatment response (defined by study authors), 17 studies reported remission rates, 35 studies reported change in symptom levels, 24 studies reported total number of patients reporting adverse effects, 24 studies reported sleepiness/drowsiness, 6 studies reported agitation/anxiety, 3 studies reported suicide wishes/gestures/attempts, 4 studies reported average score/change in quality of life/satisfaction, 30 studies reported dropouts due to a lack of efficacy, and 33 studies reported dropouts due to adverse effects. Studies were not included in the analyses if they did not report data on the specified outcome or if the authors did not fully report the specified outcome and could not be contacted for additional information.

There were no studies that reported data on falls, hypotension, subjective memory impairment, or number of participants experiencing withdrawal symptoms. Studies that reported zero events in both treatment arms for an outcome were not included the in analyses for that outcome because they provided no valuable information on treatment effect [86]. This included 8 studies that reported zero deaths in both treatment arms [99, 101, 104, 108, 109, 114, 129, 132] and one study [109] that reported zero deaths by suicide in both treatment arms.

4.3 Risk of Bias of Included Studies

Figures 2 and 3 are a graph and summary of the risk of bias of the included studies, respectively. For the domain *random sequence generation*, 13 studies specified how their randomization sequence was generated and received low risk of bias, while random sequence generation was unclear for 25 studies. Methods for *allocation concealment* were specified in 8 studies, receiving low risk of bias, while it was unclear in the remaining 30 studies. Often studies would only specify that they were 'double-blind'. In these cases, a judgment whether the bias was high, low, or unclear was made by the reviewer to assess whether there was reasonable evidence for concern that blinding was

compromised for participants, personnel, or outcome assessors in any way. In total, 27 studies received a low risk of bias, and 11 studies received an unclear risk of bias for blinding of participants and personnel and blinding of outcome assessment. Although ITT analysis was used in the majority of studies, there were no studies that received a low risk of bias for *incomplete outcome data*. This is because LOCF was the main approach to dealing with missing data. LOCF however, is limited as it carries forward the last observed value and assumes it would not have changed [90]. This approach has the potential to lead to bias and as a result, studies that used LOCF were automatically given an unclear risk of bias [90]. A high risk of bias was judged if there was not enough information to make a valid assessment or if LOCF was used and dropout rates differed significantly between groups. In total, 27 studies had an unclear risk of bias, and 11 studies had a high risk of bias in this domain. Twenty studies were given a low risk of bias in *selective outcome reporting* because they fully reported all outcomes that they specified in their methods section, protocol, or in their clinical trial registry. All other studies were given an unclear (4 studies) or a high (14 studies) risk of bias if there was not enough information to make a valid assessment, or if authors failed to report, or only partially reported (i.e., only providing p-values or describing the results as 'significant' or 'not significant') outcomes. For other sources of bias, these were rated as unclear or high risk of bias if there was not enough information to make a valid assessment, or if there was suspicion of the involvement of the funder/sponsor. In this domain, one study was given a low risk of bias because it was sponsored by the government, 13 studies had an unclear risk of bias because the sponsor/funding was not specified, and 24 studies had a high risk of bias because they were sponsored by a pharmaceutical company.

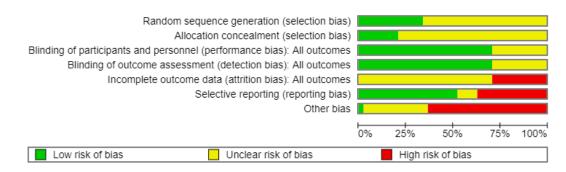


Figure 2. Risk of bias graph

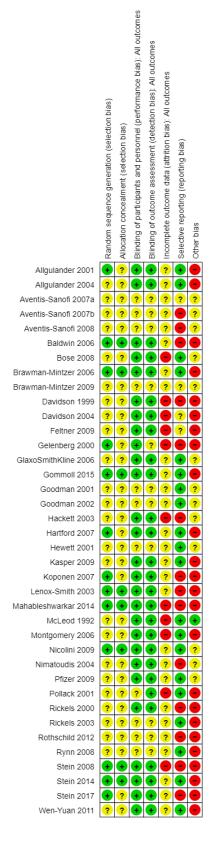


Figure 3. Risk of bias summary

4.4 Results of Meta-Analyses

Below is a description of the results from the meta-analyses. Appendix 5 lists all the studies and outcomes for which GetDataGraph Digitizer was used to extract data. In addition, to avoid unit-of-analysis issues, multi-arm studies that included antidepressants from different classes were entered twice into the analyses comparing all antidepressants to placebo, with the sample size from the placebo group being split in half for each antidepressant-placebo comparison. This was done according to the guidelines listed in the Cochrane Handbook for studies with more than two intervention groups [86]. Within the analyses comparing different classes of antidepressants, each antidepressant-placebo comparison was entered under its corresponding class, with the full sample size for the placebo group used to get the most accurate estimate of effect for that treatment class. RevMan Web however, automatically presents an estimated total effect size at the bottom of the analyses comparing different classes of antidepressants. This total effect size represents the effect size for all the antidepressants included in the analysis compared to placebo. These data, however, have been omitted as analyses comparing all antidepressants to placebo are already included for each outcome, with multi-arm studies being appropriately adjusted to avoid unit of analysis issues. Furthermore, studies that contribute multiple antidepressant-placebo comparisons into a meta-analysis are only counted as one study when considering the total number of studies that contribute to the analysis, as specified by the Cochrane Handbook [86].

The quality of evidence for the outcomes rate of treatment response measured as a reduction of at least 50% on the HAM-A, acceptability, dropouts due to a lack of efficacy, and dropouts due to adverse effects was found to be very-low. Evidence was downgraded by one level for all four outcomes due to an overall high risk of bias among the included studies. The quality of evidence was downgraded by one level for rate of treatment response and acceptability due to high heterogeneity. This review also focused on those with a primary diagnosis of GAD and mostly excluded those with comorbidities, resulting in downgrading the quality of evidence by one level for indirectness for all four outcomes. The quality of evidence was not downgraded for imprecision. Many studies were sponsored by a pharmaceutical company which can potentially lead to sponsorship

bias therefore this domain was also downgraded by one level. Appendix 6 shows the GRADE quality of evidence table produced using GRADEpro, with justifications for the evaluations.

4.4.1 Rate of Treatment Response

Figures 4 and 5 show the pooled rate of treatment response - measured as a reduction of at least 50% on the HAM-A - for the different antidepressants compared to placebo. There was very low-quality evidence showing a benefit with all antidepressants over placebo in treatment response measured as a reduction of at least 50% on the HAM-A scale (RR, 1.39: 95% CI: 1.27, 1.52; studies = 21; participants = 7,556). This analysis had substantial heterogeneity ($I^2 = 64\%$; p < 0.00001).

Analyses among different classes of antidepressants all showed a benefit over placebo: SSRIs (RR, 1.51: 95% CI: 1.20, 1.90; $I^2 = 73\%$; studies = 4; participants = 1,226), SNRIs (RR, 1.34: 95% CI: 1.21, 1.47; $I^2 = 50\%$; studies = 14; participants = 4,659), and 'Other' antidepressants (RR, 1.44: 95% CI: 1.11, 1.88; $I^2 = 85\%$; studies = 6; participants = 2,093). Heterogeneity ranged from moderate-considerable. The test for subgroup interaction suggested that the effect sizes were similar across classes of antidepressants for response ($I^2 = 0\%$; p = 0.59). The Cochrane Handbook suggests that at least 10 studies should be included in each subgroup (in this case, each antidepressants class) in order to produce meaningful results [86]. Consequentially, more studies in the SSRI and 'Others' subgroups are needed to better detect subgroup differences.

	Antidepre	essants	Place	Risk ratio	Risk ratio Risk ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI		
Allgulander 2001	273	399	60	130	5.1%	1.48 [1.22 , 1.81]	+		
Allgulander 2004	102	182	55	188	4.4%	1.92 [1.48 , 2.48]			
Bose 2008	66	125	28	67	3.6%	1.26 [0.91 , 1.75]			
Bose 2008	65	125	28	67	3.6%	1.24 [0.90 , 1.73]			
Brawman-Mintzer 2006	97	164	78	162	5.0%	1.23 [1.00 , 1.51]			
Davidson 1999	87	176	35	98	3.8%	1.38 [1.02 , 1.88]	_ . _		
Gommoll 2015	103	198	82	197	4.9%	1.25 [1.01 , 1.55]			
Hackett 2003	200	354	44	97	4.6%	1.25 [0.98 , 1.58]			
Hartford 2007	165	326	60	161	4.8%	1.36 [1.08 , 1.70]			
Kasper 2009	55	125	59	128	4.2%	0.95 [0.73 , 1.25]	-		
Koponen 2007	193	338	54	175	4.6%	1.85 [1.46 , 2.35]			
enox-Smith 2003	64	122	59	122	4.5%	1.08 [0.85 , 1.39]			
/lahableshwarkar 2014	76	149	32	77	3.8%	1.23 [0.90 , 1.67]			
Mahableshwarkar 2014	201	456	32	77	4.1%	1.06 [0.80 , 1.41]	<u> </u>		
/lontgomery 2006	68	110	45	100	4.3%	1.37 [1.06 , 1.78]	_ _		
Vicolini 2009	245	392	69	163	5.2%	1.48 [1.21 , 1.79]			
Vimatoudis 2004	22	24	6	22	1.4%	3.36 [1.68 , 6.72]			
Rothschild 2012	77	145	72	144	4.8%	1.06 [0.85 , 1.33]			
Rynn 2008	67	168	51	159	4.0%	1.24 [0.93 , 1.67]	<u> </u>		
Stein 2008	45	63	27	58	3.7%	1.53 [1.12 , 2.11]			
Stein 2014	89	139	24	65	3.5%	1.73 [1.23 , 2.44]			
Stein 2014	92	139	24	65	3.5%	1.79 [1.28 , 2.52]			
Stein 2017	164	268	32	140	3.7%	2.68 [1.95, 3.68]			
Wen-Yuan 2011	74	107	53	100	4.8%	1.30 [1.04 , 1.63]			
Total (95% CI)		4794		2762	100.0%	1.39 [1.27 , 1.52]	•		
Total events:	2690		1109				*		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Test for subgroup differer	= 7.13 (P < 0	0.00001)		1 0.2 0.5 1 2 5 10 vours placebo Favours antidep					

Figure 4. Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo

Study or Subgroup Events Total Events Total Weight IV, Random, 95% Cl IV, Random, 95% Cl 1.2.1 SSRIs Aligulander 2004 102 182 55 188 24.2% 1.92 [1.48, 2.48] Bose 2008 66 125 57 135 24.2% 1.25 [0.97, 1.62] Brawman-Mintzer 2006 97 164 78 162 27.2% 1.23 [1.00, 1.51] Stein 2014 92 139 48 131 24.4% 1.81 [1.40, 2.33] Subtotal (95% Cl) 610 616 100.0% 1.51 [1.20, 1.90] 1.30 Total events: 357 238		Antidepre	ssants	Place	ebo		Risk ratio	Risk ratio
Aligulander 2004 102 182 55 188 24.2% 1.92 [1.48, 2.48] Bose 2006 66 125 57 135 24.2% 1.25 [0.97, 1.62] Brawman-Mintzer 2006 97 164 78 162 27.2% 1.23 [1.00, 1.51] Stein 2014 92 139 48 131 24.4% 1.81 [1.40, 2.33] Subtotal (95% CI) 610 616 100.0% 1.51 [1.20, 1.90] Total events: 357 238 Heterogeneity: Tau ² = 0.04; Ch ² = 11.07, df = 3 (P = 0.01); l ² = 73% Test for overall effect: Z = 3.47 (P = 0.0005) 1.2.2 SNRis Hacket 2003 65 125 57 135 7.1% 1.23 [0.95, 1.60] Davidson 1999 87 176 35 98 6.0% 1.38 [1.02, 1.88] Hacket 2003 200 354 44 97 7.8% 1.25 [0.98, 1.58] Hacket 2007 165 326 60 161 8.1% 1.36 [1.08, 1.70] Kasper 2009 55 125 59 128 6.8% 0.95 [0.73, 1.25] Kopone 2007 193 338 54 175 7.7% 1.25 [0.98, 1.58] Hantford 2007 165 326 60 161 8.1% 1.36 [1.46, 2.35] Lenox-Smith 2003 64 122 59 122 7.4% 1.08 [0.85, 1.39] Mahableshwarkar 2014 76 149 65 154 7.6% 1.21 [0.95, 1.54] Montgomery 2006 68 110 45 100 7.1% 3.36 [1.68, 6.72] Rynn 2008 67 168 51 159 6.3% 1.24 [0.93, 1.67] Wen-Yuan 2011 74 107 53 100 8.2% 1.30 [1.04, 1.63] Subtotal (95% CI) 2915 1744 100.0% 1.34 [1.21, 1.47] Total events: 1654 717 Heterogeneilty: Tau ² = 0.02; Ch ² = 26.24, df = 13 (P = 0.02); P = 50% Test for overall effect: Z = 5.91 (P < 0.00001) 1.2.3 Other Gommol 2015 103 198 82 197 17.6% 1.25 [1.01, 1.55] Mahableshwarkar 2014 456 65 154 17.6% 1.04 [0.85, 1.29] Rothschild 2012 77 145 72 144 17.4% 1.06 [0.85, 1.23] Stein 2013 198 48 131 16.7% 175 [1.53, 1.22, 1.1] Stein 2014 89 139 48 131 16.7% 175 [1.53, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% CI) 1289 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneilty: Tau ² = 0.09; Ch ³ = 32.76, df = 5 (P < 0.00001); I ² = 85%	Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
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Total events: 1654 717 Heterogeneity: Tau ² = 0.02; Chi ² = 26.24, df = 13 (P = 0.02); I ² = 50% Test for overall effect: Z = 5.91 (P < 0.00001) 1.2.3 Other Gommoll 2015 103 198 82 197 17.6% 1.25 [1.01, 1.55] Wahableshwarkar 2014 201 456 65 154 17.6% 1.04 [0.85, 1.29] Rothschild 2012 77 145 72 144 17.4% 1.06 [0.85, 1.33] Stein 2008 45 63 27 58 15.4% 1.53 [1.12, 2.11] Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); I ² = 85%			2915		1744	100.0%		▲
Test for overall effect: $Z = 5.91 (P < 0.00001)$ 1.2.3 Other Sommoll 2015 103 198 82 197 17.6% 1.25 [1.01, 1.55] Mahableshwarkar 2014 201 456 65 154 17.6% 1.04 [0.85, 1.29] Rothschild 2012 77 145 72 144 17.4% 1.06 [0.85, 1.33] Stein 2008 45 63 27 58 15.4% 1.53 [1.12, 2.11] Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chl ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	. ,	1654						•
Test for overall effect: $Z = 5.91 (P < 0.00001)$ 1.2.3 Other Gommoll 2015 103 198 82 197 17.6% 1.25 [1.01, 1.55] Mahableshwarkar 2014 201 456 65 154 17.6% 1.04 [0.85, 1.29] Rothschild 2012 77 145 72 144 17.4% 1.06 [0.85, 1.33] Stein 2008 45 63 27 58 15.4% 1.53 [1.12, 2.11] Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chl ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	Heterogeneity: Tau ² = 0.0)2; Chi² = 26	.24. df =	13 (P = 0.0)2); ² = 5	0%		
Gommoll 2015 103 198 82 197 17.6% 1.25 [1.01, 1.55] Mahableshwarkar 2014 201 456 65 154 17.6% 1.04 [0.85, 1.29] Rothschild 2012 77 145 72 144 17.4% 1.06 [0.85, 1.33] Stein 2008 45 63 27 58 15.4% 1.53 [1.12, 2.11] Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chl ² = 32.76, df = 5 (P < 0.00001); l ² = 85% 85%	e ,			,				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.2.3 Other							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Gommoll 2015	103	198	82	197	17.6%	1.25 [1.01 , 1.55]	
Stein 2008 45 63 27 58 15.4% 1.53 [1.12, 2.11] Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% Cl) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	Mahableshwarkar 2014	201	456	65	154	17.6%	1.04 [0.85 , 1.29]	+
Stein 2014 89 139 48 131 16.7% 1.75 [1.35, 2.26] Stein 2017 164 268 32 140 15.4% 2.68 [1.95, 3.68] Subtotal (95% Cl) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	Rothschild 2012	77	145	72	144	17.4%	1.06 [0.85 , 1.33]	-
Stein 2017 164 268 32 140 15.4% 2.68 1.95, 3.68 Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); I ² = 85%	Stein 2008	45	63	27	58	15.4%	1.53 [1.12 , 2.11]	
Subtotal (95% CI) 1269 824 100.0% 1.44 [1.11, 1.88] Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); I ² = 85%	Stein 2014	89	139	48	131	16.7%	1.75 [1.35 , 2.26]	
Total events: 679 326 Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	Stein 2017	164	268	32	140	15.4%	2.68 [1.95 , 3.68]	
Heterogeneity: Tau ² = 0.09; Chi ² = 32.76, df = 5 (P < 0.00001); l ² = 85%	Subtotal (95% CI)		1269		824	100.0%	1.44 [1.11 , 1.88]	•
	Total events:	679		326				•
Test for overall effect: Z = 2.76 (P = 0.006)	Heterogeneity: Tau ² = 0.0)9; Chi² = 32	.76, df =	5 (P < 0.00	0001); l² =	85%		
	Test for overall effect: Z =	= 2.76 (P = 0	.006)					
Test for subgroup differences: Chi ² = 1.06, df = 2 (P = 0.59), l ² = 0%	Test for subgroup differer	nces: Chi² =	1.06, df =	2 (P = 0.5	i9), I² = 0	%	, F	

Figure 5. Rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment class versus placebo

4.4.2 Acceptability (total number of dropouts):

Figures 6 and 7 show the pooled acceptability for the different antidepressants compared to placebo. There was very low-quality evidence showing no difference in total number of dropouts between all antidepressants compared to placebo (RR, 1.02: 95% CI: 0.92, 1.12; studies = 34; participants = 11,598). This analysis had moderate-substantial heterogeneity (I²: 52%; p = 0.0002).

Analyses among the different classes of antidepressants did not show a difference compared to placebo: SSRIs (RR, 1.06: 95% CI: 0.95, 1.19; I²: 2%; studies = 16; participants = 5,031), SNRIs (RR, 1.03: 95% CI: 0.87, 1.21; I²: 69%; studies = 15; participants = 4,863), and 'Other' antidepressants (RR, 0.86: 95% CI: 0.61, 1.21; I²: 70%; studies = 6; participants = 2,134). Analyses among the SNRIs and 'Other' antidepressants had substantial heterogeneity whereas the analysis of the SSRI group had low heterogeneity. The test for subgroup interaction suggested that the effect size was similar between classes of antidepressants with regard to acceptability (I² = 0%; p = 0.51) although more studies with 'Other' antidepressants are needed to better detect subgroup differences.

	Antidepre	ssants	Place	ebo		Risk ratio	Risk ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Ilgulander 2001	102	411	45	130	3.8%	0.72 [0.54 , 0.96]	
ligulander 2004	41	188	51	190	3.2%	0.81 [0.57 , 1.16]	
ventis-Sanofi 2008	20	114	17	126	1.8%	1.30 [0.72 , 2.36]	
aldwin 2006	83	543	15	139	2.2%	1.42 [0.84 , 2.38]	
lose 2008	29	131	18	70	2.2%	0.86 [0.52 , 1.44]	
ose 2008	37	133	18	70	2.4%	1.08 [0.67 , 1.75]	
Brawman-Mintzer 2006	51	168	46	170	3.4%	1.12 [0.80 , 1.57]	
rawman-Mintzer 2009	12	28	7	14	1.5%	0.86 [0.44 , 1.69]	
avidson 1999	84	203	36	104	3.6%	1.20 [0.88 , 1.63]	
avidson 2004	42	161	36	159	3.0%	1.15 [0.78 , 1.70]	
eltner 2009	15	56	18	57	1.9%	0.85 [0.48 , 1.51]	
Gelenberg 2000	64	124	83	127	4.5%	0.79 [0.64 , 0.98]	
BlaxoSmithKline 2006	30	179	28	182	2.5%	1.09 [0.68 , 1.75]	
Sommoll 2015	57	201	40	201	3.3%	1.43 [1.00 , 2.03]	
Goodman 2001	32	129	33	128	2.8%	0.96 [0.63 , 1.46]	
Goodman 2002	31	149	31	145	2.6%	0.97 [0.63 , 1.51]	
lackett 2003	77	370	16	97	2.4%	1.26 [0.77 , 2.06]	
lartford 2007	136	326	62	161	4.3%	1.08 [0.86 , 1.37]	
lewett 2001	35	188	22	186	2.3%	1.57 [0.96 , 2.58]	-
asper 2009	41	125	35	128	3.1%	1.20 [0.82 , 1.75]	
enox-Smith 2003	15	123	25	120	1.9%	0.60 [0.33 , 1.08]	
lahableshwarkar 2014	50	122	18	78	2.5%	1.39 [0.87 , 2.21]	
lahableshwarkar 2014	120	468	18	78	2.5%		
		400	20	101		1.11 [0.72 , 1.71]	
Iontgomery 2006	34				2.4%	1.52 [0.94 , 2.46]	
licolini 2009	117	411	68	170	4.3%	0.71 [0.56 , 0.90]	
limatoudis 2004	5	24	11	22	1.0%	0.42 [0.17 , 1.01]	
fizer 2009	39	97	28	101	3.0%	1.45 [0.97 , 2.16]	
ollack 2001	34	161	30	163	2.7%	1.15 [0.74 , 1.78]	
Rickels 2000	83	253	19	96	2.7%	1.66 [1.07 , 2.57]	_ -
Rickels 2003	100	386	40	180	3.5%	1.17 [0.85 , 1.61]	+
othschild 2012	27	152	38	152	2.7%	0.71 [0.46 , 1.10]	
ynn 2008	75	168	50	159	3.9%	1.42 [1.07 , 1.89]	
tein 2008	5	63	4	58	0.5%	1.15 [0.32 , 4.08]	
tein 2014	26	142	17	65	2.1%	0.70 [0.41 , 1.20]	
tein 2014	23	139	17	65	2.0%	0.63 [0.36 , 1.10]	
Stein 2017	31	270	30	142	2.5%	0.54 [0.34 , 0.86]	
Ven-Yuan 2011	26	108	28	102	2.5%	0.88 [0.55 , 1.39]	
otal (95% CI)		7160		4438	100.0%	1.02 [0.92 , 1.12]	•
otal events:	1829		1118				
leterogeneity: Tau ² = 0.0)4; Chi² = 74	.93, df = 3	36 (P = 0.0	0002); I² =	52%	0.1	1 0.2 0.5 1 2 5 1
est for overall effect: Z =	= 0.37 (P = 0	.71)					er in placebo Higher in anti
	nces: Not ap					-	

