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

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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 antidepressant and placebo groups. Limited evidence also suggested a benefit of 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.

# Table of Contents

# List of Tables

# List of Figures

# List of Appendices

# 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 (NRIs), 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 low-income 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 mid-thirties, 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, MDD and pain, paid an estimated $762 more and $6073 more than people who had 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, and the 4-item Patient Health Questionnaire [1, 46]. These tools have been 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 long-term 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 meta-analyses 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 meta-analyses 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 meta-analyses 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 $I^2$ value [85]. We used the following parameters to estimate the degree of heterogeneity from the $I^2$ 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.

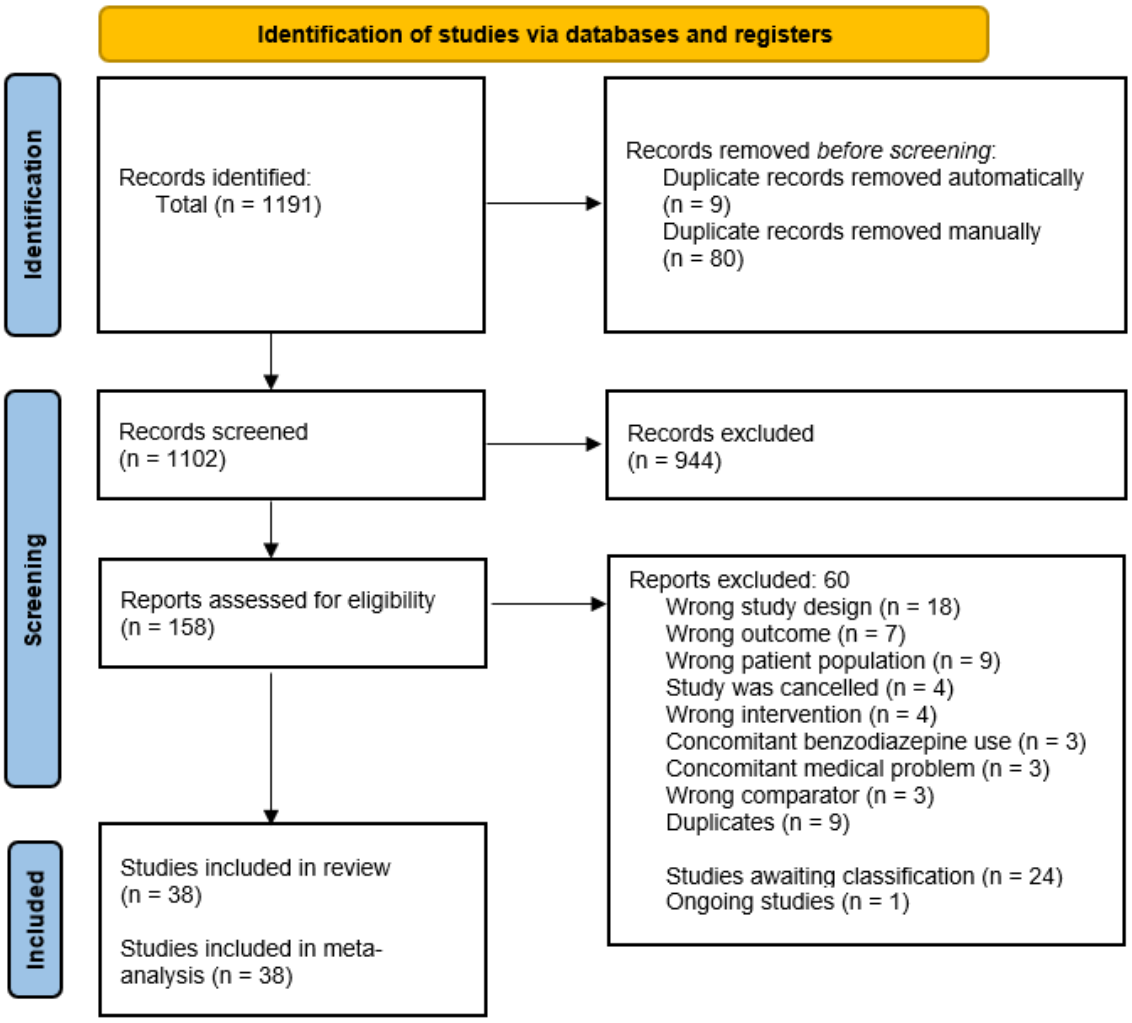


**Figure 1. PRISMA flow diagram**

## 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 |
|---|---|---|---|---|---|---|---|
| Allgulander 2001 [128] | DSM-IV | None stated | Belgium, Finland, France, Sweden, UK | Primary care and psychiatric outpatients | Placebo, 130 | 46.1 (NA); 58%, 42% | 37.5, 75 or 150 mg/day, 24 weeks |
| | | | | | Venlafaxine, 411 | 44.8 (NA); 61.3%, 38.7% | 37.5, 75 or 150 mg/day, 24 weeks |
| Allgulander 2004 [118] | DSM-IV | None stated | Australia, Canada, Denmark, Norway, Sweden | Outpatients | Placebo, 190 | 42.4 (11.5); 51%, 49% | 50-150 mg/day, 12 weeks |
| | | | | | Sertraline, 188 | 40.3 (11.1); 59%, 41% | 50-150 mg/day, 12 weeks |
| Aventis-Sanofi 2007a [108] | DSM-IV-TR | None stated | NA | Outpatients | Placebo, 122 | Total: 40.8 (12.3); Total: 66.9%, 31.1% | 20 mg/day, 8 weeks |
| | | | | | Paroxetine, 124 | | 20 mg/day, 8 weeks |
| | | | | | Amibegron, 120 | | 700 mg/day, 8 weeks |
| Aventis-Sanofi 2007b [115] | DSM-IV-TR | None stated | United States | Outpatients | Placebo, 119 | Total: 40.3 (13.9); Total: 61.9%, 38.1% | 10 mg/day, 8 weeks |
| | | | | | Escitalopram, 122 | | 10 mg/day, 8 weeks |
| | | | | | Amibegron, 118 | | 700 mg/day, 8 weeks |

**Table 1 continued**

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

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Davidson 1999 [127] | DSM-IV | None stated | United States | Outpatients | Placebo, 98 | 39.0 (11.0); 62.2%, 37.8% | 75 or 150 mg/day, 8 weeks |
| | | | | | 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 2004 [113] | DSM-IV | None stated | United States | Outpatients | Placebo, 157 | 39.5 (13.1); 52.9%, 47.1% | 10-20 mg/day, 8 weeks |
| | | | | | Escitalopram, 158 | 39.5 (12.1); 52.5%, 47.5% | 10-20 mg/day, 8 weeks |
| Feltner 2009 [107] | DSM-IV | None stated | United States | NA | Placebo, 57 | 35.0 (10.4); 54.4%, 45.6% | 20 mg/day, 4 weeks |
| | | | | | 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 2000 [120] | DSM-IV | None stated | United States | Outpatients | Placebo, 127 | 38.0 (11.0); 59%, 41% | 75-225 mg/day, 28 weeks |
| | | | | | Venlafaxine, 124 | 41.0 (12.0); 59%, 41% | 75-225 mg/day, 28 weeks |
| GlaxoSmithKline 2006 [110] | DSM-IV | None stated | Japan | Outpatients | Placebo, 170 | 40.6 (12.7); 59.1%, 40.9% | 20 mg/day, 8 weeks |
| | | | | | Paroxetine, 170 | 39.5 (12.2); 60.5%, 39.5% | 20 mg/day, 8 weeks |
| Gommoll 2015 [101] | DSM-IV-TR | Other mood disorders (not specified) | United States | Outpatients | Placebo, 201 | 40.1 (13.0); 66.2%, 33.8% | 20-40 mg/day, 8 weeks |
| | | | | | Vilazodone, 201 | 40.5 (13.2); 72.5%, 27.5% | 20-40 mg/day, 8 weeks |

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Goodman 2001 [117] | DSM-IV | None stated | United Stated | Outpatients | Placebo, 128 | 40.9 (14.0); 62.5%, 37.5% | 10-20 mg/day, 8 weeks |
| | | | | | Escitalopram, 129 | 39.6 (13.4); 59.5%, 40.5% | 10-20 mg/day, 8 weeks |
| Goodman 2002 [116] | DSM-IV | None stated | United States | Outpatients | Placebo, 145 | 38.6 (12.5); 48.6%, 51.4% | 10-20 mg/day, 8 weeks |
| | | | | | Escitalopram, 149 | 36.8 (12.2); 61.4%, 38.6% | 10-20 mg/day, 8 weeks |
| Hackett 2003 [125] | DSM-IV | None stated | NA | Outpatients | Placebo, 97 | 43 (NA); 64%, 36% | 75 or 150 mg/day, 8 weeks |
| | | | | | 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 |
| Hartford 2007 [104] | DSM-IV | None stated | United States | Outpatients | Placebo, 161 | 41.9 (14.2); 61.5%, 38.5% | 60-120 mg/day or 75-225 mg/day, 10 weeks |
| | | | | | 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 | None stated | United Kingdom, France, Ireland, Germany, Austria, Italy | 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 |

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kasper 2009 [124] | DSM-IV-TR | None stated | Belgium, Canada, France, Ireland, Italy, Netherlands, Spain, Sweden | Outpatients | Placebo, 128 | 40.2 (12.1); 61%, 39% | 75-225 mg/day, 8 weeks |
| | | | | | Venlafaxine, 125 | 42.6 (11.8); 58%, 42% | 75-225 mg/day, 8 weeks |
| | | | | | Pregabalin, 121 | 39.5 (11.9); 64%, 36% | 150-600 mg/day, 8 weeks |
| Koponen 2007 [130] | DSM-IV | None stated | Finland, France, Germany, South Africa, Spain, Sweden, United States | Outpatients | Placebo, 175 | 44.1 (13.4); 66.9%, 33.1% | 60 or 120 mg/day, 9 weeks |
| | | | | | Duloxetine, 338 | 43.6 (12.7); 68.3%, 31.7% | 60 or 120 mg/day, 9 weeks |
| Lenox-Smith 2003 [121] | DSM-IV | None stated | United Kingdom | Primary care | Placebo, 122 | 46 (NA); 56.6%, 43.4% | 75-150 mg/day, 24 weeks |
| | | | | | Venlafaxine, 122 | 48 (NA); 61.5%, 38.5% | 75-150 mg/day, 24 weeks |
| Mahablesh warkar 2014 [99] | DSM-IV-TR | None stated | United States; 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 |
| | | | | | 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 |
| McLeod 1992 [98] | DSM-III-R | None stated | NA | Volunteers | Placebo, 14 | 40.3 (7.9); 64%, 35.7% | 25-200 mg/day, 6 weeks |
| | | | | | 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 |

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Montgomery 2006 [123] | DSM-IV | None stated | Austria, Belgium, Germany, Netherlands, United Kingdom | Primary care and psychiatric outpatients | Placebo, 101 | 43.0 (12.0); 58%, 42% | 75 mg/day, 6 weeks |
| | | | | | Venlafaxine, 113 | 46.0 (12.0); 65%, 35% | 75 mg/day, 6 weeks |
| | | | | | Pregabalin, 207 | 43.4 (12.1); 62.1%, 37.9% | 400 or 600 mg/day, 6 weeks |
| Nicolini 2009 [103] | 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 |
| | | | | | Duloxetine, 242 | | 20 or 60-120 mg/day, 10 weeks |
| | | | | | Venlafaxine, 169 | | 75-225 mg/day, 10 weeks |
| Nimatoudis 2004 [122] | DSM-IV | None stated | Greece | Outpatients | Placebo, 22 | 44.0 (12.0); 68.2%, 31.8% | 75-150mg/day, 8 weeks |
| | | | | | Venlafaxine, 24 | 41.0 (14.0); 66.7%, 33.3% | 75-150mg/day, 8 weeks |
| Pfizer 2009 [109] | DSM-IV | None stated | Hungary, Italy, Korea, United States | NA | Placebo, 101 | 42.1 (12.5); 65%, 35% | 20 mg/day, 8 weeks |
| | | | | | 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 |

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pollack 2001[111] | DSM-IV | None stated | United States and Canada | Outpatients | Placebo, 163 | 41.3 (Range 19-80); 66.3%, 33.7% | 20-50 mg/day, 8 weeks |
| | | | | | Paroxetine, 161 | 39.7 (Range 19-69); 60.9%, 39.1% | 20-50 mg/day, 8 weeks |
| Rickels 2000 [126] | DSM-IV | None stated | United States | Outpatients | Placebo, 96 | 40.9 (11.3); 57%, 43% | 75, 150 or 225 mg/day, 8 weeks |
| | | | | | Venlafaxine, 253 | 40.8 (12.4); 55.3%, 44.7% | 75, 150 or 225 mg/day, 8 weeks |
| Rickels 2003 [106] | DSM-IV | None stated | United States, Canada | Outpatients | Placebo, 188 | 40.8 (12.6); 56%, 44% | 20 or 40 mg/day, 8 weeks |
| | | | | | Paroxetine, 385 | 40.4 (12.7); 55%, 45% | 20 or 40 mg/day, 8 weeks |
| Rothschild 2012 [134] | DSM-IV-TR | None stated | United States | NA | Placebo, 152 | 41.4 (12.8); 87.2%, 12.8% | 5 mg/day, 8 weeks |
| | | | | | Vortioxetine, 152 | 41.0 (14.1); 67.8%, 32.2% | 5 mg/day, 8 weeks |
| Rynn 2008 [131] | DSM-IV | None stated | United States | Outpatients | Placebo, 159 | 41.0 (14.2); 62.3%, 37.7% | 60-120 mg/day, 10 weeks |
| | | | | | Duloxetine, 168 | 42.2 (13.9); 61.3%, 38.7% | 60-120 mg/day, 10 weeks |
| Stein 2008 [132] | DSM-IV-TR | None stated | Finland, South Africa | Outpatients | Placebo, 58 | Total: 41.7 (12.2); Total: 68.6%, 31.4% | 25-50 mg/day, 12 weeks |
| | | | | | Agomelatine, 63 | | 25-50 mg/day, 12 weeks |

**Table 1 continued**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stein 2014 [81] | DSM-IV-TR | None stated | 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 |
| | | | | | Agomelatine, 139 | 43.6 (12.5); 74.8%, 25.2% | 10-20 mg/day, 12 weeks |
| | | | | | Escitalopram, 142 | 41.2 (12.5); 68.3%, 31.7% | 25-50 mg/day, 12 weeks |
| Stein 2017 [133] | 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 |
| | | | | | Agomelatine, 270 | 43.9 (14.3); 70%, 30% | 10 or 25 mg/day, 12 weeks |
| Wen-Yuan 2011 [129] | DSM-IV | None stated | China | Outpatients | Placebo, 102 | 38.0 (12.0); 54.9%, 45.1% | 60-120 mg/day, 15 weeks |
| | | | | | 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.

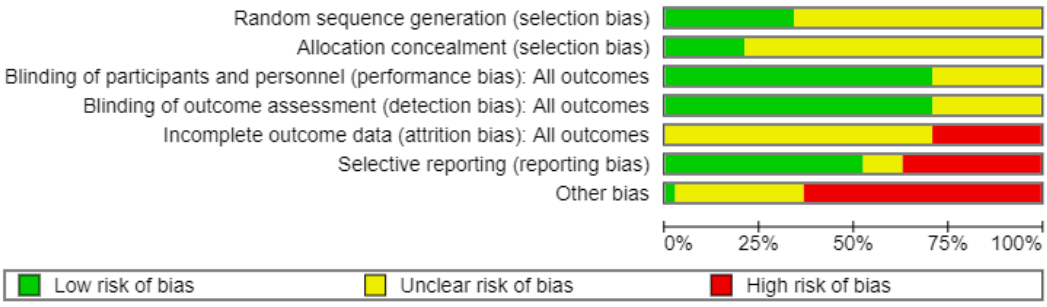


**Figure 2. Risk of bias graph**

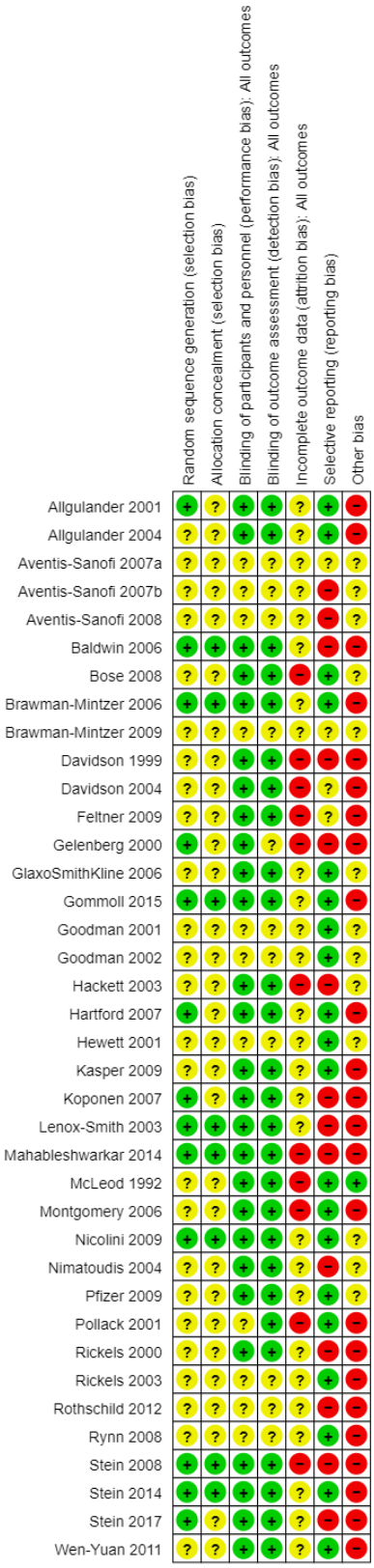


**Figure 3. Risk of bias summary**

## 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.

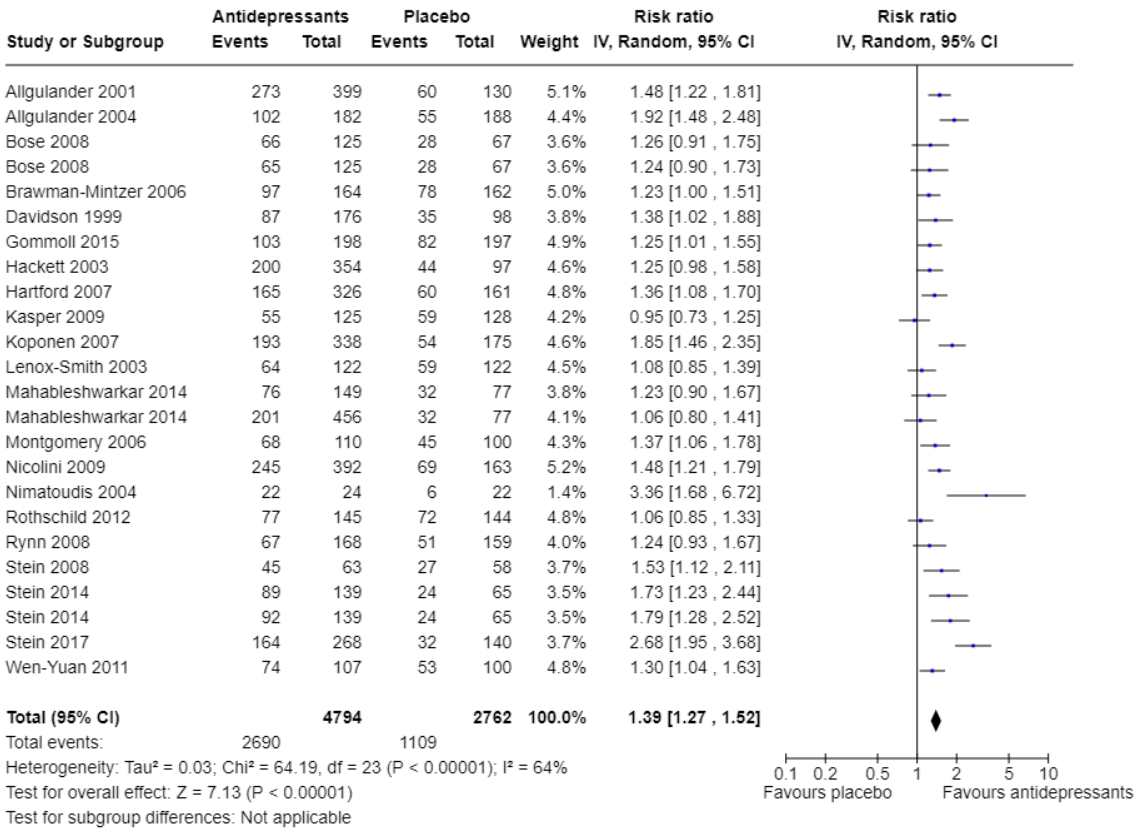


**Figure 4. Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo**

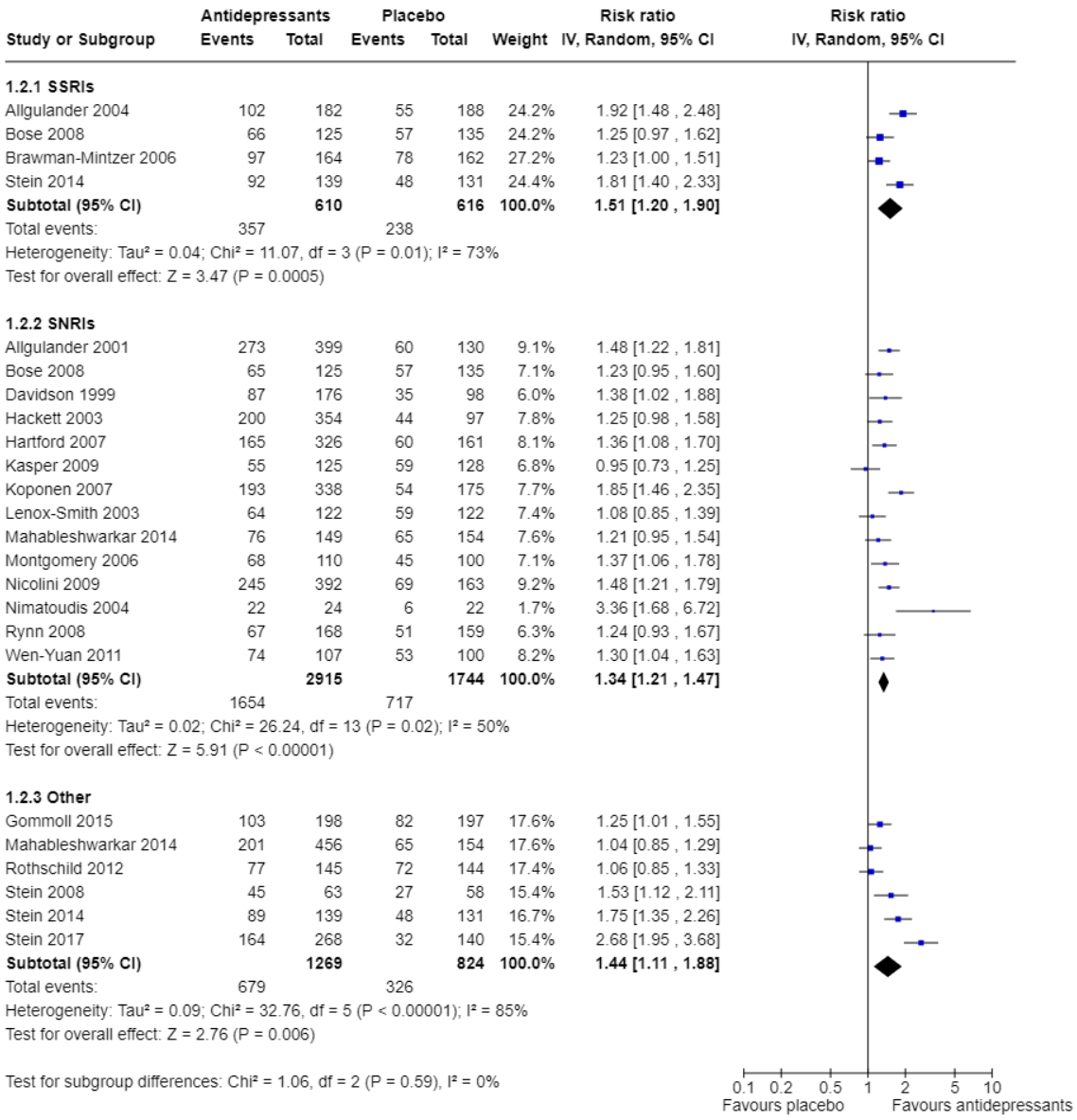


**Figure 5. Rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment class versus placebo**

### 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 ($I^2$: 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; $I^2$: 2%; studies = 16; participants = 5,031), SNRIs (RR, 1.03: 95% CI: 0.87, 1.21; $I^2$: 69%; studies = 15; participants = 4,863), and 'Other' antidepressants (RR, 0.86: 95% CI: 0.61, 1.21; $I^2$: 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 ($I^2$ = 0%; p = 0.51) although more studies with 'Other' antidepressants are needed to better detect subgroup differences.

