The Newer Anticonvulsants in the Treatment of Generalised Anxiety Disorder: A Systematic Review and Meta-Analysis

By

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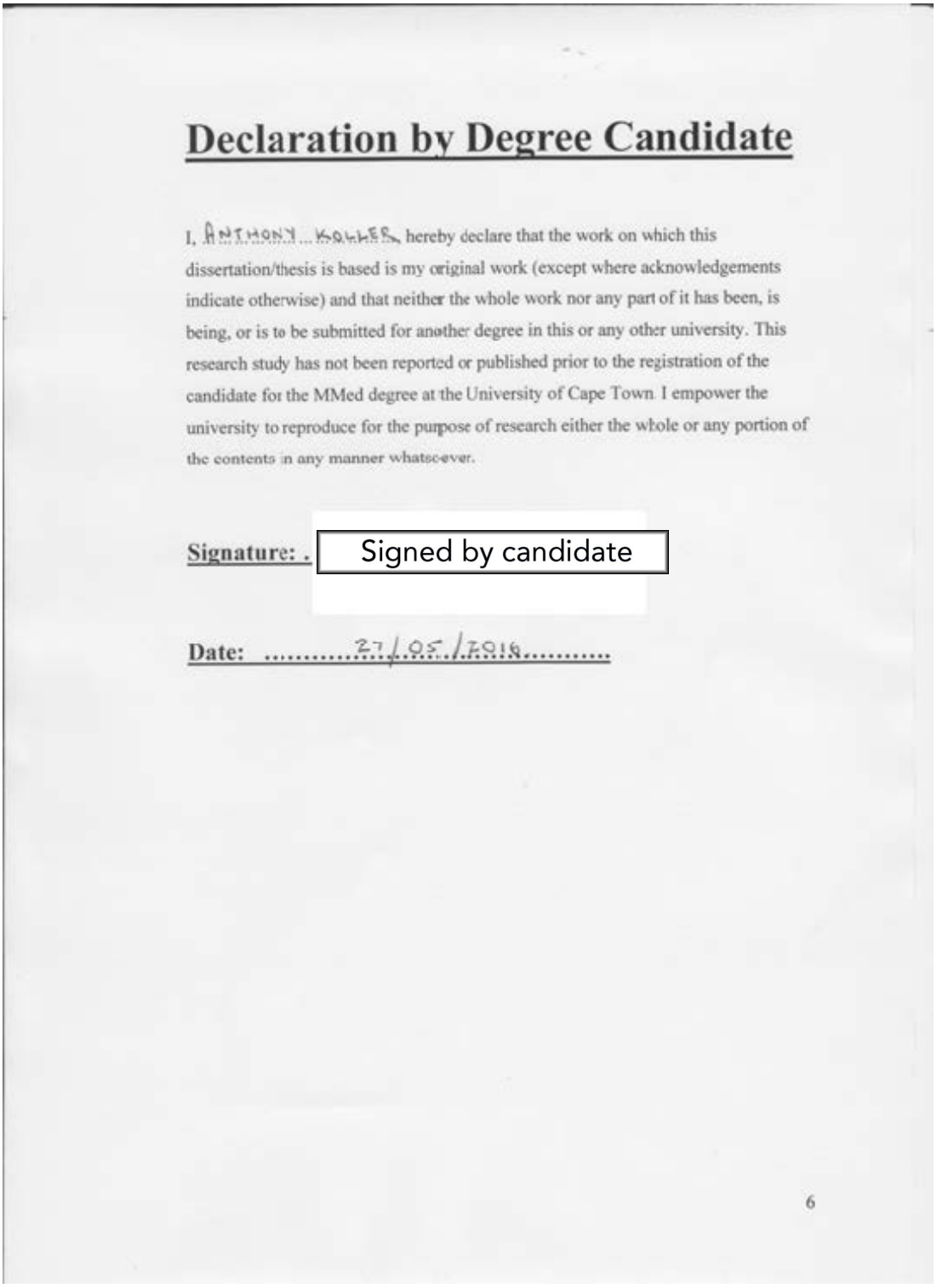
Declaration by Degree Candidate



Declaration by Degree Candidate

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Abstract

Generalised anxiety disorder (GAD) is a common, chronic and debilitating mental disorder impairing quality of life and functioning. The 1st line treatments for GAD include the selective serotonergic reuptake inhibitors (SSRIs) and the selective serotonergic noradrenergic reuptake inhibitors (SNRIs). However, they have rates of non-response ranging from 25 to 40%. There is justification to search for new and more efficacious GAD medication. It has hypothesised anticonvulsants possess anxiolytic properties based on animal studies and epilepsy trials. There is inconsistent evidence that anticonvulsants are efficacious in GAD. It was considered useful and timely to investigate this further. The newer anticonvulsants (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide) were investigated as they were considered to have a more benign side effect profile and fewer drug interactions than older anticonvulsants.