Figure 6. Acceptability for all antidepressants versus placebo

41 20 83 29 51 12 42 15 30 32 31 35 39 34 100 26 620 Chi ^z = 15.2 11 (P = 0.2 37 84 64 77	188 114 543 131 168 28 161 56 179 129 149 188 97 161 386 142 2820 23, df = 15	51 17 15 36 46 7 36 18 28 33 31 22 28 30 40 35 47 35 (P = 0.4 5 (P = 0.4 5 45 36 36 83 16		9.0% 3.3% 4.4% 6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% %	0.81 [0.57 , 1.16] 1.30 [0.72 , 2.36] 1.42 [0.84 , 2.38] 0.86 [0.56 , 1.32] 1.12 [0.80 , 1.57] 0.86 [0.44 , 1.69] 1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63] 0.79 [0.64 , 0.98]	IV, Random, 95% CI
20 83 29 51 12 42 15 30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 37 84 64 77	114 543 131 168 28 161 56 179 129 149 188 97 161 386 2820 23, df = 15 27) 411 133 203 124	17 15 36 46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	126 139 140 170 14 159 57 182 128 145 186 101 163 180 131 2211 3); ² = 2' 130 140 141 142 145 163 163 163 163 163 163 163 163	3.3% 4.4% 6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0%	1.30 [0.72, 2.36] 1.42 [0.84, 2.38] 0.86 [0.56, 1.32] 1.12 [0.80, 1.57] 0.86 [0.44, 1.69] 1.15 [0.78, 1.70] 0.85 [0.48, 1.51] 1.09 [0.68, 1.75] 0.96 [0.63, 1.46] 0.97 [0.63, 1.51] 1.57 [0.96, 2.58] 1.45 [0.97, 2.16] 1.15 [0.74, 1.78] 1.17 [0.85, 1.61] 0.69 [0.44, 1.07] 1.06 [0.95, 1.19] 0.72 [0.54, 0.96] 1.08 [0.73, 1.60] 1.20 [0.88, 1.63]	
20 83 29 51 12 42 15 30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 37 84 64 77	114 543 131 168 28 161 56 179 129 149 188 97 161 386 2820 23, df = 15 27) 411 133 203 124	17 15 36 46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	126 139 140 170 14 159 57 182 128 145 186 101 163 180 131 2211 3); ² = 2' 130 140 141 142 145 163 163 163 163 163 163 163 163	3.3% 4.4% 6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0%	1.30 [0.72, 2.36] 1.42 [0.84, 2.38] 0.86 [0.56, 1.32] 1.12 [0.80, 1.57] 0.86 [0.44, 1.69] 1.15 [0.78, 1.70] 0.85 [0.48, 1.51] 1.09 [0.68, 1.75] 0.96 [0.63, 1.46] 0.97 [0.63, 1.51] 1.57 [0.96, 2.58] 1.45 [0.97, 2.16] 1.15 [0.74, 1.78] 1.17 [0.85, 1.61] 0.69 [0.44, 1.07] 1.06 [0.95, 1.19] 0.72 [0.54, 0.96] 1.08 [0.73, 1.60] 1.20 [0.88, 1.63]	
20 83 29 51 12 42 15 30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 37 84 64 77	114 543 131 168 28 161 56 179 129 149 188 97 161 386 2820 23, df = 15 27) 411 133 203 124	17 15 36 46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	126 139 140 170 14 159 57 182 128 145 186 101 163 180 131 2211 3); ² = 2' 130 140 141 142 145 163 163 163 163 163 163 163 163	3.3% 4.4% 6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0%	1.30 [0.72, 2.36] 1.42 [0.84, 2.38] 0.86 [0.56, 1.32] 1.12 [0.80, 1.57] 0.86 [0.44, 1.69] 1.15 [0.78, 1.70] 0.85 [0.48, 1.51] 1.09 [0.68, 1.75] 0.96 [0.63, 1.46] 0.97 [0.63, 1.51] 1.57 [0.96, 2.58] 1.45 [0.97, 2.16] 1.15 [0.74, 1.78] 1.17 [0.85, 1.61] 0.69 [0.44, 1.07] 1.06 [0.95, 1.19] 0.72 [0.54, 0.96] 1.08 [0.73, 1.60] 1.20 [0.88, 1.63]	
83 29 51 12 42 15 30 32 31 35 39 34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	543 131 168 28 161 56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	15 36 46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	139 140 170 14 159 57 182 128 145 186 101 163 180 131 2211 3); I ² = 2' 130 140 104	4.4% 6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0%	1.42 [0.84 , 2.38] 0.86 [0.56 , 1.32] 1.12 [0.80 , 1.57] 0.86 [0.44 , 1.69] 1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
29 51 12 42 15 30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	131 168 28 161 56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	36 46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	140 170 14 159 57 182 128 145 186 101 163 180 131 2211 3); I ² = 2' 130 140 104	6.4% 10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% %	0.86 [0.56 , 1.32] 1.12 [0.80 , 1.57] 0.86 [0.44 , 1.69] 1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
51 12 42 15 30 32 31 35 39 34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	168 28 161 56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	46 7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	170 14 159 57 182 128 145 186 101 163 180 131 2211 3); I ² = 2' 130 140 104 127	10.2% 2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% %	1.12 [0.80 , 1.57] 0.86 [0.44 , 1.69] 1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
12 42 15 30 32 31 35 39 34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	28 161 56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	7 36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	14 159 57 182 128 145 186 101 163 180 131 2211 3); I ² = 2 130 140 104 127	2.6% 7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% %	0.86 [0.44 , 1.69] 1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
42 15 30 32 31 35 39 34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	161 56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	36 18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	159 57 182 128 145 186 101 163 180 131 2211 3); I ² = 2' 130 140 104 127	7.7% 3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.15 [0.78 , 1.70] 0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.46] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
15 30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	56 179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	18 28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	57 182 128 145 186 101 163 180 131 2211 3); ² = 2 130 140 104 127	3.5% 5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	0.85 [0.48 , 1.51] 1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
30 32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	179 129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	28 33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	182 128 145 186 101 163 180 131 2211 3); I ² = 2 ⁻ 130 140 104 127	5.2% 6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.09 [0.68 , 1.75] 0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
32 31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	129 149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	33 31 22 28 30 40 35 473 5 (P = 0.43 45 36 36 83	128 145 186 101 163 180 131 2211 3); I ² = 2 ⁻ 130 140 104 127	6.6% 6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	0.96 [0.63 , 1.46] 0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
31 35 39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	149 188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	31 22 28 30 40 35 5 (P = 0.43 45 36 36 83	145 186 101 163 180 131 2211 3); I ² = 2 ⁻ 130 140 104 127	6.0% 4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	0.97 [0.63 , 1.51] 1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
35 39 34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	188 97 161 386 142 2820 23, df = 15 27) 411 133 203 124	22 28 30 40 35 5 (P = 0.43 45 36 36 83	186 101 163 180 131 2211 3); I ² = 2 ⁻ 130 140 104 127	4.8% 7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.57 [0.96 , 2.58] 1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
39 34 100 26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	97 161 386 142 2820 23, df = 15 27) 411 133 203 124	28 30 40 35 5 (P = 0.43 45 36 36 83	101 163 180 131 2211 3); I ² = 2' 130 140 104 127	7.3% 6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.45 [0.97 , 2.16] 1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
34 100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	161 386 142 2820 23, df = 15 27) 411 133 203 124	30 40 35 5 (P = 0.43 45 36 36 83	163 180 131 2211 3); I ² = 2' 130 140 104 127	6.0% 11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.15 [0.74 , 1.78] 1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
100 26 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	386 142 2820 23, df = 15 27) 411 133 203 124	40 35 473 5 (P = 0.43 45 36 36 83	180 131 2211 3); I ² = 2 ¹ 130 140 104 127	11.2% 5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	1.17 [0.85 , 1.61] 0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
26 620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	142 2820 23, df = 15 27) 411 133 203 124	35 473 5 (P = 0.43 45 36 36 83	131 2211 3); I ² = 2 ¹ 130 140 104 127	5.8% 100.0% % 7.9% 6.6% 7.7% 9.0%	0.69 [0.44 , 1.07] 1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
620 Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	2820 23, df = 15 27) 411 133 203 124	473 5 (P = 0.43 45 36 36 83	2211 3); I ² = 2 ¹ 130 140 104 127	100.0% % 7.9% 6.6% 7.7% 9.0%	1.06 [0.95 , 1.19] 0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	23, df = 15 27) 411 133 203 124	5 (P = 0.43 45 36 36 83	3); ² = 2 ⁴ 130 140 104 127	% 7.9% 6.6% 7.7% 9.0%	0.72 [0.54 , 0.96] 1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
Chi ² = 15.2 11 (P = 0.2 102 37 84 64 77	411 133 203 124	5 (P = 0.43 45 36 36 83	130 140 104 127	7.9% 6.6% 7.7% 9.0%	1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
11 (P = 0.2 102 37 84 64 77	411 133 203 124	45 36 36 83	130 140 104 127	7.9% 6.6% 7.7% 9.0%	1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
102 37 84 64 77	411 133 203 124	36 36 83	140 104 127	6.6% 7.7% 9.0%	1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	+
37 84 64 77	133 203 124	36 36 83	140 104 127	6.6% 7.7% 9.0%	1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	+
37 84 64 77	133 203 124	36 36 83	140 104 127	6.6% 7.7% 9.0%	1.08 [0.73 , 1.60] 1.20 [0.88 , 1.63]	
84 64 77	203 124	36 83	104 127	7.7% 9.0%	1.20 [0.88 , 1.63]	+-
64 77	124	83	127	9.0%		+
77					0.79 [0.64 , 0.98]	
	370	16	97			
				5.4%	1.26 [0.77 , 2.06]	_
136	326	62	161	8.7%	1.08 [0.86 , 1.37]	
41	125	35	128	6.8%	1.20 [0.82 , 1.75]	
15	122	25	122	4.5%	0.60 [0.33 , 1.08]	
50	156	36	157	6.9%	1.40 [0.97 , 2.02]	
34	113	20	101	5.5%	1.52 [0.94 , 2.46]	—
117	411	68	170	8.6%	0.71 [0.56 , 0.90]	
5	24	11	22	2.6%	0.42 [0.17 , 1.01]	
83	253	19	96	6.0%	1.66 [1.07 , 2.57]	_ _
75	168	50	159	8.0%	1.42 [1.07 , 1.89]	
26	108	28	102	5.8%	0.88 [0.55 , 1.39]	-+-
	3047		1816	100.0%	1.03 [0.87 , 1.21]	•
946		570				
		4 (P < 0.00	001); l² =	69%		
30 (P = 0.7	(6)					
57	201	40	201	20.3%	1.43 [1.00 , 2.03]	
120	468	36	157		1.12 [0.81 , 1.55]	
27	152	38				
5	63	4				
23	139	35				
31				17.6%	• •	_
2.						
263		183				
	49, df = 5		5); ² = 70	0%		
	*					
s: Chi ² = 1	.37, df = 2	2 (P = 0.51	1), I² = 0°	%	01	0.2 0.5 1 2
	946 Chi² = 45.: 30 (P = 0.7 57 120 27 5 23 31 263 Chi² = 16.4 36 (P = 0.3	3047 946 Chi ² = 45.10, df = 14 30 (P = 0.76) 57 201 120 468 27 152 5 63 23 139 31 270 1293 263 Chi ² = 16.49, df = 5 36 (P = 0.39)	3047 946 570 Chi ² = 45.10, df = 14 (P < 0.00 0 (P = 0.76) 57 201 40 120 468 36 27 152 38 5 63 4 23 139 35 31 270 30 1293 263 183 Chi ² = 16.49, df = 5 (P = 0.006 66 (P = 0.39)	3047 1816 946 570 Chi² = 45.10, df = 14 (P < 0.0001); l² =	30471816100.0%946570 $Chi^2 = 45.10, df = 14 (P < 0.0001); I^2 = 69\%$ 30 (P = 0.76)57201402020.3%120468361572715238152181%5634585.7%231393127020314217.6%1293841263183Chi^2 = 16.49, df = 5 (P = 0.006); I^2 = 70%	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Figure 7. Acceptability by treatment class versus placebo

4.4.3 Rate of Treatment Response (defined by study authors)

Figures 8 and 9 show the pooled rate of treatment response (defined by study authors) for the different antidepressants compared to placebo. One study [120] defined treatment response as a reduction of 40% or more on the HAM-A, one study [107] defined treatment response as a score of 1 or 2 on the of Clinical Global Impression-Change (CGI-C) while the remaining 16 studies defined it as a score of 1 or 2 on the CGI-I. The analysis showed a benefit of all antidepressants over placebo in the rate of treatment response as defined by study authors (RR, 1.35: 95% CI: 1.27, 1.43; studies = 18; participants = 6,613). Heterogeneity in this analysis was low-moderate (I²: 36%; p = 0.06).

Analyses among different classes of antidepressants also showed a benefit over placebo: SSRIs (RR, 1.31: 95% CI: 1.20, 1.44; I²: 45%; studies = 10; participants = 3,661) and SNRIs (RR, 1.41: 95% CI: 1.31, 1.53; I²: 5%; studies = 8; participants = 2,693). Heterogeneity was moderate among SSRIs and low among SNRIs. Although the confidence interval for the 'Other' antidepressants included the null value, the direction of effect was towards benefit with these antidepressants compared to placebo (RR, 1.20: 95% CI: 1.00, 1.43; I²: NA; studies = 1; participants = 395). Heterogeneity could not be assessed here because only one study was included. The test for subgroup interaction suggested that the effect size was similar across classes of antidepressants in rate of treatment response as defined by study authors (I² = 40.9%; p = 0.18) however, more studies among SNRIs and 'Other' antidepressants are needed to better detect subgroup differences.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Allgulander 2001	296	399	63	130	6.3%	1.53 [1.27 , 1.84]	
Allgulander 2004	115	182	70	188	5.2%	1.70 [1.37 , 2.11]	
Baldwin 2006	387	536	87	138	8.6%	1.15 [1.00 , 1.31]	
Bose 2008	75	125	31	67	3.3%	1.30 [0.97 , 1.74]	L
Bose 2008	82	125	31	67	3.5%	1.42 [1.06 , 1.89]	
Brawman-Mintzer 2006	106	164	88	162	6.5%	1.19 [0.99 , 1.43]	
Davidson 1999	98	176	38	98	3.6%	1.44 [1.08 , 1.90]	
Davidson 2004	89	154	58	153	4.4%	1.52 [1.19 , 1.95]	
Feltner 2009	21	56	11	57	0.9%	1.94 [1.04 , 3.65]	
Gelenberg 2000	82	115	51	123	4.5%	1.72 [1.35 , 2.19]	
GlaxoSmithKline 2006	100	177	91	181	6.0%	1.12 [0.93 , 1.36]	
Gommoll 2015	119	198	99	197	6.6%	1.20 [1.00 , 1.43]	_ _
Hackett 2003	277	354	63	97	7.6%	1.20 [1.03 , 1.41]	
Hartford 2007	189	326	67	161	5.6%	1.39 [1.13 , 1.71]	
Hewett 2001	114	181	91	183	6.4%	1.27 [1.05 , 1.52]	
Lenox-Smith 2003	79	122	56	122	4.7%	1.41 [1.12 , 1.78]	
Montgomery 2006	67	110	42	100	3.7%	1.45 [1.10 , 1.91]	
Pollack 2001	100	161	77	163	5.7%	1.31 [1.07 , 1.61]	
Rickels 2003	250	385	82	180	6.7%	1.43 [1.20 , 1.70]	
Total (95% CI)		4046		2567	100.0%	1.35 [1.27 , 1.43]	
Total events:	2646		1196				'
Heterogeneity: Tau ² = 0.0	01; Chi ² = 28	3.01, df =	18 (P = 0.0	06); I² = 3	6%		
Test for overall effect: Z :				-		F	Favours placebo Favours antidepressar
Test for subgroup differe	nces: Not an	plicable					

Figure 8. Rate of treatment response (defined by study authors) for all antidepressants versus placebo

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.2.1 SSRIs							
Allgulander 2004	115	182	70	188	9.7%	1.70 [1.37 , 2.11]	
Baldwin 2006	387	536	87	138	14.7%	1.15 [1.00 , 1.31]	+
Bose 2008	75	125	62	135	8.9%	1.31 [1.04 , 1.65]	
Brawman-Mintzer 2006	106	164	88	162	11.7%	1.19 [0.99 , 1.43]	
Davidson 2004	89	154	58	153	8.3%	1.52 [1.19 , 1.95]	
Feltner 2009	21	56	11	57	1.8%	1.94 [1.04 , 3.65]	
GlaxoSmithKline 2006	100	177	91	181	10.9%	1.12 [0.93 , 1.36]	
Hewett 2001	114	181	91	183	11.5%	1.27 [1.05 , 1.52]	
Pollack 2001	100	161	77	163	10.4%	1.31 [1.07 , 1.61]	
Rickels 2003	250	385	82	180	12.0%	1.43 [1.20 , 1.70]	
Subtotal (95% CI)		2121		1540	100.0%		•
Total events:	1357		717				•
Heterogeneity: Tau ² = 0.0	01; Chi ² = 16	5.49, df =	9 (P = 0.06	5); I² = 45	%		
Test for overall effect: Z =	= 6.09 (P < 0	0.00001)					
3.2.2 SNRIS							
Allgulander 2001	296	399	63	130	16.3%	1.53 [1.27 , 1.84]	
Bose 2008	82	125	62	135	11.6%	1.43 [1.14 , 1.78]	
Davidson 1999	98	176	38	98	7.4%		_
Gelenberg 2000	82	115	51	123	10.1%	1.72 [1.35 , 2.19]	
Hackett 2003	277	354	63	97	22.6%	1.20 [1.03 , 1.41]	
Hartford 2007	189	326	67	161	13.6%	1.39 [1.13 , 1.71]	
Lenox-Smith 2003	79	122	56	122	10.7%	1.41 [1.12 , 1.78]	
Montgomery 2006	67	110	42	100	7.8%		
Subtotal (95% CI)		1727		966	100.0%	1.41 [1.31 , 1.53]	
Total events:	1170		442				•
Heterogeneity: Tau ² = 0.0	00; Chi ² = 7.	36, df = 7	(P = 0.39)	; I ² = 5%			
Test for overall effect: Z	= 8.70 (P < 0	0.00001)					
3.2.3 Other							
Gommoll 2015	119	198	99	197	100.0%	1.20 [1.00 , 1.43]	-
Subtotal (95% CI)		198			100.0%		
Total events:	119		99			• • • •	•
Heterogeneity: Not appli	cable						
Test for overall effect: Z =		0.05)					
Test for subgroup differe	nces: Chi² -	3.38 df-	= 2 (P = 0 1	18) ² = 4	0.9%	Ŀ	
rescion subgroup dillere	nues. Unit =	5.30, UI =	- 2 (P - 0.1	10), 1 4	0.376	0.2 Fav	2 0.5 1 2 5 ours placebo Favours antidepre:

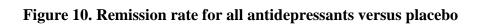
Figure 9. Rate of treatment response (defined by study authors) by treatment class versus placebo

4.4.4 Remission

Figures 10 and 11 show the pooled remission rate for the different antidepressants compared to placebo. All the studies defined remission as a HAM-A total score of 7 or less at endpoint except one [112], which defined remission as a HAM-A total score of 10 or less at endpoint. The analysis showed a benefit of all antidepressants over placebo for remission rates (RR, 1.54: 95% CI: 1.36, 1.73; studies = 17; participants = 6,286). This analysis had moderate heterogeneity (I^2 : 44%; p = 0.02).

Analyses comparing different classes of antidepressants all showed benefit over placebo: SSRIs (RR, 1.41: 95% CI: 1.22, 1.64; I²: 33%; studies = 7; participants = 2,827), SNRIs (RR, 1.57: 95% CI: 1.28, 1.92; I²: 49%; studies = 8; participants = 2,639), and 'Other' antidepressants (RR, 1.77: 95% CI: 1.27, 2.45; I²: 52%; studies = 4; participants = 1,088). Heterogeneity was low-moderate among SSRIs, moderate among SNRIs, and moderatesubstantial among the other antidepressants. The test for subgroup interaction suggested that the effect size was similar across classes of antidepressants in remission rates (I² = 0%; p = 0.41) although more studies are needed to better detect subgroup differences.

	Antidepressants Placebo					Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Allgulander 2004	56	182	34	188	5.8%	1.70 [1.17 , 2.47]
Baldwin 2006	225	536	41	138	7.7%	1.41 [1.07 , 1.86	1 -
Bose 2008	39	125	16	67	4.0%	1.31 [0.79 , 2.16	1 +
Bose 2008	39	125	16	67	4.0%	1.31 [0.79 , 2.16	1 +
Hartford 2007	86	326	31	161	5.9%	1.37 [0.95 , 1.97	1 +
Hewett 2001	90	181	85	183	9.2%	1.07 [0.86 , 1.33]	1 +
Koponen 2007	117	338	33	175	6.4%	1.84 [1.31 , 2.58]
Lenox-Smith 2003	34	122	23	122	4.4%	1.48 [0.93 , 2.36	
Nicolini 2009	172	392	32	163	6.6%	2.24 [1.61 , 3.11]
Nimatoudis 2004	15	24	2	22	0.8%	6.88 [1.77 , 26.71]
Pollack 2001	58	161	37	163	6.2%	1.59 [1.12 , 2.25	
Rickels 2003	127	385	36	180	6.7%	1.65 [1.19 , 2.28]
Rothschild 2012	38	145	32	144	5.2%	1.18 [0.78 , 1.78	1
Rynn 2008	47	168	37	159	5.8%	1.20 [0.83 , 1.74]]
Stein 2008	26	63	13	58	3.4%	1.84 [1.05 , 3.23	
Stein 2014	44	139	13	65	3.6%	1.58 [0.92 , 2.73]	1 +
Stein 2014	51	139	13	65	3.7%	1.83 [1.08 , 3.13	
Stein 2017	88	268	18	140	4.5%	2.55 [1.61 , 4.06]
Wen-Yuan 2011	46	107	32	100	6.0%	1.34 [0.94 , 1.92]	i <u>-</u>
Total (95% CI)		3926		2360	100.0%	1.54 [1.36 , 1.73]	
Total events:	1398		544				'
Heterogeneity: Tau ² =	0.03; Chi ² =	: 32.36, di	f = 18 (P =	0.02); l ²	= 44%		
Test for overall effect:	Z = 6.91 (P	< 0.0000	1)				Favours placebo Favours antidepressa
Test for subgroup diffe			,				



	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
4.2.1 SSRIs							
Allgulander 2004	56	182	34	188	11.7%	1.70 [1.17 , 2.47	∣ _
Baldwin 2006	225	536	41	138	17.7%	1.41 [1.07 , 1.86	_
Bose 2008	39	125	32	135	10.6%	•	
Hewett 2001	90	181	85	183	23.2%	-	
Pollack 2001	58	161	37	163	12.9%	1.59 [1.12 , 2.25	_ _ _
Rickels 2003	127	385	36	180	14.3%	1.65 [1.19 , 2.28	_ _ _
Stein 2014	44	139	26	131	9.7%	•	
Subtotal (95% CI)		1709		1118	100.0%		
Total events:	639		291			• • •	
Heterogeneity: Tau ² =	0.01; Chi ² =	= 8.92, df =	= 6 (P = 0.	18); l² = 3	33%		
Test for overall effect:							
4.2.2 SNRIS							
Bose 2008	39	125	32	135	13.1%	1.32 [0.88 , 1.96	
Hartford 2007	86	326		161			
Koponen 2007	117	338		175			
Lenox-Smith 2003	34	122		122			
Nicolini 2009	172	392		163		-	
Nimatoudis 2004	15	24		22		•	·
Rynn 2008	47	168		159			
Wen-Yuan 2011	46	107		100			
Subtotal (95% CI)		1602			100.0%		
Total events:	556		222				' ▼
Heterogeneity: Tau ² =		= 13 80 di		05)· 12 =	49%		
Test for overall effect:					1070		
4.2.3 Other							
Rothschild 2012	38	145	32	144	27.6%	1.18 [0.78 , 1.78	
Stein 2008	26	63		58			
Stein 2014	51	139		131		L /	
Stein 2017	88	268		140			
Subtotal (95% CI)		615			100.0%		
Total events:	203		89				·
Heterogeneity: Tau ² =		= 6.21. df		10): ² = 5	52%		
Test for overall effect:			·	,			
Toot for outpress		2 - 4 00	f - 0 /P	0.44) 12	- 00/		
Test for subgroup diffe	rences: Ch	r = 1.80, (л = 2 (Р =	0.41), I * :	= 0%		0.05 0.2 1 5 20
							Favours placebo Favours antidep

Figure 11. Remission rate by treatment class versus placebo

4.4.5 Change in Symptom Levels

Figures 12 and 13 show the pooled change in symptom levels for the different antidepressants compared to placebo. The mean difference was used as the effect measure as all studies reported scores on the Hamilton Anxiety Rating Scale. The mean change from baseline in HAM-A total score was extracted for 31 studies and the HAM-A total score at endpoint was extracted for 4 studies. The imputation method for missing SDs was required for studies Allgulander 2001 (imputed SD from study Lenox-Smith 2003), Hackett 2003 (imputed SD from study Davidson 1999), Rynn 2008 (imputed SD from study Hartford 2007), Koponen 2007 (imputed SD from study Hartford 2007), and Rickels 2000 (imputed SD from study Kasper 2009). Pooled SD was calculated and imputed for one study (Gelenberg 2000).

Overall, the analysis showed a benefit for all antidepressants over placebo in reducing GAD symptoms (MD, -2.72; 95% CI: -3.45, -2.00; studies = 35; participants = 11,519). This analysis had substantial-considerable heterogeneity (I^2 : 80%; p < 0.00001).

Analyses comparing different classes of antidepressants to placebo all showed benefit with antidepressants in reducing symptoms of GAD except for TCAs: TCAs (MD, -3.90; 95% CI: -9.49, 1.69; I²: NA; studies = 1; participants = 28); SSRIs (MD, -2.28; 95% CI: -2.98, -1.58; I²: 49%; studies = 15; participants = 4,689); SNRIs (MD, -3.04; 95% CI: -4.12, -1.97; I²: 81%; studies = 16; participants =5,244); and 'Other' (MD, -3.06; 95% CI: -5.94, -0.17; I²: 94%; studies = 6; participants = 1,980). There was moderate heterogeneity among SSRIs, substantial-considerable heterogeneity among SNRIs, considerable heterogeneity among the 'Other' antidepressants, and could not be assessed for TCAs. The test for subgroup interaction suggests the effect size was similar across classes of antidepressants in reducing GAD symptoms (I² = 0%; p = 0.63) however more studies are needed to better detect subgroup differences.

	Antic	lepressai	nts	F	Placebo			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
llgulander 2001	-15.2	8.4	399	-11	8.4	130	3.0%	-4.20 [-5.86 , -2.54]	-
Allgulander 2004	-11.7	8.1	182	-8	8.2	188	3.0%	-3.70 [-5.36 , -2.04]	
Baldwin 2006	-15.8	7.8	536	-14.2	7.8	138	3.1%	-1.60 [-3.06 , -0.14]	-
3ose 2008	-11.4	7.4	125	-9.2	7.8	67	2.6%	-2.20 [-4.47, 0.07]	_
Bose 2008	-10.9	7.5	125	-9.2	7.8	67	2.6%	-1.70 [-3.98 , 0.58]	
Brawman-Mintzer 2006	-12.7	91.8	164	-11.2	93.2	162	0.1%	-1.50 [-21.58 , 18.58]	•
awman-Mintzer 2009	10.4	6	26	9.4	7.3	14	1.5%	1.00 [-3.47 , 5.47]	
avidson 1999	13.4	7.8	174	15.6	7.2	98	2.9%	-2.20 [-4.04 , -0.36]	_
avidson 2004	-11.3	7.5	154	-7.4	7.4	153	3.0%	-3.90 [-5.57 , -2.23]	_
eltner 2009	-11	5.8	56	-7.4	5.4	57	2.7%	-3.60 [-5.67 , -1.53]	_
Selenberg 2000	-13.4	18.1	115	-8.7	21.6	123	1.3%	-4.70 [-9.75 , 0.35]	
axoSmithKline 2006	-10.3	7.7	177	-9.5	7.7	181	3.0%	-0.80 [-2.40 , 0.80]	
Sommoll 2015	-11.2	7.4	198	-9.9	7.5	197	3.1%	-1.30 [-2.77 , 0.17]	
Goodman 2001	-9.6	6.7	124	-7.7	6.8	128	3.0%	-1.90 [-3.57 , -0.23]	
Goodman 2002	-9.2	6	143	-7.6	5.9	138	3.1%	-1.60 [-2.99 , -0.21]	
lackett 2003	14.5	7.8	354	15.9	7.2	97	3.0%	-1.40 [-3.05 , 0.25]	
artford 2007	-12.1	8.7	326	-9.2	8.5	161	3.0%	-2.90 [-4.52 , -1.28]	
lewett 2001	-12.4	10.8	181	-11.3	10.8	183	2.7%	-1.10 [-3.32 , 1.12]	
asper 2009	-12.4	10.0	125	-11.7	10.0	128	2.5%	-0.30 [-2.80 , 2.20]	_
Coponen 2007	-12.7	8.8	338	-8.4	8.5	175	3.0%	-4.30 [-5.87 , -2.73]	
enox-Smith 2003	-12.7	8.4	122	-0.4	8.4	1/3	2.7%	-2.10 [-4.21 , 0.01]	
lahableshwarkar 2014	-14.1	6.5	149	-12	6.5	77	2.7%	-2.60 [-4.39 , -0.81]	
lahableshwarkar 2014	-13.9	6.5	343	-11.3	6.5	77	2.9%		
	-11.0			-11.3		14	3.0% 1.1%	-0.50 [-2.11 , 1.11]	-
IcLeod 1992		6.7	14		8.3			-3.90 [-9.49 , 1.69]	
Iontgomery 2006	-14.1	8.4	110	-11.6	8	100	2.7%	-2.50 [-4.72 , -0.28]	
licolini 2009	-15.3	8.8	392	-11.6	8.9	163	3.0%	-3.70 [-5.32 , -2.08]	-
limatoudis 2004	-19.2	1.7	24	-10.8	2.7	22	3.2%	-8.40 [-9.72 , -7.08]	-
fizer 2009	-11.1	6.6	89	-10.6	6.9	96	2.8%	-0.50 [-2.45 , 1.45]	-
ollack 2001	-13.3	10.2	161	-10.7	10.2	163	2.7%	-2.60 [-4.82 , -0.38]	
tickels 2000	-11.7	10.1	253	-9.5	10.2	96	2.6%	-2.20 [-4.59 , 0.19]	
tickels 2003	-12.3	8.6	385	-9.3	8.7	180	3.1%	-3.00 [-4.53 , -1.47]	-
tothschild 2012	-12.6	7.8	145	-13.2	7.9	144	2.9%	0.60 [-1.21 , 2.41]	+-
tynn 2008	-8.1	8.8	168	-5.9	8.5	159	2.9%	-2.20 [-4.08 , -0.32]	
Stein 2008	-16.6	8.9	63	-13.2	9.5	58	2.1%	-3.40 [-6.69 , -0.11]	
Stein 2014	-15.6	9.4	139	-10.6	9.5	65	2.3%	-5.00 [-7.79 , -2.21]	
Stein 2014	-15.6	8.2	139	-10.6	9.5	65	2.4%	-5.00 [-7.68 , -2.32]	
tein 2017	-15.9	8.5	268	-6.9	9.2	140	2.9%		-
Ven-Yuan 2011	-14.3	8.3	107	-11.8	8.3	100	2.6%	-2.50 [-4.76 , -0.24]	
otal (95% Cl)			7093			4426	100.0%	-2.72 [-3.45 , -2.00]	•
leterogeneity: Tau ² = 3.8	9; Chi ² = 1	87.96, df	= 37 (P <	0.00001);	l² = 80%				
est for overall effect: Z =	7.35 (P <	0.00001)							-20 -10 0 10
Test for subgroup differen								_	antidepressants Favours