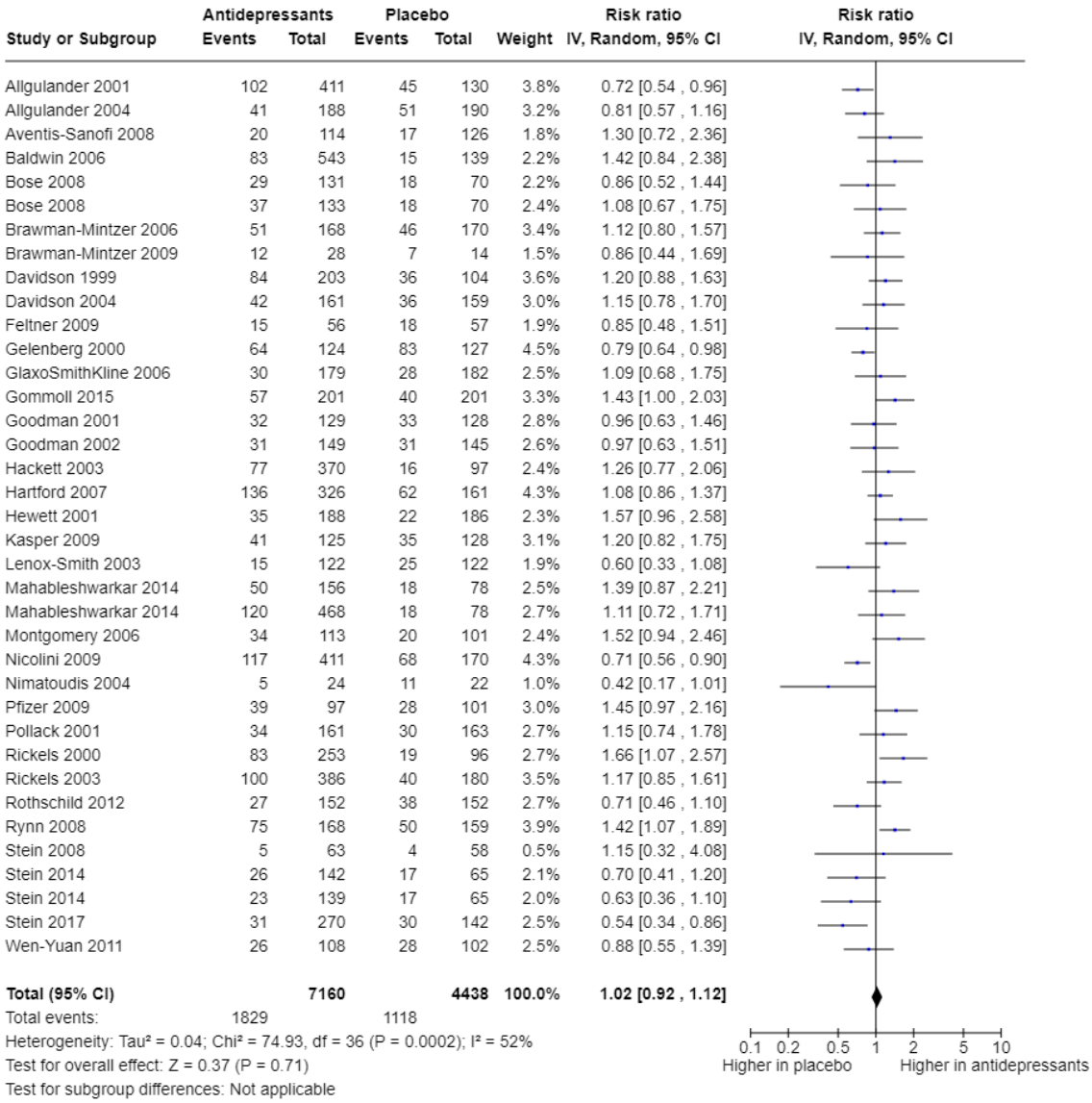


**Figure 6. Acceptability for all antidepressants versus placebo**

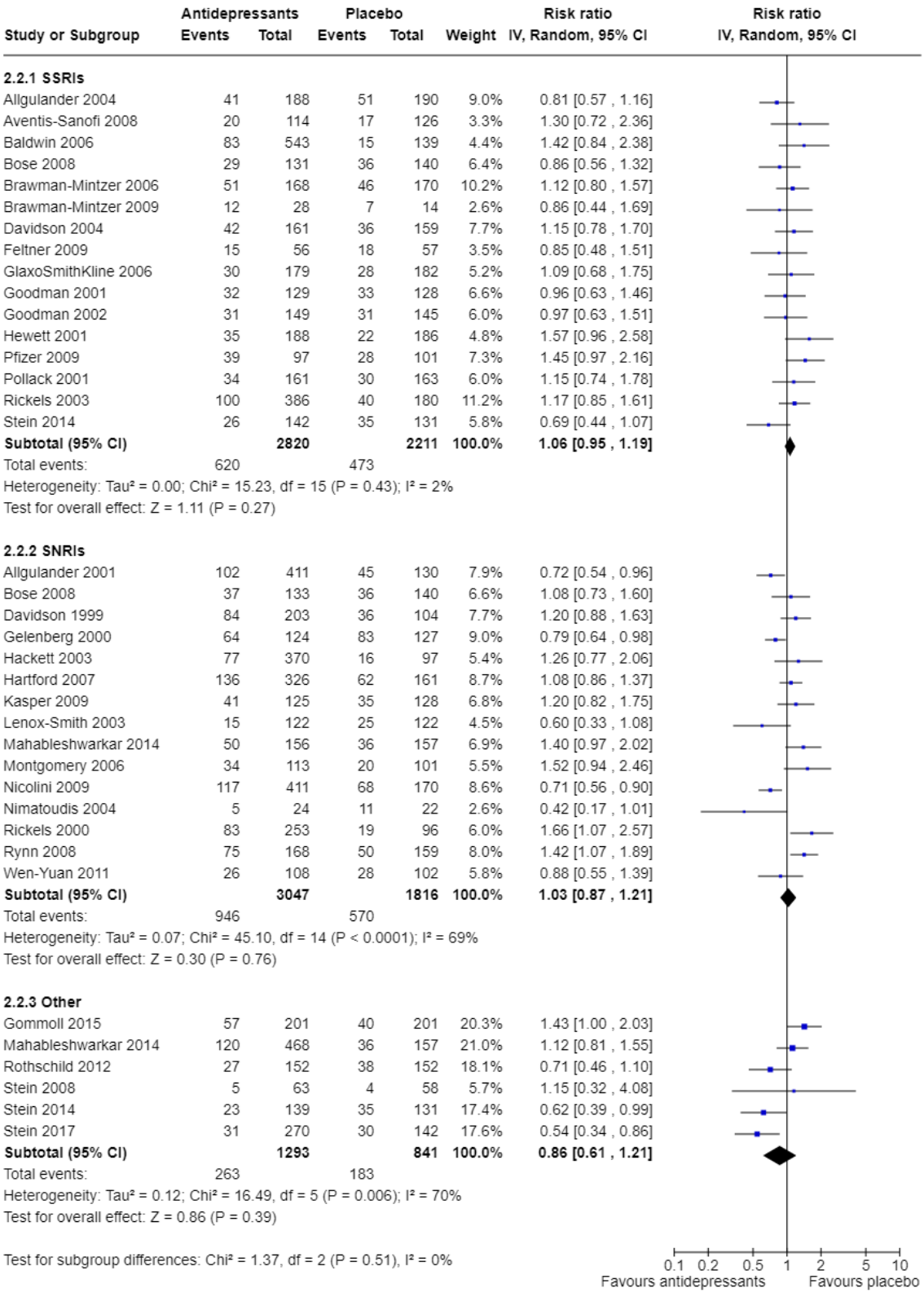


**Figure 7. Acceptability by treatment class versus placebo**

### 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 ($I^2$: 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; $I^2$: 45%; studies = 10; participants = 3,661) and SNRIs (RR, 1.41: 95% CI: 1.31, 1.53; $I^2$: 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; $I^2$: 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 ($I^2$ = 40.9%; p = 0.18) however, more studies among SNRIs and 'Other' antidepressants are needed to better detect subgroup differences.

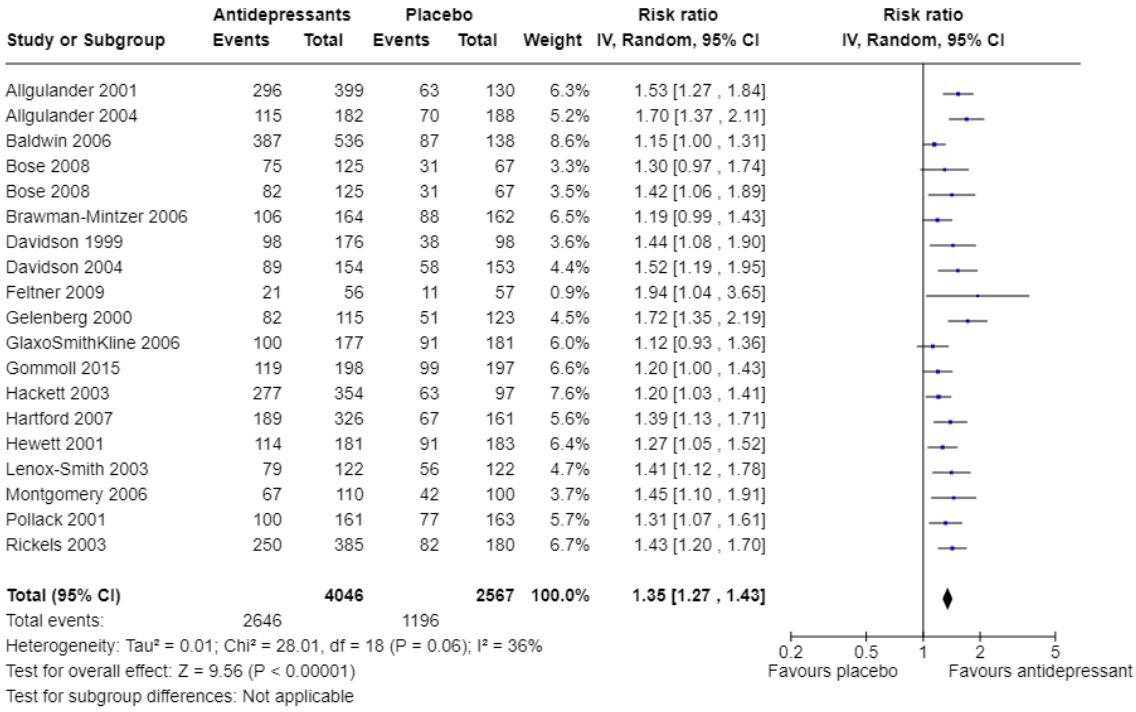


**Figure 8. Rate of treatment response (defined by study authors) for all antidepressants versus placebo**

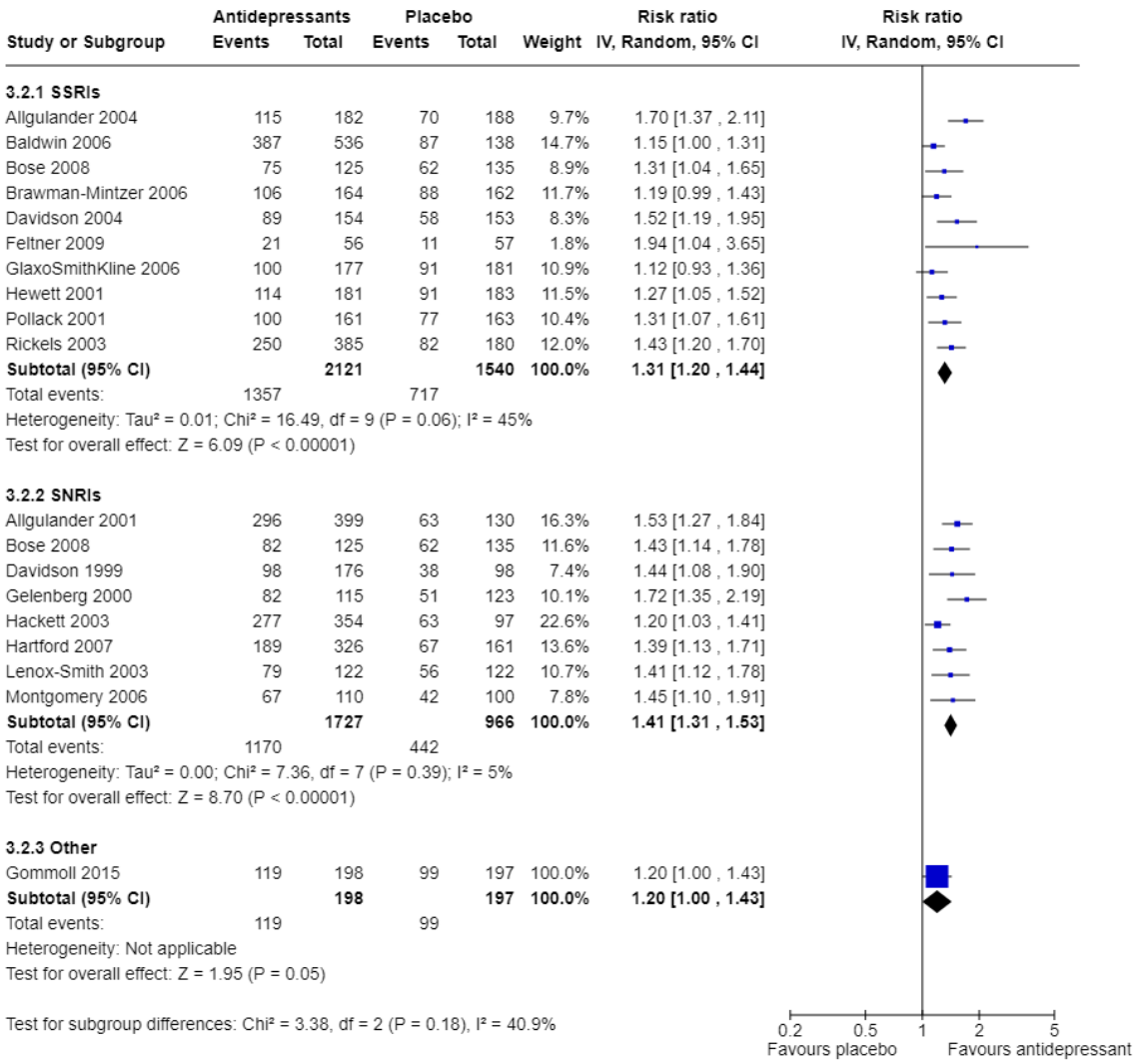


**Figure 9. Rate of treatment response (defined by study authors) by treatment class versus placebo**

### 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; $I^2$: 33%; studies = 7; participants = 2,827), SNRIs (RR, 1.57: 95% CI: 1.28, 1.92; $I^2$: 49%; studies = 8; participants = 2,639), and 'Other' antidepressants (RR, 1.77: 95% CI: 1.27, 2.45; $I^2$: 52%; studies = 4; participants = 1,088). Heterogeneity was low-moderate among SSRIs, moderate among SNRIs, and moderate-substantial among the other antidepressants. The test for subgroup interaction suggested that the effect size was similar across classes of antidepressants in remission rates ($I^2$ = 0%; p = 0.41) although more studies are needed to better detect subgroup differences.

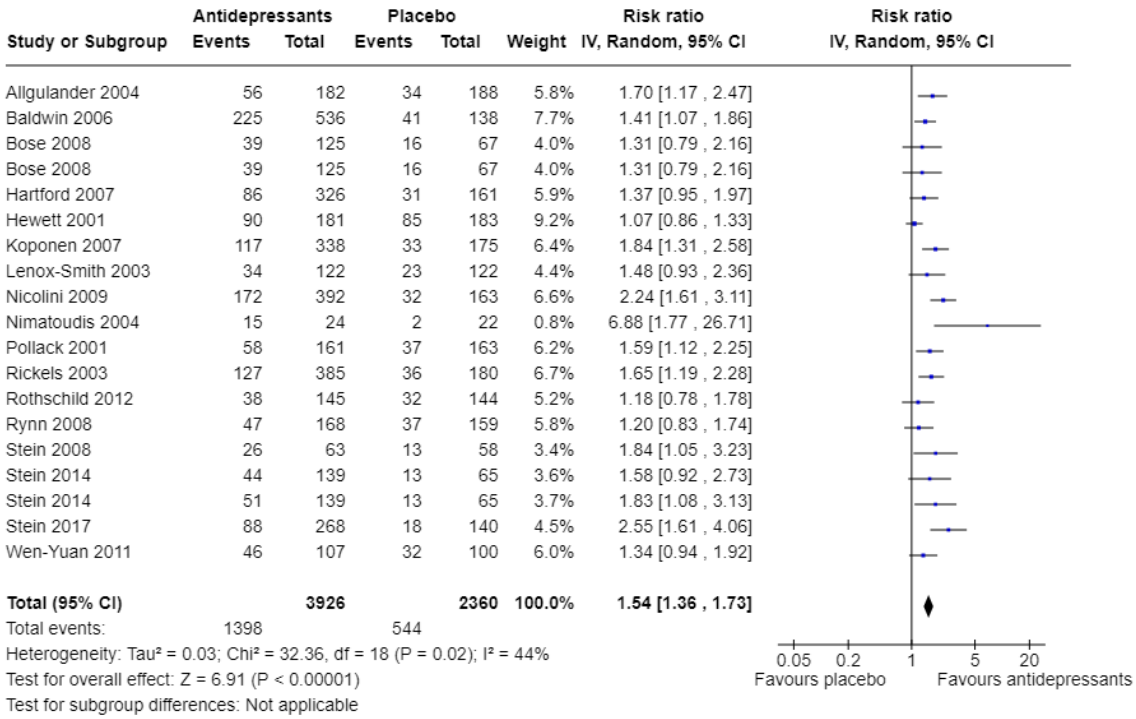


**Figure 10. Remission rate for all antidepressants versus placebo**

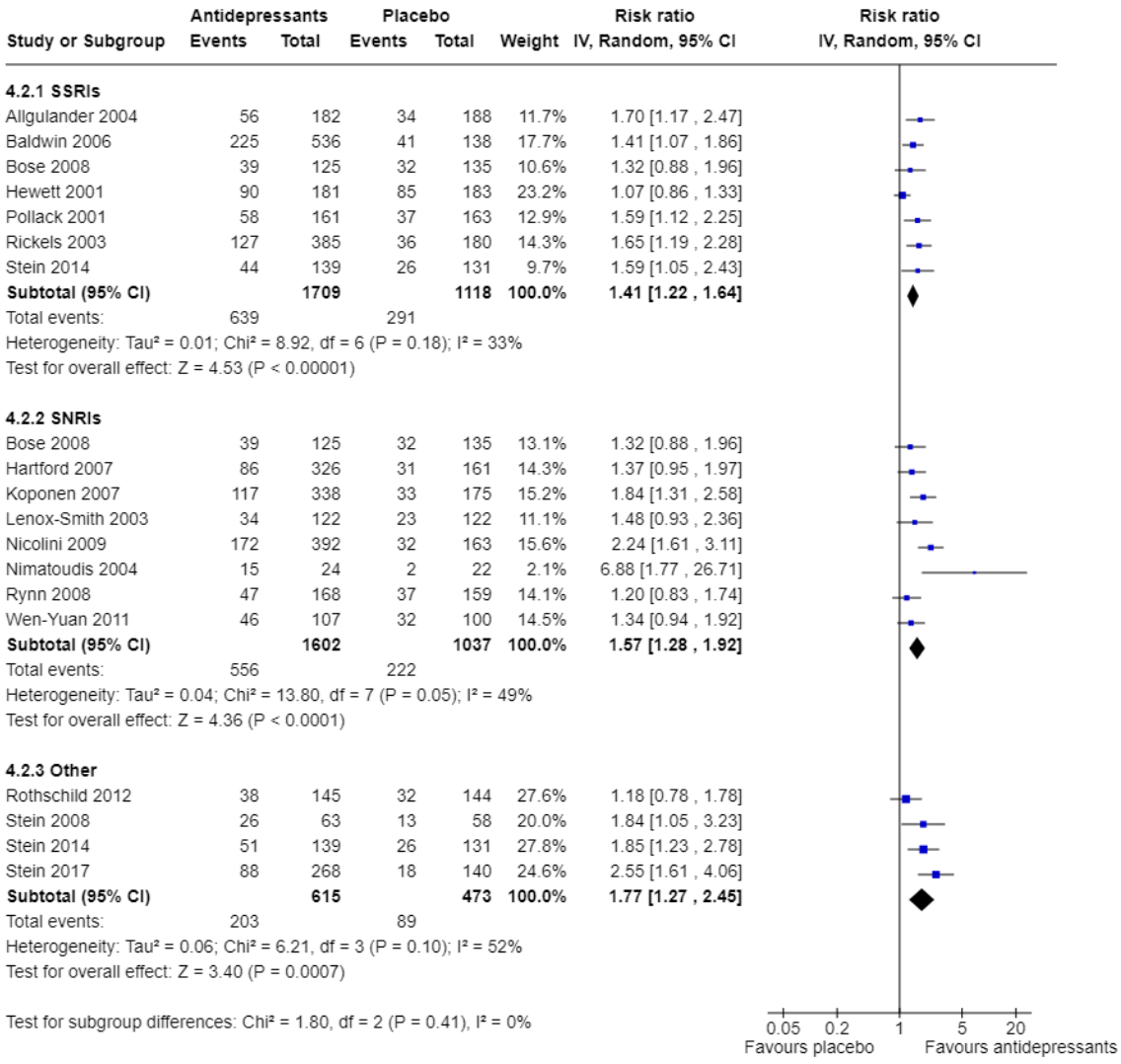


**Figure 11. Remission rate by treatment class versus placebo**

### 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; $I^2$: NA; studies = 1; participants = 28); SSRIs (MD, -2.28; 95% CI: -2.98, -1.58; $I^2$: 49%; studies = 15; participants = 4,689); SNRIs (MD, -3.04; 95% CI: -4.12, -1.97; $I^2$: 81%; studies = 16; participants =5,244); and ‘Other’ (MD, -3.06; 95% CI: -5.94, -0.17; $I^2$: 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 ($I^2 = 0\%$; $p = 0.63$) however more studies are needed to better detect subgroup differences.