This study is a systematic review and meta-analysis of the newer anticonvulsants in the treatment of GAD. The main objective was to use randomised controlled trial (RCT) data to estimate efficacy of the newer anticonvulsants in GAD. using A search strategy was designed and three separate searches conducted by the *Cochrane Depression Anxiety and Neurosis Group* of the *Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register* (CCDANCTR) and *clinicaltrials.gov* (the last search in May 2013). An updated, independent, search was conducted in May 2016 with no additional citations retrieved. 287 citations were retrieved and screened in total. Two independent raters assessed citations using the abstracts and selected trials that satisfied the inclusion criteria. 12 RCTs were included with eight using pregabalin and four using tiagabine. A single rater collated data from RCTs assisted by Covidence Systematic Review Software. All statistical analyses were performed using Review Manager.

A random effects meta-analysis was performed expressing summary statistics as effect estimates with 95% confidence intervals (CI). There were 4001 participants in total with 2516 in the anticonvulsant group and 1485 in the placebo. Primary outcomes were reduction in symptom severity using the *Hamilton Anxiety Rating Scale* (HAM-A) and treatment response using the *Clinical Global Impressions Scale-Improvement item* (CGI-I). Secondary outcome was medication acceptability. Reduction of symptom severity on the HAM-A for: the anticonvulsant group (pregabalin and tiagabine combined) was significantly favourable with a mean difference (MD) of -2.10 ([-2.83, -1.36] 95% CI); pregabalin was significantly

favourable (MD -2.86 [-3.52, -2.21] 95% CI) tiagabine was statistically insignificant (MD -0.58 [-1.41, 0.25] 95% CI). The risk ratio (RR) of treatment response using the CGI-I (RR >1 favours the anticonvulsant) for: the anticonvulsant group was significantly favourable (RR 1.23 [1.12, 1.35] 95% CI); pregabalin was significantly favourable (RR 1.35 [1.21, 1.50] 95% CI) tiagabine was statistically insignificant (RR 1.09 [0.98, 1.22] 95% CI). The RR of treatment acceptability (RR >1 favoured placebo) for: the anticonvulsant group was significantly unfavourable (RR 1.49 [1.18, 1.88] 95% CI); pregabalin was statistically insignificant (RR 1.23 [0.92, 1.65] 95% CI) tiagabine was significantly unfavourable (RR 1.95 [1.29, 2.93] 95% CI).

In conclusion, this systematic review of the newer anticonvulsants included only RCTs of pregabalin and tiagabine. The main finding was that pregabalin showed significant efficacy in reducing symptom severity and improving treatment response in GAD. Tiagabine failed to show significant efficacy in primary outcomes. Further work is needed to better clarify the place of the newer anticonvulsants in the treatment armamentarium of GAD.

Acknowledgements

Authorship of Original Protocol for the Minor Dissertation

With permission granted by the authors, the protocol for this minor dissertation was based upon the protocol originally written by Jonathan C. Ipser and Dan J. Stein, for a *Cochrane Systematic Review* entitled "*Newer anticonvulsants in the treatment of anxiety disorders*" (Ipser & Stein, 2006). However, the degree candidate completely and independently, revised and and rewrote, an entirely new protocol for this minor dissertation.

Differences between the Protocol and the Review

The systematic search that was conducted for the *Cochrane Systematic Review* included all anxiety disorders in the search parameters. This was in accordance with the original protocol. This search yielded large amounts of data. Due to the size of such a review, a decision was made to extract only data on generalised anxiety disorder, in order to narrow the scope of the review for this minor dissertation. Data regarding the results of the full search process on all anxiety disorders is displayed in the PRISMA flow diagram (Moher, Liberati, Tetzlaff, *et al.*, 2009)

Collaborators

Lisa Albert (LA) assisted the degree candidate, Anthony Koller (AK), as an independent 2nd reviewer during the review process. (LA) assisted in the selection of studies for inclusion based on title and abstract. Dan Stein (DS) coordinated and assisted during the review process and served as a third party to resolve any disputes between the raters. Anthony Koller independently performed the data extraction and analysis and was the sole author of the minor dissertation. Dan Stein served as supervisor of the degree candidate for this minor dissertation, and provided guidance and suggestions during the research study.