Figure 12. Change in symptom levels for all antidepressants versus placebo

	Antio	epressan	ts		Placebo			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.2.1 TCAs									
McLeod 1992	12.4	6.7	14	16.3	8.3	14	100.0%	-3.90 [-9.49 , 1.69]	_
Subtotal (95% CI)	12.1	0.7	14	10.0	0.0		100.0%	-3.90 [-9.49 , 1.69]	
Heterogeneity: Not applic	able		14			14	100.075	0.00 [0.40 ; 1.00]	
Test for overall effect: Z =		.17)							
5.2.2 SSRIs	44.7	0.4	400			400	0.00/	0.701.500 0.041	
Allgulander 2004	-11.7	8.1	182	-8		188	8.0%	-3.70 [-5.36 , -2.04]	-
Baldwin 2006	-15.8	7.8	536	-14.2		138	9.0%	-1.60 [-3.06 , -0.14]	-
Bose 2008	-10.9	7.5	125	-9.2		135	7.2%	-1.70 [-3.56 , 0.16]	
Brawman-Mintzer 2006	-12.7	91.8	164	-11.2		162		-1.50 [-21.58 , 18.58]	· · · · · ·
Brawman-Mintzer 2009	10.4	6	26	9.4		14	2.1%	1.00 [-3.47 , 5.47]	
Davidson 2004	-11.3	7.5	154	-7.4		153	8.0%	-3.90 [-5.57 , -2.23]	-
Feltner 2009	-11	5.8	56	-7.4		57	6.4%	-3.60 [-5.67 , -1.53]	
GlaxoSmithKline 2006	-10.3	7.7	177	-9.5		181	8.3%	-0.80 [-2.40 , 0.80]	-
Goodman 2001	-9.6	6.7	124	-7.7		128	8.0%	-1.90 [-3.57 , -0.23]	
Goodman 2002	-9.2	6	143	-7.6		138	9.3%	-1.60 [-2.99 , -0.21]	-
Hewett 2001	-12.4	10.8	181	-11.3		183	5.9%	-1.10 [-3.32 , 1.12]	-+
Pfizer 2009	-11.1	6.6	89	-10.6		96	6.9%	-0.50 [-2.45 , 1.45]	+
Pollack 2001	-13.3	10.2	161	-10.7		163	5.9%	-2.60 [-4.82 , -0.38]	
Rickels 2003	-12.3	8.6	385	-9.3		180	8.6%	-3.00 [-4.53 , -1.47]	-
Stein 2014	-15.6	8.2	139	-10.6	9.5	131	6.2%	-5.00 [-7.12 , -2.88]	
Subtotal (95% CI)			2642			2047	100.0%	-2.28 [-2.98 , -1.58]	♦
Heterogeneity: Tau ² = 0.8	6; Chi² = 27	25, df =	14 (P = 0).02); I² =	49%				
Test for overall effect: Z =	6.39 (P < 0	.00001)							
5.2.3 SNRIS									
Allgulander 2001	-15.2	8.4	399	-11	8.4	130	6.7%	-4.20 [-5.86 , -2.54]	-
Bose 2008	-11.4	7.4	125	-9.2	7.8	135	6.5%	-2.20 [-4.05 , -0.35]	_
Davidson 1999	13.4	7.8	174	15.6		98	6.5%	-2.20 [-4.04 , -0.36]	_
Gelenberg 2000	-13.4	18.1	115	-8.7		123	2.9%	-4.70 [-9.75 , 0.35]	
Hackett 2003	14.5	7.8	354	15.9		97	6.8%	-1.40 [-3.05 , 0.25]	_
Hartford 2007	-12.1	8.7	326	-9.2	8.5	161	6.8%	-2.90 [-4.52 , -1.28]	-
Kasper 2009	-12	10.1	125	-11.7		128	5.6%	-0.30 [-2.80 , 2.20]	_
Koponen 2007	-12.7	8.8	338	-8.4	8.5	175	6.9%	-4.30 [-5.87 , -2.73]	-
Lenox-Smith 2003	-14.1	8.4	122	-12		122	6.1%	-2.10 [-4.21, 0.01]	
Mahableshwarkar 2014	-13.9	6.5	149	-11.3	6.5	154	7.0%	-2.60 [-4.06 , -1.14]	-
Montgomery 2006	-14.1	8.4	110	-11.6		100	6.0%	-2.50 [-4.72 , -0.28]	_
Nicolini 2009	-15.3	8.8	392	-11.6		163	6.8%	-3.70 [-5.32 , -2.08]	_
Nimatoudis 2004	-19.2	1.7	24	-10.8		22	7.2%	-8.40 [-9.72 , -7.08]	
Rickels 2000	-11.7	10.1	253	-9.5		96	5.8%	-2.20 [-4.59 , 0.19]	
Rynn 2008	-8.1	8.8	168	-5.9		159	6.5%	-2.20 [-4.08 , -0.32]	
Wen-Yuan 2011	-14.3	8.3	107	-11.8		100	5.9%	-2.50 [-4.76 , -0.24]	
Subtotal (95% CI)	-14.0	0.0	3281	-11.0	0.0		100.0%	-3.04 [-4.12 , -1.97]	
Heterogeneity: Tau ² = 3.7	6: Chi² = 70	45 df =		000011	12 - 81%	1365	100.076	-0.04 [-4.12 , -1.07]	•
Test for overall effect: Z =			10 (1 < 0		1 - 01/0				
5.2.4 Other						10-	47.40	4 00 1 0 77 0 (77	
Gommoll 2015	-11.2	7.4	198	-9.9		197	17.4%	-1.30 [-2.77 , 0.17]	-
Mahableshwarkar 2014	-11.8	6.5	343	-11.3		154	17.6%	-0.50 [-1.74 , 0.74]	+
Rothschild 2012	-12.6	7.8	145	-13.2		144			+-
Stein 2008	-16.6	8.9	63	-13.2		58	14.7%		
Stein 2014	-15.6	9.4	139	-10.6		131	16.4%		
Stein 2017	-15.9	8.5	268	-6.9	9.2	140	17.0%	-9.00 [-10.83 , -7.17]	-
Subtotal (95% CI)			1156			824	100.0%	-3.06 [-5.94 , -0.17]	•
Heterogeneity: Tau ² = 11.	90; Chi² = 7	7.06, df =	5 (P < 0	.00001);	l² = 94%				-
Test for overall effect: Z =	2.08 (P = 0	0.04)							
				CO) 12	~~				
Test for subgroup differen	cos: Ohi2								-20 -10 0 10

Figure 13. Change in symptom levels by treatment class versus placebo

4.4.6 Total Number of Patients Reporting Adverse Effects

Figures 14 and 15 show the pooled total number of patients reporting adverse effects for the different antidepressants compared to placebo. The analysis showed a higher number of patients reporting adverse effects among all antidepressants compared to placebo (RR, 1.16; 95% CI: 1.11, 1.20; studies = 24; participants = 7,914). This analysis had low-moderate heterogeneity ($I^2 = 30\%$; p = 0.07).

Analyses among different classes of antidepressants also showed a larger number of patients reporting adverse effects in the SSRI group compared to placebo (RR, 1.15: 95% CI: 1.09, 1.20; $I^2 = 25\%$; studies = 14; participants = 4,331); the SNRI group compared to placebo (RR, 1.14: 95% CI: 1.07, 1.22; $I^2 = 40\%$; studies = 7; participants = 1,887) and among the 'Other' antidepressants compared to placebo (RR, 1.21: 95% CI: 1.11, 1.33; $I^2 = 27\%$; studies = 6; participants = 2,120). There was low heterogeneity among SSRIs and 'Other' antidepressants and low-moderate heterogeneity for SNRIs. The test for subgroup interaction suggested similarity across classes of antidepressants in terms of the total number of patients reporting adverse effects ($I^2 = 0\%$; p = 0.51) however, more studies are needed with SNRIs and 'Other' antidepressants to detect subgroup differences.

	Antidepre	essants	Place	Risk ratio	Risk ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Aventis-Sanofi 2007a	90	124	69	122	3.0%	1.28 [1.06 , 1.55]	
Aventis-Sanofi 2007b	96	122	80	119	4.1%	1.17 [1.00 , 1.37]	
Aventis-Sanofi 2008	81	113	69	124	2.9%	1.29 [1.06 , 1.57]	
Baldwin 2006	253	542	76	139	3.4%	0.85 [0.72 , 1.02]	
Bose 2008	107	127	49	68	3.7%	1.17 [0.99 , 1.38]	
Bose 2008	111	129	49	68	3.8%	1.19 [1.01 , 1.41]	
Brawman-Mintzer 2009	7	28	3	14	0.1%	1.17 [0.35 , 3.84]	
Davidson 2004	126	158	109	157	5.2%	1.15 [1.01 , 1.31]	
GlaxoSmithKline 2006	148	179	141	181	6.8%	1.06 [0.96 , 1.18]	-
Gommoll 2015	166	200	118	198	5.1%	1.39 [1.22 , 1.59]	-
Goodman 2001	110	126	94	128	5.5%	1.19 [1.05 , 1.35]	-
Goodman 2002	122	145	99	142	5.2%	1.21 [1.06 , 1.37]	-
Hartford 2007	276	326	117	161	6.6%	1.17 [1.05 , 1.29]	-
lewett 2001	108	187	91	185	3.0%	1.17 [0.97 , 1.42]	L
enox-Smith 2003.	112	122	109	121	8.5%	1.02 [0.94 , 1.10]	+
/lahableshwarkar 2014	364	467	53	77	4.0%	1.13 [0.97 , 1.33]	L
/ahableshwarkar 2014	126	154	53	77	3.7%	1.19 [1.01 , 1.41]	
Vimatoudis 2004	10	24	9	22	0.3%	1.02 [0.51 , 2.03]	
Pfizer 2009	61	97	54	100	2.1%	1.16 [0.92 , 1.48]	<u> </u>
Rickels 2003	336	386	133	180	7.3%	1.18 [1.07 , 1.30]	-
Rothschild 2012	109	148	93	151	4.0%	1.20 [1.02 , 1.40]	
Rynn 2008	140	168	116	159	5.9%	1.14 [1.02 , 1.28]	
Stein 2008	24	63	20	58	0.6%	1.10 [0.69 , 1.78]	
Stein 2014	68	139	29	65	1.2%	1.10 [0.80 , 1.51]	
Stein 2014	66	139	29	65	1.2%	1.06 [0.77 , 1.47]	_ _
Stein 2017	87	270	36	140	1.2%	1.25 [0.90 , 1.74]	<u> </u>
Wen-Yuan 2011	65	108	45	102	1.7%	1.36 [1.04 , 1.78]	
Total (95% Cl)		4791		3123	100.0%	1.16 [1.11 , 1.20]	•
Total events:	3369		1943				['
leterogeneity: Tau ² = 0.0	00; Chi ² = 37	7.21, df =	26 (P = 0.0	07); I² = 3	0%	(1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -
Fest for overall effect: Z =	= 7.58 (P < 0	0.00001)					gher in placebo Higher in antidep
Fest for subgroup differer	nces: Not ap	plicable					

Figure 14. Total number of patients reporting adverse effects for all antidepressants

versus placebo

	Antidepre	ssants	Place	bo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events		Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.2.1 SSRIs							
Aventis-Sanofi 2007a	90	124	69	122	5.2%	1.28 [1.06 , 1.55]	
Aventis-Sanofi 2007b	96	122	80	119	7.2%	1.17 [1.00 , 1.37]	_
Aventis-Sanofi 2008	81	113	69	124	5.0%		
aldwin 2006	253	542	76	139	5.9%		
lose 2008	107	127	98	136	9.5%	1.17 [1.03 , 1.33]	
rawman-Mintzer 2009	7	28		14	0.2%		
avidson 2004	126	158	109	157	9.3%		-
laxoSmithKline 2006	148	179	141	181	12.7%		-
oodman 2001	110	126	94	128	10.0%	1.19 [1.05 , 1.35]	
oodman 2002	122	145	99	142	9.4%		-
ewett 2001	108	187	91	185	5.2%	1.17 [0.97 , 1.42]	L.
fizer 2009	61	97	54	100	3.6%	1.16 [0.92 , 1.48]	
tickels 2003	336	386	133	180	13.8%		-
tein 2014	68	139	58	131	3.1%		
ubtotal (95% CI)		2473		1858	100.0%		•
otal events:	1713		1174			• • •	•
leterogeneity: Tau ² = 0.0	00; Chi ² = 17	.23, df =	13 (P = 0.1	9); l² = 28	5%		
est for overall effect: Z	= 5.66 (P < 0	.00001)					
.2.2 SNRIS	444	100	00	100	10 10/	1 10 [1 05 1 05]	
ose 2008	111	129	98	136	16.1%	1.19 [1.05 , 1.35]	-
artford 2007	276	326 122		161	19.5%		-
enox-Smith 2003 Iahableshwarkar 2014	112 126	154		121	25.0% 15.6%		Ť
limatoudis 2004	126	24		155 22	0.9%		
ynn 2008	140	168	116	159	17.6%		
ven-Yuan 2011	65	100	45	102	5.3%		-
	65	1031	40		100.0%	1.36 [1.04 , 1.78]	
ubtotal (95% CI) otal events:	840	1031	601	000	100.0%	1.14 [1.07 , 1.22]	•
eterogeneity: Tau ² = 0.0		09 df - 6		12 - 10%			
est for overall effect: Z =			(F = 0.13)	,1 = 40 /0			
0.0.045							
2.3 Other	400	000	440	400	07.00	4 00 14 00 4 50	
iommoll 2015	166	200		198	27.3%	1.39 [1.22 , 1.59]	+
lahableshwarkar 2014	364	467	107	155	31.1%		•
tothschild 2012	109	148	93	151	21.4%		
tein 2008	24	63		58	3.4%		
tein 2014	66	139		131	10.1%		
tein 2017	87	270	36	140	6.6%		+
ubtotal (95% CI)		1287		833	100.0%	1.21 [1.11 , 1.33]	•
otal events:	816		432				
leterogeneity: Tau ² = 0.0 est for overall effect: Z =			(P = 0.23);	; I² = 27%			
use for overall effect. Z -	1.5 (1 < 0						
est for subgroup differe	nces: Chi² =	1.35, df =	2 (P = 0.5	1), l² = 09	%	0.2	0.5 1 2
							depressants Favours place

Figure 15. Total number of patients reporting adverse effects by treatment class versus placebo

4.4.7 Sleepiness/Drowsiness

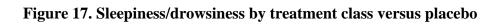
Figures 16 and 17 show the pooled number of patients reporting sleepiness/drowsiness for the different antidepressants compared to placebo. One study [107] (participants = 113) only reported sleepiness/drowsiness for the paroxetine arm but not the placebo arm and was not included in the analysis. The analysis showed more patients reporting sleepiness/drowsiness among all antidepressants compared to placebo (RR, 2.32: 95% CI: 1.93, 2.78; studies = 24; participants = 9,037). Heterogeneity was low ($I^2 = 0\%$; p = 0.79).

Analyses comparing different classes of antidepressants to placebo showed more patients reporting sleepiness/drowsiness among SSRIs (RR, 2.15: 95% CI: 1.70, 2.71; $I^2 = 0\%$; studies = 12; participants = 3,933); SNRIs (RR, 2.66: 95% CI: 1.92, 3.69; $I^2 = 5\%$; studies = 10; participants = 3,529) and 'Other' antidepressants (RR, 1.94: 95% CI: 1.16, 3.25; $I^2 = 0\%$; studies = 5; participants = 1,999) compared to placebo. Heterogeneity was low among all the analyses. The test for subgroup interaction suggested there were similar effect sizes across classes of antidepressants ($I^2 = 0\%$; p = 0.47) although more studies are needed to further investigate subgroup effects.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3aldwin 2006	35	542	3	139	2.5%	2.99 [0.93 , 9.59]	
Bose 2008	13	127	5	68	3.5%	1.39 [0.52 , 3.74]	
Bose 2008	21	129	5	68	3.9%	2.21 [0.87 , 5.61]	L
Brawman-Mintzer 2009	0	28	1	14	0.3%	0.17 [0.01 , 3.98]	←
avidson 2004	19	158	9	157	5.8%	2.10 [0.98 , 4.49]	_ . _
laxoSmithKline 2006	44	179	18	181	13.1%	2.47 [1.49 , 4.11]	-
Sommoll 2015	12	200	6	198	3.7%	1.98 [0.76 , 5.17]	
oodman 2001	16	126	7	128	4.6%	2.32 [0.99 , 5.45]	
oodman 2002	21	145	12	142	7.5%	1.71 [0.88 , 3.35]	L.
artford 2007	41	326	6	161	4.8%	3.37 [1.46 , 7.78]	
ewett 2001	13	187	0	185	0.4%	26.71 [1.60 , 446.09]	
asper 2009	6	125	3	128	1.8%	2.05 [0.52, 8.01]	
oponen 2007	16	338	2	175	1.6%	4.14 [0.96 , 17.81]	
lahableshwarkar 2014	19	154	3	77	2.4%	3.17 [0.97 , 10.37]	
1ahableshwarkar 2014	28	467	3	77	2.5%	1.54 [0.48 , 4.94]	
lontgomery 2006	4	113	3	101	1.6%	1.19 [0.27 , 5.20]	
icolini 2009	24	411	3	170	2.4%	3.31 [1.01 , 10.84]	
fizer 2009	7	97	6	100	3.0%	1.20 [0.42 , 3.45]	
ollack 2001	27	161	11	163	7.6%	2.49 [1.28 , 4.84]	
ickels 2000	64	273	12	97	10.3%	1.89 [1.07 , 3.36]	_
ickels 2003	73	386	13	180	10.7%	2.62 [1.49 , 4.60]	-
othschild 2012	9	148	3	151	2.0%	3.06 [0.85 , 11.08]	
ynn 2008	20	168	1	159	0.8%	18.93 [2.57 , 139.39]	→
tein 2014	5	141	1	65	0.7%	2.30 [0.27 , 19.33]	
tein 2014	5	139	1	65	0.7%	2.34 [0.28 , 19.61]	
Stein 2017	6	270	1	140	0.8%	3.11 [0.38 , 25.59]	
Ven-Yuan 2011	12	108	1	102	0.8%	11.33 [1.50 , 85.60]	
otal (95% Cl)		5646		3391	100.0%	2.32 [1.93 , 2.78]	•
fotal events:	560		139				
leterogeneity: Tau ² = 0.0	00; Chi² = 20	0.10, df =	26 (P = 0.7	'9); I² = 0	%		0.01 0.1 1 10 100
est for overall effect: Z =	= 8.96 (P < 0	0.00001)				ŀ	ligher in placebo Higher in antidep
est for subgroup differer	nces: Not ap	plicable					

Figure 16. Sleepiness/drowsiness for all antidepressants versus placebo

Events	Total	Events	Total		IV, Random, 95% Cl	IV, Random, 95% Cl
0.5	5.40		400	4.00/	0.00 10.00 0.001	
35	542		139	4.0%	2.99 [0.93 , 9.59]	
13	127		136	8.7%	1.39 [0.63 , 3.06]	+
-						
						—
		-			26.71 [1.60 , 446.09]	
	97	6	100	4.8%	1.20 [0.42 , 3.45]	
	161	11	163	12.1%	2.49 [1.28 , 4.84]	
73	386	13	180	17.0%	2.62 [1.49 , 4.60]	
5	141	3	131	2.7%	1.55 [0.38 , 6.35]	- _
	2277		1656	100.0%	2.15 [1.70 , 2.71]	•
273		93				
0; Chi ² = 9.	83, df = 1	1 (P = 0.55); I² = 0%	,		
6.45 (P < 0	.00001)					
21	129	10	136	18.6%	2.21 [1.08 , 4.52]	
41	326	6	161	14.0%	3.37 [1.46 , 7.78]	
6	125	3	128	5.5%	2.05 [0.52 , 8.01]	
16	338	2	175	4.8%		
19	154	6	155	12.4%		
4	113	3	101	4.8%		
24	411	3	170	7.2%		
64	273	12	97			
20						
227					2.00 [•
	52 df = 9		l ² = 5%			
		(1 0.00)	,1 0,0			
12	200	6	198	28.9%	1.98 [0.76 , 5.17]	
28	467	6	155	35.7%	1.55 [0.65 , 3.67]	
9	148	3	151	16.1%	3.06 [0.85 , 11.08]	<u> </u>
5	139	3	131	13.4%	1.57 [0.38 , 6.44]	
6			140	6.0%		
-						
60		19				\mathbf{I}
	02. df = 4		$ ^2 = 0\%$			
		(. 0.01)	,. 070			
2.010 -0						
nces: Chi² -	151 df-	2 (P = 0 4	 7) ² = 0 	%		1 0.1 1 10 1
	273 0; Chi ² = 9, 6.45 (P < 0 21 41 6 16 19 4 24 64 20 12 227 2; Chi ² = 9, 5.90 (P < 0 12 28 9 5.90 (P < 0 12 28 9 5 6 00; Chi ² = 1, 2.51 (P = 0	$\begin{array}{c} 19 & 158 \\ 44 & 179 \\ 16 & 126 \\ 21 & 145 \\ 13 & 187 \\ 7 & 97 \\ 27 & 161 \\ 73 & 386 \\ 5 & 141 \\ 2277 \\ 273 \\ 0; Chi^2 = 9.83, df = 1 \\ 6.45 (P < 0.00001) \\ \end{array}$ $\begin{array}{c} 21 & 129 \\ 41 & 326 \\ 6 & 125 \\ 16 & 338 \\ 19 & 154 \\ 4 & 113 \\ 24 & 411 \\ 64 & 273 \\ 20 & 168 \\ 12 & 108 \\ 12 & 108 \\ 12 & 108 \\ 2145 \\ 227 \\ 2; Chi^2 = 9.52, df = 9 \\ 5.90 (P < 0.00001) \\ \end{array}$ $\begin{array}{c} 12 & 200 \\ 28 & 467 \\ 9 & 148 \\ 5 & 139 \\ 6 & 270 \\ 1224 \\ 60 \\ 0; Chi^2 = 1.02, df = 4 \\ 2.51 (P = 0.01) \end{array}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$



4.4.8 Agitation/Anxiety

Figures 18 and 19 show the pooled number of patients feeling agitation/anxiety for the different antidepressants compared to placebo. One study, [81] (participants = 411) only reported this outcome for the treatment arms, but not the placebo arm therefore was not included in the analysis. Overall, limited evidence showed that there was no difference in number of participants experiencing agitation/anxiety between all antidepressants and placebo (RR, 1.06: 95% CI: 0.74, 1.53; studies = 6; participants = 2,026). There was low heterogeneity in this analysis ($I^2 = 0\%$; p = 0.41).

Limited evidence showed there were no differences in agitation/anxiety between classes of antidepressants compared to placebo: SSRIs (RR, 1.11: 95% CI: 0.60, 2.05; I²: 19%; studies = 5; participants = 1,783) and SNRIs (RR, 0.99: 95% CI: 0.57, 1.72; I²: NA; studies = 1; participants = 243). There was low heterogeneity among the SSRI group and could not be calculated for the SNRI group because there was only one study. The test for subgroup interaction suggested similarity across classes of antidepressants in patients reporting agitation/anxiety (I² = 0%; p = 0.80) although more studies are needed to detect any subgroup effects.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Allgulander 2004	19	184	18	189	35.1%	1.08 [0.59 , 2.00]
Baldwin 2006	22	542	4	139	12.0%	1.41 [0.49 , 4.03	a]
Brawman-Mintzer 2009	1	28	0	14	1.3%	1.55 [0.07 , 35.83	J
Davidson 2004	1	158	7	157	3.1%	0.14 [0.02 , 1.14	
Hewett 2001	5	187	2	185	5.0%	2.47 [0.49 , 12.59	1
Lenox-Smith 2003	21	122	21	121	43.4%	0.99 [0.57 , 1.72	2]
Total (95% CI)		1221		805	100.0%	1.06 [0.74 , 1.53	a 🔺
Total events:	69		52				- T
Heterogeneity: Tau ² = 0.0	00; Chi ² = 5.	02, df = 5	(P = 0.41)	; I ² = 0%			
Test for overall effect: Z =	= 0.31 (P = 0	0.76)					Higher in placebo Higher in antidepressa
Test for subgroup differe	nces: Not ap	plicable					

Figure 18. Agitation/anxiety for all antidepressants versus placebo

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
8.2.1 SSRIs							
Allgulander 2004	19	184	18	189	50.0%	1.08 [0.59 , 2.00]	
Baldwin 2006	22	542	4	139	25.6%	1.41 [0.49 , 4.03]	_ _
Brawman-Mintzer 2009	1	28	0	14	3.7%	1.55 [0.07 , 35.83]	
Davidson 2004	1	158	7	157	8.1%	0.14 [0.02 , 1.14]	
Hewett 2001	5	187	2	185	12.6%	2.47 [0.49 , 12.59]	
Subtotal (95% CI)		1099		684	100.0%	1.11 [0.60 , 2.05]	•
Total events:	48		31				T
Heterogeneity: Tau ² = 0.7	10; Chi ² = 4.	92, df = 4	(P = 0.30)	; I² = 19%	6		
Test for overall effect: Z	= 0.32 (P = 0).75)					
8.2.2 SNRIS							
Lenox-Smith 2003	21	122	21	121	100.0%	0.99 [0.57 , 1.72]	-
Subtotal (95% CI)		122		121	100.0%	0.99 [0.57 , 1.72]	—
Total events:	21		21				Ť
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	= 0.03 (P = 0).98)					
Test for subgroup differe	nces: Chi² =	007 df=	1 (P = 0 8	30) l ² = 0	%	00	
		e.e., ui					01 0.1 1 10 10 tidepressants Favours place

Figure 19. Agitation/anxiety by treatment class versus placebo

4.4.9 Suicide Wishes/Gestures/Attempts

Figures 20 and 21 show the pooled number of patients experiencing suicide wishes/gestures/attempts for the different antidepressants compared to placebo. Limited evidence showed no difference in suicide wishes/gestures/attempts between all antidepressants compared to placebo (RR, 0.74: 95% CI: 0.40, 1.36; studies = 3; participants = 802). There was low heterogeneity in this analysis ($I^2 = 0\%$; p = 0.40).

Limited evidence among classes of antidepressants also showed no differences compared to placebo: SSRIs (RR, 5.15: 95% CI: 0.25, 105.98; $I^2 = NA$; studies = 1; participants = 197), SNRIs (RR, 0.54: 95% CI: 0.16, 1.79; $I^2 = NA$; studies = 1; participants = 210), and 'Other' antidepressants (RR, 0.75: 95% CI: 0.36, 1.54; $I^2 = NA$; studies= 1; participants = 395). Heterogeneity could not be assessed as there was only one study in each analysis. The test for subgroup interaction suggested similarity between classes of antidepressants regarding patients experiencing suicide wishes/gestures/attempts ($I^2 = 0\%$; p = 0.40) although more studies are needed to detect subgroup differences.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Gommoll 2015	12	198	16	197	70.4%	0.75 [0.36 , 1.54]	
Pfizer 2009	2	97	0	100	4.0%	5.15 [0.25 , 105.98]	
Wen-Yuan 2011	4	108	7	102	25.6%	0.54 [0.16 , 1.79]	
Total (95% CI)		403		399	100.0%	0.74 [0.40 , 1.36]	•
Total events:	18		23				•
Heterogeneity: Tau ² =	0.00; Chi ² =	1.85, df	= 2 (P = 0.	40); I ² = 0)%		0.01 0.1 1 10 100
Test for overall effect:	Z = 0.96 (P	= 0.34)				ŀ	Higher in placebo Higher in antidepressar
Test for subgroup diffe	erences: Not	applicab	le				

Figure 20. Suicide wishes/gestures/attempts for all antidepressants versus placebo

2	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
2							
2							
_	97	0	100	100.0%	5.15 [0.25 , 105.98]		→
	97		100	100.0%	5.15 [0.25 , 105.98]		
2		0					
able							
1.06 (P :	= 0.29)						
4	108	7	102	100.0%	0.54 [0.16 , 1.79]		
	108		102	100.0%	0.54 [0.16 , 1.79]	-	
4		7				•	
able							
1.01 (P :	= 0.31)						
12	198	16	197	100.0%	0.75 [0.36 , 1.54]		
	198		197	100.0%	0.75 [0.36 , 1.54]		
12		16				•	
able							
0.79 (P =	= 0.43)						
	able 1.06 (P = 4 4 bble 1.01 (P = 12 12 bble	able 1.06 (P = 0.29) 4 108 4 108 4 1.01 (P = 0.31) 12 198 12 12 198 12 12	able 1.06 (P = 0.29) 4 108 7 108 7 4 7 ble 1.01 (P = 0.31) 12 198 16 198 16 12 16 ble	Ible 1.06 (P = 0.29) 4 108 7 102 4 7 Ible 1.01 (P = 0.31) 12 198 16 197 198 197 12 16 Ible	table $1.06 (P = 0.29)$ 4 108 7 102 100.0% 108 102 100.0% 4 7 table 1.01 (P = 0.31) 12 198 16 197 100.0% 198 197 100.0% 12 16 table 16	4 108 7 102 $100.0%$ 0.54 $[0.16, 1.79]$ 4 108 102 $100.0%$ 0.54 $[0.16, 1.79]$ 4 7 102 $100.0%$ 0.54 $[0.16, 1.79]$ 4 7 102 $100.0%$ 0.54 $[0.16, 1.79]$ 4 7 102 $100.0%$ 0.54 $[0.16, 1.79]$ 100 7 102 $100.0%$ 0.54 $[0.16, 1.79]$ 12 198 197 $100.0%$ 0.75 $[0.36, 1.54]$ 12 16 197 $100.0%$ 0.75 $[0.36, 1.54]$ 12 16 16 100 100 100 100	ble 1.06 (P = 0.29) 4 108 7 102 100.0% 0.54 [0.16, 1.79] 4 7 ble 1.01 (P = 0.31) 12 198 16 197 100.0% 0.75 [0.36, 1.54] 198 197 100.0% 0.75 [0.36, 1.54] 12 16

Figure 21.Suicide wishes/gestures/attempts by treatment class versus placebo

4.4.10 Average Score/Change in Quality of Life/Satisfaction

Figures 22 and 23 show the pooled average score/change in quality of life/satisfaction for the different antidepressants compared to placebo. All studies reported the mean change from baseline on the Q-LES-Q, therefore the mean difference was used as the effect measure. A higher score on the Q-LES-Q indicates an improved quality of life. Limited evidence showed an improvement in average score/change in quality of life/satisfaction

with antidepressants over placebo (MD, 6.51; 95% CI: 4.95, 8.07; studies = 4; participants = 1,013). There was low heterogeneity in this analysis (I^2 : 0%; p = 0.92).