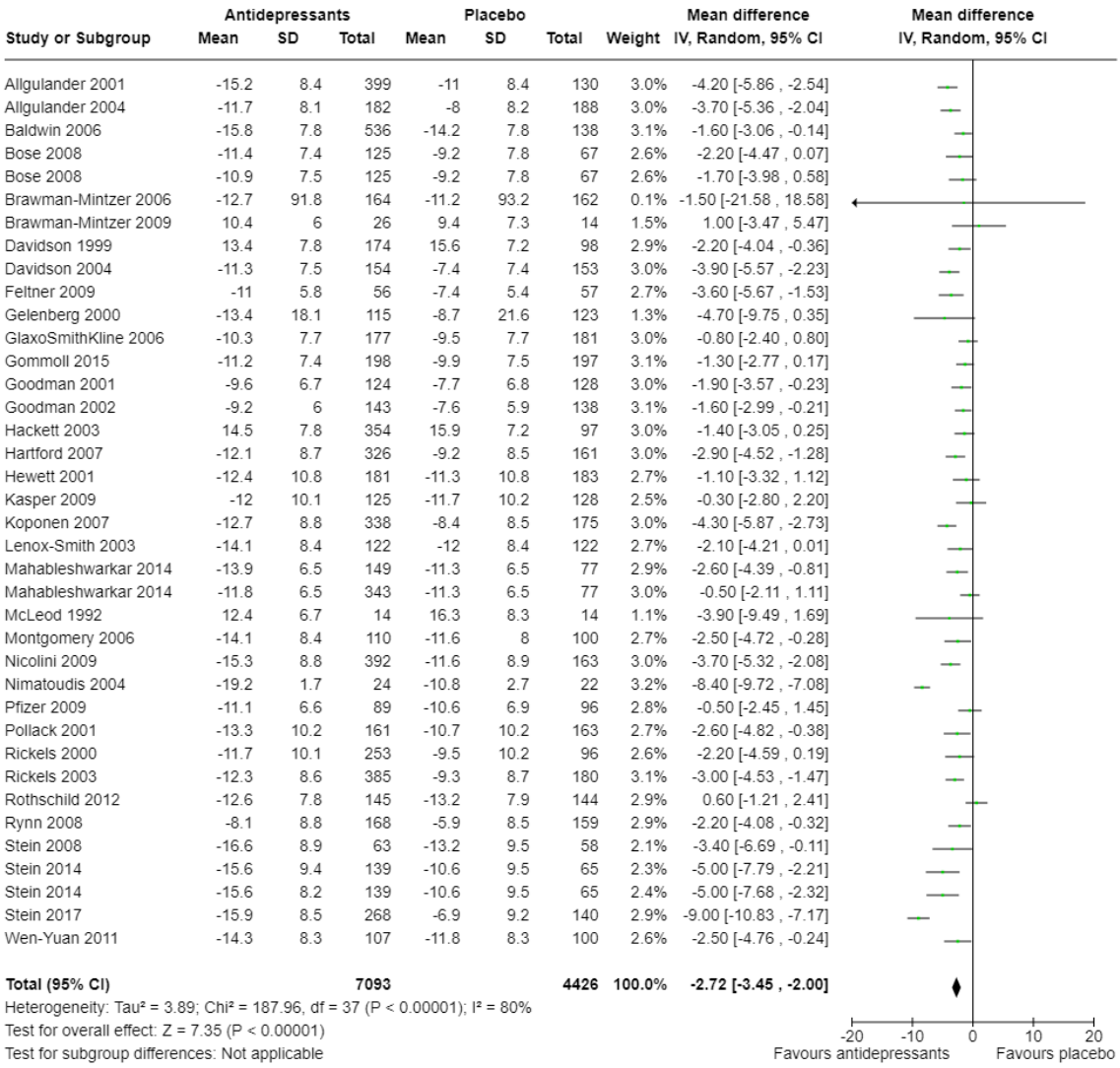


**Figure 12. Change in symptom levels for all antidepressants versus placebo**

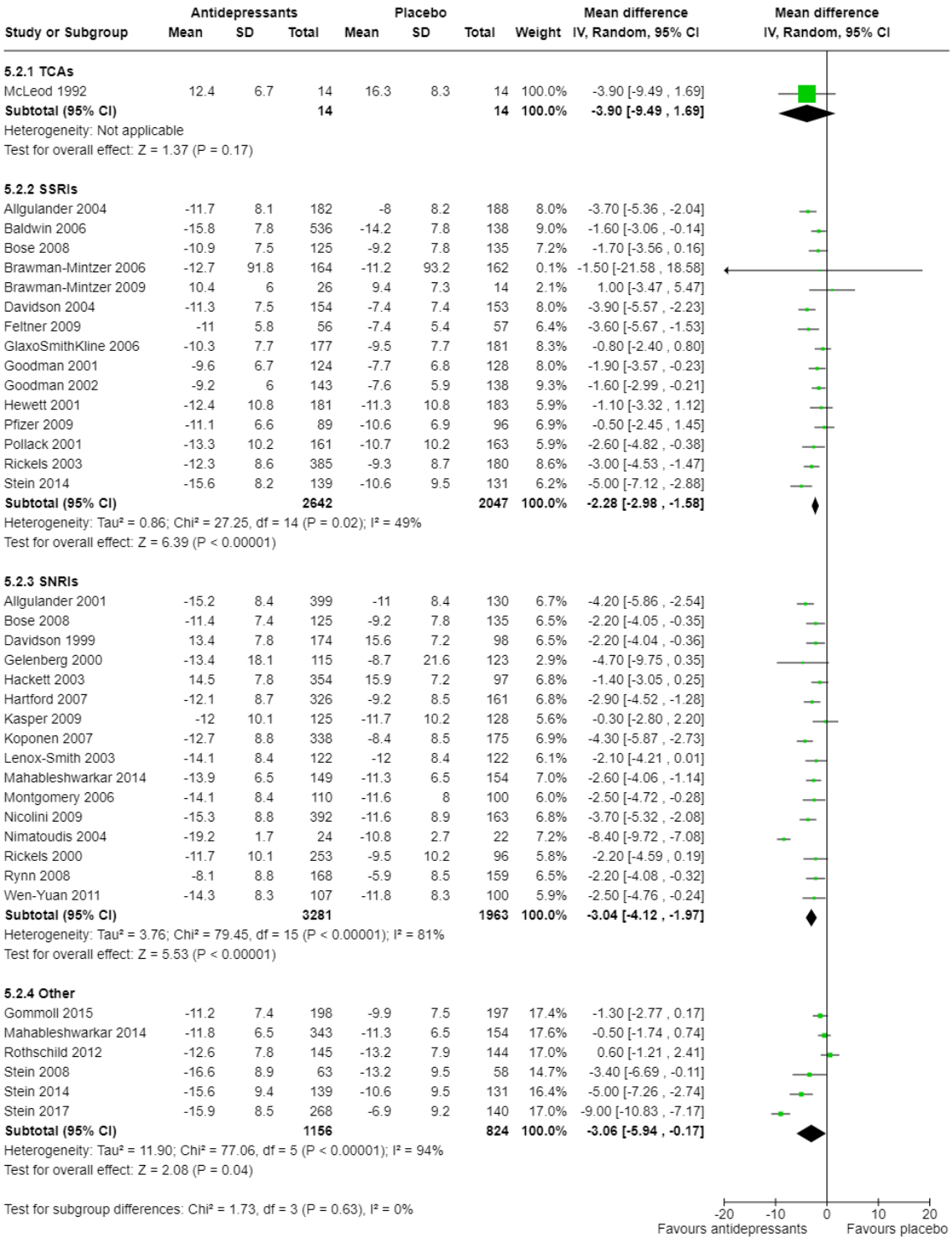


**Figure 13. Change in symptom levels by treatment class versus placebo**

### 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.

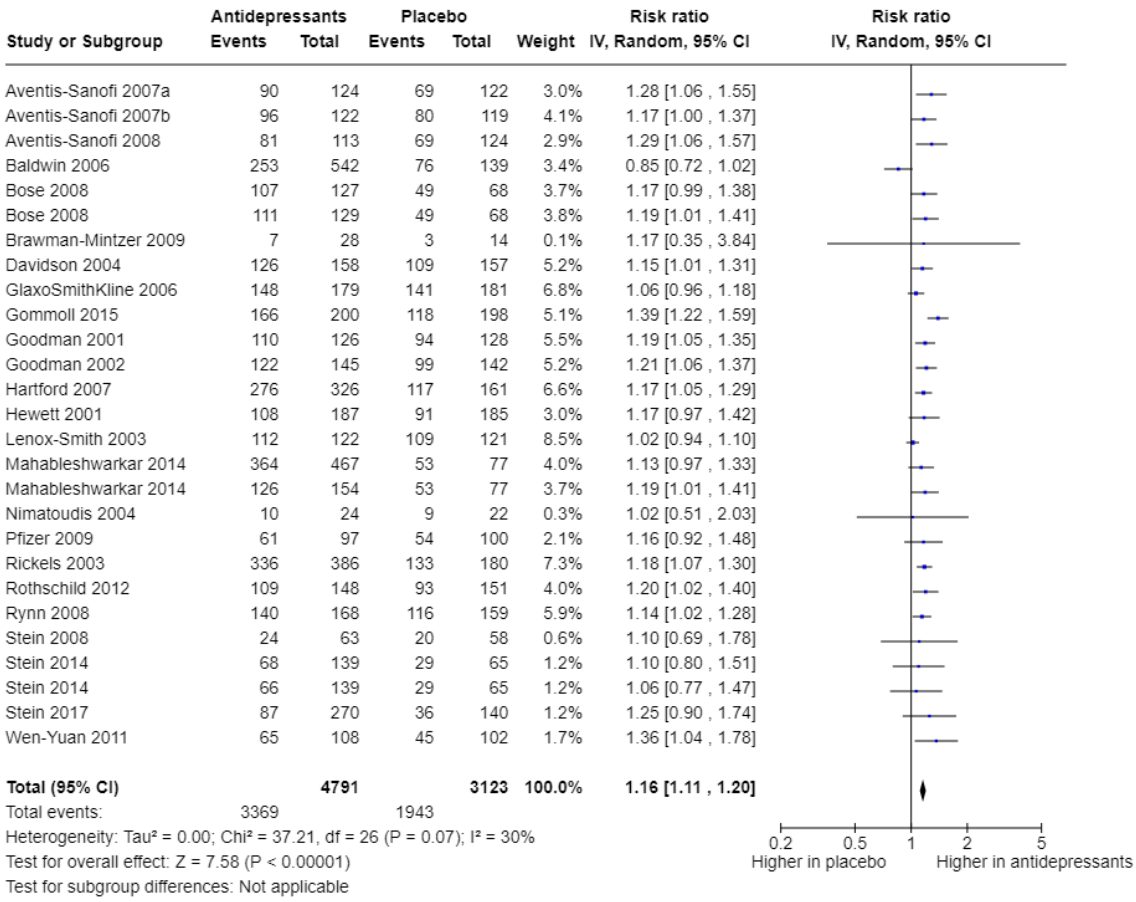


**Figure 14. Total number of patients reporting adverse effects for all antidepressants versus placebo**

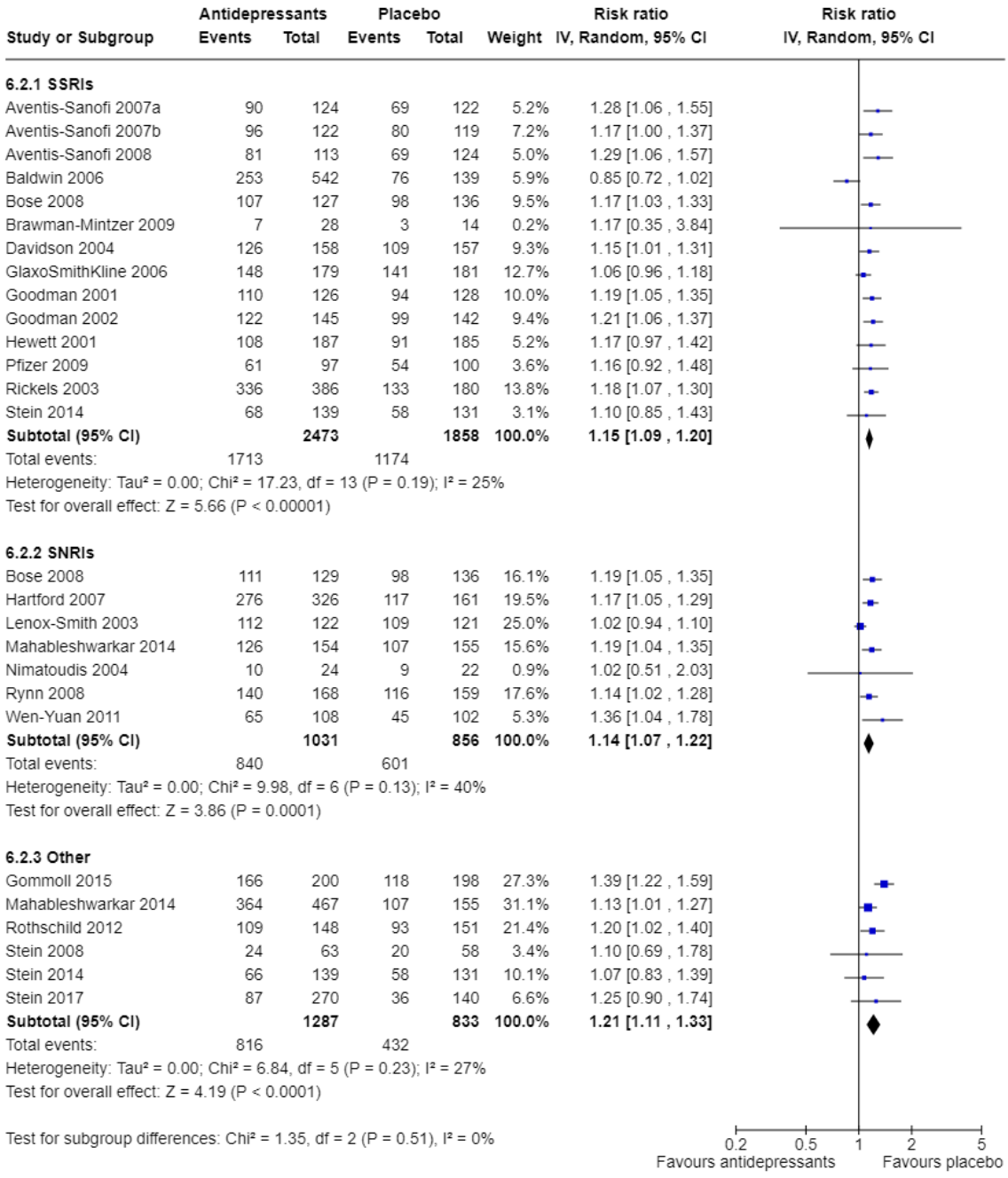


**Figure 15. Total number of patients reporting adverse effects by treatment class versus placebo**

### 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.

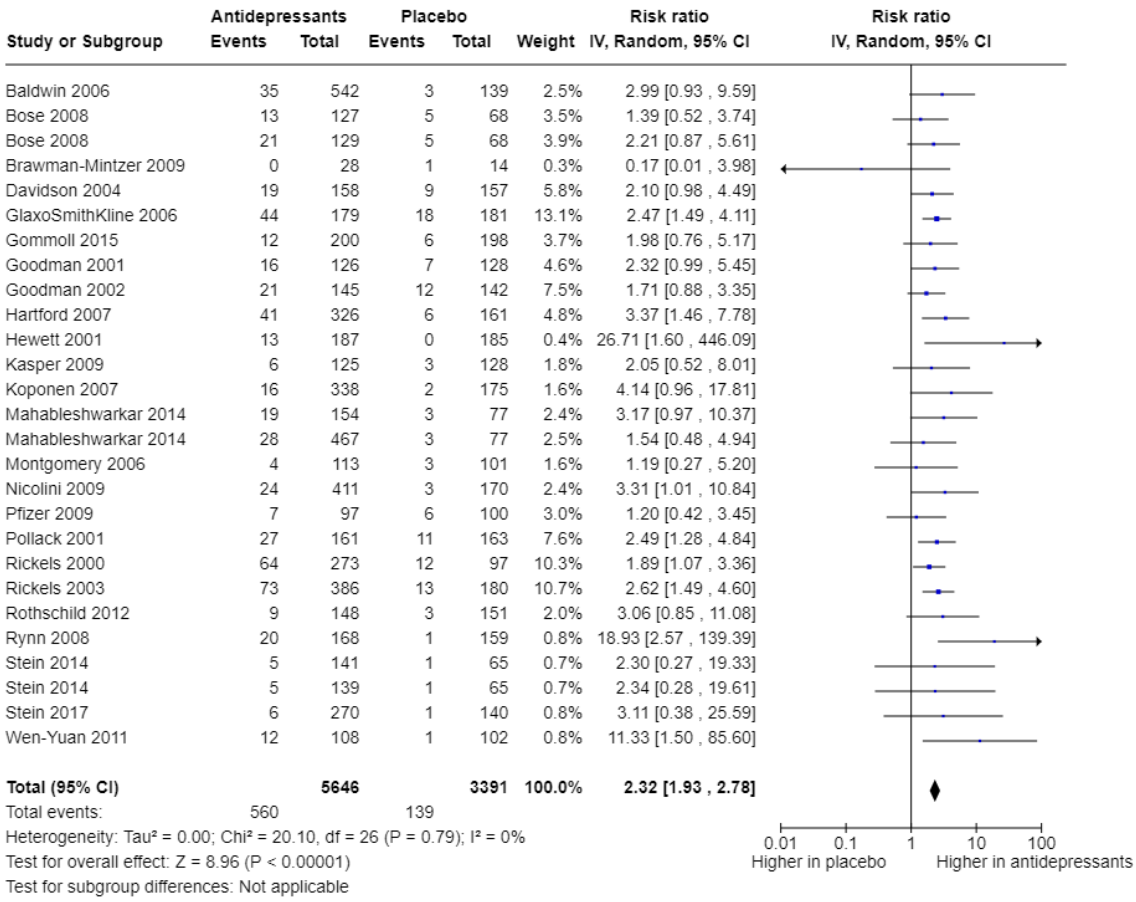


**Figure 16. Sleepiness/drowsiness for all antidepressants versus placebo**

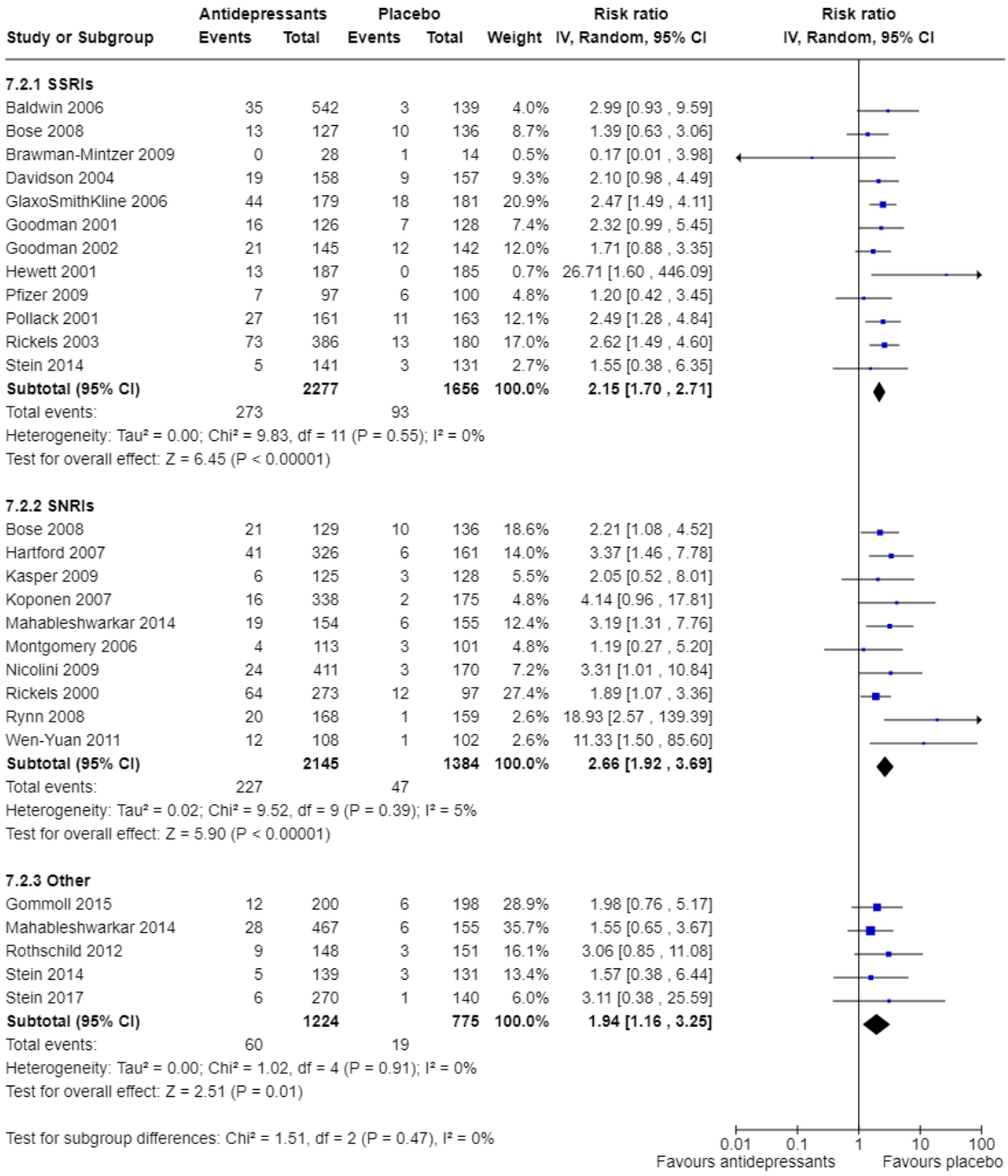


**Figure 17. Sleepiness/drowsiness by treatment class versus placebo**

### 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; $I^2$: 19%; studies = 5; participants = 1,783) and SNRIs (RR, 0.99: 95% CI: 0.57, 1.72; $I^2$: 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 ($I^2$ = 0%; p = 0.80) although more studies are needed to detect any subgroup effects.