Other individuals and Sources of Support

Sarah Dawson is the Trials Search Co-ordinator of the Cochrane Depression, Anxiety and Neurosis group, and conducted the first three searches for this review. Her efforts are acknowledged and much appreciated. Thanks to Taryn Amos for her help and advice during the review process. The MRC Research Unit on Anxiety and Stress Disorders, Cape Town, South Africa. The University of Cape Town.

Declarations of Interest

Anthony Koller has no known conflict of interest. Lisa Albert has no known conflict of interest. Jonathan C. Ipser has no known conflict of interest. Dan J. Stein has received research grants and/or consultancy honoraria from Astrazeneca, Eli-Lilly, GlaxoSmithKline, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo and Wyeth. He has participated in a number of ongoing trials and presented data from some of these trials on behalf of the sponsoring companies.

Format of the Manuscript and Citation Style

This minor dissertation is presented in *standard monograph format*. This study is a full systematic review and meta-analysis. It follows, as closely as possible, the structure set out by the Cochrane Collaboration in *The Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (Moher, Shamseer, Clarke, *et al.*, 2014). This dissertation uses the *Harvard* citation style.

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Chapter 1

Introduction and Background

Generalised anxiety disorder (GAD) is a debilitating mental disorder primarily characterised by excessive worry along with troublesome somatic strain, tension and personal distress (Allgulander, 2006; 2012). GAD has a high degree of morbidity, decreases quality of life, and results in poor social and occupational functioning. It tends to run a chronic course throughout life, with frequent relapses, and has a high degree of psychiatric co-morbidity (Allgulander, 2012; Angst, Gamma, Baldwin, *et al.*, 2009; Allgulander, 2006; Hoffman, Dukes & Wittchen, 2008).

GAD is common worldwide, with recent surveys of the general population in various parts of the world suggesting a lifetime prevalence of 4.3-5.9% and a 12-month prevalence of approximately 1-2% (Baldwin, Waldman & Allgulander, 2011)(Kessler et al. 2001) The prevalence rate of GAD in South Africa is thought to be similar to overseas rates based on data from a local study(Stein, Seedat, Herman, *et al.*, 2008).GAD has been found to be the most common anxiety disorder encountered in the primary care setting (Wittchen, Kessler, Beesdo, *et al.*, 2002). In addition, GAD is also considered the most common anxiety disorder in older age groups (Lieb, Becker & Altamura, 2005).

The level of disability associated with GAD is comparable to that of a long-term physical illness such as asthma or diabetes (Maier, Gänsicke, Freyberger, *et al.*, 2009). Hence, GAD can lead to significant increases in the utilisation of health services, increase health care expenditure and, therefore, add to the financial strain placed on an economy (Kessler, Keller & Wittchen, 2001; Stein, Seedat, Herman, *et al.*, 2008).

The Rational for the Investigation of Other Psychotropics in the Treatment of GAD

The recommended 1st line treatments for GAD include predominantly the SSRI's and SNRI's (Bandelow, Sher, Bunevicius, *et al.*, 2012; Baldwin, Anderson, Nutt, *et al.*, 2005). However, they are estimated to have high rates of non-response in the region of 25 to 40% (Baldwin, Waldman & Allgulander, 2011). Among the tricyclic antidepressants there is good evidence to support the use of imipramine in GAD (Bandelow, Boerner J, Kasper, et al., 2013). Although effective, the tricyclic antidepressants carry troublesome anticholinergic side effects and can be fatal in overdose (Bandelow, Boerner J, Kasper, et al., 2013). Numerous studies have found the 5-HT_{1A} agonist, buspirone, effective in treating GAD (Bandelow, Boerner J, Kasper, et al., 2013). However, there is conflicting evidence where it is was found inferior to venlafaxine and one controlled unsuccessful trial (Bandelow, Boerner J, Kasper, et al., 2013). The antihistamine, hydroxyzine, showed some efficacy in a small number of controlled trials, however, it never established itself as a recognised treatment option (Bandelow, Boerner J, Kasper, et al., 2013). Benzodiazepines are extremely efficacious in the short term treatment of GAD (Gould, Otto, Pollack, et al., 1997). However, their long term use is severely hampered by their potential for abuse, development of dependence and the high risk associated with a medically unsupervised withdrawal (Mula, 2011). There is some evidence supporting the use of the atypical antipsychotics in GAD, particularly quetiapine, but also including adjunctive use of risperidone and olanzapine in treatment refractory cases (Kreys & Phan, 2015; Samuel, Zimovetz, Gabriel, et al., 2011). However, the metabolic and potential extrapyramidal side effects of antipsychotics, like tardive dyskinesia, remain a problem (Kreys & Phan, 2015). There appears to be no evidence to support the use of beta-blockers such as propranolol in GAD (Steenen, van Wijk, van der Heijden, et al., 2016). Despite all the above treatment options, the majority of patients with GAD still fail to achieve remission. Hence, there is a need to continue searching other avenues for new, more effective and safer medications in the treatment of GAD.