Limited evidence also showed a benefit among different classes of antidepressants compared to placebo: SSRIs (MD, 6.70; 95% CI: 5.05, 8.35; I²: 0%; studies = 3; participants = 760) and SNRIs (MD, 5.00; 95% CI: 0.29, 9.71; I²: NA; studies = 1; participants = 253). Heterogeneity was low among SSRIs and could not be assessed for SNRIs. The test for subgroup interaction suggested similar effect sizes across the two classes of antidepressants in improving quality of life/satisfaction (I² = 0%; p = 0.51) although more studies are needed to detect subgroup differences.

	Antid	lepressa	nts	F	Placebo			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Allgulander 2004	9	13	169	2.4	11.8	171	34.8%	6.60 [3.96 , 9.24]	
Davidson 2004	8.4	8.7	154	1.7	11.2	153	48.1%	6.70 [4.46 , 8.94	I –
Feltner 2009	16.5	17.2	56	9.3	16.6	57	6.2%	7.20 [0.97 , 13.43]	I —
Kasper 2009	12.7	19	125	7.7	19.2	128	10.9%	5.00 [0.29 , 9.71]	I
Total (95% CI)			504			509	100.0%	6.51 [4.95 , 8.07]	
Heterogeneity: Tau ² =	0.00; Chi2 =	= 0.47, df	= 3 (P =	0.92); l² = (0%				•
Test for overall effect:	Z = 8.20 (P	< 0.0000)1)						-20 -10 0 10 20
Test for subgroup diffe	erences: No	t applicat	ole						Favours placebo Favours antidepres

Figure 22. Average score/change in quality of life/satisfaction for all antidepressants versus placebo

	Antid	lepressa	nts	F	Placebo			Mean difference	Mean dif	fference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Randor	m, 95% Cl
10.2.1 SSRIs										
Allgulander 2004	9	13	169	2.4	11.8	171	39.0%	6.60 [3.96 , 9.24]	
Davidson 2004	8.4	8.7	154	1.7	11.2	153	54.0%	6.70 [4.46 , 8.94]	-
Feltner 2009	16.5	17.2	56	9.3	16.6	57	7.0%	7.20 [0.97 , 13.43	1	
Subtotal (95% CI)			379			381	100.0%	6.70 [5.05 , 8.35	j l	•
Heterogeneity: Tau ² =	0.00; Chi2 :	= 0.03, df	= 2 (P =	0.99); l² = (0%			• • •	-	•
Test for overall effect:	Z = 7.96 (P	< 0.0000	1)							
10.2.2 SNRIs										
Kasper 2009	12.7	19	125	7.7	19.2	128	100.0%	5.00 [0.29 , 9.71	1	
Subtotal (95% CI)			125			128	100.0%	5.00 [0.29 , 9.71	i l	.
Heterogeneity: Not ap	plicable							• • •	-	-
Test for overall effect:		= 0.04)								
Test for subgroup diffe	erences: Ch	i² = 0.44,	df = 1 (P	= 0.51), I²	= 0%				-20 -10 C Favours placebo	10 20 Favours antidepressant

Figure 23. Average score/change in quality of life/satisfaction by treatment class versus placebo

4.4.11 Dropouts Due to Lack of Efficacy

Figures 24 and 25 show the pooled dropouts due to lack of efficacy for the main comparisons of this review. Two studies, [108] (participants = 246) and [122] (participants = 46) reported dropouts due to a lack of efficacy for only one study arm therefore, due to uncertainty in the data for the other arm, these studies were not included in this analysis. Very low-quality evidence showed that fewer participants dropped out due to a lack of efficacy in the antidepressant group compared to the placebo group (RR, 0.41: 95% CI: 0.34, 0.50; studies = 30; participants = 11,311). This analysis had low heterogeneity ($I^2 = 4\%$; p = 0.40).

Analyses of different classes of antidepressants also showed that fewer participants dropped out due to a lack of efficacy in the antidepressant group compared to the placebo group: SSRIs (RR, 0.55: 95% CI: 0.38, 0.79; $I^2 = 6\%$; studies = 14; participants = 4,832), SNRIs (RR, 0.33: 95% CI: 0.25, 0.43; $I^2 = 0\%$; studies = 13; participants = 4,775) and 'Other' antidepressants (RR, 0.49: 95% CI: 0.29, 0.83; $I^2 = 22\%$; studies = 6; participants = 2,130). Heterogeneity was low among all analyses. The test for subgroup interaction suggested similar effect sizes across classes of antidepressants in dropouts due to lack of efficacy ($I^2 = 63.0\%$; p = 0.07) although more studies are needed among the 'Other' class of antidepressants for further investigate subgroup effects.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
llgulander 2001	31	411	21	130	12.4%	0.47 [0.28 , 0.78]	-
ligulander 2004	3	184	4	189	1.8%	0.77 [0.17 , 3.39]	
ventis-Sanofi 2008	6	114	7	126	3.4%	0.95 [0.33 , 2.74]	
aldwin 2006	11	542	5	139	3.5%	0.56 [0.20 , 1.60]	
lose 2008	3	127	3	68	1.6%	0.54 [0.11 , 2.58]	
lose 2008	0	133	3	68	0.5%	0.07 [0.00 , 1.40]	•
awman-Mintzer 2006	2	164	5	162	1.5%	0.40 [0.08 , 2.01]	
avidson 2004	2	158	5	157	1.5%	0.40 [0.08 , 2.02]	
elenberg 2000	10	124	28	127	7.8%	0.37 [0.19, 0.72]	
laxoSmithKline 2006	5	179	5	182	2.6%	1.02 [0.30 , 3.45]	
ommoll 2015	2	200	1	198	0.7%	1.98 [0.18 , 21.66]	
oodman 2001	2	126	8	128	1.7%	0.25 [0.06 , 1.17]	
oodman 2002	4	145	0	142	0.5%	8.82 [0.48 , 162.24]	
ackett 2003	11	370	6	97	4.0%	0.48 [0.18 , 1.27]	
artford 2007	4	326	6	161	2.5%	0.33 [0.09 , 1.15]	
ewett 2001	0	187	5	185	0.5%	0.09 [0.01 , 1.62]	• • • • • • • • • • • • • • • • • • •
asper 2009	4	125	12	128	3.1%	0.34 [0.11 , 1.03]	
ponen 2007	9	338	23	175	6.5%	0.20 [0.10 , 0.43]	_
ahableshwarkar 2014	7	468	2	78	1.6%	0.58 [0.12 , 2.76]	
ahableshwarkar 2014	1	156		78	0.7%	0.25 [0.02 , 2.71]	
ontgomery 2006	1	113	2	101	0.7%	0.45 [0.04 , 4.85]	
icolini 2009	7	411	19	170	5.2%	0.15 [0.07 , 0.36]	
izer 2009	2	97		100	0.7%	2.06 [0.19 , 22.37]	
ollack 2001	3	161		163	2.3%	0.34 [0.09 , 1.22]	
ckels 2000	6	253		96	2.8%	0.46 [0.14 , 1.46]	
ckels 2003	13	386	8	180	5.0%	0.76 [0.32 , 1.80]	
othschild 2012	1	152	3	152	0.8%	0.33 [0.04 , 3.17]	
ynn 2008	3	168	7	159	2.2%	0.41 [0.11 , 1.54]	
tein 2008	3	63	3	58	1.6%	0.92 [0.19 , 4.38]	
tein 2014	14	139	11	65	6.8%	0.60 [0.29 , 1.24]	
tein 2014	6	142		65	4.2%	0.25 [0.10 , 0.65]	
tein 2017	9	270	20	142	6.3%	0.24 [0.11, 0.51]	
en-Yuan 2011	4	108	13	102	3.2%	0.29 [0.10 , 0.86]	
otal (95% CI)		7040		4271	100.0%	0.41 [0.34 , 0.50]	•
otal events:	189		263			_	•
leterogeneity: Tau ² = 0.0	1; Chi ² = 33	3.36, df =	32 (P = 0.4	10); I ² = 4	%		0.01 0.1 1 10 1
est for overall effect: Z =							igher in placebo Higher in ant

Figure 24. Dropouts due to lack of efficacy for all antidepressants versus placebo

Study or Subgroup	Antidepre		Place		Woight	Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	weight	IV, Random, 95% Cl	IV, Random, 95% Cl
11.2.1 SSRIs							
Allgulander 2004	3	184	4	189	5.7%	0.77 [0.17 , 3.39]	
Aventis-Sanofi 2008	6	114	7	126	10.6%	0.95 [0.33 , 2.74]	_
Baldwin 2006	11	542	5	139	11.0%	0.56 [0.20 , 1.60]	
Bose 2008	3	127	6	136	6.6%	0.54 [0.14 , 2.10]	
Brawman-Mintzer 2006	2	164	5	162	4.8%	0.40 [0.08 , 2.01]	_
Davidson 2004	2	158	5	157	4.8%	0.40 [0.08 , 2.02]	
GlaxoSmithKline 2006	5	179	5	182	8.2%	1.02 [0.30 , 3.45]	
Goodman 2001	2	126	8	128	5.3%	0.25 [0.06 , 1.17]	
Goodman 2002	4	145	0	142	1.5%	8.82 [0.48 , 162.24]	
Hewett 2001	0	187	5	185	1.5%	0.09 [0.01 , 1.62]	• • • • • • • • • • • • • • • • • • •
Pfizer 2009	2	97	1	100	2.3%	2.06 [0.19 , 22.37]	
Pollack 2001	3	161	9	163	7.4%	0.34 [0.09 , 1.22]	
Rickels 2003	13	386	8	180	15.3%	0.76 [0.32 , 1.80]	
Stein 2014	6	142	22	131	15.1%	0.25 [0.11 , 0.60]	
Subtotal (95% CI)		2712		2120	100.0%	0.55 [0.38 , 0.79]	◆
Total events:	62		90				
Heterogeneity: Tau ² = 0.0	03; Chi² = 13	.83, df =	13 (P = 0.3	9); I² = 6	%		
Test for overall effect: Z =	= 3.27 (P = 0	.001)					
11.2.2 SNRIs							
Allgulander 2001	31	411	21	130	26.2%	0.47 [0.28 , 0.78]	
Bose 2008	0	133	6	136	0.9%	0.08 [0.00 , 1.38]	
Gelenberg 2000	10	124		127	15.2%	0.37 [0.19 , 0.72]	
Hackett 2003	11	370	6	97	7.5%	0.48 [0.18 , 1.27]	
Hartford 2007	4	326	6	161	4.5%	0.33 [0.09 , 1.15]	
Kasper 2009	4	125		128	5.8%	0.34 [0.11 , 1.03]	
Koponen 2007	. 9	338	23	175	12.5%	0.20 [0.10 , 0.43]	
Mahableshwarkar 2014	1	156	4	157	1.5%	0.25 [0.03 , 2.23]	
Montgomery 2006	1	113	2	101	1.2%	0.45 [0.04 , 4.85]	
Nicolini 2009	7	411	19	170	9.8%	0.15 [0.07 , 0.36]	
Rickels 2000	6	253	5	96	5.2%	0.46 [0.14 , 1.46]	
Rynn 2008	3	168	7	159	3.9%	0.41 [0.11 , 1.54]	
Wen-Yuan 2011	4	108	13	102	5.9%	0.29 [0.10 , 0.86]	
Subtotal (95% CI)		3036			100.0%		
Total events:	91		152		100.070	0.00 [0.20 , 0.40]	•
Heterogeneity: Tau ² = 0.0		74 df = 1		3): $ ^2 = 0\%$			
Test for overall effect: Z =			- (,,			
11 2 3 Other							
11.2.3 Other Gommoll 2015	2	200	4	100	1 50/	1 08 [0 10 01 66]	
	2	200 468	1 4	198 157	4.5%	1.98 [0.18 , 21.66]	
Mahableshwarkar 2014 Rothschild 2012	1	468	4	157 152	14.9% 5.0%	0.59 [0.17 , 1.98] 0.33 [0.04 , 3.17]	
Stein 2008	3	152	3		5.0% 9.8%		
				63 121		1.09 [0.23 , 5.17]	
Stein 2014 Stein 2017	14	139	22	131			
Stein 2017	9	270	20		29.3% 100.0%		
Subtotal (95% CI)	20	1287	50	843	100.0%	0.49 [0.29 , 0.83]	\blacksquare
Total events:	36 00: Chiž = 6	10 df - 5	53 (D = 0.27)	12 - 000			
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =			(P = 0.27)	, 1- = 22%)		
reaction overlain encot. Z -	2.04 (1 - 0						
Test for subgroup differe	nces: Chi² =	5.40, df =	2 (P = 0.0	7), I² = 63	3.0%		0.01 0.1 1 10 100
							Higher in placebo Higher in antidepres

Figure 25. Dropouts due to lack of efficacy by treatment class versus placebo

4.4.12 Dropouts Due to Adverse Effects

Figures 26 and 27 show the pooled dropouts due to adverse effects for the different antidepressants compared to placebo. Very low-quality evidence showed that more participants dropped out due to adverse effects with all the antidepressants compared to placebo (RR, 2.17: 95% CI: 1.81, 2.59; studies = 33; participants = 12,097). This analysis had low heterogeneity ($I^2 = 25\%$; p = 0.09).

Analyses looking at the effect among different classes of antidepressants also showed that more participants dropped out due to adverse effects among the antidepressant groups compared to placebo: SSRIs (RR, 1.98: 95% CI: 1.51, 2.61; $I^2 = 23\%$; studies = 16; participants = 5,315), SNRIs (RR, 2.42: 95% CI: 1.81, 3.22; $I^2 = 50\%$; studies = 14; participants = 5,078) and 'Other' antidepressants (RR, 2.26: 95% CI: 1.33, 3.85; $I^2 = 0\%$; studies = 6; participants = 2,130). The SSRIs and 'Other' antidepressants had low heterogeneity while the SNRI analysis showed moderate-substantial heterogeneity. The test for subgroup interaction suggested that there were similar effect sizes across classes of antidepressants regarding the total number of patients dropping out due to adverse effects ($I^2 = 0\%$; p = 0.61) although more studies are needed for further investigation.

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Allqulander 2001	44	411	14	130	5.5%	0.99 [0.56 , 1.75]	
Allgulander 2004	15	184	19	189	4.7%	0.81 [0.43 , 1.55]	
Aventis-Sanofi 2007a	11	124		122	2.9%	1.55 [0.62 , 3.86]	
ventis-Sanofi 2007b	10	122		119	3.0%	1.22 [0.50 , 2.98]	
ventis-Sanofi 2008	11	113	4	124	2.1%	3.02 [0.99 , 9.21]	
aldwin 2006	42	542	4	139	2.5%	2.69 [0.98 , 7.38]	
3ose 2008	17	129	3	68	1.9%	2.99 [0.91 , 9.84]	
lose 2008	9	127		68	1.7%	1.61 [0.45 , 5.74]	
Brawman-Mintzer 2006	9	164	3	162	1.7%	2.96 [0.82 , 10.75]	
avidson 1999	50	203	10	104	4.8%	2.56 [1.36 , 4.84]	
Davidson 2004	14	158	8	157	3.3%	1.74 [0.75 , 4.03]	
Gelenberg 2000	30	124		127	5.9%	1.71 [1.01 , 2.90]	
GlaxoSmithKline 2006	22	179		182	3.1%	3.73 [1.55 , 8.98]	
Gommoll 2015	22	200		198	3.4%	3.11 [1.36 , 7.12]	
Goodman 2001	14	126	4	128	2.2%	3.56 [1.20 , 10.51]	
Goodman 2002	8	145		142	1.6%	2.61 [0.71, 9.65]	
lackett 2003	40	370		97	2.5%	2.62 [0.96 , 7.15]	
lartford 2007	41	326		161	2.0%		
lewett 2001	18	187		185	1.4%		
asper 2009	22	125		128	3.5%		
oponen 2007	45	338		175	2.5%	5.82 [2.13 , 15.93]	
lahableshwarkar 2014	30	468		78	1.4%	2.50 [0.61 , 10.25]	
lahableshwarkar 2014	23	156		78	1.4%	5.75 [1.39 , 23.77]	
Iontgomery 2006	23	113		101	4.3%	2.06 [1.03 , 4.11]	
licolini 2009	44	411	15	170	5.6%	1.21 [0.69 , 2.12]	
fizer 2009	6	97		100	2.0%		
ollack 2001	17	161	6	163	3.0%	2.87 [1.16 , 7.09]	
Rickels 2000	49	253		96	3.8%		
Rickels 2003	44	386		180	5.0%	1.71 [0.93 , 3.16]	
Rothschild 2012	4	152		152	1.0%	2.00 [0.37 , 10.76]	
ynn 2008	34	162		159	5.1%	2.48 [1.36 , 4.52]	
stein 2008	1	63		58	0.3%		
tein 2000	10	141	2	65	1.3%	2.30 [0.52 , 10.22]	
tein 2014	3	139		65	1.0%	0.70 [0.12 , 4.10]	
tein 2017	4	270		142	0.6%		
Ven-Yuan 2011	13	108		102	1.8%	4.09 [1.20 , 13.94]	
ren Tuan 2011	13	100	5	102	1.0 /0	4.00[1.20, 10.04]	
Total (95% CI)		7483		4614	100.0%	2.17 [1.81 , 2.59]	•
otal events:	799		223				
leterogeneity: Tau ² = 0.0			35 (P = 0.0)9); I ² = 2;	5%	0.0	
est for overall effect: Z =	= 8.46 (P < 0	.00001)				High	er in placebo Higher in ant

Figure 26. Dropouts due to adverse effects for all antidepressants versus placebo

Study or Subgroup	Antidepre Events	essants Total	Place Events	ebo Total	Weight	Risk ratio IV, Random, 95% Cl	Risk ratio IV, Random, 95% Cl
orady of Subgroup	Evenits	iotai	Evenus	iotai	weight	11, Nandoni, 35% Cl	
12.2.1 SSRIs							
Allgulander 2004	15	184	19	189	10.8%	0.81 [0.43 , 1.55]	
Aventis-Sanofi 2007a	11	124	7	122	6.7%	1.55 [0.62 , 3.86]	
Aventis-Sanofi 2007b	10	122	8	119	7.0%	1.22 [0.50 , 2.98]	
Aventis-Sanofi 2008	11	113	4	124	4.9%	3.02 [0.99 , 9.21]	
Baldwin 2006	42	542	4	139	5.8%	2.69 [0.98 , 7.38]	
Bose 2008	9	127	7	136	6.3%	1.38 [0.53 , 3.59]	
Brawman-Mintzer 2006	9	164	3	162	3.9%	2.96 [0.82 , 10.75]	
Davidson 2004	14	158	8	157	7.6%	1.74 [0.75 , 4.03]	
GlaxoSmithKline 2006	22	179	6	182	7.1%	3.73 [1.55 , 8.98]	
Goodman 2001	14	126	4	128	5.2%	3.56 [1.20 , 10.51]	
Goodman 2002	8	145	3	142	3.8%	2.61 [0.71, 9.65]	
Hewett 2001	18	187	2	185	3.2%	8.90 [2.10 , 37.83]	
Pfizer 2009	6	97	5	100	4.7%	1.24 [0.39 , 3.92]	
Pollack 2001	17	161	6	163	6.8%	2.87 [1.16 , 7.09]	
Rickels 2003	44	386	12	180	11.5%	1.71 [0.93 , 3.16]	
Stein 2014	10	141	4	131	4.8%	2.32 [0.75 , 7.23]	
Subtotal (95% CI)	.0	2956	4		100.0%	1.98 [1.51 , 2.61]	
Total events:	260	2000	102	2000			-
Heterogeneity: Tau ² = 0.1		58 df=		19)· l² = ?	3%		
			10 (1 = 0.		0.70		
Test for overall effect: Z =	- +.32 (F < l						
12.2.2 SNRIs							
Allgulander 2001	44	411	14	130	9.5%	0.99 [0.56 , 1.75]	_ _
Bose 2008	17	129	7	136	6.5%	2.56 [1.10 , 5.97]	
Davidson 1999	50	203	10	104	8.7%	2.56 [1.36 , 4.84]	
Gelenberg 2000	30	124	18	127	10.0%	1.71 [1.01 , 2.90]	_ _
Hackett 2003	40	370	4	97	5.3%	2.62 [0.96 , 7.15]	
Hartford 2007	41	326	3	161	4.4%	6.75 [2.12 , 21.46]	
Kasper 2009	22	125	7	128	6.8%	3.22 [1.43 , 7.26]	
Koponen 2007	45	338	4	175	5.3%	5.82 [2.13 , 15.93]	
Mahableshwarkar 2014	23	156		157	5.1%	5.79 [2.05 , 16.35]	
Montgomery 2006	23	113	10	101	8.1%	2.06 [1.03 , 4.11]	
Nicolini 2009	44	411	15	170	9.6%	1.21 [0.69 , 2.12]	_
Rickels 2000	49	253	7	96	7.4%	2.66 [1.25 , 5.66]	7-
Rynn 2008	34	168		159	9.1%	2.48 [1.36 , 4.52]	_
Wen-Yuan 2011	13	108	3	102	4.0%	4.09 [1.20 , 13.94]	
	15	3235	5		100.0%		
Subtotal (95% CI)	475	3235	110	1045	100.0%	2.42 [1.81 , 3.22]	▼
Total events:	475 14: Chi2 – 26	00 df -	119 12 (D = 0 (00): 12 - E	0.0/		
Heterogeneity: Tau ² = 0.1 Test for overall effect: 7 :			13 (F = 0.0	<i>52)</i> , 1 [–] – 0	0 /0		
Test for overall effect: Z =	- 0.02 (P < l						
12.2.3 Other							
Gommoll 2015	22	200	7	198	41.4%	3.11 [1.36 , 7.12]	
Mahableshwarkar 2014	30	468	4	157	26.9%	2.52 [0.90 , 7.03]	—
Rothschild 2012	4	152	2	152	10.0%	2.00 [0.37 , 10.76]	
Stein 2008	1	63		58	2.8%	2.77 [0.11 , 66.57]	
Stein 2014	3	139		131		0.71 [0.16 , 3.10]	
Stein 2017	4	270		142	6.0%	2.10 [0.24 , 18.64]	
Subtotal (95% CI)	4	1292			100.0%	2.26 [1.33 , 3.85]	
Total events:	64	1202	18	000		2.20 [-
Heterogeneity: Tau ² = 0.1		03 df = 5		· 12 = 0%			
Test for overall effect: Z =			. 0.70	,,, 070			
TESTION OVERALL ELICUL. Z -	- 5.00 (F - 0						
Test for subgroup differe	nces: Chi² =	0.97. df =	2 (P = 0.6	51), l ² = 0	%	0.	
		J.J., UI -	- U = U.C			0	

Figure 27. Dropouts due to adverse effects by treatment class versus placebo

4.5 Subgroup Analyses

The following subgroup analyses were used to assess potential sources of heterogeneity among the analyses comparing all antidepressants to placebo for the primary outcomes, specifically (i) rate of treatment response measured as a reduction of at least 50% on the HAM-A and (ii) acceptability. Subgroup analysis for diagnostic criteria was not performed due to a limited number of studies using diagnostic criteria other than the DSM-IV and DSM-IV-TR. Subgroup analysis for elderly participants was not performed because no studies investigated patients over 65 years of age.

4.5.1 Treatment Setting

Figures 28 and 29 display subgroup analyses for the two primary outcomes, rate of treatment response measured as a reduction of at least 50% on the HAM-A and acceptability by treatment setting. There was a benefit of antidepressants compared to placebo in response for outpatients (RR, 1.47: 95% CI: 1.31, 1.64; $I^2 = 66\%$, studies = 16; participants = 5,525) and for primary care and psychiatric outpatients (RR, 1.44: 95% CI: 1.23, 1.69; $I^2 = 0\%$; studies = 2; participants = 739) but no difference was found between antidepressants and placebo for primary care patients (RR, 1.08: 95% CI: 0.85, 1.39; $I^2 = NA$; studies = 1; participants = 244). Heterogeneity was substantial among the outpatient analysis, low for the primary care and psychiatric outpatient analysis and could not be assessed for primary care analysis due to limited studies. The test for subgroup interaction suggested similar effect sizes across the treatment settings are needed for further investigation of the effect of treatment setting on rate of treatment response.

Figure 29 displays the acceptability by treatment setting. The results suggested that there were no differences in acceptability between the antidepressant group compared to the placebo group among all treatment settings: outpatients (RR, 1.01: 95% CI: 0.91, 1.13; $I^2 = 53\%$; studies = 26; participants = 9,166), primary care and psychiatric outpatients (RR, 1.02: 95% CI: 0.49, 2.12; $I^2 = 85\%$; studies = 2; participants = 755), and primary care patients (RR, 0.86: 95% CI: 0.44, 1.69; $I^2 = NA$; studies = 1; participants = 42). Moderate-substantial heterogeneity was found among the outpatient subgroup and

substantial-considerable heterogeneity was found among the primary care and psychiatric outpatient subgroup. Heterogeneity could not be assessed for the primary care patient subgroup. The test for subgroup interaction suggested similar effect sizes across the treatment settings ($I^2 = 0\%$; p = 0.89) however, more studies are needed among subgroups for further investigation.