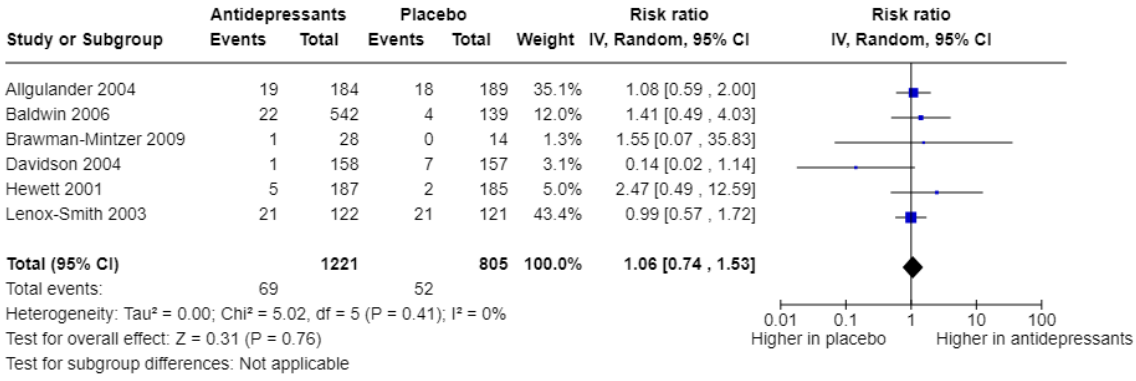


**Figure 18. Agitation/anxiety for all antidepressants versus placebo**

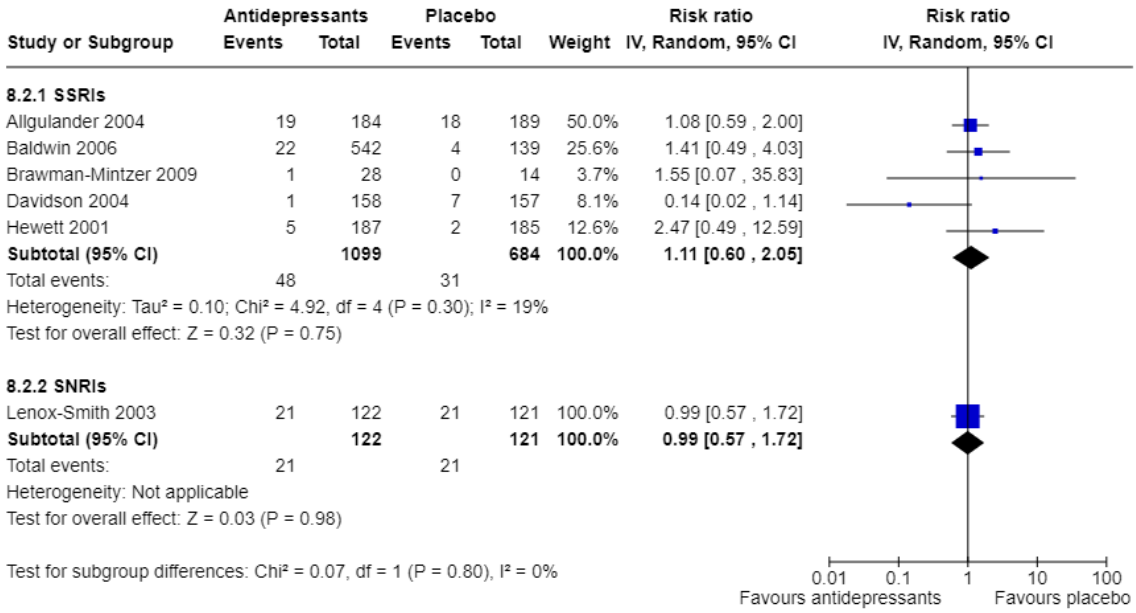


**Figure 19. Agitation/anxiety by treatment class versus placebo**

## 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.

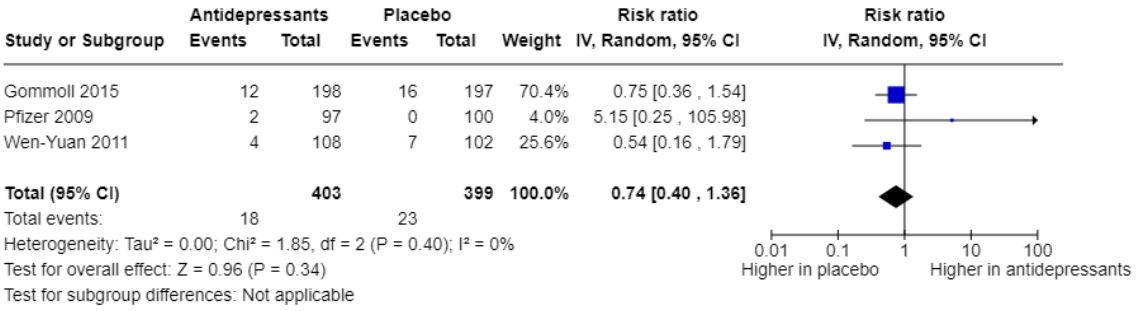


**Figure 20. Suicide wishes/gestures/attempts for all antidepressants versus placebo**

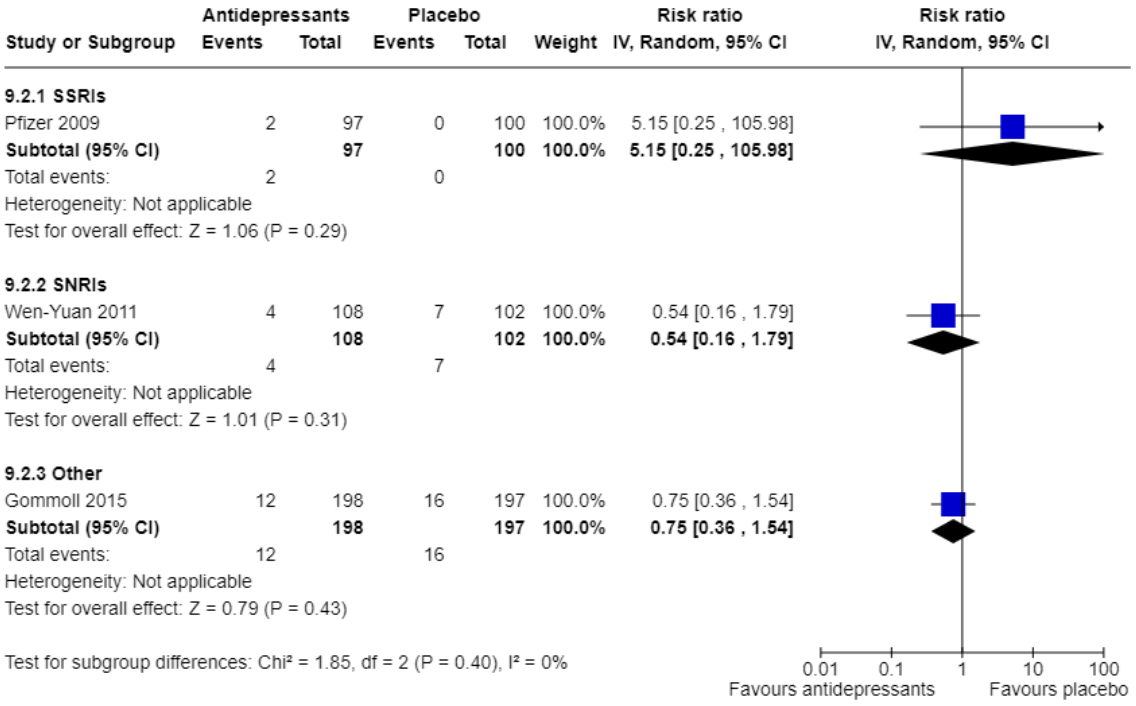


**Figure 21.Suicide wishes/gestures/attempts by treatment class versus placebo**

## 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; $I^2$: 0%; studies = 3; participants = 760) and SNRIs (MD, 5.00; 95% CI: 0.29, 9.71; $I^2$: 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 ($I^2$ = 0%; p = 0.51) although more studies are needed to detect subgroup differences.

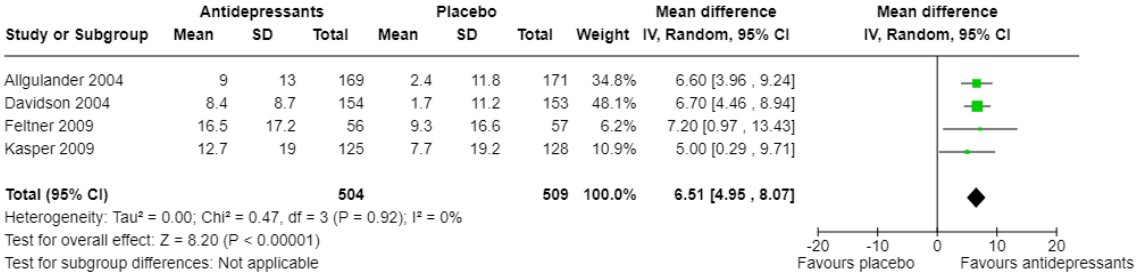


**Figure 22. Average score/change in quality of life/satisfaction for all antidepressants versus placebo**

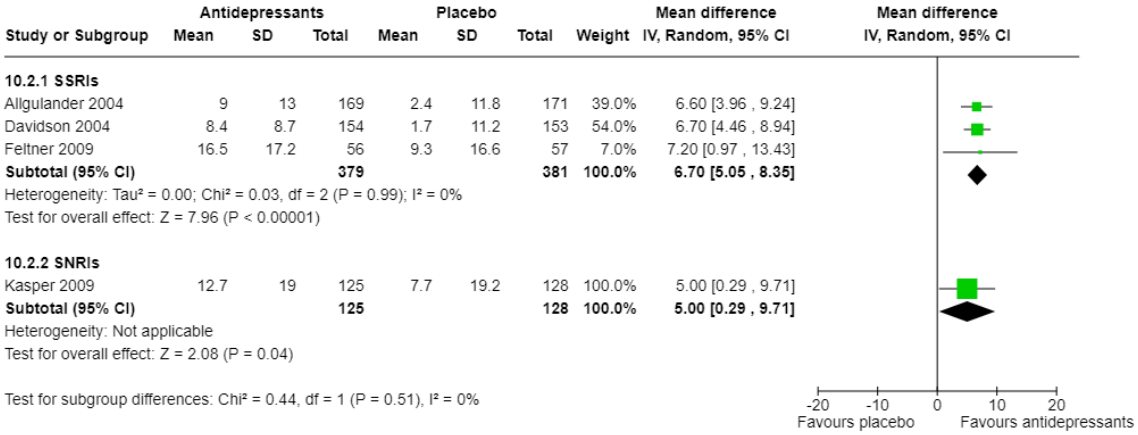


**Figure 23. Average score/change in quality of life/satisfaction by treatment class versus placebo**

### 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.

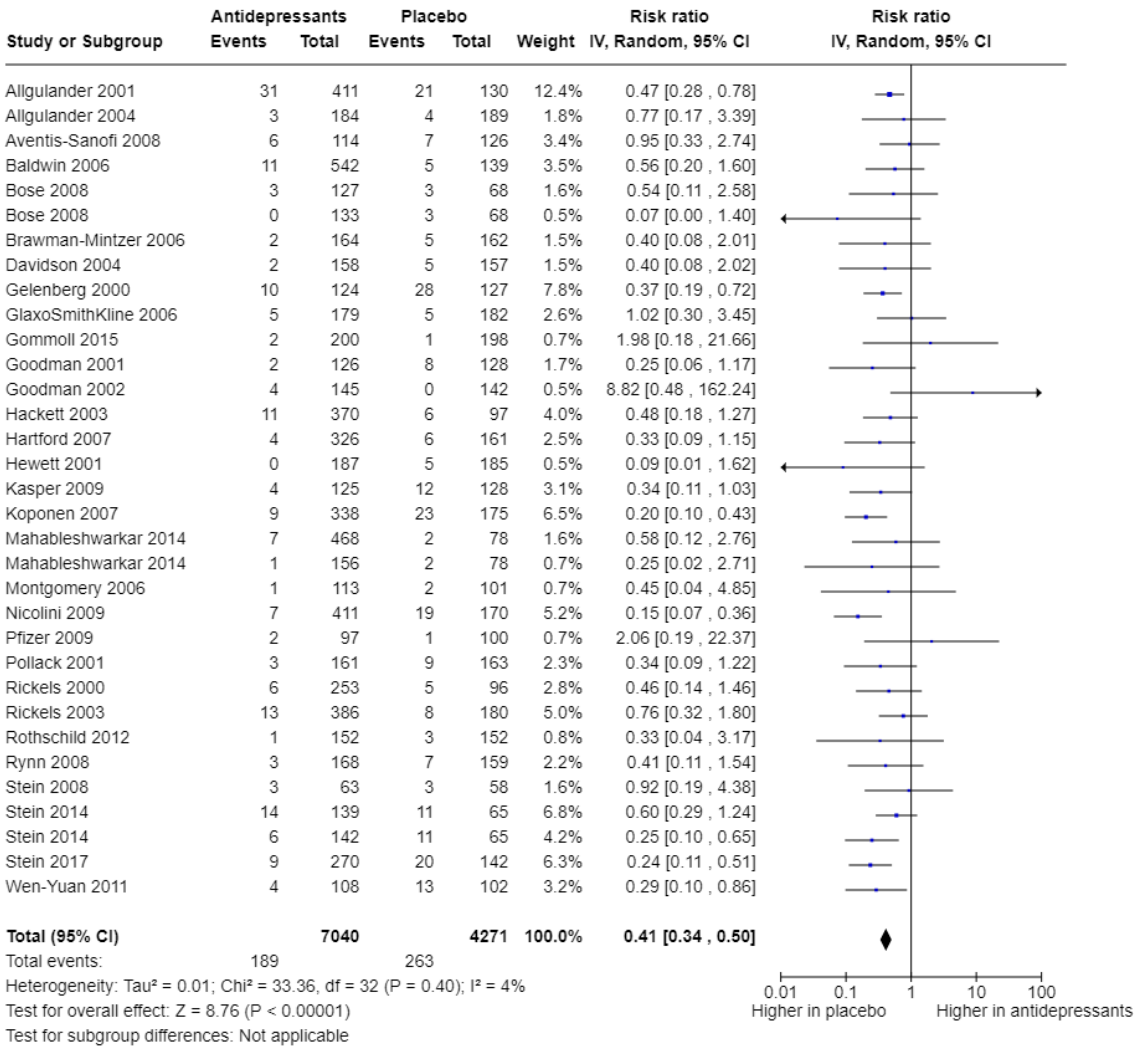


**Figure 24. Dropouts due to lack of efficacy for all antidepressants versus placebo**

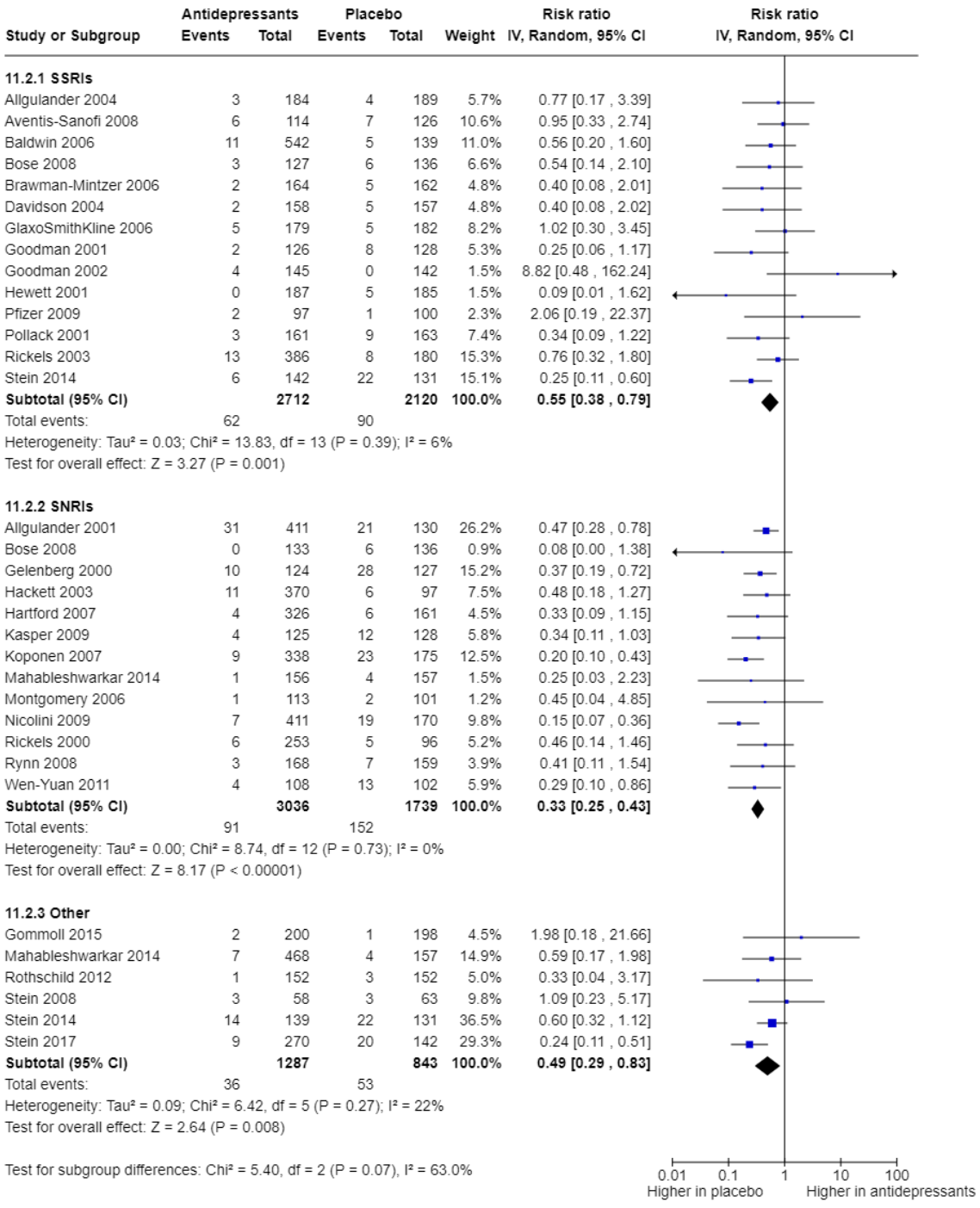


**Figure 25. Dropouts due to lack of efficacy by treatment class versus placebo**

### 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.

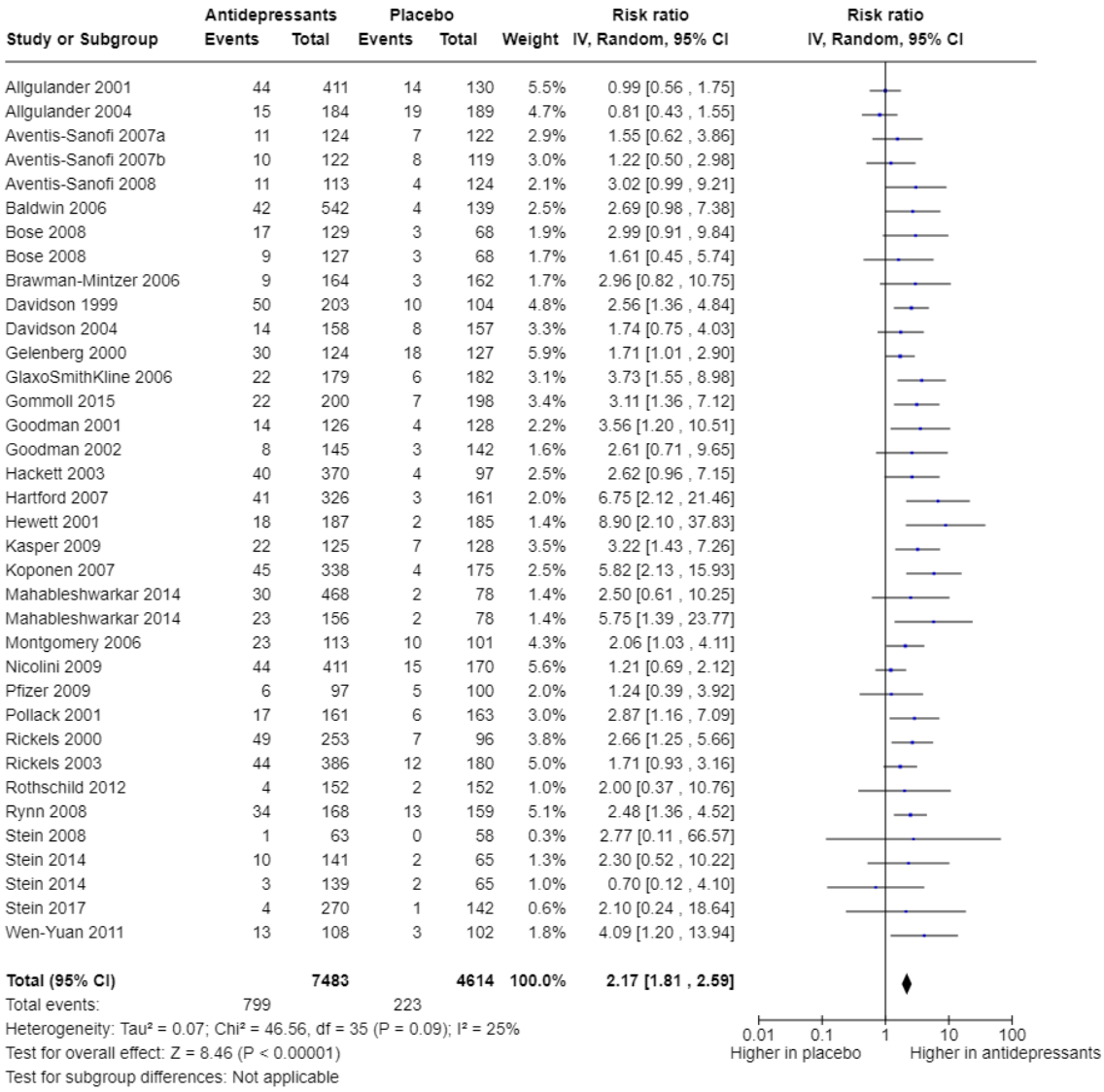


**Figure 26. Dropouts due to adverse effects for all antidepressants versus placebo**

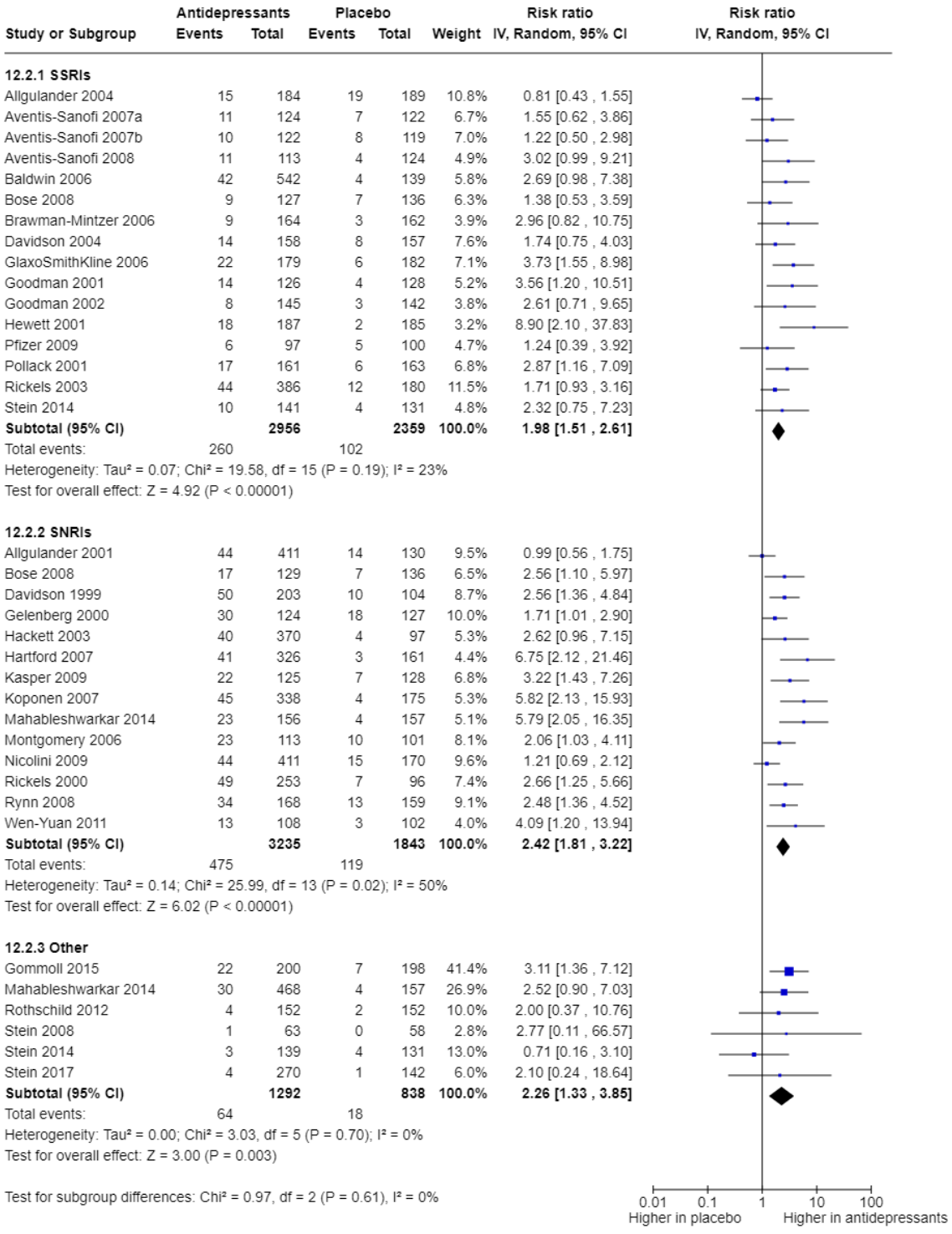


**Figure 27. Dropouts due to adverse effects by treatment class versus placebo**

## 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 ($I^2$ = 58.5%; p = 0.09) however, more studies among different 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.