The Rational for Investigating the Newer Anticonvulsants as Interventions in GAD

In this review the newer anticonvulsants are defined as those brought to market from 1985 onwards which includes felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide. It is hypothesised that these agents may possess anxiolytic properties. This suggestion is based on observations from their use in clinical trials for other indications as well some early data from animal studies. In addition, the currently postulated mechanisms as to how these agents might work, forms a theoretical basis for explaining how they might act as anxiolytics.

There is evidence from animal studies which supports the anxiolytic properties of some of the newer anticonvulsants (Lamberty, Falter, Gower, *et al.*, 2003; Mirza, Bright, Stanhope, *et al.*, 2005). There is supporting evidence from epilepsy trials in which patients displayed improved mood and reduced anxiety after treatment with various newer anticonvulsants (Smith, Chadwick, Baker, *et al.*, 1993) . There is some evidence to suggest that the newer anticonvulsants may be more benign and have a lower side effect burden (Besag, 2001). There is preliminary evidence that suggests that the newer anticonvulsants may pose less risks of drug-drug interactions compared to older agents (French, Kanner, Bautista, *et al.*, 2004; LaRoche & Helmers, 2004).

Although the precise mechanism of action of how an anticonvulsant may produce anxiolysis is not fully clear, various hypotheses exist. It is known from research in epilepsy that sensitisation and “kindling of neurons occur when repeated stimuli of the same neurons leads to a decrease in their firing threshold (Post, 2007). The link of the ictal “kindling” phenomenon to mood disorders has been frequently suggested in the past. It is possible that such a mechanism may also underlie the formation of abnormal neuronal firing in the circuits posited to be involved in anxiety disorders (Post, 2007).

Hence, the reduction in "kindling" by anticonvulsants could result in reduced firing of the abnormal neuronal circuits implicated in GAD and thereby result in anxiolysis. This would specifically involve reducing excessive neuronal activity in several key areas and circuits including: the amygdala; the hippocampus and the cortico-striatal-thalamo-cortical (CSTC) circuits (Post, 2007; Grunze, 2008; Stahl, 2004a). The "kindling" process is thought to primarily involve excessive activity of the excitatory neurotransmitter glutamate and decreased activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Ashton & Young, 2003). Anticonvulsants are thought to lead to a reduction in glutamatergic activity and an increase in GABAergic activity (Ashton & Young, 2003). In keeping with this, there is evidence suggesting anticonvulsant therapy demonstrates side effects that are in accordance with raised GABAergic and decreased glutamatergic activity (Ketter, Post & Theodore, 1999).

Anticonvulsants are complicated molecules with the majority having multiple mechanisms of action. Still, the current evidence supports the hypothesis that anticonvulsants produce anxiolysis primarily by increasing GABAergic activity and regulating voltage-sensitive calcium channels (VSCC's) (Aroniadou-Anderjaska, Qashu & Braga, 2006; Goddard, Narayan, Woods, *et al.*, 1996). Conversely, although barbiturates, vigabatrin, tiagabine and topiramate, for instance, can be considered GABAergic compounds, this property alone does not ensure they will all act as anxiolytics (Mula, 2011). It is possible that this is due to the complexity of the circuits and various receptor subtypes that comprise the GABAergic system (Mula, 2011). Additionally, the varied and complex mechanisms of action of anticonvulsants make predicting their potential side effects difficult. For example, the four GABAergic compounds mentioned above, particularly topiramate, happen to be associated with significant cognitive impairment, but this side effect is not associated with all GABAergic anticonvulsants (Mula & Trimble, 2009).