	Antidepressants		Placebo			Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.3.1 Outpatients							
Allgulander 2004	102	182	55	188	5.0%	1.92 [1.48 , 2.48]	-
Bose 2008	66	125	28	67	4.1%	1.26 [0.91 , 1.75]	_ _
Bose 2008	65	125	28	67	4.1%	1.24 [0.90 , 1.73]	_ <u>_</u>
Brawman-Mintzer 2006	97	164	78	162	5.8%	1.23 [1.00 , 1.51]	
Davidson 1999	87	176	35	98	4.4%	1.38 [1.02 , 1.88]	
Gommoll 2015	103	198	82	197	5.7%	1.25 [1.01 , 1.55]	_
Hackett 2003	200	354	44	97	5.3%	1.25 [0.98 , 1.58]	
Hartford 2007	165	326	60	161	5.5%	1.36 [1.08 , 1.70]	-
Kasper 2009	55	125	59	128	4.8%	0.95 [0.73 , 1.25]	_
Koponen 2007	193	338	54	175	5.3%	1.85 [1.46 , 2.35]	_
Nicolini 2009	245	392	69	163	5.9%	1.48 [1.21, 1.79]	-
Nimatoudis 2004	22	24	6	22	1.5%	3.36 [1.68 , 6.72]	
Rynn 2008	67	168		159	4.6%	1.24 [0.93 , 1.67]	
Stein 2008	45	63		58	4.2%		
Stein 2014	89	139		65	3.9%	1.73 [1.23 , 2.44]	
Stein 2014	92	139		65	4.0%		
Stein 2017	164	268		140	4.2%		
Wen-Yuan 2011	74	107		100	5.5%		
Subtotal (95% CI)		3413		2112	84.0%		
Total events:	1931	••••	809		•• //		•
		75 df =)001) [.] ² =	66%		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	04; Chi² = 49			0001); l² =	66%		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	04; Chi² = 49			0001); I² =	66%		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care	04; Chi² = 49 = 6.81 (P < 0	.00001)	17 (P < 0.0				
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003	04; Chi² = 49	.00001) 122	17 (P < 0.0	122	5.1%	1.08 [0.85 , 1.39]	-
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI)	04; Chi² = 49 = 6.81 (P < 0 64	.00001)	17 (P < 0.0			1.08 [0.85 , 1.39] 1.08 [0.85 , 1.39]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events:	04; Chi ² = 49 = 6.81 (P < 0 64 64	.00001) 122	17 (P < 0.0	122	5.1%		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable	.00001) 122 122	17 (P < 0.0	122	5.1%		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable	.00001) 122 122	17 (P < 0.0	122	5.1%		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z =	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0	.00001) 122 122 .52)	17 (P < 0.0 59 59	122	5.1%		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and 	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0	.00001) 122 122 .52)	17 (P < 0.0 59 59 nts	122	5.1%		•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI)	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric	.00001) 122 122 .52) outpatie	17 (P < 0.0 59 59 nts 60	122 122	5.1% 5.1 %	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and p Allgulander 2001	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric 273	.00001) 122 122 .52) outpatie 399	17 (P < 0.0 59 59 nts 60	122 122 130	5.1% 5.1% 5.9%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78]	
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and [Allgulander 2001 Montgomery 2006	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric 273	.00001) 122 122 .52) outpatie 399 110	17 (P < 0.0 59 59 nts 60	122 122 130 100	5.1% 5.1% 5.9% 5.0%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and (Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events:	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric 273 68 341	.00001) 122 122 .52) outpatie 399 110 509	17 (P < 0.0 59 59 nts 60 45 105	122 122 130 130 230	5.1% 5.1% 5.9% 5.0%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78]	★
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and (Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events: Heterogeneity: Tau ² = 0.0	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric 273 68 341 00; Chi ² = 0.2	.00001) 122 122 .52) outpatie 399 110 509 21, df = 1	17 (P < 0.0 59 59 nts 60 45 105	122 122 130 130 230	5.1% 5.1% 5.9% 5.0%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and (Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events: Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 psychiatric 273 68 341 00; Chi ² = 0.2	.00001) 122 122 .52) outpatie 399 110 509 21, df = 1 .00001)	17 (P < 0.0 59 59 105 45 (P = 0.65)	122 122 130 100 230 ; 1 ² = 0%	5.1% 5.1% 5.9% 5.0% 10.9%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78] 1.44 [1.23 , 1.69]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and (Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events: Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Total (95% CI)	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 273 68 341 00; Chi ² = 0.2 = 4.55 (P < 0	.00001) 122 122 .52) outpatie 399 110 509 21, df = 1	17 (P < 0.0 59 59 105 45 (P = 0.65)	122 122 130 100 230 ; 1 ² = 0%	5.1% 5.1% 5.9% 5.0%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78] 1.44 [1.23 , 1.69]	 ↓
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and j Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events: Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Total (95% CI) Total events:	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 273 68 341 00; Chi ² = 0.2 = 4.55 (P < 0 2336	.00001) 122 122 .52) outpatie 399 110 509 21, df = 1 .00001) 4044	17 (P < 0.0 59 59 105 (P = 0.65) 973	122 122 130 130 230 ; ² = 0% 2464	5.1% 5.1% 5.9% 5.0% 10.9%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78] 1.44 [1.23 , 1.69] 1.44 [1.31 , 1.58]	
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.3.2 Primary care Lenox-Smith 2003 Subtotal (95% CI) Total events: Heterogeneity: Not applic Test for overall effect: Z = 1.3.3 Primary care and (Allgulander 2001 Montgomery 2006 Subtotal (95% CI) Total events: Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Total (95% CI)	04; Chi ² = 49 = 6.81 (P < 0 64 64 cable = 0.64 (P = 0 273 68 341 00; Chi ² = 0.2 = 4.55 (P < 0 2336 03; Chi ² = 54	.00001) 122 122 .52) outpatie 399 110 509 21, df = 1 .00001) 4044 .50, df = 1	17 (P < 0.0 59 59 105 (P = 0.65) 973	122 122 130 130 230 ; ² = 0% 2464	5.1% 5.1% 5.9% 5.0% 10.9%	1.08 [0.85 , 1.39] 1.48 [1.22 , 1.81] 1.37 [1.06 , 1.78] 1.44 [1.23 , 1.69] 1.44 [1.31 , 1.58]	

Figure 28. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment setting

Ctudy or Cubaroup	-	ssants	Place		Majaht	Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.3.1 Outpatients							
Allgulander 2004	41	188	51	190	3.8%	0.81 [0.57 , 1.16]	
Baldwin 2006	83	543	15	139	2.6%	1.42 [0.84 , 2.38]	
Bose 2008	29	131	18	70	2.6%	0.86 [0.52 , 1.44]	
Bose 2008	37	133	18	70	2.8%	1.08 [0.67 , 1.75]	
Brawman-Mintzer 2006	51	168	46	170	4.0%	1.12 [0.80 , 1.57]	
Davidson 1999	84	203	36	104	4.2%	1.20 [0.88 , 1.63]	
Davidson 2004	42	161	36	159	3.5%	1.15 [0.78 , 1.70]	_ _
Gelenberg 2000	64	124	83	127	5.2%	0.79 [0.64 , 0.98]	-
GlaxoSmithKline 2006	30	179	28	182	2.9%	1.09 [0.68 , 1.75]	
Gommoll 2015	57	201	40	201	3.8%	1.43 [1.00 , 2.03]	
Goodman 2001	32	129	33	128	3.3%		
Goodman 2002	31	149	31	145	3.1%	0.97 [0.63 , 1.51]	
Hackett 2003	77	370	16	97	2.8%		
Hartford 2007	136	326	62	161	5.0%		
Hewett 2001	35	188	22	186	2.8%		
Kasper 2009	41	125	35	128	3.6%		
Lenox-Smith 2003	15	122		122	2.2%		
Nicolini 2009	117	411	68	170	4.9%		
Nimatoudis 2004	5	24	11	22	1.2%		
Pollack 2001	34	161	30	163	3.1%		
Rickels 2000	83	253	19	96	3.1%		
Rickels 2003	100	386	40	180	4.1%		
Rynn 2008	75	168 63	50	159	4.5%		
Stein 2008	5		4	58	0.7%		
Stein 2014	26	142	17	65	2.5%		
Stein 2014	23	139	17	65	2.4%		
Stein 2017	31	270		142	3.0%		
Wen-Yuan 2011	26	108	28	102	3.0%		
Subtotal (95% CI)		5565		3601	90.9%	1.01 [0.91 , 1.13]	•
Total events:	1410		909		500/		
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =			27 (P = 0.0	J005); I² =	53%		
0.0.0 Duineanu anna							
2.3.2 Primary care Brawman-Mintzer 2009	12	28	7	14	1.8%	0.86 [0.44 4.60]	
	12		1				
Subtotal (95% CI)	10	28	7	14	1 .8 %	0.86 [0.44 , 1.69]	
Total events:	12 2010		7				
Heterogeneity: Not appli		(22)					
Test for overall effect: Z =	= 0.45 (P = 0	.66)					
2.3.3 Primary care and	psychiatric	outpatie	nts				
Allgulander 2001	102	411	45	130	4.4%	0.72 [0.54 , 0.96]	
Montgomery 2006	34	113	20	101	2.8%	1.52 [0.94 , 2.46]	—
Subtotal (95% CI)		524		231	7.3%	1.02 [0.49 , 2.12]	
Total events:	136		65			-	
Heterogeneity: Tau ² = 0.2	24; Chi² = 6.8		(P = 0.009	9); I² = 85	%		
Test for overall effect: Z =	= 0.05 (P = 0	.96)					
Total (95% CI)		6117		3846	100.0%	1.00 [0.90 , 1.12]	
Total events:	1558		981				
Heterogeneity: Tau ² = 0.0	05; Chi² = 66	.02, df =	30 (P = 0.0	0002); l² =	55%		
Test for overall effect: Z =							gher in placebo Higher in antidepres
Test for subgroup differen					~		

Figure 29. Subgroup analysis for acceptability by treatment setting

4.5.2 Studies with Patients who have Comorbidities

Figures 30 and 31 display subgroup analyses for the two primary outcomes, rate of treatment response measured as a reduction of at least 50% on the HAM-A and acceptability among patients with and without psychiatric comorbidities. There was a benefit of antidepressants over placebo for response in patients without psychiatric comorbidities (RR, 1.41: 95% CI: 1.28, 1.57; $I^2 = 68\%$; studies = 19; participants = 6,777) and with psychiatric comorbidities (RR, 1.25; 95% CI: 1.07, 1.46; $I^2 = 0\%$; studies = 2; participants = 779). There was substantial heterogeneity among studies without patients with comorbidities. The test for subgroup interaction suggested similar effect sizes across the subgroups ($I^2 = 39.3\%$; p = 0.20) however, more studies that include patients with psychiatric comorbidities are needed to further investigate the effects of psychiatric comorbidities on response.

Figure 31 displays the acceptability for patients with and without psychiatric comorbidities. The results suggested that there are no differences in the total number of dropouts among the antidepressant group and placebo group in patients without psychiatric comorbidities (RR, 1.01: 95% CI: 0.91, 1.12; $I^2 = 53\%$; studies = 32; participants = 10,792) and with psychiatric comorbidities (RR, 1.15: 95% CI: 0.86, 1.55; $I^2 = 25\%$; studies = 2; participants = 806). The former analysis had moderate-substantial heterogeneity while the latter had low heterogeneity. The test for subgroup interaction suggested similar effect sizes across the subgroups ($I^2 = 0\%$; p = 0.40) however, more studies that include patients with secondary psychiatric comorbidities are needed to further investigate the effects of psychiatric comorbidities on acceptability.

	Antidepre	ssants	Place	ebo		Risk ratio	Risk ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
.4.1 Without comorbidi	ties								
Allgulander 2001	273	399	60	130	5.1%	1.48 [1.22 , 1.81]			
Allgulander 2004	102	182	55	188	4.4%	1.92 [1.48 , 2.48]			
Brawman-Mintzer 2006	97	164	78	162	5.0%	1.23 [1.00 , 1.51]			
avidson 1999	87	176	35	98	3.8%	1.38 [1.02 , 1.88]	_ _		
lackett 2003	200	354	44	97	4.6%	1.25 [0.98 , 1.58]	L.		
artford 2007	165	326	60	161	4.8%	1.36 [1.08 , 1.70]			
asper 2009	55	125	59	128	4.2%	0.95 [0.73 , 1.25]	_		
oponen 2007	193	338	54	175	4.6%	1.85 [1.46 , 2.35]			
enox-Smith 2003	64	122	59	122	4.5%	1.08 [0.85 , 1.39]			
/lahableshwarkar 2014	76	149	32	77	3.8%	1.23 [0.90 , 1.67]			
/lahableshwarkar 2014	201	456	32	77	4.1%	1.06 [0.80 , 1.41]	_		
Iontgomery 2006	68	110	45	100	4.3%	1.37 [1.06 , 1.78]			
Vicolini 2009	245	392	69	163	5.2%	1.48 [1.21 , 1.79]	-		
Vimatoudis 2004	22	24	6	22	1.4%	3.36 [1.68 , 6.72]			
Rothschild 2012	77	145	72	144	4.8%	1.06 [0.85 , 1.33]	_		
tynn 2008	67	168	51	159	4.0%	1.24 [0.93 , 1.67]	L		
tein 2008	45	63	27	58	3.7%	1.53 [1.12 , 2.11]			
Stein 2014	89	139	24	65	3.5%	1.73 [1.23 , 2.44]			
tein 2014	92	139	24	65	3.5%	1.79 [1.28 , 2.52]			
tein 2017	164	268		140		2.68 [1.95 , 3.68]			
Ven-Yuan 2011	74	107	53	100	4.8%	1.30 [1.04 , 1.63]			
ubtotal (95% CI)		4346		2431	87.9%	1.41 [1.28 , 1.57]			
otal events:	2456		971				•		
eterogeneity: Tau ² = 0.0		73. df = 3		0001): l²	= 68%				
est for overall effect: Z =			(,, -					
.4.2 With comorbidities									
Bose 2008	, 66	125	28	67	3.6%	1.26 [0.91 , 1.75]			
30se 2008	65	125		67	3.6%	1.24 [0.90 , 1.73]			
ommoll 2015	103	125		197	3.6% 4.9%		1		
Subtotal (95% CI)	103	448	02	331	4.9% 12.1%	1.25 [1.01 , 1.55]			
otal events:	234	440	138	331	14.170	1.25 [1.07 , 1.46]	▼		
leterogeneity: Tau ² = 0.0		00 df - 0		12 - 00/					
est for overall effect: Z =			(= 1.00)	, 1 - 0 %					
esti or overall ellect. Z =	2.01 (P = 0	.000)							
lotal (95% CI)		4794		2762	100.0%	1.39 [1.27 , 1.52]	•		
Total events:	2690		1109			L			
	3: Chi ² = 64	19 df = 1	23 (P < 0.0	0001) 12	= 64%	0.1	0.2 0.5 1 2 5 10		
eterogeneity: Tau ² = 0.03 est for overall effect: Z =			20 (1 . 0.0				0.2 0.5 1 2 5 10 ours placebo Favours antide		

Figure 30. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A for patients with and without comorbidities

Study or Subgroup	Antidepre Events	essants Total	Place Events	ebo Total	Weight	Risk ratio IV, Random, 95% Cl	Risk ratio IV, Random, 95% Cl
citaly of cabilitup	Lients	iotai	Litents	iotai		11, Randoni, 80% Of	
2.4.1 Without comorbid	ities						
Allgulander 2001	102	411	45	130	3.8%	0.72 [0.54 , 0.96]	
Allgulander 2004	41	188	51	190	3.2%	0.81 [0.57 , 1.16]	
Aventis-Sanofi 2008	20	114	17	126	1.8%	1.30 [0.72 , 2.36]	
Baldwin 2006	83	543	15	139	2.2%	1.42 [0.84 , 2.38]	
Brawman-Mintzer 2006	51	168	46	170	3.4%	1.12 [0.80 , 1.57]	_
Brawman-Mintzer 2009	12	28	7	14	1.5%	0.86 [0.44 , 1.69]	
Davidson 1999	84	203	36	104	3.6%	1.20 [0.88 , 1.63]	
Davidson 2004	42	161	36	159	3.0%	1.15 [0.78 , 1.70]	_ _
Feltner 2009	15	56	18	57	1.9%	0.85 [0.48 , 1.51]	
Gelenberg 2000	64	124	83	127	4.5%	0.79 [0.64, 0.98]	
GlaxoSmithKline 2006	30	179	28	182	2.5%	1.09 [0.68 , 1.75]	
Goodman 2001	32	129	33	128	2.8%	0.96 [0.63 , 1.46]	
Goodman 2002	31	149	31	145	2.6%	0.97 [0.63 , 1.51]	
Hackett 2003	77	370	16	97	2.4%	1.26 [0.77 , 2.06]	
Hartford 2007	136	326	62	161	4.3%	1.08 [0.86 , 1.37]	
Hewett 2001	35	188	22	186	2.3%	1.57 [0.96 , 2.58]	
Kasper 2009	41	125	35	128	3.1%	1.20 [0.82 , 1.75]	
Lenox-Smith 2003	15	123		120	1.9%	0.60 [0.33 , 1.08]	
Mahableshwarkar 2014	50	156	18	78	2.5%	1.39 [0.87 , 2.21]	
Mahableshwarkar 2014	120	468	18	78	2.5%		
		466	20	101		1.11 [0.72 , 1.71]	
Montgomery 2006	34				2.4%	1.52 [0.94 , 2.46]	
Nicolini 2009	117	411	68	170	4.3%	0.71 [0.56 , 0.90]	
Nimatoudis 2004	5	24	11	22	1.0%	0.42 [0.17 , 1.01]	
Pfizer 2009	39	97	28	101	3.0%	1.45 [0.97 , 2.16]	
Pollack 2001	34	161	30	163	2.7%	1.15 [0.74 , 1.78]	
Rickels 2000	83	253	19	96	2.7%	1.66 [1.07 , 2.57]	_
Rickels 2003	100	386	40	180	3.5%	1.17 [0.85 , 1.61]	+
Rothschild 2012	27	152	38	152	2.7%	0.71 [0.46 , 1.10]	
Rynn 2008	75	168		159	3.9%	1.42 [1.07 , 1.89]	
Stein 2008	5	63	4	58	0.5%	1.15 [0.32 , 4.08]	
Stein 2014	26	142	17	65	2.1%	0.70 [0.41 , 1.20]	
Stein 2014	23	139	17	65	2.0%	0.63 [0.36 , 1.10]	
Stein 2017	31	270	30	142	2.5%	0.54 [0.34 , 0.86]	
Wen-Yuan 2011	26	108	28	102	2.5%	0.88 [0.55 , 1.39]	
Subtotal (95% CI)		6695		4097	92.1%	1.01 [0.91 , 1.12]	•
Total events:	1706		1042				
Heterogeneity: Tau ² = 0.0	05; Chi² = 70).65, df = (33 (P = 0.0	0001); l² =	53%		
Test for overall effect: Z =	= 0.17 (P = 0	0.86)					
2.4.2 With comorbiditie	s						
Bose 2008	29	131	18	70	2.2%	0.86 [0.52 , 1.44]	
Bose 2008	37	133	18	70	2.4%	1.08 [0.67 , 1.75]	
Gommoll 2015	57	201	40	201	3.3%	1.43 [1.00 , 2.03]	L
Subtotal (95% CI)		465		341	7.9%	1.15 [0.86 , 1.55]	
Total events:	123		76				
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	02; Chi² = 2.			; ² = 25%	5		
Total (95% CI)		7160		4438	100.0%	1.02 [0.92 , 1.12]	•
Total events:	1829		1118				[
Heterogeneity: Tau ² = 0.0	04; Chi² = 74	1.93, df = 3).71)	36 (P = 0.0	0002); I² =	52%	0	.1 0.2 0.5 1 2 5 10

Figure 31. Subgroup analysis for acceptability for patients with and without psychiatric comorbidities

4.5.3 Duration of Treatment

Figures 32 and 33 display subgroup analyses for the two primary outcomes, rate of treatment response measured as a reduction of at least 50% on the HAM-A and acceptability by treatment duration. There was a benefit of antidepressants over placebo in response among studies lasting for 12 weeks or less (RR, 1.41: 95% CI: 1.27, 1.57; $I^2 = 67\%$; studies = 18; participants = 6,576) and in studies lasting more than 12 weeks (RR, 1.30; 95% CI: 1.09, 1.54; $I^2 = 46\%$; studies = 3; participants = 980). There was substantial heterogeneity in the former analysis and moderate heterogeneity in the latter analysis. The test for subgroup interaction suggested similar effect sizes across the subgroups ($I^2 = 0\%$; p = 0.41) although more studies lasting longer than 12 weeks are needed for further investigation.

Figure 33 displays the acceptability for antidepressants compared to placebo by treatment duration. The results suggested that there were no differences between antidepressants and placebo in acceptability in studies lasting 12 weeks or less (RR, 1.07: 95% CI: 0.96, 1.18; $I^2 = 46\%$; studies = 30; participants = 10,352) with moderate heterogeneity. In studies lasting more than 12 weeks, there were less total people dropping out in the antidepressant group compared to the placebo group (RR, 0.76: 95% CI: 0.65, 0.89; $I^2 = 0\%$; studies = 4; participants = 1,246) with low heterogeneity. The test for subgroup interaction was significant ($I^2 = 92.1\%$; p = 0.0004), suggesting that there may be effect modification by treatment duration on acceptability. However, considering the much larger number of studies lasting 12 weeks or less compared to those lasting longer than 12 weeks (30 trials, 10,352 participants versus 4 trials, 1,246 participants), this result requires further investigation with more studies lasting more than 12 weeks.

	Antidepre	ssants	Place	ebo		Risk ratio	Risk ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.5.1 12 weeks or less							
Allgulander 2004	102	182	55	188	4.4%	1.92 [1.48 , 2.48]	
Bose 2008	66	125	28	67	3.6%	1.26 [0.91 , 1.75]	
Bose 2008	65	125	28	67	3.6%	1.24 [0.90 , 1.73]	
Brawman-Mintzer 2006	97	164	78	162	5.0%	1.23 [1.00 , 1.51]	_ _
Davidson 1999	87	176	35	98	3.8%	1.38 [1.02 , 1.88]	
Gommoll 2015	103	198	82	197	4.9%	1.25 [1.01 , 1.55]	_ _
lackett 2003	200	354	44	97	4.6%	1.25 [0.98 , 1.58]	_ _
Hartford 2007	165	326	60	161	4.8%	1.36 [1.08 , 1.70]	
Kasper 2009	55	125	59	128	4.2%	0.95 [0.73 , 1.25]	_
Koponen 2007	193	338	54	175	4.6%	1.85 [1.46 , 2.35]	
Mahableshwarkar 2014	76	149	32	77	3.8%	1.23 [0.90 , 1.67]	
Mahableshwarkar 2014	201	456	32	77	4.1%	1.06 [0.80 , 1.41]	_
Montgomery 2006	68	110	45	100	4.3%	1.37 [1.06 , 1.78]	
Nicolini 2009	245	392	69	163	5.2%	1.48 [1.21 , 1.79]	-
Nimatoudis 2004	22	24	6	22	1.4%	3.36 [1.68 , 6.72]	
Rothschild 2012	77	145	72	144	4.8%	1.06 [0.85 , 1.33]	_
Rynn 2008	67	168	51	159	4.0%	1.24 [0.93 , 1.67]	L
Stein 2008	45	63	27	58	3.7%	1.53 [1.12 , 2.11]	
Stein 2014	89	139	24	65	3.5%	1.73 [1.23 , 2.44]	
Stein 2014	92	139	24	65	3.5%	1.79 [1.28 , 2.52]	
Stein 2017	164	268	32	140	3.7%	2.68 [1.95 , 3.68]	
Subtotal (95% CI)		4166		2410	85.6%	1.41 [1.27 , 1.57]	
otal events:	2279		937			• • •	•
leterogeneity: Tau ² = 0.0	04: Chi ² = 59	.92. df = 2	20 (P < 0.0)0001); l²	= 67%		
est for overall effect: Z =			,	,,			
.5.2 More than 12 weel	ks						
Allgulander 2001	273	399	60	130	5.1%	1.48 [1.22 , 1.81]	-
enox-Smith 2003	64	122		122		1.08 [0.85 , 1.39]	
Ven-Yuan 2011	74	107		100	4.8%	1.30 [1.04 , 1.63]	
Subtotal (95% CI)		628		352		1.30 [1.09 , 1.54]	
Total events:	411		172		/ v		▼
Heterogeneity: Tau ² = 0.0		71. df = 2		: l² = 46%			
Test for overall effect: Z =							
Total (95% CI)		4794		2762	100.0%	1.39 [1.27 , 1.52]	
Total events:	2690		1109			• • •	
Heterogeneity: Tau ² = 0.0	03; Chi ² = 64	.19, df = 2	23 (P < 0.0)0001); l²	= 64%	H	0.2 0.5 1 2 5 1
Test for overall effect: Z =			,	<i>,,</i>			burs placebo Favours antic
Test for subgroup differe	÷		1 (P = 0.4	1), l² = 0	%		,
		,	(· • • ·	,,			

Figure 32. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment duration

Study or Subgroup	Antidepre Events	ssants Total	Place Events		Weight	Risk ratio IV, Random, 95% Cl	Risk ratio IV, Random, 95% Cl
craay of cangloup	Lients	iotai	Litents	iotai		11, Nandolli, 2076 Of	
2.5.1 12 weeks or less							
Allgulander 2004	41	188	51	190	3.2%	0.81 [0.57 , 1.16]	
Aventis-Sanofi 2008	20	114	17	126	1.8%	1.30 [0.72 , 2.36]	
Baldwin 2006	83	543	15	139	2.2%	1.42 [0.84 , 2.38]	+
Bose 2008	29	131	18	70	2.2%	0.86 [0.52 , 1.44]	
Bose 2008	37	133	18	70	2.4%	1.08 [0.67 , 1.75]	_
Brawman-Mintzer 2006	51	168	46	170	3.4%	1.12 [0.80 , 1.57]	- -
Brawman-Mintzer 2009	12	28	7	14	1.5%	0.86 [0.44 , 1.69]	
Davidson 1999	84	203	36	104	3.6%	1.20 [0.88 , 1.63]	+
Davidson 2004	42	161	36	159	3.0%	1.15 [0.78 , 1.70]	_ -
Feltner 2009	15	56	18	57	1.9%	0.85 [0.48 , 1.51]	
GlaxoSmithKline 2006	30	179	28	182	2.5%	1.09 [0.68 , 1.75]	_ _
Gommoll 2015	57	201	40	201	3.3%	1.43 [1.00 , 2.03]	_ _
Goodman 2001	32	129	33	128	2.8%	0.96 [0.63 , 1.46]	
Goodman 2002	31	149	31	145	2.6%	0.97 [0.63 , 1.51]	
Hackett 2003	77	370	16	97	2.4%	1.26 [0.77 , 2.06]	_ _
Hartford 2007	136	326	62	161	4.3%	1.08 [0.86 , 1.37]	
Hewett 2001	35	188	22	186	2.3%	1.57 [0.96 , 2.58]	
Kasper 2009	41	125	35	128	3.1%	1.20 [0.82 , 1.75]	
Mahableshwarkar 2014	50	156	18	78	2.5%	1.39 [0.87 , 2.21]	
Mahableshwarkar 2014	120	468	18	78	2.7%	1.11 [0.72 , 1.71]	
Montgomery 2006	34	113	20	101	2.4%	1.52 [0.94 , 2.46]	
Nicolini 2009	117	411	68	170	4.3%	0.71 [0.56 , 0.90]	
Nimatoudis 2004	5	24	11	22	1.0%	0.42 [0.17 , 1.01]	
Pfizer 2009	39	97	28	101	3.0%	1.45 [0.97 , 2.16]	
Pollack 2001	34	161	30	163	2.7%	1.15 [0.74 , 1.78]	
		253	19		2.7%		
Rickels 2000	83			96		1.66 [1.07 , 2.57]	
Rickels 2003	100	386	40	180	3.5%	1.17 [0.85 , 1.61]	+
Rothschild 2012	27	152	38	152	2.7%	0.71 [0.46 , 1.10]	
Rynn 2008	75	168	50	159	3.9%	1.42 [1.07 , 1.89]	
Stein 2008	5	63	4	58	0.5%	1.15 [0.32 , 4.08]	
Stein 2014	26	142	17	65	2.1%	0.70 [0.41 , 1.20]	
Stein 2014	23	139	17	65	2.0%	0.63 [0.36 , 1.10]	
Stein 2017	31	270	30	142	2.5%	0.54 [0.34 , 0.86]	— — [
Subtotal (95% CI) Total events:	1622	6395	937	3957	87.3%	1.07 [0.96 , 1.18]	•
Heterogeneity: Tau ² = 0.0		80 df = '		03)· 12 = /	16%		
Test for overall effect: Z =			52 (1 - 0.0	,00),1	+0 /0		
2.5.2 More than 12 week	s						
Allgulander 2001	102	411	45	130	3.8%	0.72 [0.54 , 0.96]	
Gelenberg 2000	64	124	83	127	4.5%	0.79 [0.64 , 0.98]	-
Lenox-Smith 2003	15	122	25	122	1.9%	0.60 [0.33 , 1.08]	
Wen-Yuan 2011	26	108	28	102	2.5%	0.88 [0.55 , 1.39]	
Subtotal (95% CI)		765		481	12.7%	0.76 [0.65 , 0.89]	
Total events:	207		181				•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	0; Chi² = 1.2			; ² = 0%			
Total (95% Cl)		7160		4438	100.0%	1.02 [0.92 , 1.12]	•
Total events:	1829		1118				ľ
		00 46	36 (P = 0.0	00001-12	500/		

Figure 33. Subgroup analysis for acceptability by treatment duration

4.6 Sensitivity Analyses

4.6.1 High/Unclear Risk of Bias in Random Allocation or Blinding

Figures 34 and 35 display sensitivity analyses among the two primary outcomes after removing studies with an unclear or high risk of bias rating in the domains *random sequence generation* and *blinding of participants and personnel*.

Figure 34 shows that removing 10 studies with an unclear or high risk of bias did not substantially change rate of treatment response (RR, 1.45; 95% CI: 1.28, 1.64; $I^2 = 67\%$; studies = 11; participants = 4,745) compared to the original analysis (Figure 4 (RR, 1.39; 95% CI: 1.27, 1.52; $I^2 = 64\%$; studies = 21; participants = 7,556)).