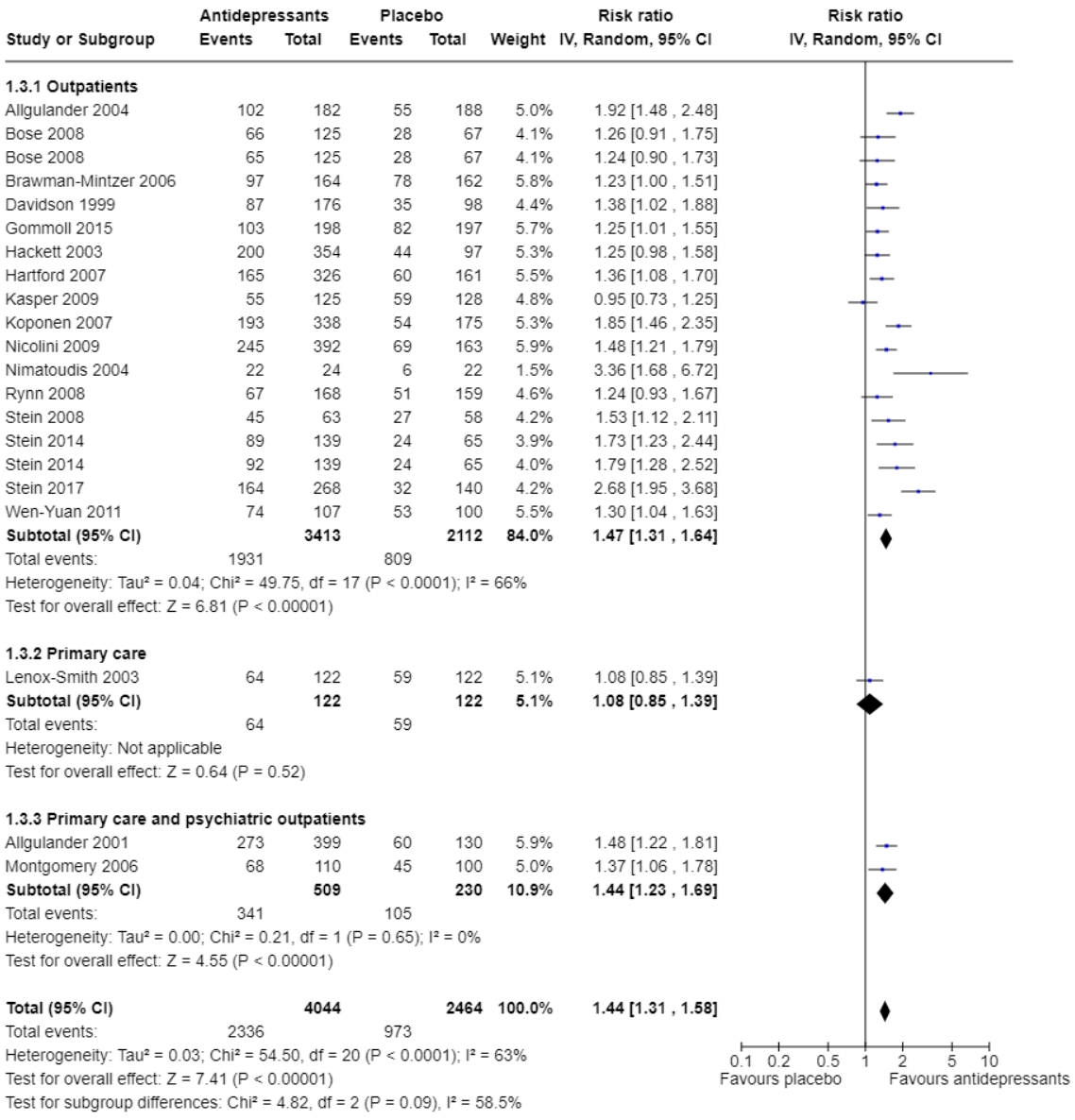


**Figure 28. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment setting**

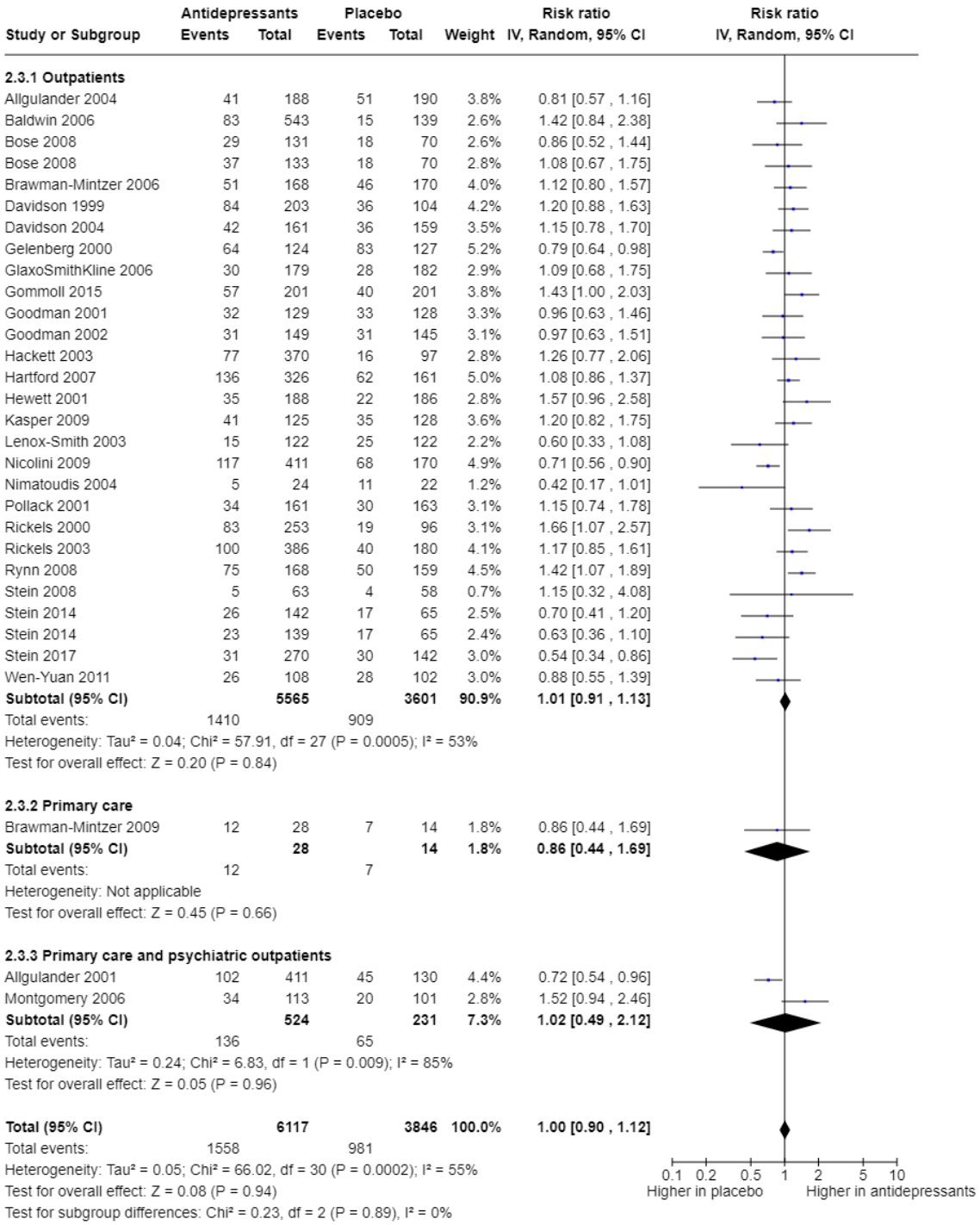


**Figure 29. Subgroup analysis for acceptability by treatment setting**

### 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 psychiatric comorbidities and low heterogeneity among studies with 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.

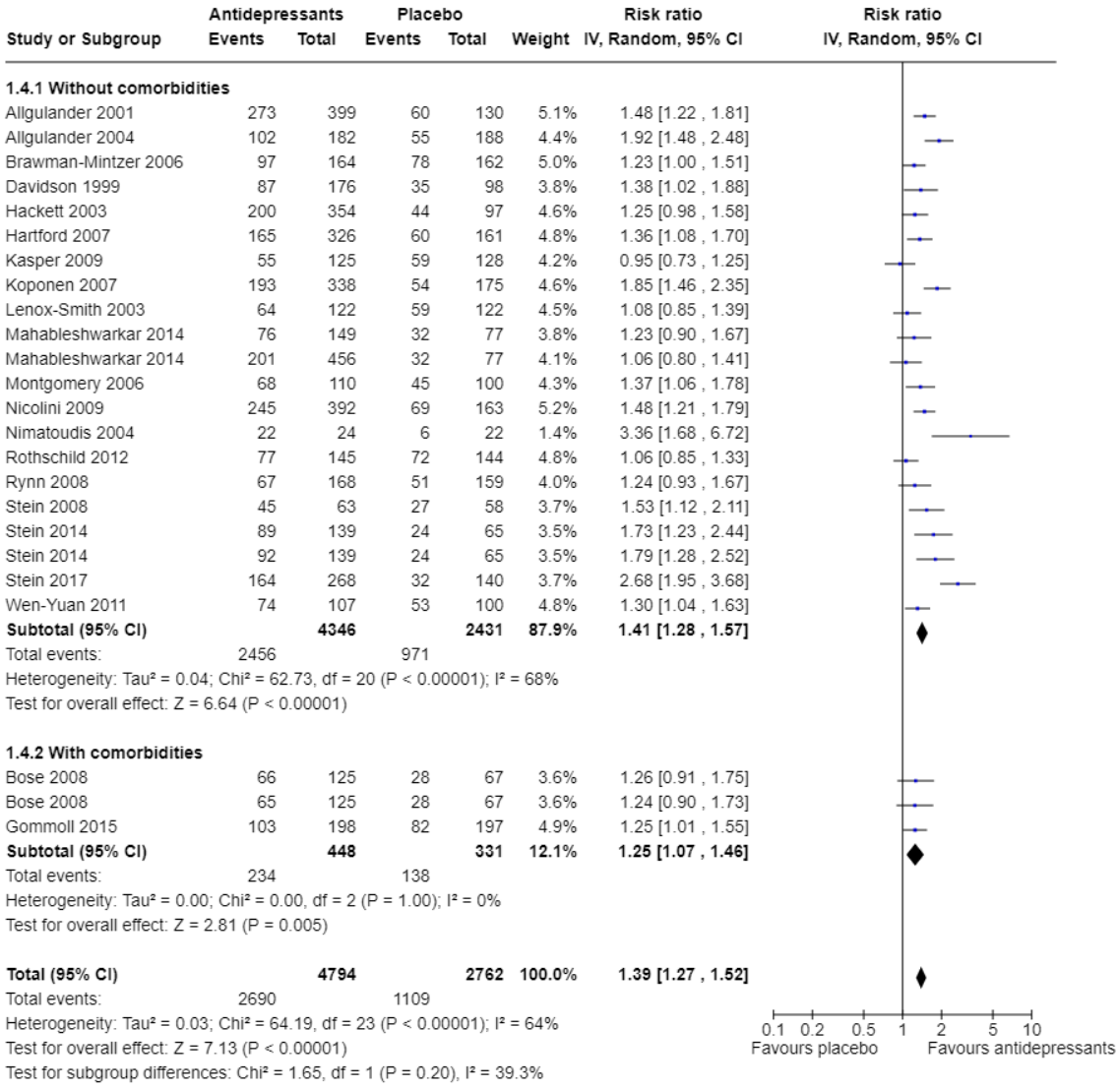


**Figure 30. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A for patients with and without comorbidities**

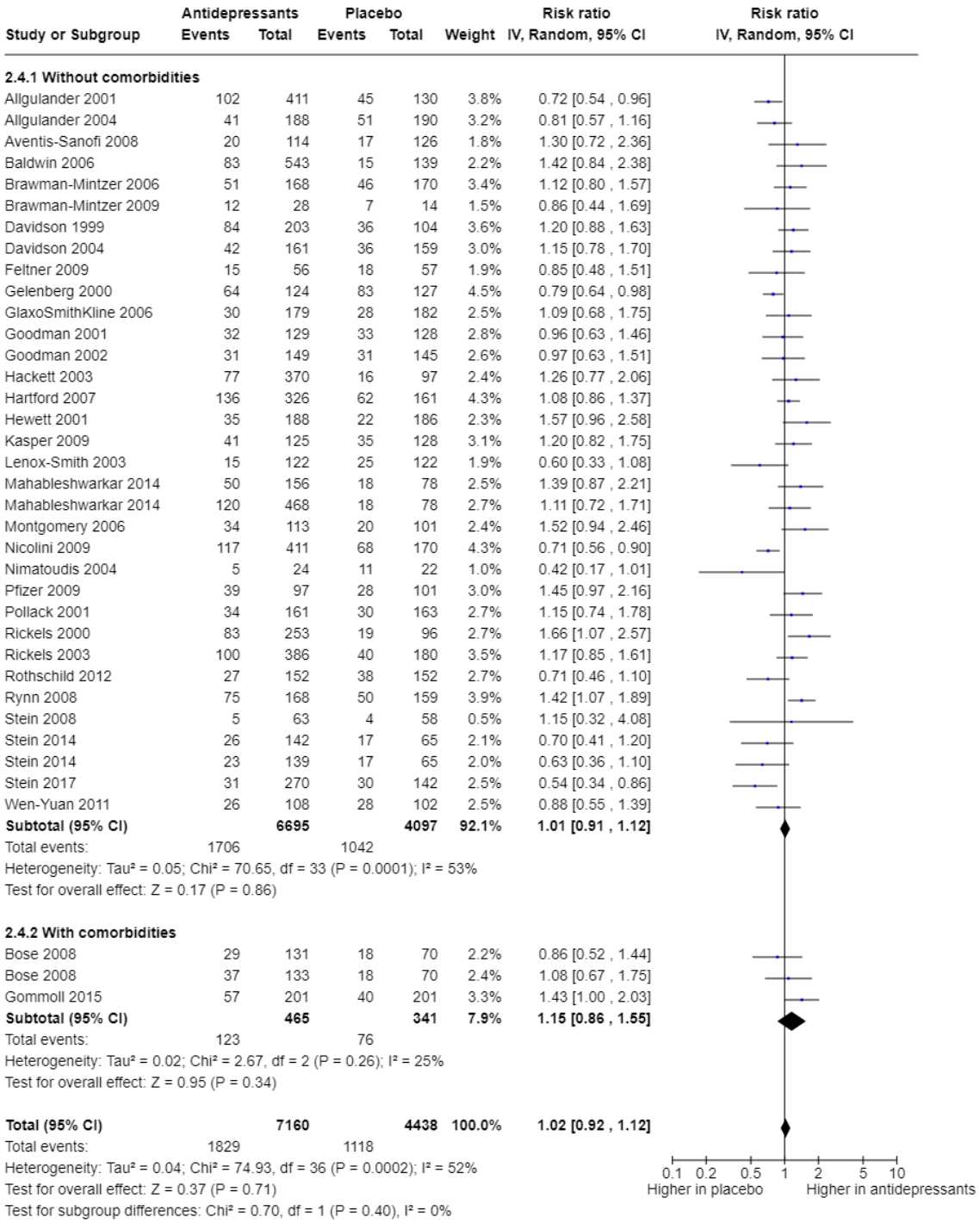


**Figure 31. Subgroup analysis for acceptability for patients with and without psychiatric comorbidities**

### 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.

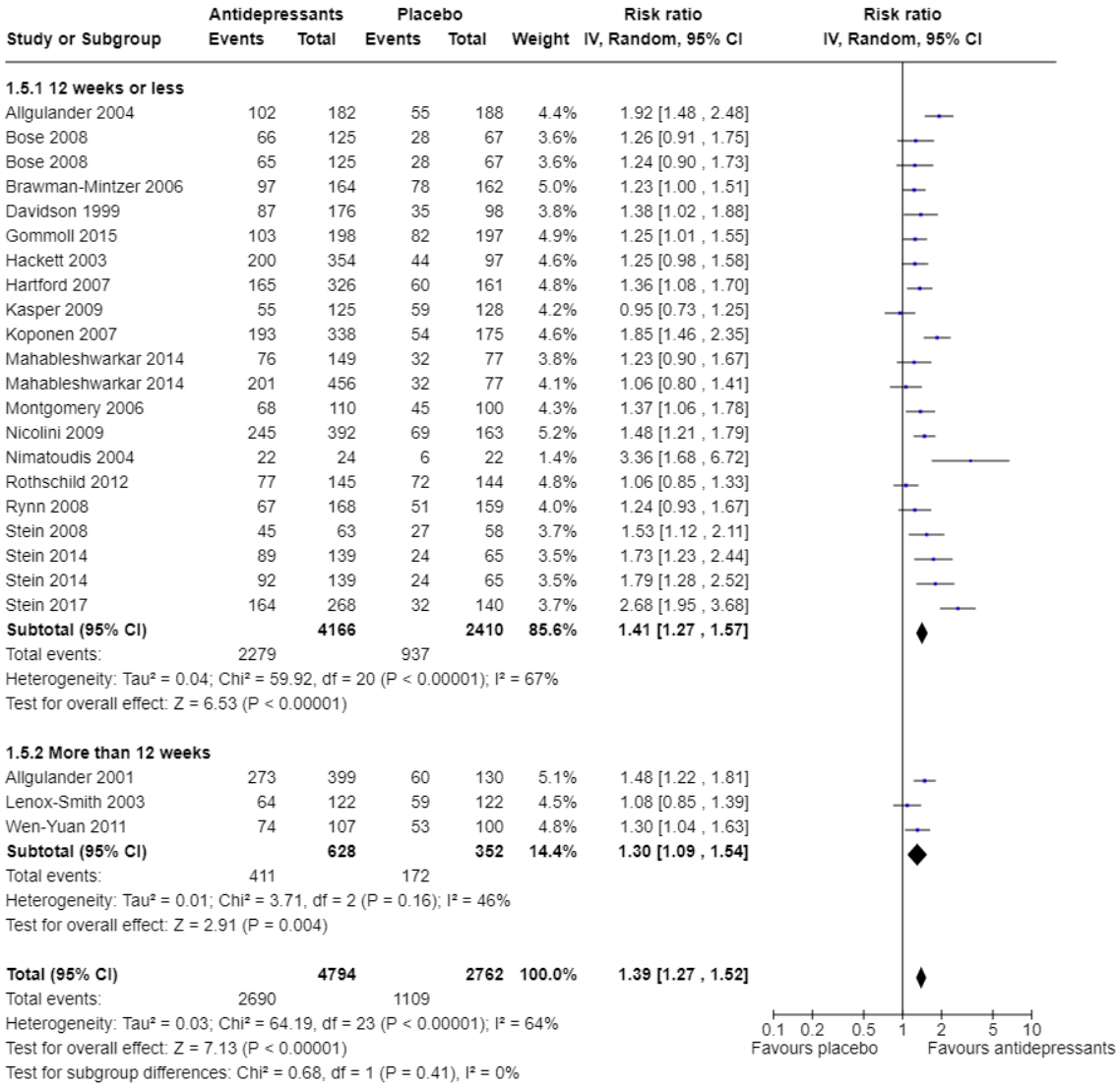


**Figure 32. Subgroup analysis for rate of treatment response measured as a reduction of at least 50% on the HAM-A by treatment duration**