The mechanism of modulating neuronal VSCC's seems to be highly efficacious in reduction of anxiety symptoms (Stahl, 2004a; Mula, 2011). This mechanism of action is not a new development as a number of existing anticonvulsants are thought to block VSCC's to some extent in addition to having other effects (Mula, 2011). However, there are particular anticonvulsants that are thought to act only via the modulation of the N and P/Q subtypes of VSCC's. These particular calcium channels, which are located presynaptically, are critical for the regulation of neurotransmitter release. More precisely, it is the the $\alpha_2\delta$ subunits, of the N and P/Q calcium channels, which are thought to play a critical role in the pathophysiology of anxiety (Stahl, 2004a). $\alpha_2\delta$ subunits, when opened by a current, allow an influx of calcium molecules into the nerve terminal, leading to the release of glutamate into the synapse via excitation-secretion coupling. It is hypothesised that through modulation of $\alpha_2\delta$ subunits, excessive glutamatergic activity in abnormal circuits in GAD can be dampened, while still allowing normal levels of glutamate neurotransmission to occur once the situation is stabilised (Stahl, 2004a).

Gabapentin and pregabalin are known as $\alpha_2\delta$ ligands. They are believed to bind to open N and P/Q calcium channels that are firing excessively and causing elevated glutamatergic activity (Stahl, 2004b). These agents are thought to modulate these calcium channels by binding to the $\alpha_2\delta$ subunits, reducing the influx of calcium into the cell, thereby normalising excessive glutamatergic activity, and theoretically producing anxiolysis (Stahl, 2004a; Mula, 2011). Once the aberrant neurocircuitry in GAD is stabilised, the $\alpha_2\delta$ ligands are believed to maintain a physiological level of glutamatergic activity through ongoing regulation of the stabilised VSCC's (Stahl, 2004b).

The Importance and Utility of This Review

For many reasons, a systematic review of the efficacy of anticonvulsants in GAD is useful at this time, as the last such reviews of these agents in anxiety disorders were many years ago (Mula, 2011; Pande, Pollack, Crockatt, et al., 2007; Kinrys & Wygant, 2005; Van Ameringen, Mancini, Pipe, et al., 2004a). The review conducted by Mula (2011) noted that in many instances the evidence base was thin, consisting mostly of case reports and open label studies with few randomised controlled trials. The review highlighted that there were problems associated with the existing trials. Some were methodologically unsound in that they lacked sufficient sample size, utilised different assessment scales, lacked a placebo control or did not account for comorbidities (Mula, 2011). As a result there were inconsistent findings regarding the efficacy of anticonvulsants in GAD. Overall, Mula (2011) felt that the study of anticonvulsants in anxiety disorders including GAD warranted further investigation.

It is hoped that the evidence base has matured since the last reviews were undertaken and that higher quality data may be available. With this in mind, it could be valuable to obtain a more recent reflection of the usefulness of the newer anticonvulsants in GAD. Conducting a methodologically rigorous systematic review and meta-analysis investigating the efficacy and acceptability of these agents in GAD should provide such information.

Objectives: Purpose of this study

A) Use RCT data to evaluate the net effects of the newer anticonvulsants in enhancing treatment response and reducing symptom severity in GAD.

B) To establish whether the efficacy and acceptability of specific anticonvulsants are superior to others in GAD.

Overview of the Newer Anticonvulsants Considered in This Systematic Review

Felbamate

Felbamate received approval from the Food and Drug Administration (FDA), for the treatment for epilepsy, first among the the newer anticonvulsants considered in this review (LaRoche & Helmers, 2004). The mechanism of action of felbamate is thought to based on the modulation of both sodium and calcium voltage-sensitive channels leading to inhibition of glutamatergic activity and, to a lesser extent, potentiation of GABAergic activity (Mula, 2011). Unfortunately, felbamate is associated with significant risks of both hepatotoxicity and development of aplastic anaemia (Borowicz, Piskorska, Kimber-Trojnar, *et al.*, 2004). This has curtailed its use in epilepsy and possibly investigation into its use in other disorders. No evidence was found regarding the use of felbamate in other psychiatric conditions such as mood or other anxiety disorders.