Figure 35 shows that removing 22 studies with an unclear or high risk of bias did not substantially change acceptability (RR, 0.90; 95% CI: 0.77, 1.06; $I^2 = 62\%$; studies = 12; participants = 5,250) compared to the original analysis (Figure 7 (RR, 1.02; 95% CI: 0.92, 1.12; $I^2 = 52\%$; studies = 34; participants = 11,598)).

	Antidepre	essants	Place	ebo		Risk ratio	Risk ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEF
✓ Allgulander 2001	273	399	60	130	9.1%	1.48 [1.22 , 1.81]	-	• ? • • ? •
× Allgulander 2004	102	182	55	188	0.0%	1.92 [1.48 , 2.48]		?? 🖶 🖶 ? 🖶
× Bose 2008	66	125	28	67	0.0%	1.26 [0.91 , 1.75]		? ? 🖶 🖶 🖶
× Bose 2008	65	125	28	67	0.0%	1.24 [0.90 , 1.73]		?? 🖶 🖶 🖶 🤃
✓ Brawman-Mintzer 2006	97	164	78	162	8.9%	1.23 [1.00 , 1.51]		
× Davidson 1999	87	176	35	98	0.0%	1.38 [1.02 , 1.88]		? ? 🖶 🖶 🖨 🖨
✓ Gommoll 2015	103	198	82	197	8.7%	1.25 [1.01 , 1.55]		
× Hackett 2003	200	354	44	97	0.0%	1.25 [0.98 , 1.58]		? ? 🖶 🖶 🖨 🖨
✓ Hartford 2007	165	326	60	161	8.4%	1.36 [1.08 , 1.70]		• ? • • ? • (
× Kasper 2009	55	125	59	128	0.0%	0.95 [0.73 , 1.25]		? ? 🖶 🖶 ? 🖶 (
✓ Koponen 2007	193	338	54	175	8.1%	1.85 [1.46 , 2.35]		🖶 ? 🖶 🖶 ? 🛑 (
✓ Lenox-Smith 2003	64	122	59	122	8.0%	1.08 [0.85 , 1.39]		
✓ Mahableshwarkar 2014	76	149	32	77	6.8%	1.23 [0.90 , 1.67]		
✓ Mahableshwarkar 2014	201	456	32	77	7.2%	1.06 [0.80 , 1.41]		
× Montgomery 2006	68	110	45	100	0.0%	1.37 [1.06 , 1.78]		? ? 🖶 🖶 🖨 🖨
✓ Nicolini 2009	245	392	69	163	9.1%	1.48 [1.21 , 1.79]	-	
× Nimatoudis 2004	22	24	6	22	0.0%	3.36 [1.68 , 6.72]		? ? 🖶 🖶 ? 🖨
× Rothschild 2012	77	145	72	144	0.0%	1.06 [0.85 , 1.33]		? ? ? ? ? 🔴
× Rynn 2008	67	168	51	159	0.0%	1.24 [0.93 , 1.67]		?????
✓ Stein 2008	45	63	27	58	6.6%	1.53 [1.12 , 2.11]		
✓ Stein 2014	89	139	24	65	6.2%	1.73 [1.23 , 2.44]	_	
✓ Stein 2014	92	139	24	65	6.2%	1.79 [1.28 , 2.52]	<u> </u>	
✓ Stein 2017	164	268	32	140	6.6%	2.68 [1.95, 3.68]		+ ? + + ? +
× Wen-Yuan 2011	74	107	53	100	0.0%	1.30 [1.04 , 1.63]		?? 🖶 🖶 ? 🖶
Total (95% CI)		3153		1592	100.0%	1.45 [1.28 , 1.64]		
Total events:	1807		633				•	
Heterogeneity: Tau ² = 0.03;	Chi ² = 36.3	9, df = 12	(P = 0.000)	3); l² = 6	7%	, H	1 0.2 0.5 1 2 5	-1 10
Test for overall effect: Z = 5								idepressants
Test for subgroup difference		· · · · ·						
0 P		-						
Risk of bias legend								

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 34. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo without studies with high/unclear risk of bias

	Antidepre	ssants	Place	bo		Risk ratio	Risk ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEF
/ Allgulander 2001	102	411	45	130	9.3%	0.72 [0.54 , 0.96]	_	• ? • • ? •
< Allgulander 2004	41	188	51	190	0.0%	0.81 [0.57 , 1.16]	-	??
Aventis-Sanofi 2008	20	114	17	126	0.0%	1.30 [0.72 , 2.36]		2 2 2 2 2 8
Baldwin 2006	83	543	15	139	5.7%	1.42 [0.84 , 2.38]	_	
(Bose 2008	29	131	18	70	0.0%	0.86 [0.52 , 1.44]	-	2 2 8 8 8 8
Bose 2008	37	133	18	70	0.0%	1.08 [0.67 , 1.75]		
Brawman-Mintzer 2006	51	168	46	170	8.5%	1.12 [0.80 , 1.57]	_	
Brawman-Mintzer 2009	12	28	7	14	0.0%	0.86 [0.44 , 1.69]		222222
Davidson 1999	84	203	36	104	0.0%	1.20 [0.88 , 1.63]		2 2 8 8 8 8
Davidson 2004	42	161	36	159	0.0%	1.15 [0.78 , 1.70]		
Feltner 2009	15	56	18	57	0.0%	0.85 [0.48 , 1.51]		
Gelenberg 2000	64	124	83	127	10.8%	0.79 [0.64 , 0.98]	-	
GlaxoSmithKline 2006	30	179	28	182	0.0%	1.09 [0.68 , 1.75]	-	
Gommoll 2015	57	201	40	201	8.2%	1.43 [1.00 , 2.03]		
Goodman 2001	32	129	33	128	0.2%	0.96 [0.63 , 1.46]	-	
Goodman 2002	31	149	31	145	0.0%	0.97 [0.63 , 1.51]		2 2 2 2 2 4
Hackett 2003	77	370	16	97	0.0%			
Hartford 2005	136	326	62	161	10.4%	1.26 [0.77 , 2.06] 1.08 [0.86 , 1.37]		
Hewett 2001	35	188	22	186	0.0%		-	
Kasper 2009	41	125	35	128		1.57 [0.96 , 2.58]		0 0 0 0 0 0
Lenox-Smith 2003	41	125	25	120	0.0% 4.9%	1.20 [0.82 , 1.75]		
/ Mahableshwarkar 2014	50	122	25 18	78		0.60 [0.33 , 1.08]		
Mahableshwarkar 2014 Mahableshwarkar 2014	120	468	10		6.4%	1.39 [0.87 , 2.21]	+	
				78	6.9%	1.11 [0.72 , 1.71]		
Montgomery 2006	34 117	113 411	20 68	101	0.0%	1.52 [0.94 , 2.46]		
Nicolini 2009				170	10.3%	0.71 [0.56 , 0.90]	-	
Nimatoudis 2004	5	24	11	22	0.0%	0.42 [0.17 , 1.01]		? ? 🖶 🖶 ? 🖨
Pfizer 2009	39	97	28	101	0.0%	1.45 [0.97 , 2.16]		
Pollack 2001	34	161	30	163	0.0%	1.15 [0.74 , 1.78]		3 3 3 🔒 🖨 🖶
Rickels 2000	83	253	19	96	0.0%	1.66 [1.07 , 2.57]		3 5 6 6 5 5
Rickels 2003	100	386	40	180	0.0%	1.17 [0.85 , 1.61]		???????
Rothschild 2012	27	152	38	152	0.0%	0.71 [0.46 , 1.10]		???????
< Rynn 2008	75	168	50	159	0.0%	1.42 [1.07 , 1.89]		????????
/ Stein 2008	5	63	4	58	1.5%	1.15 [0.32 , 4.08]		• • • • •
Stein 2014	26	142	17	65	5.5%	0.70 [0.41 , 1.20]		• • • • • ? •
Stein 2014	23	139	17	65	5.3%	0.63 [0.36 , 1.10]		• • • • ? •
Stein 2017	31	270	30	142	6.5%	0.54 [0.34 , 0.86]		😑 ? 🖶 🖶 ? 🖨
Wen-Yuan 2011	26	108	28	102	0.0%	0.88 [0.55 , 1.39]		?? 🖶 🖶 ? 🖶
otal (95% CI)		3544		1706	100.0%	0.90 [0.77 , 1.06]	•	
otal events:	880		488			-	•	
leterogeneity: Tau ² = 0.05; C	Chi² = 34.20), df = 13	(P = 0.001)	; I² = 629	6	01	0.2 0.5 1 2 5	10
								tidepressants
est for overall effect: Z = 1.2							· · · · ·	

(A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 35. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo without studies with high/unclear risk of bias

4.6.2 Dropout Rate >20%

Figures 36 and 37 display how the analyses for rate of treatment response measured as reduction of at least 50% on the HAM-A and acceptability for all antidepressants versus placebo, respectively, were affected by removing studies with a greater than 20% dropout rate.

Figure 36 shows that removing 16 studies with more than 20% dropout rate did not substantially change the rate of treatment response (RR, 1.59; 95% CI: 1.22, 2.06; $I^2 =$ 79%; studies = 5; participants = 1,632) compared to the original analysis (Figure 4 (RR, 1.39; 95% CI: 1.27, 1.52; $I^2 = 64\%$; studies = 21; participants = 7,556)).

Figure 37 shows that removing 24 studies with more than 20% dropout rate did not substantially change acceptability (RR, 0.97; 95% CI: 0.77, 1.23; $I^2 = 52\%$; studies = 10; participants = 3,636) compared to the original analysis (Figure 7 (RR, 1.02; 95% CI: 0.92, 1.12; $I^2 = 52\%$; studies = 34; participants = 11,598)).

tudy or Subgroup	Events	Total		Placebo				
<u> </u>			Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI	ABCDEF
	273	399	60	130	0.0%	1.48 [1.22 , 1.81]		+ ? + + ? +
Allgulander 2004	102	182	55	188	0.0%	1.92 [1.48 , 2.48]		?? 🖶 🖶 ? 🖶
Bose 2008	66	125	28	67	0.0%	1.26 [0.91 , 1.75]		?? 🗣 🖶 🖶
Bose 2008	65	125	28	67	0.0%	1.24 [0.90 , 1.73]		?? 🖶 🖶 🖶 🖶
Brawman-Mintzer 2006	97	164	78	162	0.0%	1.23 [1.00 , 1.51]		
Davidson 1999	87	176	35	98	0.0%	1.38 [1.02 , 1.88]		?? 🔁 🖶 🛑 🛑
Gommoll 2015	103	198	82	197	0.0%	1.25 [1.01 , 1.55]		+++++++++++++++++++++++++++++++++++++++
Hackett 2003	200	354	44	97	18.2%	1.25 [0.98 , 1.58]		?? 🕈 🖶 🖨 🖨
Hartford 2007	165	326	60	161	0.0%	1.36 [1.08 , 1.70]		
Kasper 2009	55	125	59	128	0.0%	0.95 [0.73 , 1.25]		?? 🖶 🖶 ? 🖶
Koponen 2007	193	338	54	175	0.0%	1.85 [1.46 , 2.35]		🖶 ? 🖶 🖶 ? 🖨
Lenox-Smith 2003	64	122	59	122	17.9%	1.08 [0.85 , 1.39]	-	🗧 🖶 🖶 🗧 🤗 🛑
Mahableshwarkar 2014	76	149	32	77	0.0%	1.23 [0.90 , 1.67]		
Mahableshwarkar 2014	201	456	32	77	0.0%	1.06 [0.80 , 1.41]		
Montgomery 2006	68	110	45	100	0.0%	1.37 [1.06 , 1.78]		?? 🖶 🖶 🖶 🖶
Nicolini 2009	245	392	69	163	0.0%	1.48 [1.21 , 1.79]		+++++++++++++++++++++++++++++++++++++++
Nimatoudis 2004	22	24	6	22	0.0%	3.36 [1.68 , 6.72]		?? 🖶 🖶 ? 🖨
Rothschild 2012	77	145	72	144	0.0%	1.06 [0.85 , 1.33]		?????
Rynn 2008	67	168	51	159	0.0%	1.24 [0.93 , 1.67]		??????
Stein 2008	45	63	27	58	16.3%	1.53 [1.12 , 2.11]		
Stein 2014	89	139	24	65	15.7%	1.73 [1.23 , 2.44]		• • • • ? •
Stein 2014	92	139	24	65	15.7%	1.79 [1.28 , 2.52]		••••
Stein 2017	164	268	32	140	16.2%	2.68 [1.95 , 3.68]		\varTheta ? 🗣 🗣 ? 🖨
Wen-Yuan 2011	74	107	53	100	0.0%	1.30 [1.04 , 1.63]		?? 🖶 🖶 ? 🖶
otal (95% CI)		1085		547	100.0%	1.59 [1.22 , 2.06]		
otal events:	654		210				•	
eterogeneity: Tau ² = 0.08; (Chi² = 23.31	1, df = 5 (F	P = 0.0003); l² = 79	%	0 1	0.2 0.5 1 2 5	⊣ 10
est for overall effect: Z = 3.4				-				idepressants
est for subgroup differences		1 A A A A A A A A A A A A A A A A A A A						

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 36. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all

antidepressants versus placebo excluding studies with more than 20% dropout rate

Study or Subgroup	Antidepre Events		Placel Events		Weight	Risk ratio IV, Random, 95%	Risk CI IV, Rando		RiskofBias ABCDEF(
× Allgulander 2001	102	411	45	130	0.0%	0.72 [0.54 , 0	.96]		
× Allgulander 2004	41	188	51	190	0.0%	0.81 [0.57 , 1	.16]		??
✓ Aventis-Sanofi 2008	20	114	17	126	8.4%	1.30 [0.72 , 2		-	2 2 2 2 2 0
✓ Baldwin 2006	83	543	15	139	9.6%	1.42 [0.84 , 2	.38]		
× Bose 2008	29	131	18	70	0.0%	0.86 [0.52 , 1			2 2 8 8 8 8 8
× Bose 2008	37	133	18	70	0.0%	1.08 [0.67 , 1	.75]		2 2 8 8 6 6 6
× Brawman-Mintzer 2006	51	168	46	170	0.0%	1.12 [0.80 , 1	.57]		
× Brawman-Mintzer 2009	12	28	7	14	0.0%	0.86 [0.44 , 1	.69]		???????
× Davidson 1999	84	203	36	104	0.0%	1.20 [0.88 , 1	.63]		2 2 8 8 8 8 8
× Davidson 2004	42	161	36	159	0.0%	1.15 [0.78 , 1	.70]		? ? 🖶 🖶 🖨 ? 🤅
× Feltner 2009	15	56	18	57	0.0%	0.85 [0.48, 1	.51]		2 2 8 8 8 2 4
× Gelenberg 2000	64	124	83	127	0.0%	0.79 [0.64 , 0	.98]		
GlaxoSmithKline 2006	30	179	28	182	10.4%	1.09 [0.68 , 1	.75]	_	? ? + + ? + (
X Gommoll 2015	57	201	40	201	0.0%	1.43 [1.00 , 2			
X Goodman 2001	32	129	33	128	0.0%	0.96 [0.63 , 1			2 2 2 2 2 4
× Goodman 2002	31	149	31	145	0.0%	0.97 [0.63 , 1			2 2 2 2 2 4
✓ Hackett 2003	77	370	16	97	10.1%	1.26 [0.77 , 2		-	2 2 🔒 🖶 🖨 🖨
× Hartford 2007	136	326	62	161	0.0%	1.08 [0.86 , 1		-	
✓ Hewett 2001	35	188	22	186	10.0%	1.57 [0.96 , 2	-		? ? ? ? ? .
× Kasper 2009	41	125	35	128	0.0%			-	2 2 4 4 2 4
✓ Lenox-Smith 2003	15	122	25	122	8.5%	0.60 [0.33 , 1			
× Mahableshwarkar 2014	50	156	18	78	0.0%				
× Mahableshwarkar 2014	120	468	18	78	0.0%	1.11 [0.72 , 1			
× Montgomery 2006	34	113	20	101	0.0%	1.52 [0.94 . 2			2 2 8 8 8 8 8
× Nicolini 2009	117	411	68	170	0.0%	0.71 [0.56, 0			
× Nimatoudis 2004	5	24	11	22	0.0%	0.42 [0.17 , 1			2 2 4 4 2 4
× Pfizer 2009	39	97	28	101	0.0%	1.45 [0.97 , 2			228828
Pollack 2001	34	161	30	163	11.0%	1.15 [0.74 , 1		-	2 2 2 🗕 🖨 🖨
X Rickels 2000	83	253	19	96	0.0%	1.66 [1.07 , 2	-	-	2 2 4 4 2 4
X Rickels 2003	100	386	40	180	0.0%	1.17 [0.85 , 1			2 2 2 2 2 4
X Rothschild 2012	27	152	38	152	0.0%	0.71 [0.46 , 1			22222
× Rynn 2008	75	168	50	159	0.0%	1.42 [1.07 , 1			2 2 2 2 2 4
✓ Stein 2008	5	63	4	58	2.9%	1.15 [0.32 , 4	-	_	
✓ Stein 2014	26	142	17	65	9.3%	0.70 [0.41 , 1			
✓ Stein 2014	23	139	17	65	9.0%	0.63 [0.36 , 1	•		
✓ Stein 2017	31	270	30	142	10.7%	0.54 [0.34 , 0		-	• ? • • ? •
X Wen-Yuan 2011	26	108	28	102	0.0%	0.88 [0.55 , 1	-		2 2 8 8 2 8
Total (95% CI)		2291		1345	100.0%	0.97 [0.77 , 1	.23]		
Total events:	379		221			•			
Heterogeneity: Tau ² = 0.08; (, df = 10 (l² = 52%			0.1 0.2 0.5	2 5 1	0
Test for overall effect: Z = 0.2							Higher in placebo	Higher in anti	
Test for subgroup differences							2	-	-

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 37. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo excluding studies with more than 20% dropout rate

4.6.3 Missing Standard Deviations

Figure 38 displays how the analysis for change in symptom levels for all antidepressants versus placebo was affected by removing 6 studies for which the SD had to be imputed or pooled from other studies.

The results suggested that removing studies with imputed or pooled SD did not substantially change the analysis (MD, -2.66; 95% CI: -3.50, -1.82; $I^2 = 83\%$; studies = 29; participants = 9,112) compared to the original (Figure 16 (MD, -2.72; 95% CI: -3.45, -2.00; $I^2 = 80\%$; studies = 35; participants = 11,519)).

	Antid	lepressa	nts	F	Placebo			Mean difference	Mean difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEF
× Allgulander 2001	-15.2	8.4	399	-11	8.4	130	0.0%	-4.20 [-5.86 , -2.54]		
✓ Allgulander 2004	-11.7	8.1	182	-8	8.2	188	3.5%	-3.70 [-5.36 , -2.04]	-	?? 🖶 🖶 ? 🖶
✓ Baldwin 2006	-15.8	7.8	536	-14.2	7.8	138	3.6%	-1.60 [-3.06 , -0.14]	-	
✓ Bose 2008	-11.4	7.4	125	-9.2	7.8	67	3.1%	-2.20 [-4.47 , 0.07]		2 2 🖶 🖶 🖶 🕄
✓ Bose 2008	-10.9	7.5	125	-9.2	7.8	67	3.1%	-1.70 [-3.98 , 0.58]		2 2 🖶 🖶 🛑 😫 🤅
✓ Brawman-Mintzer 2006	-12.7	91.8	164	-11.2	93.2	162	0.2%	-1.50 [-21.58 , 18.58]	• •	
✓ Brawman-Mintzer 2009	10.4	6	26	9.4	7.3	14	1.9%	1.00 [-3.47 , 5.47]		???????
✓ Davidson 1999	13.4	7.8	174	15.6	7.2	98	3.4%	-2.20 [-4.04 , -0.36]		2 2 🔒 🖶 🖨 🖨
✓ Davidson 2004	-11.3	7.5	154	-7.4	7.4	153	3.5%	-3.90 [-5.57 , -2.23]		? ? 🖶 🖶 🖨 ? 🤅
✓ Feltner 2009	-11	5.8	56	-7.4	5.4	57	3.3%	-3.60 [-5.67 , -1.53]	-	?? 🔒 🖨 🗭 ? 🕻
X Gelenberg 2000	-13.4	18.1	115	-8.7	21.6	123	0.0%	-4.70 [-9.75 , 0.35]		
✓ GlaxoSmithKline 2006	-10.3	7.7	177	-9.5	7.7	181	3.5%	-0.80 [-2.40 , 0.80]	-	?? 🔒 🖨 ? 🖨 1
✓ Gommoll 2015	-11.2	7.4	198	-9.9	7.5	197	3.6%	-1.30 [-2.77, 0.17]	_	
✓ Goodman 2001	-9.6	6.7	124	-7.7	6.8	128	3.5%	-1.90 [-3.570.23]		?????
✓ Goodman 2002	-9.2	6	143	-7.6	5.9	138	3.7%	-1.60 [-2.99 , -0.21]	-	2 2 2 2 2 4 4
× Hackett 2003	14.5	7.8	354	15.9	7.2	97	0.0%	-1.40 [-3.05 , 0.25]		
✓ Hartford 2007	-12.1	8.7	326	-9.2	8.5	161	3.5%	-2.90 [-4.52 , -1.28]	-+-	
✓ Hewett 2001	-12.4	10.8	181	-11.3	10.8	183		-1.10 [-3.32 , 1.12]		· · · · · · ·
✓ Kasper 2009	-12	10.1	125	-11.7	10.2	128	3.0%	-0.30 [-2.80 , 2.20]		2 2
× Koponen 2007	-12.7	8.8	338	-8.4	8.5	175	0.0%	-4.30 [-5.87 , -2.73]		
✓ Lenox-Smith 2003	-14.1	8.4	122	-12	8.4	122		-2.10 [-4.21, 0.01]	-+-	
✓ Mahableshwarkar 2014	-13.9	6.5	149	-11.3	6.5	77	3.4%		-	
✓ Mahableshwarkar 2014	-11.8	6.5	343	-11.3	6.5	77	3.5%	-0.50 [-2.11 , 1.11]		
✓ McLeod 1992	12.4	6.7	14	16.3	8.3	14		-3.90 [-9.49 , 1.69]		2 2
✓ Montgomery 2006	-14.1	8.4	110	-11.6	8	100		-2.50 [-4.72 , -0.28]		2 2
√ Nicolini 2009	-15.3	8.8	392	-11.6	8.9	163		-3.70 [-5.32 , -2.08]		
✓ Nimatoudis 2004	-19.2	1.7	24	-10.8	2.7	22		-8.40 [-9.72 , -7.08]	_	
✓ Pfizer 2009	-11.1	6.6	89	-10.6	6.9	96		-0.50 [-2.45 , 1.45]	-]	2 2
✓ Pollack 2001	-13.3	10.2	161	-10.7	10.2	163			T	2 2 2
× Rickels 2000	-11.7	10.1	253	-9.5	10.2	96		-2.20 [-4.59 , 0.19]		
✓ Rickels 2003	-12.3	8.6	385	-9.3	8.7	180		-3.00 [-4.53 , -1.47]	+	? ? ? ? ? 🖨
✓ Rothschild 2012	-12.6	7.8	145	-13.2	7.9	144		0.60 [-1.21 , 2.41]		2 2 2 2 2 4
× Rynn 2008	-8.1	8.8	168	-5.9	8.5	159		-2.20 [-4.08 , -0.32]		
✓ Stein 2008	-16.6	8.9	63	-13.2	9.5	58		-3.40 [-6.69 , -0.11]		
✓ Stein 2008	-10.0	9.4	139	-10.6	9.5	65		-5.00 [-7.79 , -2.21]		
✓ Stein 2014	-15.6	8.2	139	-10.6	9.5	65		-5.00 [-7.68 , -2.32]		
✓ Stein 2014 ✓ Stein 2017	-15.0	8.5	268	-10.0	9.2	140		-9.00 [-10.83 , -7.17]		
✓ Stell 2017 ✓ Wen-Yuan 2011	-15.9	8.3	200	-0.9	8.3	140		-2.50 [-4.76 , -0.24]	-	
V Well-Tuali 2011	-14.5	0.0	107	-11.0	0.0	100	3.176	-2.50 [-4.76 , -0.24]	-	C C U U C U (
Total (95% CI)			5466			3646	100.0%	-2.66 [-3.50 , -1.82]	♦	
Heterogeneity: Tau ² = 4.52;			31 (P < 0.	00001); l²	= 83%					
Test for overall effect: Z = 6.									-20 -10 0 10	20
Test for subgroup difference	s: Not appl	icable						Favours	antidepressants Favours pl	acebo
Risk of bias legend										

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 38. Sensitivity analysis with risk of bias assessment: Change in symptom levels excluding studies with imputed SD

4.6.4 **Fixed-Effect Models**

Figures 39 and 40 display how the analyses for rate of treatment response measured as reduction of at least 50% on the HAM-A and acceptability for all antidepressants versus placebo, respectively, were affected by using a fixed-effects analysis instead of a random effects analysis.

Figure 39 shows that a fixed effects analysis did not substantially change rate of treatment response (RR, 1.37; 95% CI: 1.30, 1.45; $I^2 = 64\%$; studies = 21; participants = 7,556) compared to the original analysis (Figure 4 (RR, 1.39; 95% CI: 1.27, 1.52; $I^2 = 64\%$; studies = 21; participants = 7,556)).

Figure 40 shows that a fixed effects analysis did not substantially change acceptability (RR, 1.01; 95% CI: 0.94, 1.07; $I^2 = 52\%$; studies = 34; participants = 11,598) compared to the original analysis (Figure 7 (RR, 1.02; 95% CI: 0.92, 1.12; $I^2 = 52\%$; studies = 34; participants = 11,598)).