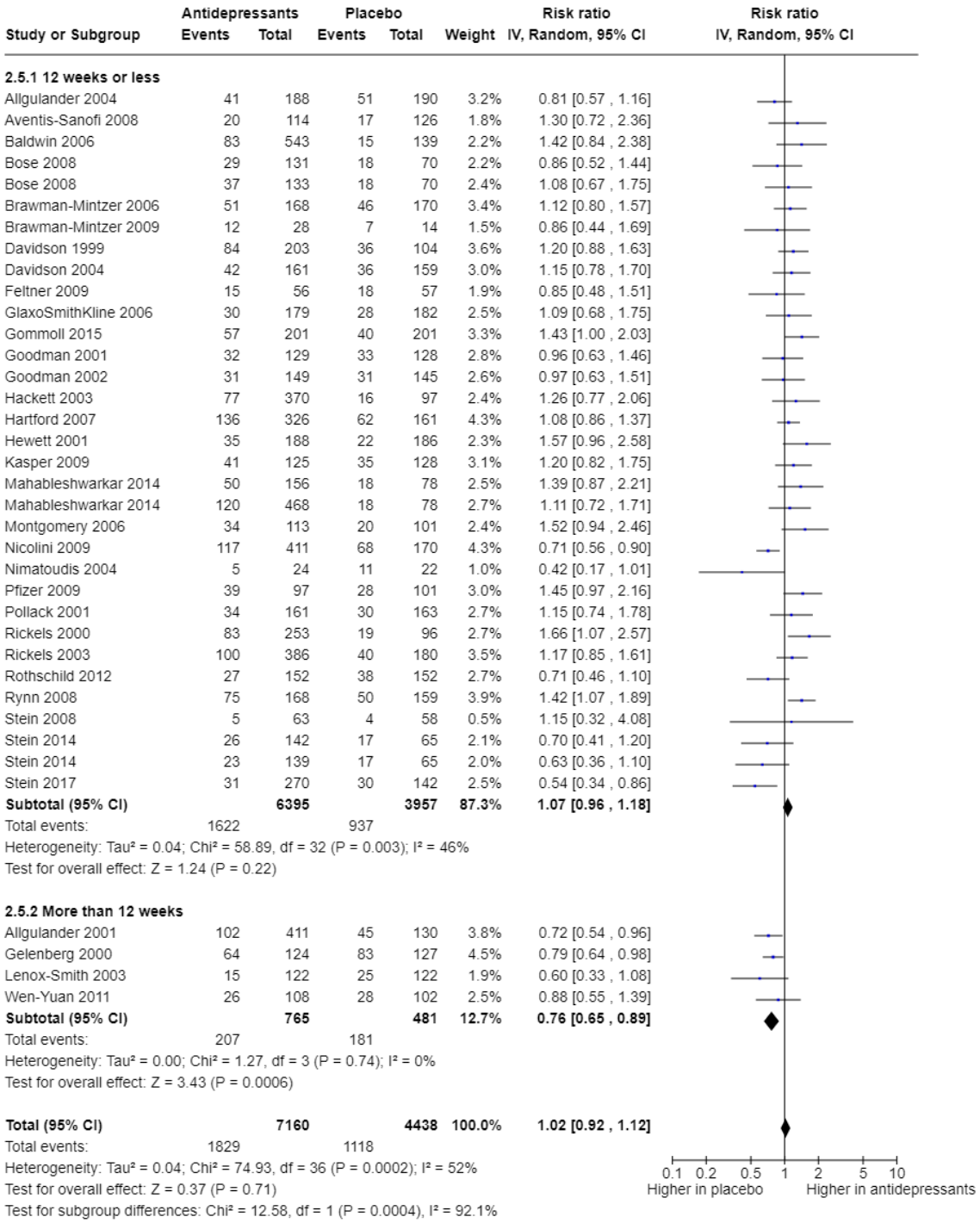


**Figure 33. Subgroup analysis for acceptability by treatment duration**

## 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)).

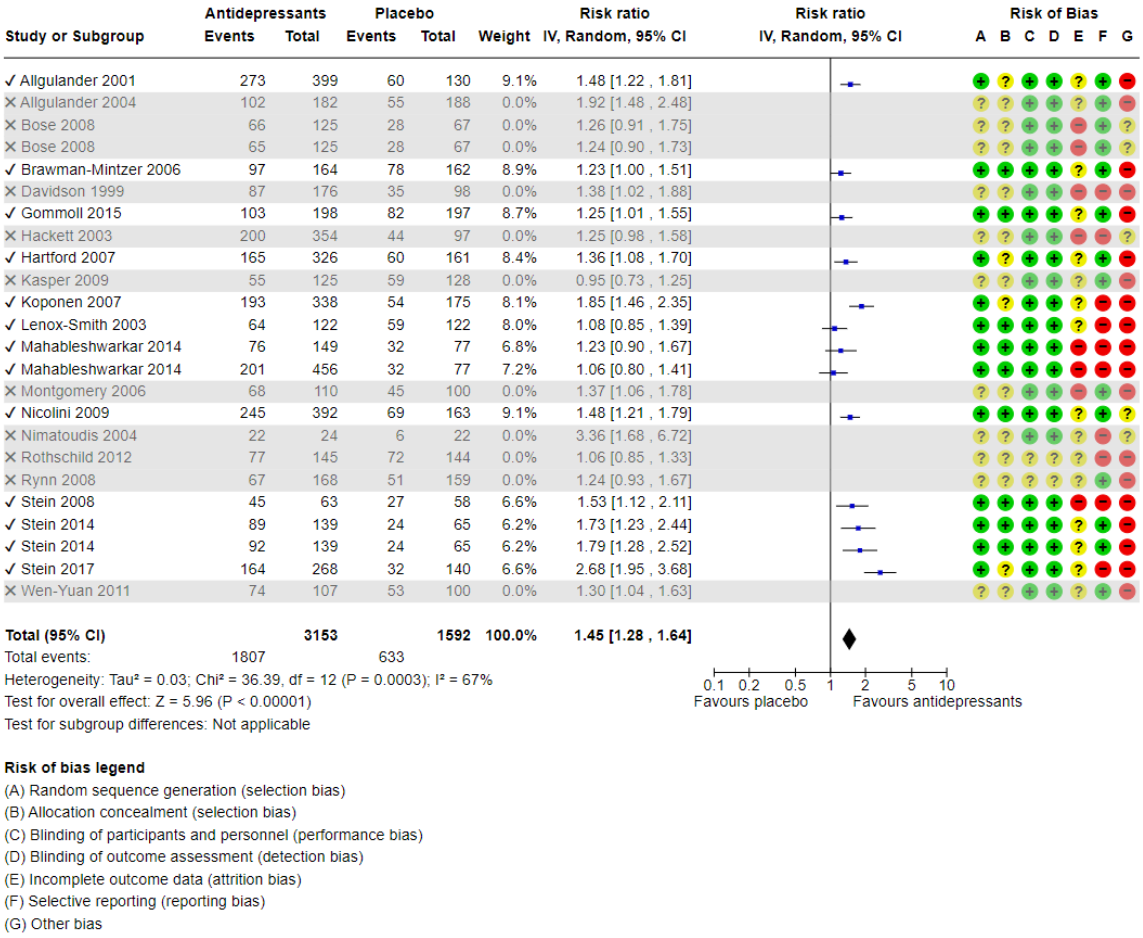


**Figure 34. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo without studies with high/unclear risk of bias**

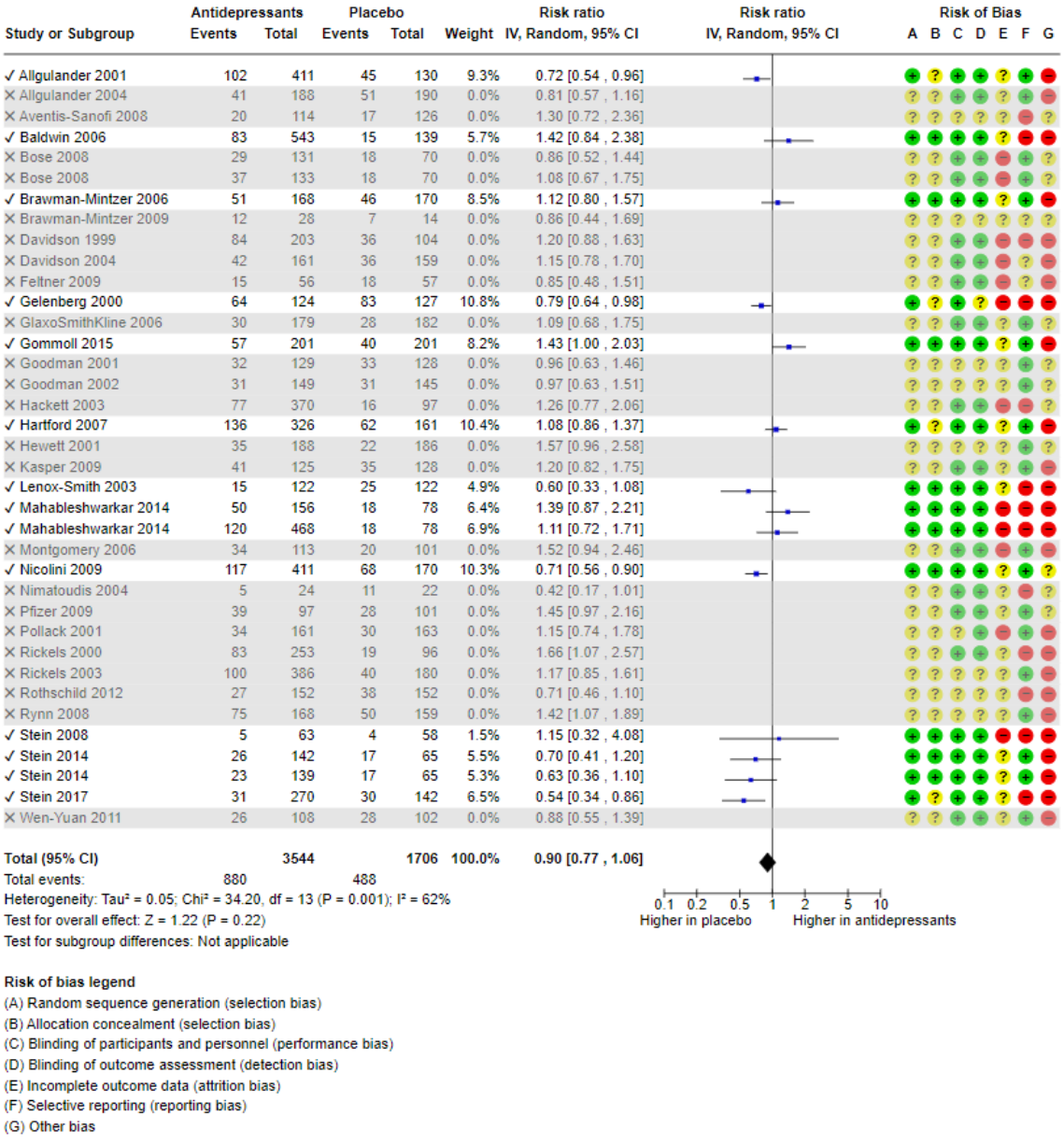


**Figure 35. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo without studies with high/unclear risk of bias**

### 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)).

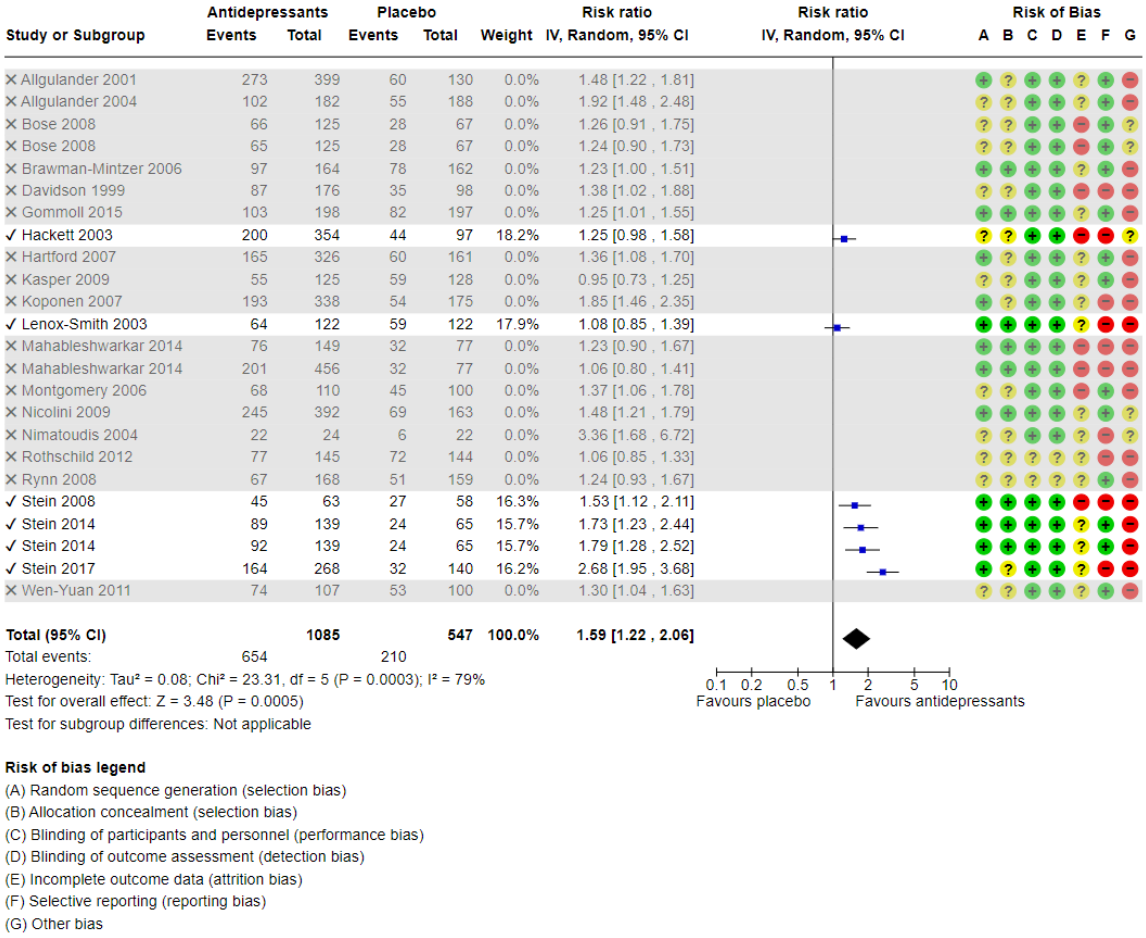


**Figure 36. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo excluding studies with more than 20% dropout rate**

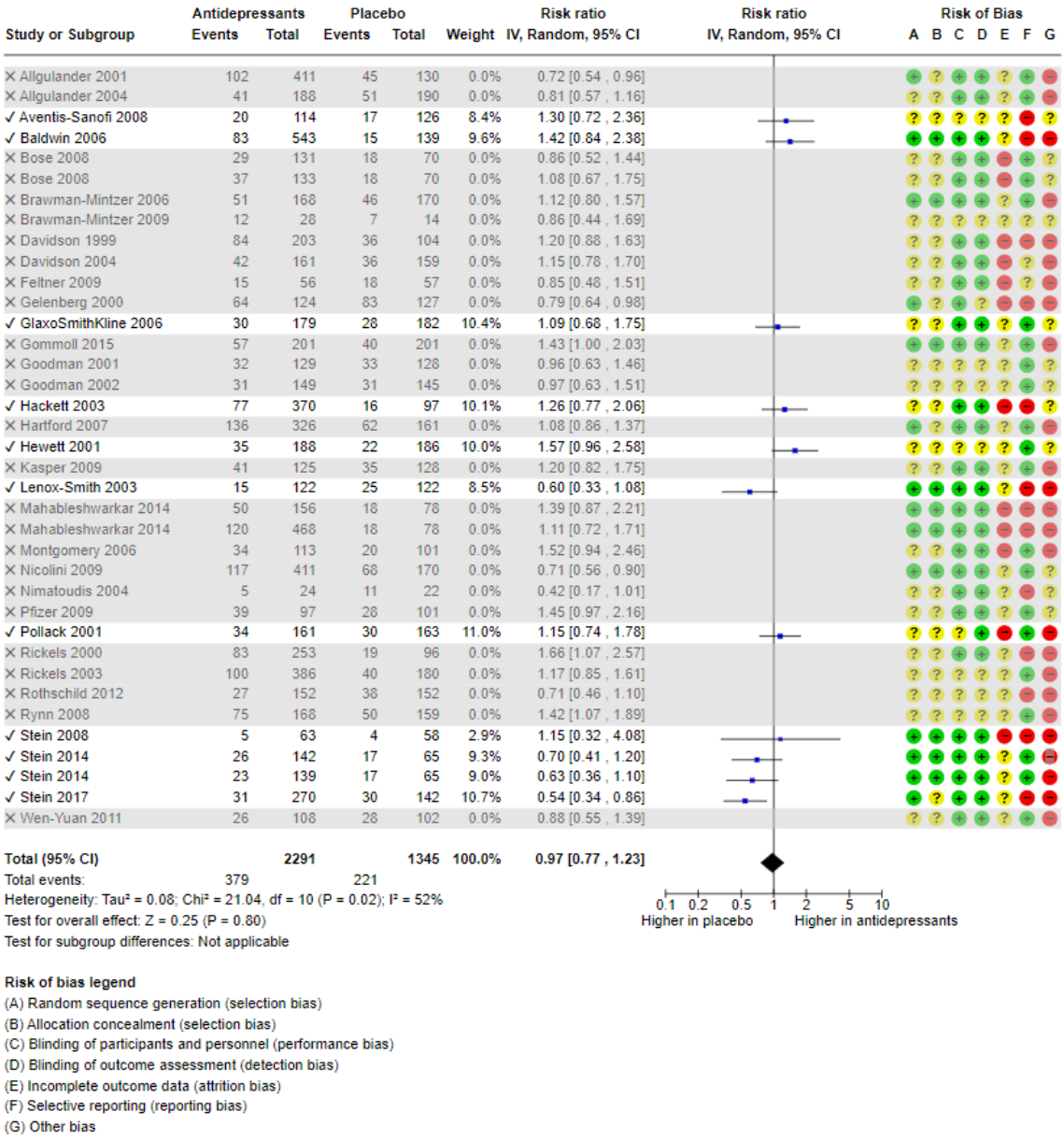


**Figure 37. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo excluding studies with more than 20% dropout rate**

### 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)).

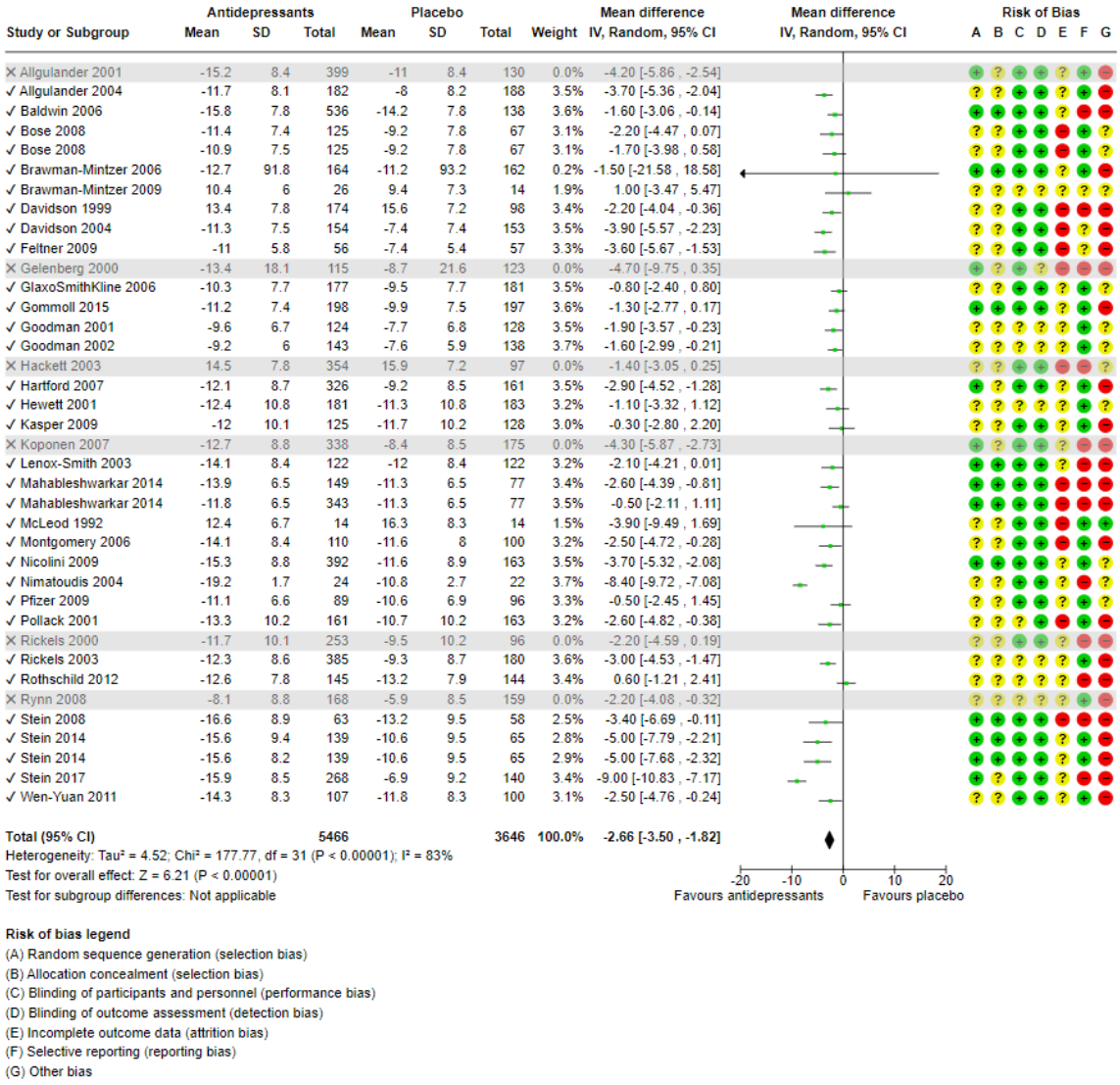


**Figure 38. Sensitivity analysis with risk of bias assessment: Change in symptom levels excluding studies with imputed SD**

## 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)).

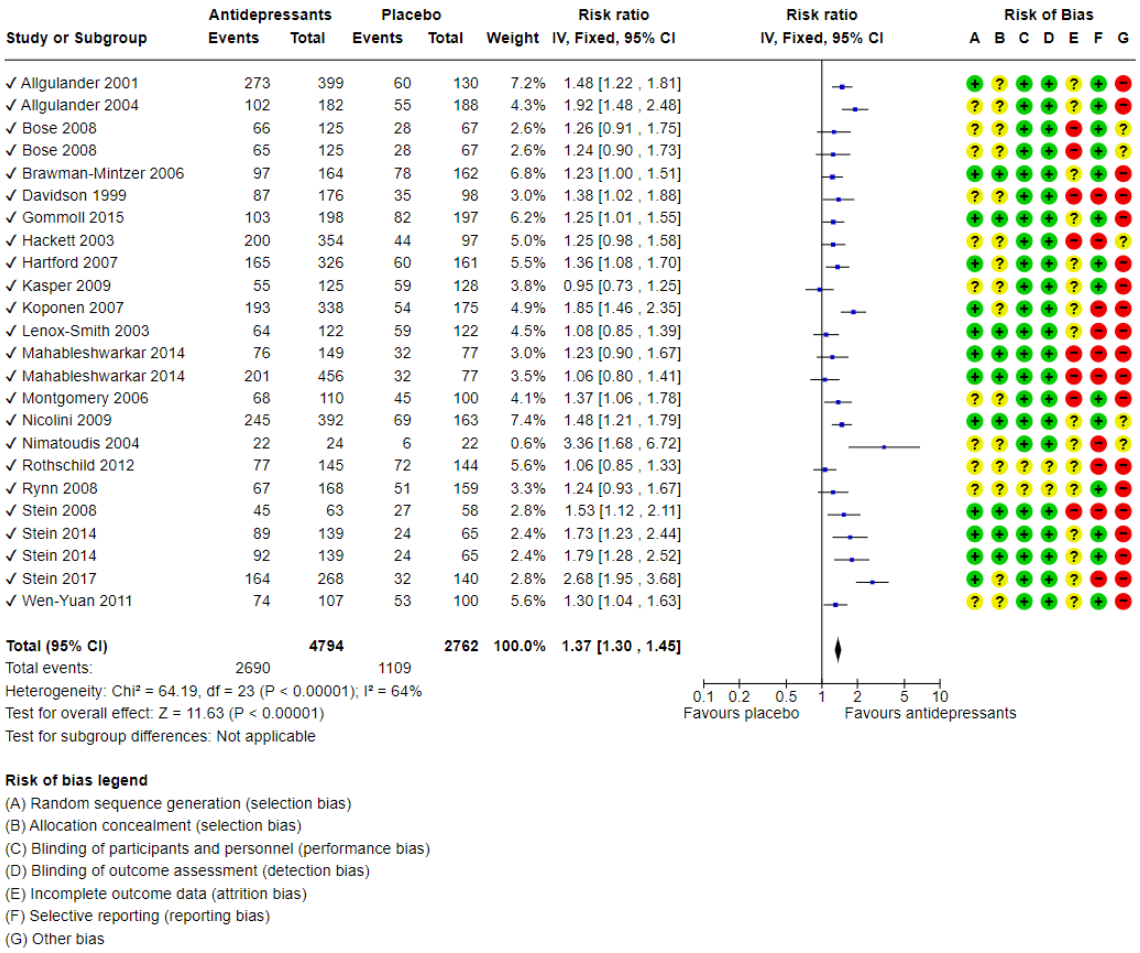


**Figure 39. Sensitivity analysis with risk of bias assessment: Rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo using fixed effects model**

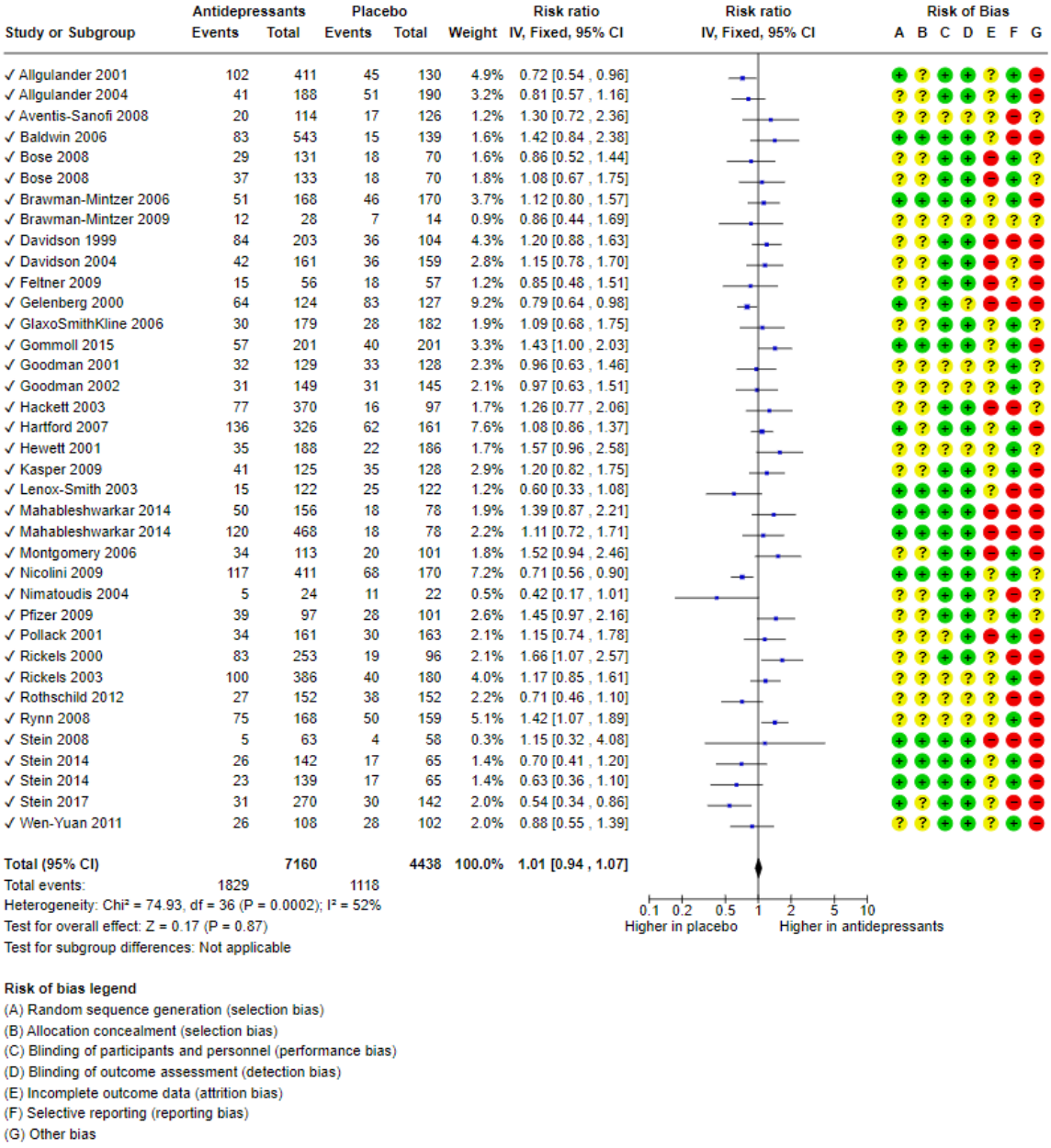


**Figure 40. Sensitivity analysis with risk of bias assessment: Acceptability for all antidepressants versus placebo using fixed effects model**

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.