Gabapentin

As discussed above, gabapentin is an $\alpha_2\delta$ ligand which binds to N and P/Q VSCC's located on the presynaptic neuronal membrane. Through this action, it is thought to regulate the influx of calcium into cells and thereby prevent excessive glutamatergic activity in neurocircuits related to anxiety. Some promising evidence is known to exist for gabapentin's efficacy in other anxiety disorders such as social anxiety disorder, panic disorder and posttraumatic stress disorder (PTSD) (Urbano, Spiegel, Laguerta, et al., 2009; Pollack, Matthews & Scott, 1998; Joos & Zeeck, 2013; Hamner, Brodrick & Labbate, 2001).

Lamotrigine

The structure of the lamotrigine molecule is unlike other anticonvulsants (Ipser & Stein, 2006). The mechanism of action of lamotrigine is thought to include the modulation of voltage-sensitive sodium channels (VSSC's), the modulation of VSCC's, glutamatergic inhibition and GABAergic potentiation (Mula, 2011; Stahl, 2013). It has already proved to be successful, in a number of RCT's and reviews, in the treatment of mood disorders (Boylan, Devinsky, Barry, et al., 2002). Even in other anxiety disorders, data is mainly limited to small open label studies and case reports. However, its showed some promising data, from a small RCT in the treatment of PTSD (Hertzberg, Butterfield, Feldman, et al., 1999). Unfortunately, lamotrigine is associated with a small, but significant, risk of developing Steven-Johnsons syndrome of about 1%. It is estimated that Steven-Johnsons syndrome can lead to mortality rates of between 5% to 15% (Ghislain & Roujeau, 2002; Ipser & Stein, 2006).

Levetiracetam

Levetiracetam is known to bind with strong affinity to the synaptic vesicle protein known as SV2A and thereby modulate the process of exocytosis of neurotransmitters (Stahl, 2013). It is also postulated to reduce the action of negative modulators of GABA-gated and glycine-gated channels as well as have some effects on N type calcium channels (Stahl, 2013). On the basis of its mechanism of action, it is thought that levetiracetam may possess anxiolytic properties. There is some, generally poor quality, data of its use in anxiety disorders. There is data, although conflicting, on its effectiveness in SAD (Stein, Ravindran, Simon, et al., 2010; Zhang, Connor & Davidson, 2005; Simon, Worthington, Doyle, et al., 2004). There was some positive data in using levetiracetam in treatment resistant PTSD (Kinrys, Wygant, Pardo, et al., 2006).

Oxcarbazepine

Oxcarbazepine is not a metabolite but rather the 10-keto analogue of carbamazepine (Stahl, 2013). Its mechanism of action involves binding to and modulating VSSC's, some binding and modulation of VSSC's and producing some degree of glutamatergic inhibition (Mula, 2011; Stahl, 2013). Unlike carbamazepine, oxcarbazepine does not seem to be associated with leukopenia, aplastic anaemia, hepatotoxicity and dangerous skin rashes and seems to have fewer drug-drug interactions (Stahl, 2013). Its most significant risk is hyponatraemia which can occur in up to 3% of patients (Stahl, 2013). There are some case reports and anecdotal evidence that suggest oxcarbazepine has potential efficacy in PTSD and panic disorder (Berigan, 2002; Windhaber & Dantendorfer, 1997).

Pregabalin

Pregabalin is an $\alpha_2\delta$ ligand which binds to N and P/Q VSCC's on presynaptic membranes and thereby modulates calcium influx and glutamatergic neurotransmission. It shares this mechanism of action with gabapentin but its effect appears to be more potent (Stahl, 2013). Evidence seems to suggest its side effect profile is comparatively mild compared to the other newer anticonvulsants. Its side effects are mainly limited to sedation, dizziness and a moderate degree of weight gain (Stahl, 2013). It is useful that pregabalin has few, if any, pharmacokinetic drug interactions as it is excreted, unchanged, renally, and does not undergo hepatic metabolism (Stahl, 2013). There already existed, in 2011, an evidence base supporting the efficacy of pregabalin in treating GAD (Mula, 2011). However, the data on pregabalin has continued to grow since then. Pregabalin is officially approved for the treatment of GAD in Europe, however, does not yet have FDA approval in the United States. It has shown efficacy in treating chronic pain and is approved by the FDA for the treatment of fibromyalgia syndrome (Sommer, Häuser, Alten, et al., 2012). It appears to show efficacy in other anxiety disorders such SAD, has been investigated as an adjunct in treating major depressive disorder (MDD) and to facilitate the withdrawal process of benzodiazepine dependent patients (Feltner, Pollack, Davidson, et al., 2000; Vitali, Tedeschini, Mistretta, et al., 2013; Bobes, Rubio, Terán, et al., 2012).