	Antidepre	essants	Place	bo		Risk ratio	Ris	k ratio		Ri	sk of	Bia	s
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixe	ed, 95% Cl	Α	в	C D	Е	F
✓ Allgulander 2001	273	399	60	130	7.2%	1.48 [1.22 , 1.81]	+	•	? (• •	?	•
✓ Allgulander 2004	102	182	55	188	4.3%	1.92 [1.48 , 2.48]		?	? (• •	?	•
✓ Bose 2008	66	125	28	67	2.6%	1.26 [0.91 , 1.75]		?	? (• •	•	•
✓ Bose 2008	65	125	28	67	2.6%	1.24 [0.90 , 1.73]		?	? (• •	•	•
✓ Brawman-Mintzer 2006	97	164	78	162	6.8%	1.23 [1.00 , 1.51	1	_			• •	?	•
✓ Davidson 1999	87	176	35	98	3.0%	1.38 [1.02 , 1.88]		?	? (• •	•	•
✓ Gommoll 2015	103	198	82	197	6.2%	1.25 [1.01 , 1.55]	_	•	•	• •	?	•
✓ Hackett 2003	200	354	44	97	5.0%	1.25 [0.98 , 1.58]		?	?	• •	•	•
✓ Hartford 2007	165	326	60	161	5.5%	1.36 [1.08 , 1.70]		•	?	• •	?	•
✓ Kasper 2009	55	125	59	128	3.8%	0.95 [0.73 , 1.25	- 1	+	?	?	• •	?	•
✓ Koponen 2007	193	338	54	175	4.9%	1.85 [1.46 , 2.35]		•	?	• •	?	
✓ Lenox-Smith 2003	64	122	59	122	4.5%	1.08 [0.85 , 1.39]	_			• •	?	
✓ Mahableshwarkar 2014	76	149	32	77	3.0%	1.23 [0.90 , 1.67]			•	• •	•	•
✓ Mahableshwarkar 2014	201	456	32	77	3.5%	1.06 [0.80 , 1.41]	-		•	• •	•	•
✓ Montgomery 2006	68	110	45	100	4.1%	1.37 [1.06 , 1.78]		?	?	• •	•	•
✓ Nicolini 2009	245	392	69	163	7.4%	1.48 [1.21 , 1.79]	-	•	•	•	?	•
✓ Nimatoudis 2004	22	24	6	22	0.6%	3.36 [1.68 , 6.72]		. ?	?	• •	?	•
✓ Rothschild 2012	77	145	72	144	5.6%	1.06 [0.85 , 1.33]	+	?	? (? ?	?	•
✓ Rynn 2008	67	168	51	159	3.3%	1.24 [0.93 , 1.67]		?	? (? ?	?	•
✓ Stein 2008	45	63	27	58	2.8%	1.53 [1.12 , 2.11]				• •	•	
✓ Stein 2014	89	139	24	65	2.4%	1.73 [1.23 , 2.44]			•	• •	?	•
✓ Stein 2014	92	139	24	65	2.4%	1.79 [1.28 , 2.52]		•	•	• •	?	•
✓ Stein 2017	164	268	32	140	2.8%	2.68 [1.95 , 3.68	1		•	?	•	?	
✓ Wen-Yuan 2011	74	107	53	100	5.6%	1.30 [1.04 , 1.63]		?	? (• •	?	•
Total (95% CI)		4794		2762	100.0%	1.37 [1.30 , 1.45	1	•					
Total events:	2690		1109					1					
Heterogeneity: Chi ² = 64.19	9, df = 23 (P	< 0.00001	l); l² = 64%				0.1 0.2 0.5	1 2 5	10				
Test for overall effect: Z = 1	1.63 (P < 0.0	00001)					Favours placebo	Favours a		sants			
Test for subgroup difference	es: Not appli	cable											

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 39. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo using fixed effects model

	Antidepre	ssants	Placet	00		Risk ratio	D	Risk ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95	% CI	IV, Fixed, 95% CI	ABCDEFG
✓ Allgulander 2001	102	411	45	130	4.9%	0.72 [0.54 ,	0.961	-	• ? • • ? • •
✓ Allgulander 2004	41	188		190	3.2%	0.81 [0.57 ,	-		? ? ? .
✓ Aventis-Sanofi 2008	20	114		126	1.2%	1.30 [0.72 ,	-		2 2 2 2 2 0 0
✓ Baldwin 2006	83	543		139	1.6%	1.42 [0.84 ,	-		
✓ Bose 2008	29	131	18	70	1.6%	0.86 [0.52]	-		2 2
✓ Bose 2008	37	133		70	1.8%	1.08 [0.67 ,	-		2 2
✓ Brawman-Mintzer 2006	51	168		170	3.7%	1.12 [0.80 ,	-		
✓ Brawman-Mintzer 2009	12	28		14	0.9%	0.86 [0.44 ,	-		
✓ Davidson 1999	84	203		104	4.3%	1.20 [0.88 ,			? ?
✓ Davidson 2004	42	161	36	159	2.8%	1.15 [0.78 ,	-	T	2 2
✓ Feltner 2009	15	56		57	1.2%	0.85 [0.48 ,			2 2
✓ Gelenberg 2000	64	124		127	9.2%	0.79 [0.64 ,	-		
✓ GlaxoSmithKline 2006	30	179		182	1.9%	1.09 [0.68 ,	-	-	2 2 4 4 2 4 3
✓ GlaxoSiminitane 2000 ✓ Gommoll 2015	57	201	40	201	3.3%	1.43 [1.00 ,	-		
✓ Goodman 2001	32	129		128	2.3%	0.96 [0.63 ,			
✓ Goodman 2001	32	129		145	2.3%	0.96 [0.63 ,		-1-	
✓ Goodman 2002 ✓ Hackett 2003	77	370		97	1.7%		-	-1-	??????? ???
✓ Hacken 2003 ✓ Hartford 2007	136	326		161		1.26 [0.77 ,	-		
					7.6%	1.08 [0.86 ,	-		
✓ Hewett 2001	35	188		186	1.7%	1.57 [0.96 ,			· · · · · · · · · · · · · · · · · · ·
✓ Kasper 2009	41	125		128	2.9%	1.20 [0.82 ,	-	- +	? ? ● ● ? ●
✓ Lenox-Smith 2003	15	122		122	1.2%	0.60 [0.33 ,			
✓ Mahableshwarkar 2014	50	156		78	1.9%	1.39 [0.87 ,	-	+	
✓ Mahableshwarkar 2014	120	468		78	2.2%	1.11 [0.72 ,	-		
✓ Montgomery 2006	34	113		101	1.8%	1.52 [0.94 ,	-		?? 🕈 🖶 🖶 🗬
✓ Nicolini 2009	117	411	68	170	7.2%	0.71 [0.56 ,	-		$\bullet \bullet \bullet \bullet \bullet ? \bullet ?$
✓ Nimatoudis 2004	5	24		22	0.5%	0.42 [0.17 ,			?? 🗣 🗣 ? 🖨 ?
✓ Pfizer 2009	39	97	28	101	2.6%	1.45 [0.97 ,	-		?? 🕈 🖶 ? 🖶 ?
✓ Pollack 2001	34	161	30	163	2.1%	1.15 [0.74 ,	-		????
✓ Rickels 2000	83	253		96	2.1%	1.66 [1.07 ,	-		2 3 🖶 🖶 3 🖷 🕯
✓ Rickels 2003	100	386		180	4.0%	1.17 [0.85 ,	-	+	3 3 3 3 3 4
✓ Rothschild 2012	27	152		152	2.2%	0.71 [0.46 ,	-		??????
✓ Rynn 2008	75	168		159	5.1%	1.42 [1.07 ,	-		???????
✓ Stein 2008	5	63		58	0.3%	1.15 [0.32 ,	-		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet$
✓ Stein 2014	26	142		65	1.4%	0.70 [0.41 ,			
✓ Stein 2014	23	139		65	1.4%	0.63 [0.36 ,			•••••
✓ Stein 2017	31	270	30	142	2.0%	0.54 [0.34 ,	0.86]		🕒 ? 🖶 🖶 ? 🖨 🧲
✓ Wen-Yuan 2011	26	108	28	102	2.0%	0.88 [0.55 ,	1.39]		?? 🕈 🖶 ? 🖶 🍯
Total (95% CI)		7160		4438	100.0%	1.01 [0.94 ,	1.07]		
Total events:	1829		1118					Ĭ	
Heterogeneity: Chi ² = 74.93	, df = 36 (P	= 0.0002)	; I² = 52%					0.1 0.2 0.5 1 2 5 1	0
Test for overall effect: Z = 0	.17 (P = 0.87	7)					н	ligher in placebo Higher in anti	
Test for subgroup difference	es: Not appli	cable							
Risk of bias legend									
(A) Random sequence gene	eration (sele	ction bias	6						
(B) Allocation concealment			/						
(C) Blinding of participants			mance bias						
(D) Blinding of outcome ass									
(E) Incomplete outcome dat			10.3)						
(F) Selective reporting (repo		103/							
(G) Other bias	ming bias)								

Figure 40. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo using fixed effects model

Furthermore, a Mantel-Haenszel fixed-effect model was run post-hoc on outcomes that were found to be 'rare' as an exploratory analysis to test the robustness of the results of the random effects model for certain outcomes. The Cochrane Handbook does not specify a threshold for which events are considered 'rare', so this was done on analyses comparing all antidepressants versus placebo for the outcomes *agitation/anxiety* and *suicide wishes/gestures/attempts*. Both these outcomes had fewer than 10 studies contributing to the meta-analysis and had some arms with 'zero' cells. The Mantel-Haenszel fixed effects model is thought to have better statistical properties when there are few, or rare, events [86]. The Mantel-Haenszel fixed effect analysis for agitation/anxiety was not substantially different compared to the original analysis (RR, 1.02; 95% CI: 0.72, 1.46; $I^2 = 1\%$; studies = 6; participants = 2,026). The Mantel-Haenszel fixed effect analysis for suicide wishes/gestures/attempts was not substantially different from the original analysis (RR, 0.77; 95% CI: 0.43, 1.40; $I^2 = 0\%$; studies = 3; participants = 802).

4.7 Publication Bias

This section displays funnel plots which were used to assess publication bias among meta-analyses for which more than 10 studies contributed to the analysis. The funnel plots were created using RevMan Web and were assessed visually for asymmetry. There were 9 outcomes which had more than 10 studies: rate of treatment response measured as a reduction of at least 50% on the HAM-A (Figure 41), acceptability (Figure 42), rate of treatment response (defined by study authors) (Figure 43), remission rate (Figure 44), change in symptom levels (Figure 45), total number of patients reporting adverse effects (Figure 46), sleepiness/drowsiness (Figure 47), dropouts due to a lack of efficacy (Figure 48) and dropouts due to adverse effects (Figure 49). All the funnel plots assessed were for the analyses comparing all antidepressants to placebo. Figures 41-46 and 49 show clustering near the top of the plot suggesting there was small-study bias. Figures 47 and 48 show a more symmetric plot, although Figure 47 suggests that small negative studies may have been missed. Funnel plots for the outcomes agitation/anxiety, suicide wishes/gestures/attempts, and average score/change in quality of life/satisfaction were not assessed because less than 10 studies contributed to the analyses.

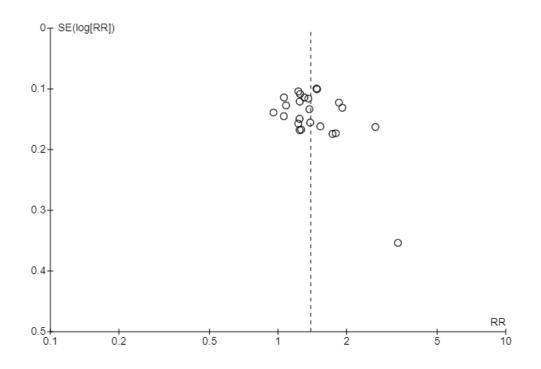


Figure 41. Funnel plot for rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo

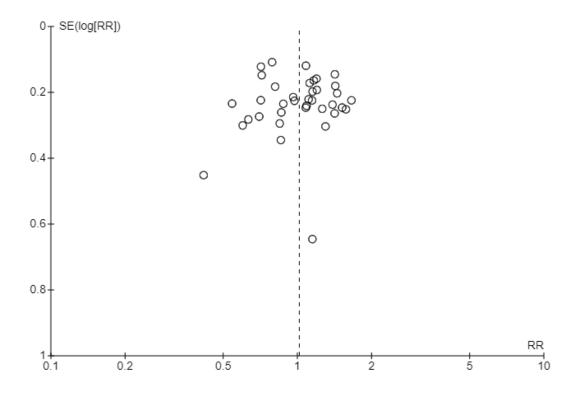


Figure 42. Funnel plot for acceptability for all antidepressants versus placebo

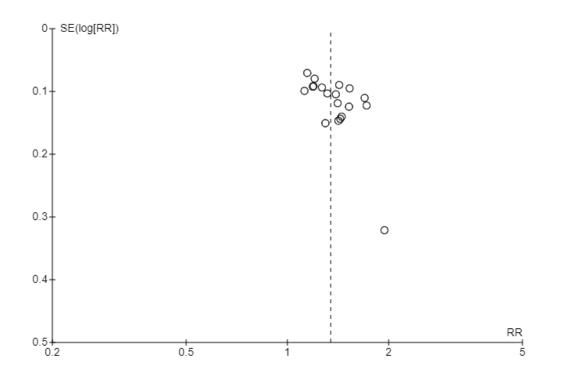


Figure 43. Funnel plot for rate of treatment response (defined by study authors) for all antidepressants versus placebo

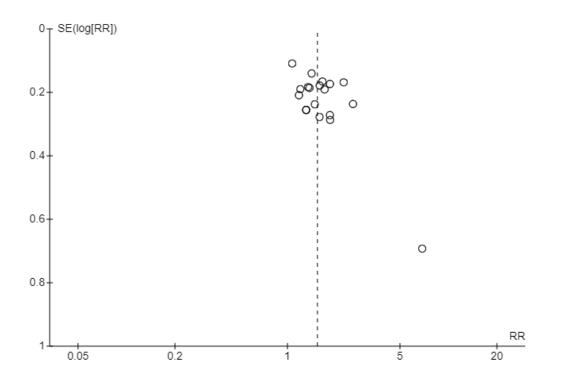


Figure 44. Funnel plot for remission rate for all antidepressants versus placebo

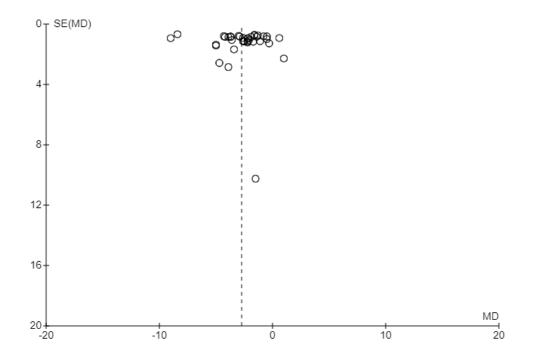


Figure 45. Funnel plot for change in symptom levels for all antidepressants versus placebo

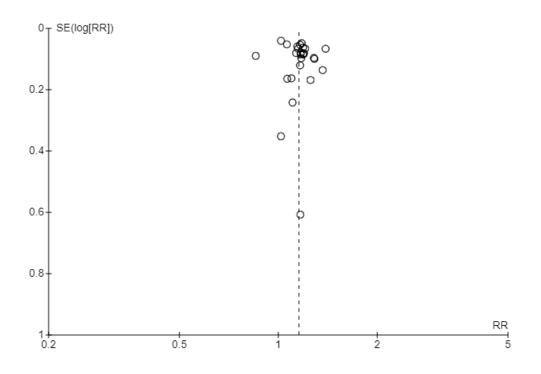


Figure 46. Funnel plot for total number of patients reporting adverse effects for all antidepressants versus placebo

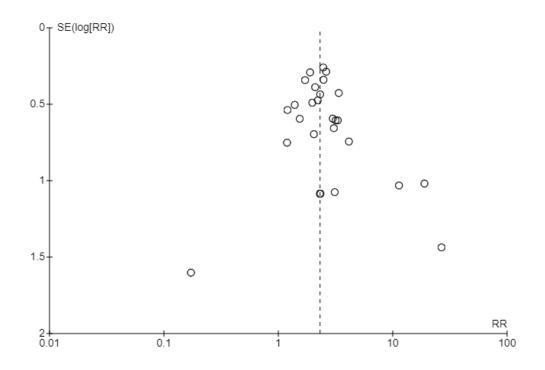


Figure 47. Funnel plot for sleepiness/drowsiness for all antidepressants versus placebo

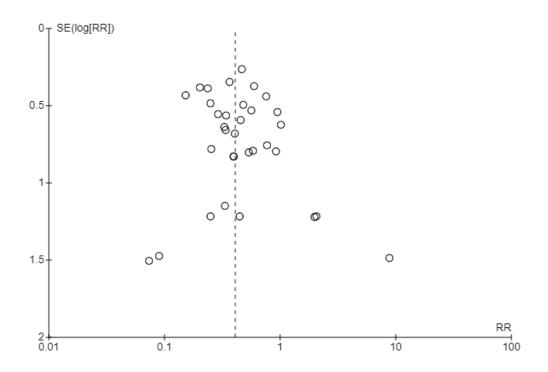


Figure 48. Funnel plot for dropouts due to lack of efficacy for all antidepressants versus placebo

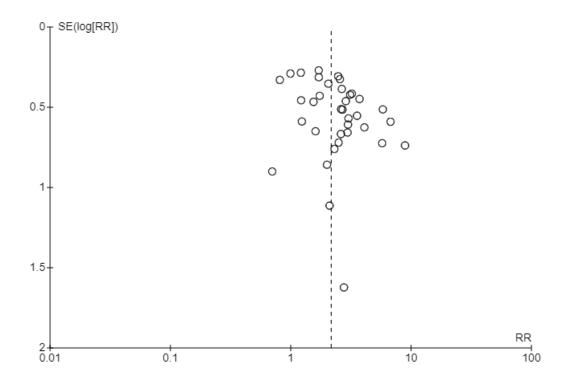


Figure 49. Funnel plot for dropouts due to adverse effects for all antidepressants versus placebo

Chapter 5

5 Discussion

5.1 Summary of Main Results

A total of 38 studies were included in this review (12,570 participants). For the two primary outcomes, there was very low-quality evidence showing a benefit for all antidepressants over placebo in rate of treatment response measured as a 50% or more reduction on the HAM-A scale. Analyses of different classes of antidepressants (SSRIs, SNRIs, and 'Others') also showed a benefit over placebo. There was very low-quality evidence showing no difference between all antidepressants and placebo for acceptability. Similar results were found among different classes of antidepressants (SSRIs, SNRIs, and 'Others').

Secondary outcomes showed a benefit for all antidepressants over placebo for the rate of treatment response (defined by study authors). Similar results were found for SSRIs and SNRIs. A trend towards benefit was seen for the 'Other' antidepressants but the confidence interval included the potential for a null effect. All antidepressants and different classes of antidepressants (SSRIs, SNRIs, and 'Others') also showed a benefit over placebo for remission rates. Similar results were found for changes in symptom levels, although one study looking at TCAs (imipramine) showed no benefit in reducing symptom levels compared to placebo.

Limited evidence showed improvements with SSRIs, SNRIs and all antidepressants over placebo, in quality of life measures. Quality of life measures allow researchers to understand the impact of the treatments on patients' lives, such as their overall functioning, wellbeing, and satisfaction, from the perspective of the patient [135, 136]. In this review, the Q-LES-Q was used as the primary patient-reported quality of life measure. The Q-LES-Q rates the patient's overall satisfaction in subjective domains such as family and social relationships, physical health, work, economic status, daily functioning etc. The Q-LES-Q was chosen because it has previously shown good psychometric properties in GAD as well as good reliability, validity and stability in other

psychiatric disorders [136]. Other measures of quality of life that were not used in our review tend to be more disorder specific and less generalizable compared to the Q-LES-Q [136].

In general, more patients reported adverse effects in the antidepressant group compared to the placebo group. This was consistent among all classes of antidepressants (SSRIs, SNRIs, 'Others'). Regarding specific adverse effects, more patients reported sleepiness/drowsiness among all antidepressants compared to placebo and among each class of antidepressant (SSRIs, SNRIs, 'Others') compared to placebo. There were no differences between all antidepressants and placebo and classes of antidepressants and placebo in patients reporting suicide wishes/gestures/attempts and in patients reporting agitation/anxiety. However, the number of events was too low to rule out a possible difference.

Very-low quality evidence showed fewer people dropping out due to a lack of efficacy in the antidepressant group compared to the placebo group. Similar results were found among different classes of antidepressants (SSRIs, SNRIs, and 'Others'). Antidepressants seemed to be less tolerable than placebo, as analyses looking at all antidepressants and different classes of antidepressants (SSRIs, SNRIs and 'Others') showed higher dropouts due to adverse effects compared to placebo, although the quality of evidence was judged to be very-low.

5.2 Overall Completeness and Applicability of Evidence

The comprehensive search was able to identify a number of published and unpublished studies for inclusion in this review. These studies reported on many of the predefined outcomes in the protocol and predominantly compared SSRIs, SNRIs, and 'Other' antidepressants to placebo. The SSRIs that were investigated were escitalopram, paroxetine, and sertraline. The SNRIs that were investigated were duloxetine and venlafaxine, while imipramine was the only TCA that was included. 'Other' antidepressants that studies investigated were agomelatine, vilazodone, and vortioxetine. This allowed for a considerable number of patients to be included, and useful information

to be derived, for these classes of antidepressants on several predefined efficacy and acceptability measures.

Despite the comprehensive search, no studies were found comparing MAOIs, NaSSAs, NDRIs or NRIs to placebo. There were also no studies that were included that compared the following SSRIs to placebo: fluoxetine, fluvoxamine, and citalopram; the following SNRIs to placebo: desvenlafaxine and milnacipran; and the following TCAs to placebo: amitriptyline, amoxapine, clomipramine, desipramine, dosulepin/dothiepin, doxepin, lofepramine, maprotiline, nortriptyline, proptriptyline, and trimipramine. 'Other' antidepressants for which no studies were included were: trazodone, nefazodone, mianserin, maprotiline, and non-conventional herbal products.

Furthermore, no data that could be synthesized were found for the following outcomes: falls, hypotension, death by suicide, subjective memory impairment, deaths, and total number of patients experiencing withdrawal. This precluded the ability for any conclusions to be made about these outcomes.

The inclusion and exclusion criteria may have limited the applicability of the results. For example, patients with other medical comorbidities were excluded from this review. Although other secondary psychiatric comorbidities were allowed, only two studies included patients with other secondary psychiatric comorbidities. Given that many people with GAD often suffer from other psychiatric and medical comorbidities, the population in this review may not be representative of the typical GAD population. For example, people with GAD often experience comorbid pain syndromes, hypertension, and cardiovascular and gastric conditions [4]. Some psychiatric conditions that have been found to be commonly comorbid among people with GAD are major depressive disorder, social phobia, specific phobia, bipolar disorder, alcohol abuse disorder, and panic disorder [137, 138]. Future reviews and studies may consider also including participants with such comorbid conditions.

Studies that were included in this review also inherently had their own inclusion criteria that further limited the applicability of the results. Studies often excluded patients taking other medications, to prevent interference with the study results. The high frequency of

comorbidities among people with GAD often leads to the use of additional medications. For example, it is common in clinical practice for those initiating treatment with an SSRI or SNRI to also take a benzodiazepine as adjunctive treatment to provide faster relief of symptoms while waiting for the effects of the antidepressants to begin [139]. Conversely, people with comorbid GAD and bipolar disorder may also take additional mood stabilizers [140]. Studies included in this review, however, largely excluded concomitant use of psychotropic drugs to prevent interference with the study drug, and ultimately, the study findings.

Most of the included studies restricted their patient population to those who met criteria for moderate to severe GAD. It is possible that baseline severity moderates the efficacy (measured using the HAM-A) of antidepressants in GAD. For example, one study found that, after 8 weeks, those with higher baseline severity showed greater symptom reductions compared to those with lower baseline severity [141]. Unfortunately, no longer term studies were found (i.e., longer than 28 weeks). Nevertheless, this is important to consider, as the results of this review may not be applicable to those who may still have considerable anxiety symptoms but did not meet the minimum baseline severity that was required for inclusion among the individual studies.

5.3 Quality of Evidence

The quality of evidence was assessed for four outcomes based on GRADE guidelines. The outcomes chosen were: (i) rate of treatment response measured as a reduction of at least 50% on the HAM-A, (ii) acceptability, (iii) dropouts due to a lack of efficacy, and (iv) dropouts due to adverse effects. The results of this review were considered very lowquality based on GRADE methodology. This means that we have very low confidence that the effect estimates for the two primary outcomes and for dropouts due to lack of efficacy and adverse effects, are close to the true effect. The evidence for risk of bias was downgraded because a large proportion of studies in the review had an unclear or high risk of bias in several domains. No studies had an overall low risk of bias and the distribution of risk of bias among the domains differed between studies. Many studies failed to describe random sequence generation and allocation concealment, resulting in an unclear risk of bias. This highlights the need for more rigorous reporting criteria. Furthermore, there were some concerns with incomplete outcome data as many studies had a high dropout rate. Selective outcome reporting was also a concern. One study [105] that mentioned it would report the rate of treatment response, measured as a reduction of at least 50% on the HAM-A, did not report the LOCF data for the antidepressant group compared to placebo at endpoint. Other studies [99, 122, 126, 132] mentioned they would report the rate of treatment response (defined as a CGI-I score of 1 or 2) but either failed to report it altogether, failed to report the significance, or failed to report the direction of the relationship. One study [114] only mentioned that antidepressants showed significant improvements compared to placebo in remission rates defined as a score of 1 on CGI-I, without giving more details. Another study [99] only mentioned that there were no differences between the antidepressant and placebo groups in remission rate defined as a HAM-A total score of 7 or less. One study [125] only mentioned that sleepiness/drowsiness was an adverse effect that was frequently experienced by the participants, but no other details were provided. It was unclear why acceptability, dropouts due to lack of efficacy, and dropouts due to adverse effects were not reported in some studies. The authors of all these studies were contacted for details, but only two replied and could not provide additional information. The general lack of information and inconsistency in the findings between the studies made it difficult to determine how, and whether, their inclusion may have affected the results of the meta-analyses in this review. However, given the small sample size of the studies with missing information relative to the large sample size for each outcome, it is unlikely that their inclusion would have greatly affected the results. The exception is with the outcome *average change in quality* of life/satisfaction. Three studies [102, 114, 119] only mentioned that the antidepressant showed improvements over placebo in Q-LES-Q scores but the data for each treatment group were not fully reported and could not be extracted. One study found a significant improvement while the other two did not. Given the relatively small sample size for the meta-analysis of this outcome, two studies that found nonsignificant results may have slightly attenuated the effect estimate. One study [130] said it would report this outcome but did not.

Furthermore, the quality of evidence for inconsistency was downgraded by one level for rate of treatment response and acceptability due to substantial (64%) and moderate (52%)

heterogeneity, respectively. Dropouts due to a lack of efficacy and dropouts due to adverse effects had low heterogeneity, therefore the quality of evidence was not downgraded. Heterogeneity can occur for several reasons, including clinical and methodological differences between studies. Although this review had strict inclusion and exclusion criteria, studies in this review differed in terms of the baseline severity of the participants, drug types, dosages, length of follow up, settings, and risk of bias among others. Although random-effects meta-analysis accounts for some unexplained heterogeneity, this should still be investigated to see whether the effects differ between samples with heterogeneous characteristics. In the current review, none of the sensitivity and subgroup analyses substantially affected the results compared to the original analysis, although the power of the subgroup analyses were generally limited due to a lack of sufficient number of studies across all subgroups. Future studies should consider further investigating potential sources of heterogeneity. For example, different drug dosages were not investigated in this review but could cause differences in effect. Further investigations of sources of heterogeneity could provide stronger conclusions about why it may be occurring and whether effects differ among different subgroups.

Participants with other serious medical comorbidities were excluded from this review and there were limited studies that included participants with secondary psychiatric comorbidities. Since many people with GAD also suffer from other medical and psychiatric comorbidities, the quality of evidence was downgraded by one level for indirectness. Future reviews and even RCTs, should investigate the efficacy of antidepressants without excluding participants with comorbidities which were discussed above. This would increase the applicability of the results and increase the confidence that the effect estimates are representative of the true effect in the general population.

Imprecision refers to the precision of the effect estimates [92]. When evaluating imprecision, it is important to consider the 95% confidence interval, the optimal information size (OIS), the event rate and sample size for each treatment group, and the threshold for appreciable benefit and harm [92]. The optimal information size requires the total number of patients included in a review to be more than a standard sample size calculation to have higher confidence in the precision of the results [92]. For

dichotomous outcomes, the GRADE handbook suggests a threshold of appreciable benefit and harm of 25% [92]. Based on this threshold, all four outcomes met the minimum total sample size (or OIS) criteria [142]. Furthermore, the effect estimates for rate of treatment response, dropouts due to lack of efficacy, and dropouts due to adverse effects excluded the null value and their 95% CIs also excluded the threshold for appreciable benefit/harm. Therefore, these outcomes were not downgraded for imprecision. Lastly, although the effect estimate for acceptability did include the null value, the 95% CIs did not include the threshold for appreciable benefit/harm and so was not downgraded for imprecision. Sample sizes and events rates were also relatively large for each outcome assessed, which further increased our confidence that the quality of evidence should not be downgraded for imprecision.

Finally, the quality of evidence was downgraded by one level for sponsorship bias for all four outcomes due to many studies being sponsored by a pharmaceutical company. This may have led to an overestimation of the effect estimates, as positive results are more likely to be published if the study is commercially sponsored [93, 94]. On the other hand, studies that are publicly funded are more likely to be published regardless of the results therefore, if future reviews could include more such studies, this may provide more comprehensive estimates of the effect [93].

Antidepressants are currently considered first-line treatments for GAD based on their favorable performance in the literature. However, the very low-quality evidence found in this review should be considered. Future studies should be conducted with more rigor and transparency and treatment guidelines should consider the quality of evidence when making recommendations. This would allow clinicians to have higher confidence when recommending treatment regimens to their patients.

5.4 Review Limitations

This review is not without limitations. Although a thorough search of electronic databases was conducted, bibliographies were not searched, and we did not reach out to experts in the field. There was some asymmetry in the funnel plots suggesting that small studies may have been missed during the search process. Small studies with non-

significant results or serious adverse effects will sometimes get rejected by the journal or not be submitted for publication entirely, which could lead to an overestimation of the benefits and an underestimation of harms [143-145].