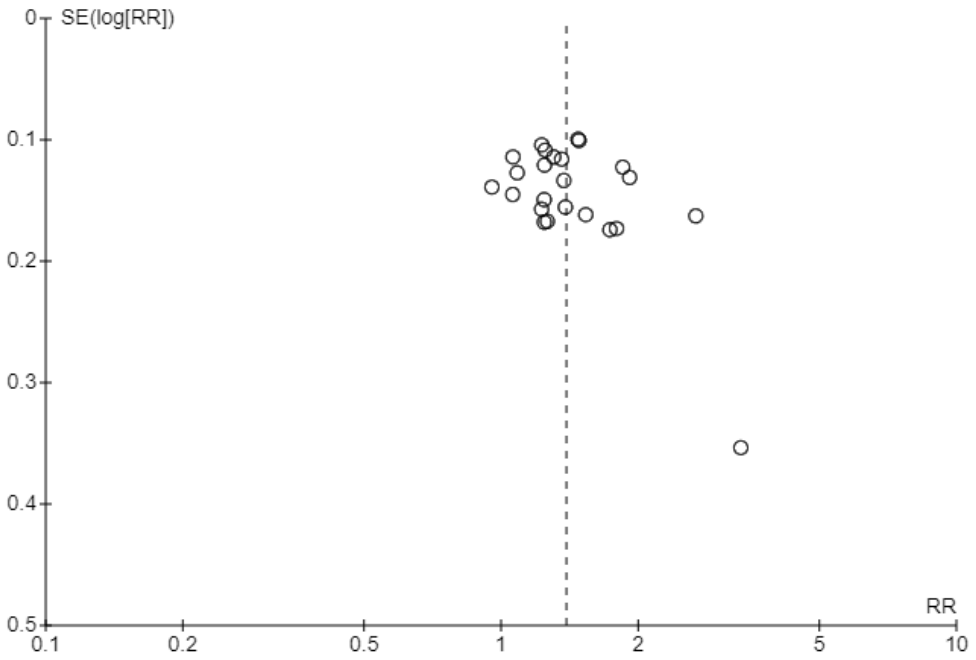


**Figure 41. Funnel plot for rate of treatment response measured as a reduction of at least 50% on the HAM-A for all antidepressants versus placebo**

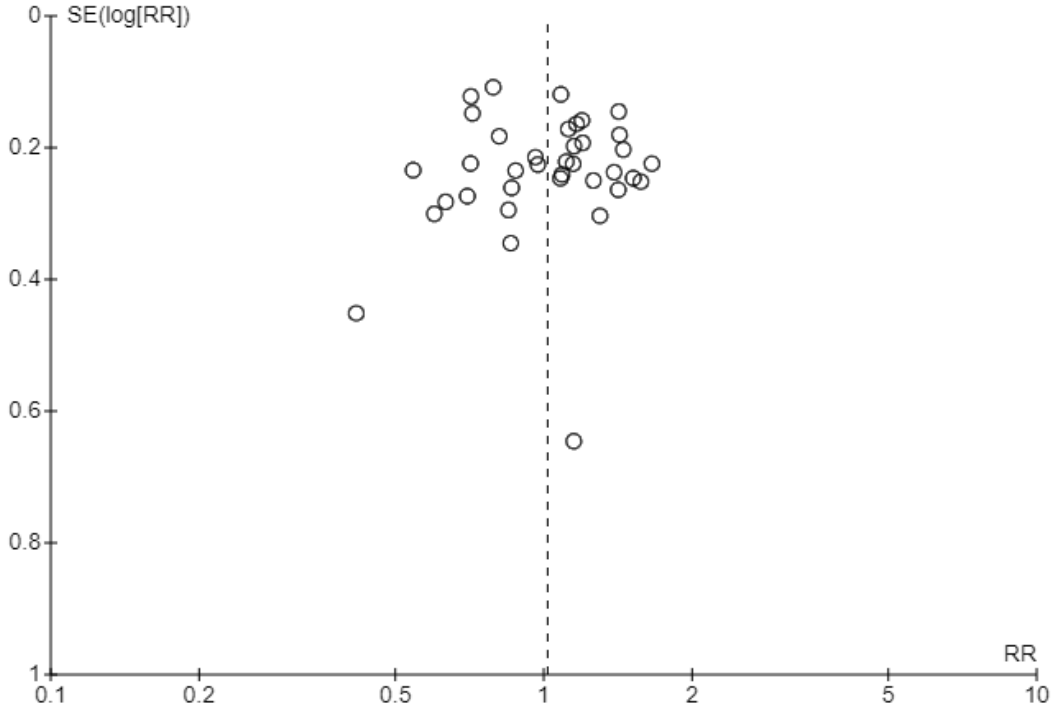


**Figure 42. Funnel plot for acceptability for all antidepressants versus placebo**

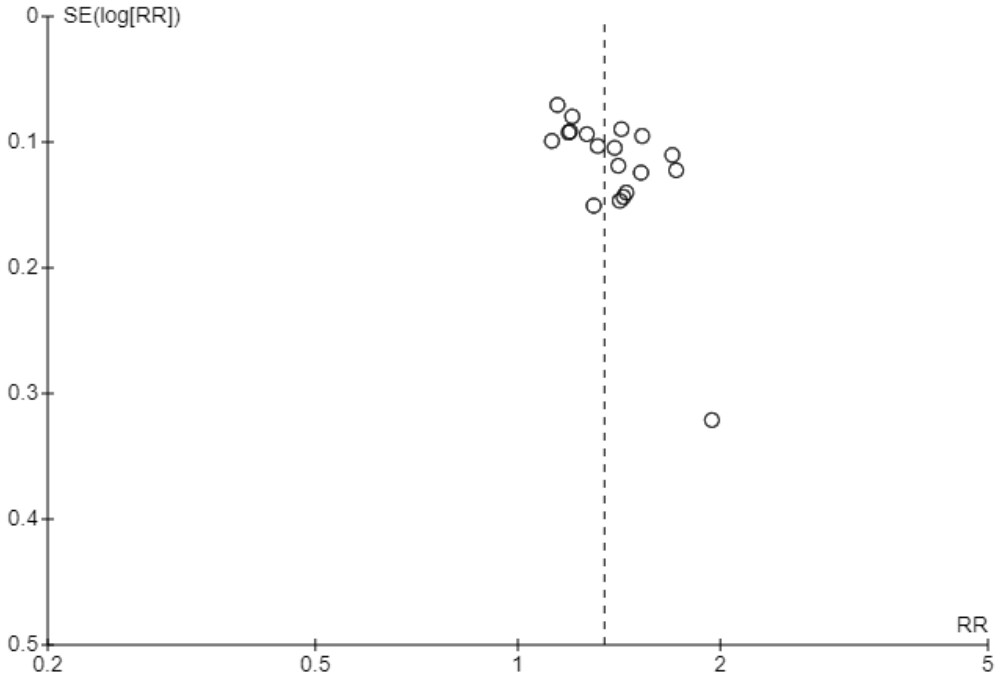


**Figure 43. Funnel plot for rate of treatment response (defined by study authors) for all antidepressants versus placebo**

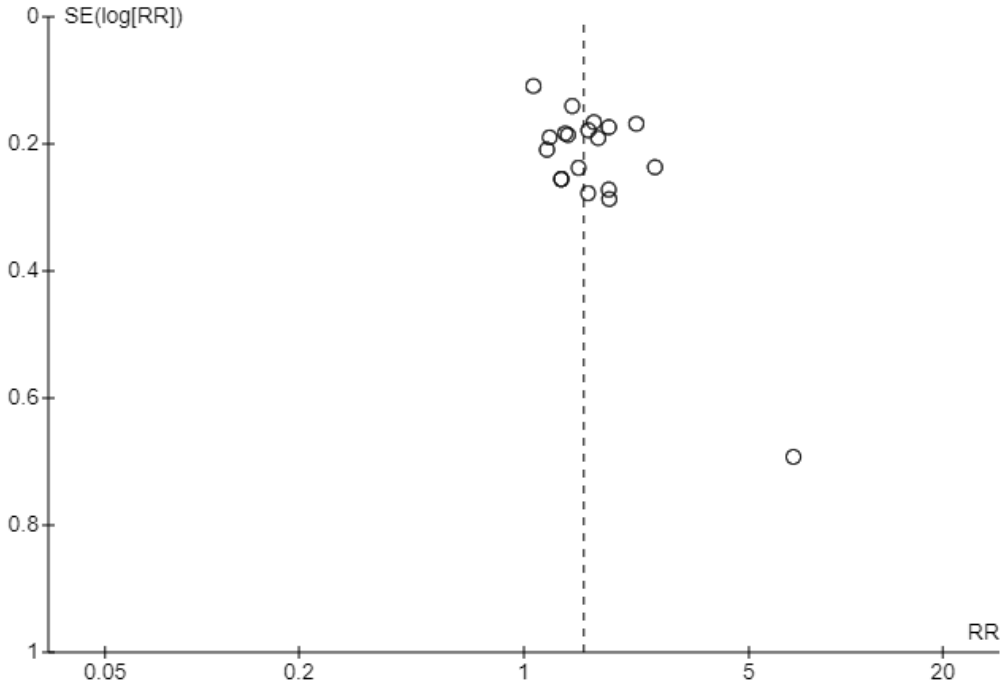


**Figure 44. Funnel plot for remission rate for all antidepressants versus placebo**

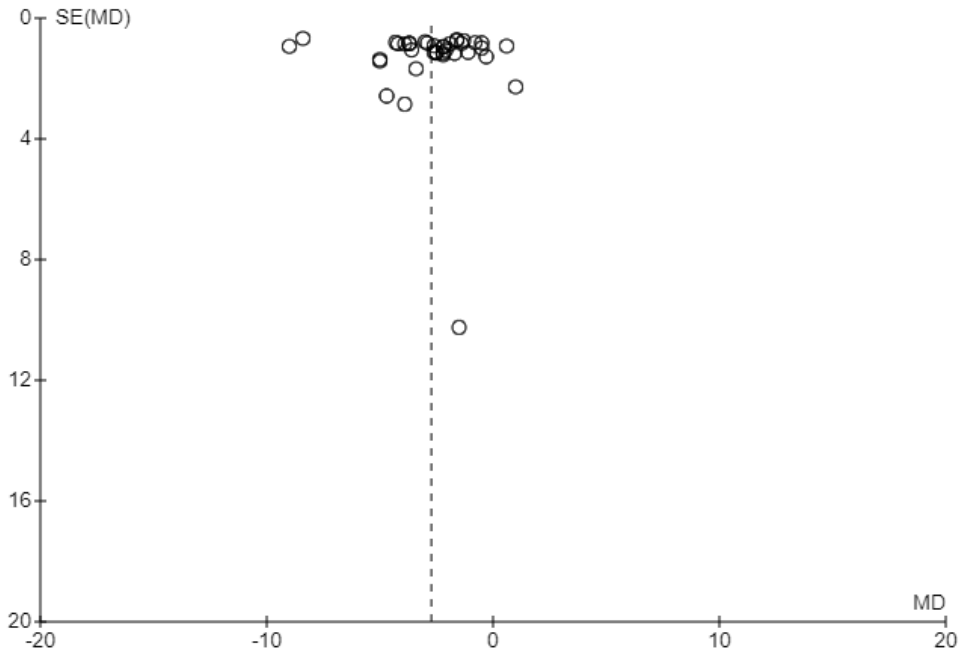


**Figure 45. Funnel plot for change in symptom levels for all antidepressants versus placebo**

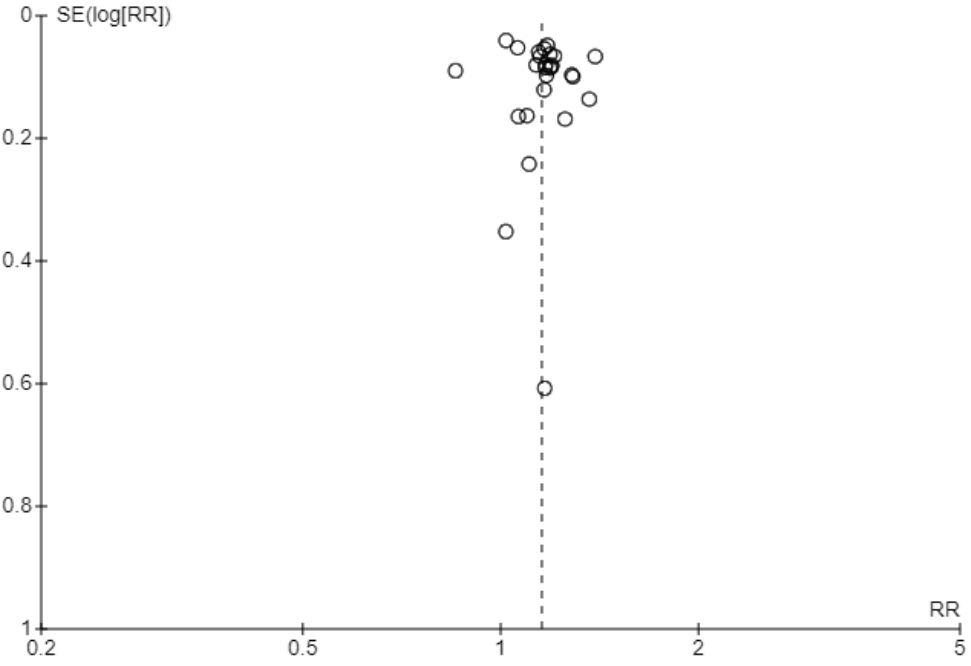


**Figure 46. Funnel plot for total number of patients reporting adverse effects for all antidepressants versus placebo**

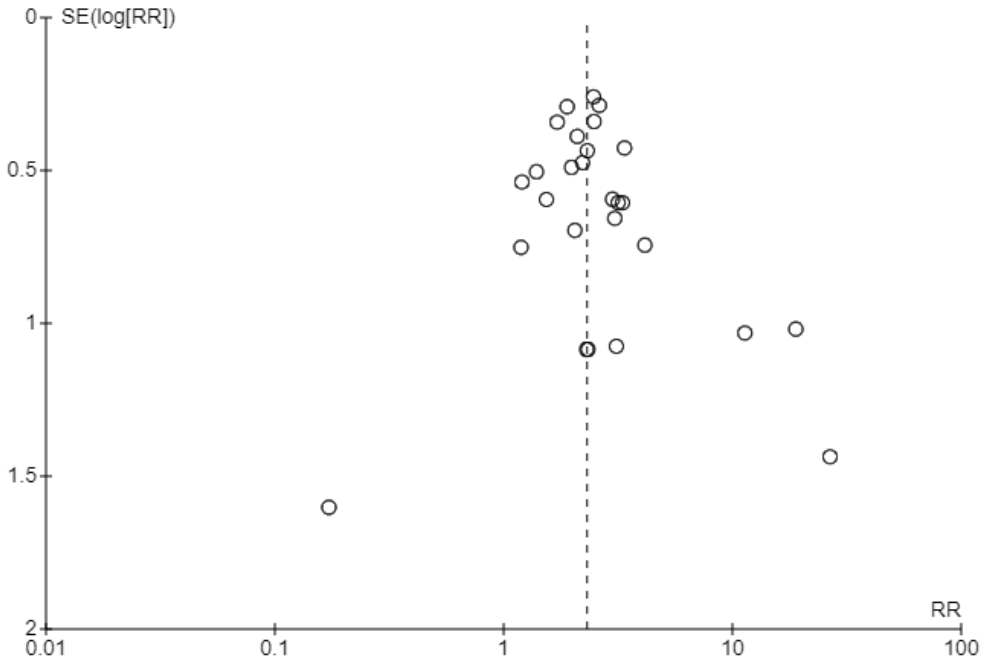


**Figure 47. Funnel plot for sleepiness/drowsiness for all antidepressants versus placebo**

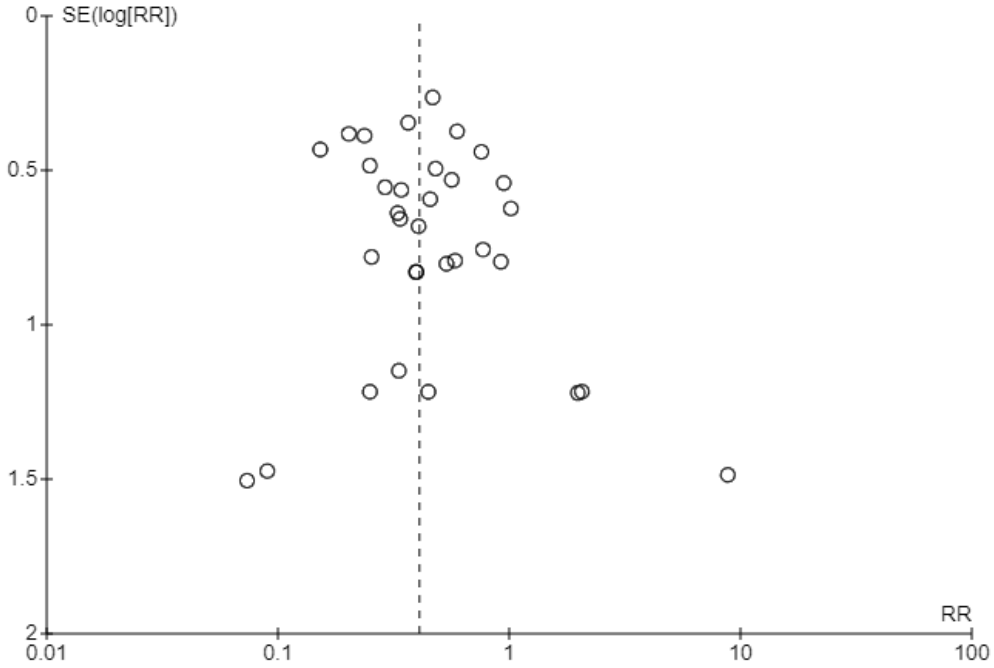


**Figure 48. Funnel plot for dropouts due to lack of efficacy for all antidepressants versus placebo**

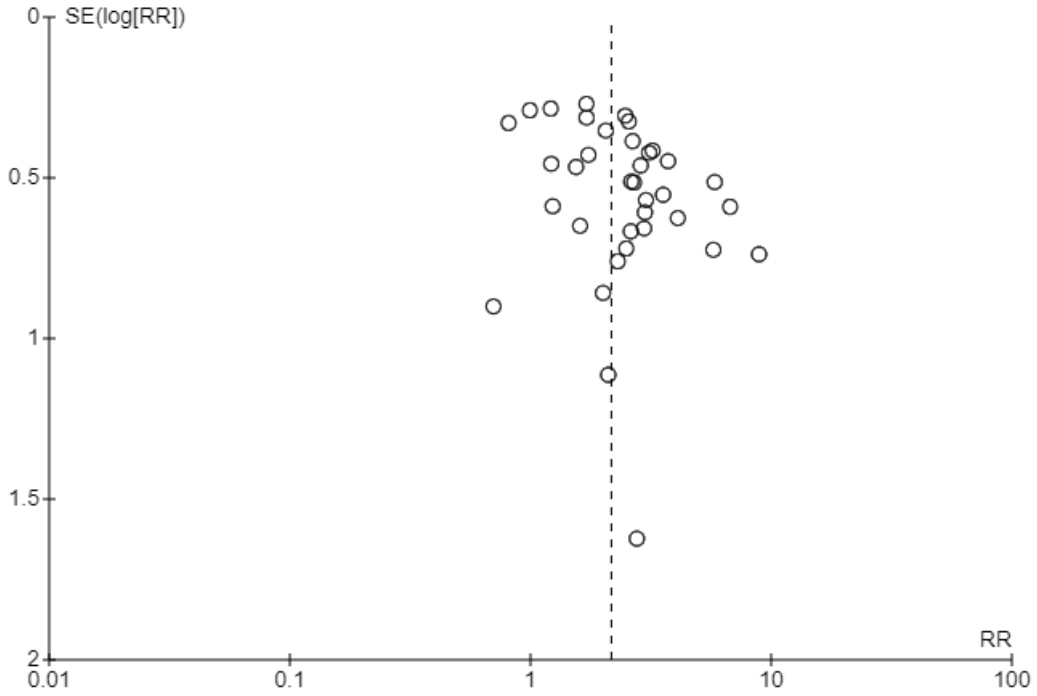


**Figure 49. Funnel plot for dropouts due to adverse effects for all antidepressants versus placebo**

# 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 low-quality 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 meta-analysis 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 long-term 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 antidepressant and placebo groups. Limited evidence also suggested a benefit of 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.

# References


1. DeMartini, J., G. Patel, and T.L. Fancher, *Generalized Anxiety Disorder.* Ann Intern Med, 2019. **170**(7): p. Itc49-itc64.

2. Ruscio, A.M., et al., *Cross-sectional Comparison of the Epidemiology of DSM-5 Generalized Anxiety Disorder Across the Globe.* JAMA Psychiatry, 2017. **74**(5): p. 465-475.

3. Crocq, M.A., *The history of generalized anxiety disorder as a diagnostic category.* Dialogues Clin Neurosci, 2017. **19**(2): p. 107-116.

4. Katzman, M.A., et al., *Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders.* BMC Psychiatry, 2014. **14 Suppl 1**(Suppl 1): p. S1.

5. Maron, E. and D. Nutt, *Biological markers of generalized anxiety disorder.* Dialogues Clin Neurosci, 2017. **19**(2): p. 147-158.

6. Bandelow, B., et al., *Efficacy of treatments for anxiety disorders: a meta-analysis.* Int Clin Psychopharmacol, 2015. **30**(4): p. 183-92.

7. Garakani, A., et al., *Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options.* Front Psychiatry, 2020. **11**: p. 595584.

8. Rickels, K. and M. Rynn, *Pharmacotherapy of generalized anxiety disorder.* J Clin Psychiatry, 2002. **63 Suppl 14**: p. 9-16.

9. Baldwin, D.S., et al., *An international survey of reported prescribing practice in the treatment of patients with generalised anxiety disorder.* World J Biol Psychiatry, 2012. **13**(7): p. 510-6.

10. Gomez, A.F., A.L. Barthel, and S.G. Hofmann, *Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review.* Expert Opin Pharmacother, 2018. **19**(8): p. 883-894.

11. Sheffler, Z.M., P. Patel, and S. Abdijadid, *Antidepressants*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

12. Hariton, E. and J.J. Locascio, *Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials.* Bjog, 2018. **125**(13): p. 1716.

13. Gopalakrishnan, S. and P. Ganeshkumar, *Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare.* J Family Med Prim Care, 2013. **2**(1): p. 9-14.

14. Schmitt, R., et al., *The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis.* Braz J Psychiatry, 2005. **27**(1): p. 18-24.

15. Baldwin, D., et al., *Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis.* Bmj, 2011. **342**: p. d1199.

16. Slee, A., et al., *Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis.* Lancet, 2019. **393**(10173): p. 768-777.

17. He, H., et al., *Comparative efficacy and acceptability of first-line drugs for the acute treatment of generalized anxiety disorder in adults: A network meta-analysis.* J Psychiatr Res, 2019. **118**: p. 21-30.

18. Showraki, M., T. Showraki, and K. Brown, *Generalized Anxiety Disorder: Revisited.* Psychiatr Q, 2020. **91**(3): p. 905-914.

19. Newman, M.G. and S.J. Llera, *A novel theory of experiential avoidance in generalized anxiety disorder: a review and synthesis of research supporting a contrast avoidance model of worry.* Clin Psychol Rev, 2011. **31**(3): p. 371-82.

20. Gerlach, A.L. and A.T. Gloster, *Worry, generalized anxiety disorder (GAD), and their importance.* Generalized Anxiety Disorder and Worrying: A Comprehensive Handbook for Clinicians and Researchers, 2020: p. 1-8.

21. Newman, M.G., et al., *Worry and generalized anxiety disorder: a review and theoretical synthesis of evidence on nature, etiology, mechanisms, and treatment.* Annu Rev Clin Psychol, 2013. **9**: p. 275-97.

22. Nordahl, H., T. Vollset, and O. Hjemdal, *An empirical test of the metacognitive model of generalized anxiety disorder.* Scand J Psychol, 2022.

23. Madonna, D., et al., *Structural and functional neuroimaging studies in generalized anxiety disorder: a systematic review.* Braz J Psychiatry, 2019. **41**(4): p. 336-362.

24. Sartori, S.B. and N. Singewald, *Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders.* Pharmacol Ther, 2019. **204**: p. 107402.

25. Munir, S. and V. Takov, *Generalized Anxiety Disorder*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

26. Craske, M.G., et al., *Anxiety disorders.* Nat Rev Dis Primers, 2017. **3**: p. 17024.

27. Hoge, E.A., et al., *Cross-cultural differences in somatic presentation in patients with generalized anxiety disorder.* J Nerv Ment Dis, 2006. **194**(12): p. 962-6.

28. Lewis-Fernández, R., et al., *Culture and the anxiety disorders: recommendations for DSM-V.* Depress Anxiety, 2010. **27**(2): p. 212-29.

29. Lijster, J.M., et al., *The Age of Onset of Anxiety Disorders.* Can J Psychiatry, 2017. **62**(4): p. 237-246.

30. Grant, B.F., et al., *Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions.* Psychol Med, 2005. **35**(12): p. 1747-59.

31. Andreescu, C. and S. Lee, *Anxiety Disorders in the Elderly.* Adv Exp Med Biol, 2020. **1191**: p. 561-576.

32. Watterson, R.A., et al., *Descriptive Epidemiology of Generalized Anxiety Disorder in Canada.* Can J Psychiatry, 2017. **62**(1): p. 24-29.

33. Hunt, C., C. Issakidis, and G. Andrews, *DSM-IV generalized anxiety disorder in the Australian National Survey of Mental Health and Well-Being.* Psychol Med, 2002. **32**(4): p. 649-59.

34. Gale, C. and O. Davidson, *Generalised anxiety disorder.* Bmj, 2007. **334**(7593): p. 579-81.

35. Pelletier, L., et al., *The burden of generalized anxiety disorder in Canada.* Health Promot Chronic Dis Prev Can, 2017. **37**(2): p. 54-62.