This review also used a confirmatory approach to measure adverse effects. This means that certain adverse effects for which data were to be collected were chosen a priori. Although these adverse effects were chosen because they are considered the most clinically relevant, this approach to measuring adverse effects may be limited in that it cannot account for unanticipated adverse effects [86]. A future review may consider a more exploratory approach to investigating the adverse effects of antidepressants to gain a more comprehensive understanding of their risks.

5.5 Limitations of Included Studies

Varying rates of placebo response are also a growing concern in GAD trials [146]. Placebo response has been found to range between 18-67% in GAD trials, making it difficult to establish the efficacy of active treatments [146]. Several factors could be causing high rates of placebo response. Some of these include natural fluctuations and variations in the disorder, exogenous factors that could exacerbate symptoms, and even having frequent contact with clinical staff which may lead to symptom improvement [146, 147]. High rates of placebo response can decrease drug-placebo differences in randomized controlled trials and suggests that new antidepressants are not as effective as older antidepressants or that older antidepressants are not as effective as they used to be [146, 147]. It is difficult to determine whether the studies included in this review were subject to high rates of placebo response and exactly how that may have affected the results. The efficacy of antidepressants in this review showed benefit over placebo in treatment response, therefore, if the studies were subject to high placebo response, it's possible that the differences in effect sizes were even larger.

Attrition bias was also a concern in this review because many studies had high dropout rates. Attrition bias can result in biased effect estimates because the outcome among those who dropped out is unknown and must be inferred [148]. If the reason for dropout is related to the study treatment and is imbalanced between the two treatment groups, this

further exacerbates the concern for biased estimates. About half the studies in this review did not discuss whether dropouts were balanced between groups and whether reasons for dropouts differed between groups. Even fewer studies discussed whether the authors thought that those who dropped out differed from those who remained in the study. This made it difficult to determine the degree of bias due to incomplete outcome data for many studies, resulting in an unclear or high risk of bias judgement. Nevertheless, the sensitivity analysis in this review suggested that removing studies with more than 20% dropout rates did not substantially change the rate of treatment responses measured as a reduction of at least 50% on the HAM-A, and acceptability.

Furthermore, there are three general approaches that can be used to analyze missing data: complete case analysis, imputation methods, and analysis of incomplete data. Complete case analysis assumes that data are missing at random and is often discouraged in psychopharmacology trials [148]. Some examples of imputation methods are: LOCF and multiple imputation. LOCF uses the last observed value before the dropout and carries it forward, assuming that no change would have occurred [148]. Multiple imputation on the other hand, does incorporate uncertainty in the imputed data [148]. Mixed-effects models are a method of analyzing incomplete data and can account for data not missing at random by modeling the missing data into the analysis [148]. Despite the existence of mixed-effects models which may be considered a preferable strategy for dealing with missing data, psychopharmacological research still heavily relies on LOCF as their main analytic strategy. This was no exception in this review, as LOCF was the commonly used strategy for dealing with missing data among the included studies. This approach is limited as it does not account for uncertainty in the imputed data and can lead to bias in either direction [148]. It is difficult to assess how this analysis may have affected the results in this review. However, studies were judged to have unclear or high risk of bias as a consequence. Future studies should consider using more appropriate methods such as multiple imputation to reduce the potential for biased study findings.

5.6 Alignment of Findings with other Studies or Reviews

Overall, results of this meta-analysis generally agree with the results of other systematic reviews and meta-analyses investigating antidepressants compared to placebo for the treatment of GAD. This review adds to the overall understanding of the efficacy and acceptability of antidepressants in the treatment of GAD and provides more detailed information of their tolerability profiles.

The review by Schmitt et al., (2005) investigated imipramine, paroxetine, venlafaxine, and sertraline [14]. They found a benefit of antidepressants over placebo in risk of non-response to treatment which is in line with our finding of higher treatment response with antidepressants. They defined treatment response as a score of 1 or 2 on the CGI, which was also the common definition of treatment response found in this review.

Schmitt et al., (2005) defined acceptability as the total number of people dropping out during the trials and post-randomization exclusions, and specific side-effects. They found no differences in acceptability between all antidepressants and for each type of antidepressant compared to placebo. This result concurs with this review as we also found no differences between antidepressants and placebo in acceptability measured as the total number of dropouts. In terms of adverse effects, they investigated common adverse effects only for venlafaxine, as it was the only antidepressant for which there was more than one study. They found that those taking venlafaxine were more likely to report nausea, dry mouth, insomnia, constipation, somnolence, anorexia, sexual dysfunction, and flatulence. Although our review did not look at all these potential adverse effects and did not specifically look at individual antidepressants, there was a higher risk of patients reporting somnolence among SNRIs compared to placebo.

It is evident that the study by Schmitt et al., (2005) is limited in that they only included a total of 8 studies looking at imipramine, paroxetine, venlafaxine, and sertraline. Our review was able to retrieve many more studies and with more antidepressants, thus a more comprehensive analysis was done.

Gomez et al., (2018) investigated the efficacy of SSRIs and SNRIs compared to placebo in reducing anxiety symptoms as measured by the HAM-A [10]. They found that SSRIs and SNRIs were more effective than placebo and were similar in magnitude. These findings are consistent with the current review. The study by Gomez et al., (2018) did not evaluate the safety and tolerability of antidepressants and therefore could not be compared to results of the current review. The current review also investigated other classes of antidepressants, while the review Gomez et al., (2018) was restricted to SSRIs and SNRIs.

Several other reviews have directly compared antidepressants to placebo in the treatment of generalized anxiety disorder. Some network meta-analyses on pharmacological treatments have included antidepressants as a part of their analyses and have generally found that antidepressants have better efficacy and variable tolerability compared to placebo [16, 17]. Slee et al., (2019) for example, included agomelatine, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, imipramine, maprotiline, mirtazapine, paroxetine, sertraline, venlafaxine, vilazodone, and vortioxetine as a part of their analysis. They compared each individual antidepressant to placebo and generally found them to have better efficacy at reducing GAD symptoms. The exceptions were imipramine, maprotiline, vilazodone and vortioxetine whose 95% CIs included the potential for no difference. Acceptability, measured as the odds of not completing the study, showed mostly no difference with placebo, with the exception of paroxetine and vilazodone, which showed worse tolerability compared to placebo.

He et al., (2019) also conducted a network meta-analysis on the efficacy and acceptability of first line treatments in GAD. In particular, their review included studies on duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, vilazodone, and vortioxetine. Similarly to Slee et al., (2017), He et al., (2019) did not pool the results of their included studies but conducted individual comparisons for each drug-placebo pair. They found greater improvement in symptoms and response with antidepressants compared to placebo, except with fluoxetine and vortioxetine, which had no difference compared to placebo. There were also no differences between antidepressants and placebo in acceptability, except with vilazodone, which had worse acceptability than placebo.

Tolerability, measured as the number of patients dropping out due to adverse effects, was higher among the antidepressants, except with fluoxetine, sertraline and vortioxetine which showed no difference.

Network meta-analyses are advantageous in that they can compare the relative effectiveness of several interventions both directly, and indirectly. The two network meta-analyses by He et al., (2019) and Slee et al., (2017) discussed above were limited in the variety of outcomes that they investigated as they did not investigate improvements in functioning (i.e., quality of life) and specific adverse effects. Moreover, a network metaanalysis comparing the relative efficacy of antidepressants only, could also provide valuable information to clinicians who have patients that do not respond well to other treatments. Future research should consider conducting a network meta-analysis that compares antidepressants to other antidepressants (and potentially other pharmacological and non-pharmacological treatments) on a wide range of outcomes. However, network meta-analyses are not without limitations. For example, the validity of indirect comparisons in network meta-analyses strongly depends on the transitivity assumption. This assumption requires trials that being used for indirect comparisons to be similar with respect to their effect modifiers [86, 149]. Otherwise, indirect comparisons should not be made. Attempts to improve transitivity can also be challenging if there are a few number of studies included in each comparison [149]. Nevertheless, a network meta-analysis would allow clinicians and researchers to gain a more comprehensive understanding of how various pharmacotherapies compare to each other and which result in the best outcomes for people with GAD.

This was the first systematic review and meta-analysis since Schmitt et al., (2005) to attempt to compare all antidepressants (and only antidepressants) to placebo in the treatment of GAD. Other studies, as described above, have either restricted their analysis to first-line treatments, or the main purpose was to perform a network meta-analysis among all pharmacotherapies.

5.7 Authors Conclusions

5.7.1 Implications for Practice

The results from the meta-analyses investigating rate of treatment response, remission rates, and reduction in symptom levels suggest that antidepressants may be more effective than placebo at treating GAD. Antidepressants were also comparable to placebo in the total number of dropouts (acceptability) and had fewer dropouts due to lack of efficacy. However, antidepressants may be less tolerable than placebo, as they had greater dropouts due to adverse effects.

Applying a clinically meaningful interpretation of these results is difficult as it depends on the perspective of the person who is considering it and what their goals are [150]. Clinicians, patients, policy makers, and health economists for example, may place different emphasis on factors such as the availability of other interventions, the condition of the patients, the risk-to-benefit ratio, and the cost of treatment [150]. Nonetheless, the results of this review add to the growing literature on antidepressants in the treatment of GAD. Although a recommendation for practice cannot be made based on the results of this review, we can use its findings as a resource to help guide healthcare decisions and future research.

5.7.2 Implications for Research

This review helped to identify some important limitations that currently exist in the literature and some implications for future studies. To briefly summarize some of the points mentioned above, the very low-quality evidence found in this review should urge future research to be conducted with higher methodological standards to enhance confidence in study and review findings. Also, an exploratory approach that investigates adverse effects should be considered to capture any unanticipated adverse effects that may be associated with the treatment [86]. High heterogeneity was also a concern for some outcomes in this review, and sensitivity and subgroup analyses were not sufficient in explaining the excess heterogeneity. Future studies may consider other potential sources of heterogeneity such as different drug dosages. Furthermore, the extensive amount of research sponsored by pharmaceutical companies indicates that more publicly

sponsored studies need to be conducted to reduce the potential for bias. Finally, a network meta-analysis could be done given that the quality of the data and the characteristics of the included studies meet the transitivity and coherence requirements needed for valid results to be derived. A network meta-analysis would allow researchers to investigate head-to-head comparisons among antidepressants and establish how they compare to each other.

Psychotherapy has also been considered for the treatment of GAD. Although there is strong evidence supporting the use of psychotherapy over placebo in the treatment of GAD, evidence directly comparing psychotherapy to pharmacotherapy is lacking [4]. The few studies that have compared psychotherapy to pharmacotherapy, however, have shown that their efficacy is similar in magnitude [4]. Furthermore, only a few studies have investigated the effects of combined psycho- and pharmacotherapy in the treatment of GAD and have found conflicting results [4]. Given this evidence, current guidelines generally recommend that psychotherapy can be used if pharmacotherapies are ineffective and do not recommend combined therapy in the treatment of GAD [4]. More studies in the future should directly compare psychotherapy to pharmacotherapies to clearly establish which is more effective and investigate whether their use in combination is more effective than pharmacotherapy or psychotherapy alone. There is also a lack of evidence investigating different variables that could affect the efficacy of psychotherapy (such as population, setting, treatment duration, frequency etc.) and future studies should take these factors into consideration as well.

Furthermore, outcomes such as agitation/anxiety, suicide wishes/gestures/attempts and average score/change in quality of life/satisfaction were not as commonly reported as some other outcomes. Considering GAD is a very debilitating disorder, with high rates of suicide, these outcomes may be considered important to patients when choosing a treatment. More research should investigate these outcomes with antidepressants.

The subgroup analyses were also limited in the number of included studies. This limits the ability to investigate whether the effects of treatment differed between clinical groups. For example, the double-blind period in most of the studies that were eligible for this review had a duration of 12 weeks or less. Given that antidepressants can take roughly 4-8 weeks to provide relief of symptoms and up to 12 weeks to experience a full response to treatment, trials of longer duration are needed to better understand the longterm effects of treatment and how long treatment should be continued for [4].

Moreover, GAD is also a chronic and persistent mental disorder as illustrated by a study that found the probability of achieving recovery among people with GAD was 58%, and the probability of recurrence among those who had recovered was 45% after 12 years of follow up [151]. Relapse prevention studies are generally longer in duration and provide insight into the long-term efficacy of antidepressants. In particular, studies on duloxetine [152], escitalopram [153], vortioxetine [154], paroxetine [155], and venlafaxine [156, 157] have all found lower relapse rates in those who continued the antidepressant for at least 6 months after an open-label period compared to those who switched to placebo. In other words, the risk of relapse was reduced in those who continued taking the antidepressants after initially responding to treatment during the open-label period. These results suggest that continuing to take the medication even after achieving response/remission may be beneficial in preventing relapse and maintaining efficacy. More such studies are needed to understand the benefits and drawbacks of long-term treatment with antidepressants.

Our search also did not identify many studies investigating the effects of antidepressants compared to placebo in older adults. Only one unpublished trial [100] was identified among veterans aged over 60. One systematic review and meta-analysis investigating pharmacotherapies among older adults in GAD found that antidepressants have significantly more responders compared to placebo [158]. However, the authors only identified five studies comparing antidepressants to placebo in this population. Older adults tend to have more cognitive decline and medical comorbidities that require them to take additional medications and that may affect their response to treatment and induce drug-drug interactions. As such, future research should be done on this population to identify the best treatment options.

5.8 Conclusion

This review adds to the growing literature on antidepressants in the treatment of GAD. This review compared the efficacy, acceptability, tolerability, quality of life, and specific adverse effects of antidepressants and placebo in the treatment of GAD. The results of the meta-analysis suggested that antidepressants may be more effective than placebo at reducing symptoms of GAD, and in achieving treatment response and remission. Antidepressants were also found to have similar acceptability to placebo but may be less tolerable as more people reported experiencing adverse effects and more people taking antidepressants treatment dropped out due to adverse effects. Some specific adverse effects such as sleepiness/drowsiness were also more frequently reported among antidepressants and limited evidence suggested a similar number of people experiencing agitation/anxiety and suicide wishes/gestures/attempts between the antidepressants over placebo in improving quality of life.

The very-low quality of evidence that was found warrants caution and careful consideration when interpreting the findings of this review. Higher quality evidence is needed so that clinicians can have increased confidence in the treatment of their patients. This review identified some important gaps in the literature on antidepressants in GAD and can be used as a tool to guide future research.

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Appendices

Appendix 1: Search Strategy

CCMD-CTR-References

#1. (general* NEAR2 anxi* or GAD)

#2. antidepress* or anti-depress* or "anti depress*" or MAOI* or RIMA* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) NEAR (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic*

#3. Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233

#4. Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or "St John*") or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or ("Lu AA21004" or Vortioxetine) or "Lu AA24530" or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin*

#5. Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone

#6. (#1 and (#2 or #3 or #4 or #5))

MEDLINE ALL

(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <u>http://ovidsp.ovid.com/</u>

Date range: 1946 to October 20, 2022

Date searched: 22nd October 2022

Records retrieved: 687

- 1 *Anxiety Disorders/ (24914)
- 2 Anxiety Disorders/dt [Drug Therapy] (5405)
- 3 ((general* adj2 anxi*) or GAD).ti,ab,kf. (21059)
- 4 or/1-3 (42562)
- 5 exp Antidepressive Agents/ (158209)
- 6 exp Neurotransmitter Uptake Inhibitors/ (154672)
- 7 exp Monoamine Oxidase Inhibitors/ (22528)

8 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. (236833)

9 (serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*).mp. (475050)

- 10 (uptake or re-uptake).mp. (449062)
- 11 9 and 10 (61850)

12 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin* or Dothiepin or Doxepin* or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lu AA21004 or Vortioxetine or Lu AA24530 or LY2216684 or Edivoxetine or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or

Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp. (112144)

- 13 5 or 6 or 7 or 8 or 11 or 12 (451731)
- 14 4 and 13 (5110)
- 15 randomized controlled trial.pt. (579185)
- 16 randomi#ed.ti,ab,kf. (751604)
- 17 controlled clinical trial.pt. (95077)
- 18 Double-Blind Method/ (173344)
- 19 clinical trials as topic.sh. (200471)
- 20 randomly.ab. (393763)

21 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,kf. (269931)

- 22 trial.ti,kf. (291288)
- 23 (animals not (humans and animals)).sh. (5023551)
- 24 or/15-22 (1531971)
- 25 24 not 23 (1416231)
- 26 (placebo* or dummy or sugar pill).mp. (259201)
- 27 14 and 25 and 26 (687)

Embase

via Ovid <u>http://ovidsp.ovid.com/</u>

Date range: 1974 to 2022 October 20

Date searched: 22nd October 2022

Records retrieved: 935

- 1 *anxiety disorder/ (24794)
- 2 anxiety disorder/dt [Drug Therapy] (12695)

- 3 generalized anxiety disorder/ (13938)
- 4 ((general* adj2 anxi*) or GAD).ti,ab,kw. (30051)
- 5 or/1-4 (64151)
- 6 exp antidepressant agent/ (542965)
- 7 exp serotonin uptake inhibitor/ (302315)
- 8 exp serotonin noradrenalin reuptake inhibitor/ (202288)
- 9 exp noradrenalin uptake inhibitor/ (251434)

10 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin* or Dothiepin or Doxepin* or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lu AA21004 or Vortioxetine or Lu AA24530 or LY2216684 or Edivoxetine or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Vigualine or Zalospirone).mp. (260282)

11 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).mp. (374928)

12 or/6-11 (734512)

13 major clinical study/ (4639494)

14 Randomized controlled trial/ (733077)

- 15 Controlled clinical study/ (467336)
- 16 double blind procedure/ (199840)
- 17 randomization/ (95355)
- 18 (RCT or randomi#ed).ti,ab,kw. (1086039)

19 ((at random or random*) adj2 (allocat* or assign* or divide* or division or number)).ti,ab,kw. (329369)

20 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw. (261848)

- 21 or/13-20 (5843011)
- 22 ((animal or nonhuman) not (human and (animal or nonhuman))).de. (6224878)
- 23 21 not 22 (5686058)
- 24 5 and 12 and 23 (4596)
- 25 (placebo* or dummy or sugar pill).mp. (509246)
- 26 24 and 25 (1170)
- 27 elsevier.cr. (29206743)
- 28 26 and 27 (1119)

29 (random* adj sampl* adj7 ("cross section*" or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9159)

30 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.) (324230)

31 (((case adj control*) and random*) not randomi?ed controlled).ti,ab. (20366)

- 32 (Systematic review not (trial or study)).ti. (225598)
- 33 (review.ab. and review.pt.) not trial.ti. (1033830)
- 34 or/29-33 (1514911)
- 35 28 not 34 (935)

APA PsycINFO

via Ovid http://ovidsp.ovid.com/

Date range: 1806 to October Week 3 2022

Date searched: 22nd October 2022

Records retrieved: 353

- 1 generalized anxiety disorder/ (3442)
- 2 ((general* adj2 anxi*) or GAD).ti,ab,id. (14609)
- 3 *anxiety disorders/ (16026)
- 4 1 or 2 or 3 (27484)
- 5 exp antidepressant drugs/ (41005)

6 neurotransmitter uptake inhibitors/ or exp serotonin norepinephrine reuptake inhibitors/ or exp serotonin reuptake inhibitors/ (14356)

- 7 exp monoamine oxidase inhibitors/ (2299)
- 8 exp tricyclic antidepressant drugs/ (6493)

9 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).ti,ab,id,hw. (75055)

10 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine or Clorgyline or Clovoxamine or CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin* or Dothiepin or Doxepin* or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluoxamine or Hyperforin or Hypericum or St John* or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lu AA21004 or Vortioxetine or Lu AA24530 or LY2216684 or Edivoxetine or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).ti,ab,id,hw. (38290)

- 11 or/5-10 (95598)
- 12 4 and 11 (2306)

13 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,id. (58796)

- 14 trial.ti,id. (41651)
- 15 randomi#ed.ti,ab,id. (100128)

16 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).ti,ab,id.(28612)

- 17 or/13-16 (165038)
- 18 (placebo* or dummy or sugar pill).ti,ab,id,hw. (44515)

19 12 and 17 and 18 (353)

Cochrane Central Register of Controlled Trials (CENTRAL)

via The Cochrane Library, Wiley http://www.cochranelibrary.com/

Issue 10 of 12, October 2022

Date searched: 22nd October 2022

Records retrieved: 949

#1 (generalised or generalized) near anxiety:ti,ab,kw 3894

- #2 GAD:ab 2537
- #3 #1 or #2 4786

#4 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Amfebutamone or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or Chlorimipramin* or Clomipramin* or Clomipramine or Clorgyline or Clovoxamine or

CX157 or Tyrima or Demexiptiline or Deprenyl or Desipramine* or Pertofrane or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin* or Dothiepin or Doxepin* or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or Hyperforin or Hypericum or (St next John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or "Lu AA21004" or Vortioxetine or "Lu AA24530" or LY2216684 or Edivoxetine or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone) 28414

#5 antidepress* or anti-depress* or MAOI* or monoamine next oxidase next inhibit* or ((serotonin or norepinephrine or noradrenaline or nor next epinephrine or nor next adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or reuptake)) or noradrenerg* or antiadrenergic or anti next adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic* 28369

#6 #4 or #5 43961

#7 #3 and #6 in Trials 949

Appendix 2: Data Extraction Template

-	red as a reduction o	f at least 50% on the Hamilt	ton Anxiety	
Scale (HAM-A)				
	ENDPOINT	ENDPOINT		
	n	Ν		
Placebo				
Intervention				
Acceptability (numb	er of dropouts): nun	ber of participants who dro	opped out	
_ • •	• · ·	al number of randomized p		
0		-	-	
(total dropouts)				
(total dropouts)	ENDPOINT			
(total dropouts)	ENDPOINT n	N		
(total dropouts) Placebo		N		
× • /		N		
Placebo	n			
Placebo Intervention	n			

Placebo			
Intervention			
Remission			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Change in symptom level	S		
	ENDPOINT		
	Mean	SD	Ν
Placebo			
Intervention			
Total number of patients	reporting adverse effects	5	
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Sleepiness/drowsiness			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Falls			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Hypotension			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Agitation/anxiety			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Suicide wishes/gestures/at			
	ENDPOINT	N	
D1 1	n	N	
Placebo			
Intervention			
Completed suicide	ENIDDOINT		
	ENDPOINT	NT	
	n	N	

Placebo			
Intervention			
Subjective memory i	mpairment		
	ENDPOINT		
	n	Ν	
Placebo			
Intervention			
Average score/chang	e in quality of life/satis	faction	
	ENDPOINT		
	mean	SD	N
Placebo			
Intervention			
Death			
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Total number of par	ticipants experiencing	withdrawal sympto	oms
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Dropouts due to inef	•		
	ENDPOINT		
	n	N	
Placebo			
Intervention			
Dropouts due to adv			
	ENDPOINT		
	n	N	
Placebo			
Intervention			

Appendix 3: Formulas

Formula 1: Convert standard error of a mean (from within an intervention group) to a standard deviation (Cochrane Handbook section 6.5.2.2):

$$SD = SE \ x \sqrt{N}$$

Where; SD = standard deviation of the group mean, SE = standard error of the group mean, N = sample size of the group of interest

Formula 2: Convert 95% confidence interval of a mean (from within an intervention group) to a standard deviation (Cochrane Handbook section 6.5.2.2):

$$SD = \sqrt{N} x \frac{(upper limit - lower limit)}{3.92}$$

Where; SD = standard deviation of the group mean, N = sample size of the group of interest

Formula 3: Combining summary statistics across groups (Cochrane Handbook section 6.5.2.10):

Combined sample size:

 $N_1 + N_2$

Combined mean:

$$\frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

Combined SD:

$$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}}$$

Where; N_1 , M_1 , SD_1 are the sample size, mean, and standard deviation of Group 1 and N_2 , M_2 , SD_2 are the sample size, mean, and standard deviation of Group 2

Study Design	Quality of	Lower if	Higher if	
	Evidence			
Randomized trial	High	Risk of Bias:	Large Effect	
(automatically		-1 if serious	+1 if large	
begins at 'high'		-2 if very serious	+2 if very large	
quality)		Inconsistency:		
	Moderate	-1 if serious	Dose Response	
		-2 if very serious	+1 if evidence of a	
		Indirectness:	gradient	
		-1 if serious		
Observational study	Low	-2 if very serious	All plausible confounding	
(automatically	Low	Imprecision:	+1 would reduce a	
begins at 'low'		-1 if serious	demonstrated effect or	
quality)		-2 if very serious	+1 would suggest a	
quality)	Very Low	Publication Bias:	spurious effect when	
		-1 if serious	results show no effect	
		-2 if very serious		

Appendix 4. GRADE Quality Assessment Criteria

Appendix 5. Data Extracted Using GetDataGraph Digitizer	Appendix 5	. Data E	Extracted	Using	GetDataGrap	oh Digitizer
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Study ID	Outcome	Intervention	Values extracted from
			GetDataGraph Digitizer
Allgulander	% responders measured as a	Placebo	46.32%
2001	reduction of at least 50% on		
	the HAM-A at endpoint		
	the mining of a chapoint	Venlafaxine	37.5 mg: 68.76%
			75 mg: 61.53%
			150 mg: 74.70%
		Placebo	48.30%

	% responders (defined by	Venlafaxine	37.5 mg: 75.15%
	study authors) at endpoint		75 mg: 66.01%
			150 mg: 81.23%
Baldwin	% responders (defined by	Placebo	63.04%
2006	study authors) at endpoint	Escitalopram	5 mg: 70.77%
			10 mg: 78.26%
			20 mg: 74.15%
		Paroxetine	20 mg: 65.94%
	% patients in remission at	Placebo	29.67%
	endpoint	Escitalopram	5 mg: 44.0%
			10 mg: 47.76%
			20 mg: 33.13%
		Paroxetine	20 mg: 43.16%
Gelenberg	% responders (defined by	Placebo	41.45%
2000	study authors) at endpoint	Venlafaxine	75-225 mg: 71.30%
Lenox-	HAM-A total score at	Placebo	16.01
Smith 2003	endpoint	Venlafaxine	75 mg: 13.89
Nicolini	% of patients reporting	Placebo	1.68%
2009	sleepiness/drowsiness	Duloxetine	20 mg: 3.61%
			60-120 mg: 8.23%
		Venlafaxine	75-225 mg: 4.75%
Koponen	% of patients reporting	Placebo	1.11%
2007	sleepiness/drowsiness	Duloxetine	60 mg: 3.60%
			120 mg: 5.96%

Appendix 6. GRADE Quality of Evidence Assessment

Participants (studies)	i) Risk of bias	(i) Inconsistency	() Indirectness	1) Imprecision	Other considerations	Overall certainty of evidence
Rate of treatment respo	nse measured as a redu	uction of at least 50% on	the Hamilton Anxiety Ratin	g Scale (HAM-A)		
7556 (24 RCTs)	serious ^a	serious ^b	serious ^c	not serious	publication bias strongly suspe cted ^d	OOO Very low
Acceptability						
11598 (34 RCTs)	serious ^a	serious ^e	serious ^c	not serious	publication bias strongly suspe cted ^d	⊕OOO Very low
Dropouts due to a lack o	of efficacy					
11311 (30 RCTs)	serious ^a	not serious	serious ^c	not serious	publication bias strongly suspe cted ^d	OOO Very low
Dropouts due to adverse	e effects					
12097 (33 RCTs)	serious ^a	not serious	serious ^c	not serious	publication bias strongly suspe cted ^d	OOO Very low

^a Evidence was downgraded by one level due to many studies in the analyses having an unclear or high risk of bias in several domains.

^b Evidence was downgraded by one level due to substantial heterogeneity (64%).

^c Evidence was downgraded by one level because patients with comorbidities were excluded.

^d Evidence was downgraded by one level because many studies in the analysis were sponsored by pharmaceutical companies.

^e Evidence was downgraded by one level due to moderate-substantial heterogeneity (52%)

Curriculum Vitae

Name:	Katarina Kopcalic
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2021-2023 M.Sc.
	The University of Washington Seattle, Washington, USA 2016-2020 B.A.
Honors and Awards:	Western Graduate Research Scholarship 2021-2022
Related Work Experience	Graduate Research Assistant, Dr. Piotr Wilk Lab The University of Western Ontario 2022-2023
	Teaching Assistant, Systematic Reviews The University of Western Ontario 2023
	Teaching Assistant, Biology 1001A The University of Western Ontario 2021