36. Lieb, R., E. Becker, and C. Altamura, *The epidemiology of generalized anxiety disorder in Europe.* Eur Neuropsychopharmacol, 2005. **15**(4): p. 445-52.

37. Szuhany, K.L. and N.M. Simon, *Anxiety Disorders: A Review.* Jama, 2022. **328**(24): p. 2431-2445.

38. Weisberg, R.B., *Overview of generalized anxiety disorder: epidemiology, presentation, and course.* J Clin Psychiatry, 2009. **70 Suppl 2**: p. 4-9.

39. Revicki, D.A., et al., *Humanistic and economic burden of generalized anxiety disorder in North America and Europe.* J Affect Disord, 2012. **140**(2): p. 103-12.

40. Sareen, J., et al., *Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults.* Arch Gen Psychiatry, 2005. **62**(11): p. 1249-57.

41. Kanwar, A., et al., *The association between anxiety disorders and suicidal behaviors: a systematic review and meta-analysis.* Depress Anxiety, 2013. **30**(10): p. 917-29.

42. Bruce, S.E., et al., *Infrequency of "pure" GAD: impact of psychiatric comorbidity on clinical course.* Depress Anxiety, 2001. **14**(4): p. 219-25.

43. Wittchen, H.U., et al., *[Generalized anxiety disorder in primary care. Patterns of healthcare utilization in Germany].* MMW Fortschr Med, 2012. **154 Suppl 3**: p. 77-84.

44. Zhu, B., et al., *The cost of comorbid depression and pain for individuals diagnosed with generalized anxiety disorder.* J Nerv Ment Dis, 2009. **197**(2): p. 136-9.

45. Remes, O., et al., *Generalised anxiety disorder and hospital admissions: findings from a large, population cohort study.* BMJ Open, 2018. **8**(10): p. e018539.

46. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder: the GAD-7.* Arch Intern Med, 2006. **166**(10): p. 1092-7.

47. Shear, M.K., *Generalized anxiety disorder in ICD-11.* World Psychiatry, 2012. **11**(Suppl 1): p. 82-88.

48. Tyrer, P. and D. Baldwin, *Generalised anxiety disorder.* Lancet, 2006. **368**(9553): p. 2156-66.

49. El Khoury, J.R., E.A. Baroud, and B.A. Khoury, *The revision of the categories of mood, anxiety and stress-related disorders in the ICD-11: a perspective from the Arab region.* Middle East Current Psychiatry, 2020. **27**(1).

50. Strawn, J.R., et al., *Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review.* Expert Opin Pharmacother, 2018. **19**(10): p. 1057-1070.

51. Bandelow, B., et al., *The German Guidelines for the treatment of anxiety disorders: first revision.* Eur Arch Psychiatry Clin Neurosci, 2022. **272**(4): p. 571-582.

52. Stefan, S., et al., *Cognitive-behavioral therapy (CBT) for generalized anxiety disorder: Contrasting various CBT approaches in a randomized clinical trial.* J Clin Psychol, 2019. **75**(7): p. 1188-1202.

53. Carpenter, J.K., et al., *Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials.* Depress Anxiety, 2018. **35**(6): p. 502-514.

54. Hunot, V., et al., *Psychological therapies for generalised anxiety disorder.* Cochrane Database Syst Rev, 2007. **2007**(1): p. Cd001848.

55. Cuijpers, P., et al., *Psychological treatment of generalized anxiety disorder: a meta-analysis.* Clin Psychol Rev, 2014. **34**(2): p. 130-40.

56. Bandelow, B., et al., *Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders.* World J Biol Psychiatry, 2007. **8**(3): p. 175-87.

57. Black, D.W., *Efficacy of combined pharmacotherapy and psychotherapy versus monotherapy in the treatment of anxiety disorders.* CNS Spectr, 2006. **11**(10 Suppl 12): p. 29-33.

58. Xie, Z.J., et al., *The efficacy of group cognitive-behavioural therapy plus duloxetine for generalised anxiety disorder versus duloxetine alone.* Acta Neuropsychiatr, 2019. **31**(6): p. 316-324.

59. Borkovec, T.D. and E. Costello, *Efficacy of applied relaxation and cognitive-behavioral therapy in the treatment of generalized anxiety disorder.* J Consult Clin Psychol, 1993. **61**(4): p. 611-9.

60. Borkovec, T.D., et al., *A component analysis of cognitive-behavioral therapy for generalized anxiety disorder and the role of interpersonal problems.* J Consult Clin Psychol, 2002. **70**(2): p. 288-98.

61. Arntz, A., *Cognitive therapy versus applied relaxation as treatment of generalized anxiety disorder.* Behav Res Ther, 2003. **41**(6): p. 633-46.

62. Dugas, M.J., et al., *A randomized clinical trial of cognitive-behavioral therapy and applied relaxation for adults with generalized anxiety disorder.* Behav Ther, 2010. **41**(1): p. 46-58.

63. Ost, L.G. and E. Breitholtz, *Applied relaxation vs. cognitive therapy in the treatment of generalized anxiety disorder.* Behav Res Ther, 2000. **38**(8): p. 777-90.

64. Leichsenring, F., et al., *Short-term psychodynamic psychotherapy and cognitive-behavioral therapy in generalized anxiety disorder: a randomized, controlled trial.* Am J Psychiatry, 2009. **166**(8): p. 875-81.

65. Durham, R.C., et al., *Cognitive therapy, analytic psychotherapy and anxiety management training for generalised anxiety disorder.* Br J Psychiatry, 1994. **165**(3): p. 315-23.

66. Ooi, S.L., P. Henderson, and S.C. Pak, *Kava for Generalized Anxiety Disorder: A Review of Current Evidence.* J Altern Complement Med, 2018. **24**(8): p. 770-780.

67. Woelk, H. and S. Schläfke, *A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder.* Phytomedicine, 2010. **17**(2): p. 94-9.

68. Kasper, S., et al., *Lavender oil preparation Silexan is effective in generalized anxiety disorder--a randomized, double-blind comparison to placebo and paroxetine.* Int J Neuropsychopharmacol, 2014. **17**(6): p. 859-69.

69. Melaragno, A.J., *Pharmacotherapy for Anxiety Disorders: From First-Line Options to Treatment Resistance.* Focus (Am Psychiatr Publ), 2021. **19**(2): p. 145-160.

70. Preti, A., et al., *The lifetime prevalence and impact of generalized anxiety disorders in an epidemiologic Italian National Survey carried out by clinicians by means of semi-structured interviews.* BMC Psychiatry, 2021. **21**(1): p. 48.

71. Wilson, T.K. and J. Tripp, *Buspirone*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

72. Guaiana, G., C. Barbui, and A. Cipriani, *Hydroxyzine for generalised anxiety disorder.* Cochrane Database Syst Rev, 2010(12): p. Cd006815.

73. Greenblatt, H.K. and D.J. Greenblatt, *Gabapentin and Pregabalin for the Treatment of Anxiety Disorders.* Clin Pharmacol Drug Dev, 2018. **7**(3): p. 228-232.

74. Berlin, R.K., P.M. Butler, and M.D. Perloff, *Gabapentin Therapy in Psychiatric Disorders: A Systematic Review.* Prim Care Companion CNS Disord, 2015. **17**(5).

75. Moraczewski, J. and K.K. Aedma, *Tricyclic Antidepressants*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

76. Chu, A. and R. Wadhwa, *Selective Serotonin Reuptake Inhibitors*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

77. Singh, D. and A. Saadabadi, *Venlafaxine*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

78. Dhaliwal, J.S., B.C. Spurling, and M. Molla, *Duloxetine*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

79. Jilani, T.N., et al., *Mirtazapine*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

80. Huecker, M.R., A. Smiley, and A. Saadabadi, *Bupropion*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

81. Stein, D.J., et al., *Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study.* J Clin Psychiatry, 2014. **75**(4): p. 362-8.

82. Buoli, M., et al., *Agomelatine for the treatment of generalized anxiety disorder.* Expert Opin Pharmacother, 2017. **18**(13): p. 1373-1379.

83. Zareifopoulos, N. and I. Dylja, *Efficacy and tolerability of vilazodone for the acute treatment of generalized anxiety disorder: A meta-analysis.* Asian J Psychiatr, 2017. **26**: p. 115-122.

84. Shin, J.J. and A. Saadabadi, *Trazodone*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL).

85. Guaiana, G., C. Barbui, and R. Abouhassan, *Antidepressants versus placebo for generalised anxiety disorder (GAD).* Cochrane Database of Systematic Reviews, 2018(2).

86. *Cochrane Handbook for Systematic Reviews of Interventions*, T.J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, Editor. 2022, Cochrane.

87. Furukawa, T.A., et al., *Imputing missing standard deviations in meta-analyses can provide accurate results.* J Clin Epidemiol, 2006. **59**(1): p. 7-10.

88. Bighelli, I., et al., *Antidepressants versus placebo for panic disorder in adults.* Cochrane Database of Systematic Reviews, 2018. **2018**(4).

89. Guaiana, G., et al., *Agomelatine versus other antidepressive agents for major depression.* Cochrane Database Syst Rev, 2013(12): p. Cd008851.

90. *Cochrane Handbook for Systematic Reviews of Interventions*, G.S. Higgins JPT, Editor. 2011, The Cochrane Collaboration

91. Hróbjartsson, A., et al., *Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors.* Bmj, 2012. **344**: p. e1119.

92. Schünemann, H., et al., *The GRADE handbook*. 2013, Cochrane Collaboration London, UK.

93. Mavridis, D. and G. Salanti, *Exploring and accounting for publication bias in mental health: a brief overview of methods.* Evid Based Ment Health, 2014. **17**(1): p. 11-5.

94. Dickersin, K., *The existence of publication bias and risk factors for its occurrence.* Jama, 1990. **263**(10): p. 1385-9.

95. Guyatt, G., et al., *GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables.* J Clin Epidemiol, 2011. **64**(4): p. 383-94.

96. Lee, Y.H., *An overview of meta-analysis for clinicians.* The Korean Journal of Internal Medicine, 2018. **33**(2): p. 277-283.

97. Page MJ, M.J., Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*. 2021: BMJ; 372:n71.

98. McLeod, D.R., et al., *Effects of alprazolam and imipramine on parasympathetic cardiac control in patients with generalized anxiety disorder.* Psychopharmacology (Berl), 1992. **107**(4): p. 535-40.

99. Mahableshwarkar, A.R., et al., *A randomised, double-blind, placebo-controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder.* Int J Clin Pract, 2014. **68**(1): p. 49-59.

100. Brawman-Mintzer, O., *Pharmacological Treatment of Generalized Anxiety Disorder in the Elderly [NCT00701675]*. 2009, VA Office of Research and Development.

101. Gommoll, C., et al., *Vilazodone in patients with generalized anxiety disorder: a double-blind, randomized, placebo-controlled, flexible-dose study.* Int Clin Psychopharmacol, 2015. **30**(6): p. 297-306.

102. Bose, A., et al., *Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder.* Depress Anxiety, 2008. **25**(10): p. 854-61.

103. Nicolini, H., et al., *Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial.* Psychol Med, 2009. **39**(2): p. 267-76.

104. Hartford, J., et al., *Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial.* Int Clin Psychopharmacol, 2007. **22**(3): p. 167-74.

105. Baldwin, D.S., A.K. Huusom, and E. Maehlum, *Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study.* Br J Psychiatry, 2006. **189**: p. 264-72.

106. Rickels, K., et al., *Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study.* Am J Psychiatry, 2003. **160**(4): p. 749-56.

107. Feltner, D.E., et al., *Clinical evaluation of the Daily Assessment of Symptoms-Anxiety (DAS-A): a new instrument to assess the onset of symptomatic improvement in generalized anxiety disorder.* CNS Neurosci Ther, 2009. **15**(1): p. 12-8.

108. *An Eight-Week, Double-Blind, Placebo-Controlled, Multicenter Study With Paroxetine (20 mg q24) as Positive Control, Evaluating the Efficacy, Safety and Tolerability of a Fixed Dose of SR58611A (350 mg q12) in Outpatients With Generalized Anxiety Disorder (NCT00266747)*. 2007, Aventis-Sanofi.

109. *Phase 3, Randomized, Double-Blind, Parallel Group, 10-Week, Placebo Controlled Fixed Dose Study of PD 0332334 and Paroxetine Evaluating the Efficacy and Safety of PD 0332334 for the Treatment of Generalized Anxiety Disorder*. 2009, Pfizer.

110. *Clinical Evaluation of BRL29060A (Paroxetine Hydrochloride Hydrate) in Generalized Anxiety Disorder (GAD) -A Double-blind, Placebo-controlled, Comparative Study*. 2006, GlaxoSmithKline.

111. Pollack, M.H., et al., *Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial.* J Clin Psychiatry, 2001. **62**(5): p. 350-7.

112. Hewett, K., Adams, A., Bryson, H., et al, *A double-blind, placebo controlled study to evaluate the efficacy and tolerability of paroxetine in patients with Generalised Anxiety Disorder (GAD) [poster]*. 2001: 7th World Congress of Biological Psychiatry, Jul 1-6, Berlin.

113. Davidson, J.R., et al., *Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study.* Depress Anxiety, 2004. **19**(4): p. 234-40.

114. *An Eight-Week, Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled Study, with Escitalopram as an Active Control, to Evaluate the Efficacy, Safety, and Tolerability of a Saredutant 100 mg Dose Once Daily, in Patients with Generalized Anxiety Disorder (EFC5583)*. 2008, Aventis-Sanofi.

115. *An eight-week, double-blind, placebo-controlled, multicenter study with escitalopram (10 mg qd) as positive control, evaluating the efficacy, safety, tolerability of a fixed dose of SR58611A (350 mg q12) in outpatients with Generalized Anxiety Disorder (NCT00252343)*. 2007, Aventis-Sanofi.

116. Goodman, W.K., Bose, A., Wang, Q., *Flexible-dose comparison of the safety and efficacy of escitalopram and placebo in the treatment of generalised anxiety disorder*. 2002, Forest Laboratories.

117. Goodman, W.K., Bose, A., Wang, Q., *Flexible-dose comparison of the safety and efficacy of Lu 26-054 (Escitalopram) and placebo in the treatment of generalized anxiety disorder*. 2001, Forest Laboratories.

118. Allgulander, C., et al., *Efficacy of sertraline in a 12-week trial for generalized anxiety disorder.* Am J Psychiatry, 2004. **161**(9): p. 1642-9.

119. Brawman-Mintzer, O., et al., *Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study.* J Clin Psychiatry, 2006. **67**(6): p. 874-81.

120. Gelenberg, A.J., et al., *Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: A 6-month randomized controlled trial.* Jama, 2000. **283**(23): p. 3082-8.

121. Lenox-Smith, A.J. and A. Reynolds, *A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care.* Br J Gen Pract, 2003. **53**(495): p. 772-7.

122. Nimatoudis, I., et al., *Remission rates with venlafaxine extended release in Greek outpatients with generalized anxiety disorder. A double-blind, randomized, placebo controlled study.* Int Clin Psychopharmacol, 2004. **19**(6): p. 331-6.

123. Montgomery, S.A., et al., *Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicenter, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine.* J Clin Psychiatry, 2006. **67**(5): p. 771-82.

124. Kasper, S., et al., *Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: results of a double-blind, placebo-controlled 8-week trial.* Int Clin Psychopharmacol, 2009. **24**(2): p. 87-96.

125. Hackett, D., V. Haudiquet, and E. Salinas, *A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder.* Eur Psychiatry, 2003. **18**(4): p. 182-7.

126. Rickels, K., et al., *Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder.* Am J Psychiatry, 2000. **157**(6): p. 968-74.

127. Davidson, J.R., et al., *Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder.* J Clin Psychiatry, 1999. **60**(8): p. 528-35.

128. Allgulander, C., D. Hackett, and E. Salinas, *Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study.* Br J Psychiatry, 2001. **179**: p. 15-22.

129. Wu, W.Y., et al., *Duloxetine versus placebo in the treatment of patients with generalized anxiety disorder in China.* Chin Med J (Engl), 2011. **124**(20): p. 3260-8.

130. Koponen, H., et al., *Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians.* Prim Care Companion J Clin Psychiatry, 2007. **9**(2): p. 100-7.

131. Rynn, M., et al., *Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial.* Depress Anxiety, 2008. **25**(3): p. 182-9.

132. Stein, D.J., A.A. Ahokas, and C. de Bodinat, *Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study.* J Clin Psychopharmacol, 2008. **28**(5): p. 561-6.

133. Stein, D.J., et al., *Efficacy and safety of agomelatine (10 or 25 mg/day) in non-depressed out-patients with generalized anxiety disorder: A 12-week, double-blind, placebo-controlled study.* Eur Neuropsychopharmacol, 2017. **27**(5): p. 526-537.

134. Rothschild, A.J., et al., *Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States.* Eur Neuropsychopharmacol, 2012. **22**(12): p. 858-66.

135. Addington-Hall, J. and L. Kalra, *Who should measure quality of life?* Bmj, 2001. **322**(7299): p. 1417-20.

136. Wyrwich, K.W., et al., *Assessment of quality of life enjoyment and satisfaction questionnaire-short form responder thresholds in generalized anxiety disorder and bipolar disorder studies.* Int Clin Psychopharmacol, 2011. **26**(3): p. 121-9.

137. Noyes Jr, R., *Comorbidity in generalized anxiety disorder.* Psychiatric Clinics of North America, 2001. **24**(1): p. 41-55.

138. Simon, N.M., *Generalized anxiety disorder and psychiatric comorbidities such as depression, bipolar disorder, and substance abuse.* Journal of Clinical Psychiatry, 2009. **70**(2): p. 10-14.

139. Rapaport, M.H., et al., *Time to response in generalized anxiety disorder in a naturalistic setting: combination therapy with alprazolam orally disintegrating tablets and serotonin reuptake inhibitors compared to serotonin reuptake inhibitors alone.* Psychiatry (Edgmont), 2006. **3**(12): p. 50-9.

140. Coplan, J.D., et al., *Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches.* World J Psychiatry, 2015. **5**(4): p. 366-78.

141. de Vries, Y.A., et al., *Initial severity and antidepressant efficacy for anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder: An individual patient data meta-analysis.* Depress Anxiety, 2018. **35**(6): p. 515-522.

142. Guyatt, G.H., et al., *GRADE guidelines 6. Rating the quality of evidence--imprecision.* J Clin Epidemiol, 2011. **64**(12): p. 1283-93.

143. Siddaway, A.P., A.M. Wood, and L.V. Hedges, *How to Do a Systematic Review: A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses.* Annu Rev Psychol, 2019. **70**: p. 747-770.

144. Mlinarić, A., M. Horvat, and V. Šupak Smolčić, *Dealing with the positive publication bias: Why you should really publish your negative results.* Biochem Med (Zagreb), 2017. **27**(3): p. 030201.

145. Turner, E.H., *Publication bias, with a focus on psychiatry: causes and solutions.* CNS Drugs, 2013. **27**(6): p. 457-68.

146. Piercy, M.A., et al., *Placebo response in anxiety disorders.* Ann Pharmacother, 1996. **30**(9): p. 1013-9.

147. Kasper, S. and M. Dold, *Factors contributing to the increasing placebo response in antidepressant trials.* World Psychiatry, 2015. **14**(3): p. 304-6.

148. Leon, A.C., et al., *Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology.* Biol Psychiatry, 2006. **59**(11): p. 1001-5.

149. Cipriani, A., et al., *Conceptual and technical challenges in network meta-analysis.* Ann Intern Med, 2013. **159**(2): p. 130-7.

150. Keefe, R.S., et al., *Defining a clinically meaningful effect for the design and interpretation of randomized controlled trials.* Innov Clin Neurosci, 2013. **10**(5-6 Suppl A): p. 4s-19s.

151. Bruce, S.E., et al., *Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study.* Am J Psychiatry, 2005. **162**(6): p. 1179-87.

152. Davidson, J.R., et al., *Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial.* Eur Neuropsychopharmacol, 2008. **18**(9): p. 673-81.

153. Allgulander, C., I. Florea, and A.K. Huusom, *Prevention of relapse in generalized anxiety disorder by escitalopram treatment.* Int J Neuropsychopharmacol, 2006. **9**(5): p. 495-505.

154. Baldwin, D.S., H. Loft, and I. Florea, *Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder.* Int Clin Psychopharmacol, 2012. **27**(4): p. 197-207.

155. Stocchi, F., et al., *Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder.* J Clin Psychiatry, 2003. **64**(3): p. 250-8.

156. Hackett, D., C. White, and E. Salinas. *Relapse prevention in patients with generalised anxiety disorder (GAD) by treatment with venlafaxine ER*. in *Poster presented at 1st International Forum on Mood and Anxiety Disorders, Monte Carlo*. 2000.

157. Rickels, K., et al., *Time to relapse after 6 and 12 months' treatment of generalized anxiety disorder with venlafaxine extended release.* Arch Gen Psychiatry, 2010. **67**(12): p. 1274-81.

158. Gonçalves, D.C. and G.J. Byrne, *Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis.* J Anxiety Disord, 2012. **26**(1): p. 1-11.

# 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 http://ovidsp.ovid.com/

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 reuptake 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 http://ovidsp.ovid.com/

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 Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine 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 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).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 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 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 re-uptake)) 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

| **Response rate measured as a reduction of at least 50% on the Hamilton Anxiety Scale (HAM-A)** | | |
|---|---|---|
| | ENDPOINT | |
| | n | N |
| Placebo | | |
| Intervention | | |
| **Acceptability (number of dropouts): number of participants who dropped out during the trial as a proportion of the total number of randomized participants (total dropouts)** | | |
| | ENDPOINT | |
| | n | N |
| Placebo | | |
| Intervention | | |
| **Response rate (defined by study authors)** | | |
| | ENDPOINT | |
| | N | N |

| | | | |
|---|---|---|---|
| Placebo | | | |
| Intervention | | | |
| **Remission** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Change in symptom levels** | | | |
| | ENDPOINT | | |
| | Mean | SD | N |
| Placebo | | | |
| Intervention | | | |
| **Total number of patients reporting adverse effects** | | | |
| | 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/attempts** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Completed suicide** | | | |
| | ENDPOINT | | |
| | n | N | |

| | | | |
|---|---|---|---|
| Placebo | | | |
| Intervention | | | |
| **Subjective memory impairment** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Average score/change in quality of life/satisfaction** | | | |
| | ENDPOINT | | |
| | mean | SD | N |
| Placebo | | | |
| Intervention | | | |
| **Death** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Total number of participants experiencing withdrawal symptoms** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Dropouts due to inefficacy** | | | |
| | ENDPOINT | | |
| | n | N | |
| Placebo | | | |
| Intervention | | | |
| **Dropouts due to adverse effects** | | | |
| | 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:

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

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

**Appendix 4. GRADE Quality Assessment Criteria**

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

**Appendix 5. Data Extracted Using GetDataGraph Digitizer**

| Study ID | Outcome | Intervention | Values extracted from GetDataGraph Digitizer |
|---|---|---|---|
| Allgulander 2001 | % responders measured as a reduction of at least 50% on the HAM-A at endpoint | Placebo | 46.32% |
| | | Venlafaxine | **37.5 mg:** 68.76%<br>**75 mg:** 61.53%<br>**150 mg:** 74.70% |
| | | Placebo | 48.30% |

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

## Appendix 6. GRADE Quality of Evidence Assessment

| Participants (studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Overall certainty of evidence |
|---|---|---|---|---|---|---|
| **Rate of treatment response measured as a reduction of at least 50% on the Hamilton Anxiety Rating Scale (HAM-A)** | | | | | | |
| 7556 (24 RCTs) | serious [a] | serious [b] | serious [c] | not serious | publication bias strongly suspected [d] | ⨁◯◯◯ Very low |
| **Acceptability** | | | | | | |
| 11598 (34 RCTs) | serious [a] | serious [e] | serious [c] | not serious | publication bias strongly suspected [d] | ⨁◯◯◯ Very low |
| **Dropouts due to a lack of efficacy** | | | | | | |
| 11311 (30 RCTs) | serious [a] | not serious | serious [c] | not serious | publication bias strongly suspected [d] | ⨁◯◯◯ Very low |
| **Dropouts due to adverse effects** | | | | | | |
| 12097 (33 RCTs) | serious [a] | not serious | serious [c] | not serious | publication bias strongly suspected [d] | ⨁◯◯◯ 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

| | |
|---|---|
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