Topiramate

Topiramate is thought to act via multiple mechanisms including the modulation of VSSC's and VSCC's, acting as a carbonic anhydrase inhibitor and enhancing GABAergic as well as reducing glutamatergic activity (Stahl, 2006). Topiramate has significant side effects limiting its use. It can cause troublesome sedation and is thought to produce cognitive impairment generally more severe compared to other anticonvulsants. It can potentially result in a metabolic acidosis and has been associated with the development of kidney stones (Stahl, 2006; Brunbech & Sabers, 2002). There is some early but conflicting evidence for its use in PTSD, SAD and obsessive compulsive disorder (OCD) (Berlant, 2000; 2004; Van Ameringen, Mancini, Pipe, et al., 2004b; Rubio, Jimenez-Arriero, Martinez-Gras, et al., 2006). Topiramate use can potentially lead to significant weight loss. This has resulted in the off-label use of topiramate as a weight-loss agent, with some clinicians prescribing it to counteract antipsychotic-associated weight gain.

Tiagabine

Tiagabine is believed to work via selectively blocking the reuptake of GABA by transporters at the presynaptic region of neurons and on glial cells (Stahl, 2006). It is thought to primarily potentiate the GABAergic system and not affect any other neurotransmitters systems or ion channels directly (Mula, 2011). Tiagabine may have troublesome side effects including sedation, cognitive impairment and the development of new onset seizures in patients without epilepsy (Stahl, 2014). It is also thought to potentially pose a long-term ophthalmological risk through its binding to melanin (Stahl, 2006). Tiagabine is mainly metabolised by the hepatic cytochrome enzyme CYP450 3A4. The induction or inhibition of this enzyme by other drugs makes tiagabine susceptible to significant fluctuations in its plasma level. Frequently used psychotropics including many of the mood-stabilising anticonvulsants and common antidepressants can alter CYP450 3A4 activity (Stahl, 2006). Tiagabine had received earlier attention regarding its potential efficacy in GAD supported by an early, but growing evidence base (Mula, 2011). The evidence at that time was limited to a few RCTs, open label studies and case series (Kinrys & Wygant, 2005). There is small body of evidence of the use of tiagabine in other anxiety disorders, including PTSD and SAD, but is mostly limited to open label studies and case series (Crane, 2003; Zwanzger, Eser, Nothdurfter, et al., 2009; Taylor, 2003; Dunlop, Papp, Garlow, et al., 2007; Kinrys & Wygant, 2005).

Vigabatrin

The mechanism of action of vigabatrin is thought to occur via the inhibition of GABA transaminase leading to an increase in the total amount of GABA in the brain (Zwanzger & Rupprecht, 2005). Vigabatrin is not a benign medication with visual field abnormalities occurring in up to 33% of patients (Kalviainen, Nousiainen, Mantyjarvi, *et al.*, 1999). There seems to be some low-level evidence suggesting its possible efficacy in panic disorder (Zwanzger, Baghai, Boerner, et al., 2001).

Zonisamide

Zonisamide can be structurally classified as a sulfonamide (Leppik, 2004). Many details remain unknown regarding the mechanism of action of zonisamide. It is thought to modulate VSSC's via an unknown mechanism (Stahl, 2014).T-type VSCC's, which perform a function that is currently unclear, are believed to be modulated by zonisamide (Stahl, 2014). Additionally it is thought that zonisamide increases the release of dopamine and serotonin as well as acting as a carbonic anhydrase inhibitor (Stahl, 2006). Its side-effects may include marked sedation, a risk of life-threating skin rashes including Steven-Johnson syndrome, development of kidney stones and a risk of blood dyscrasias (Stahl, 2006). It is metabolised partly CYP450 3A4 and therefore its plasma concentration is liable to be affected by the inducers and inhibitors of this enzyme (Stahl, 2006). There is some low-level evidence for its use in treatment refractory anxiety from an open-label, pilot study with ten patients (Kinrys, Vasconcelos e Sa & Nery, 2007). Zonisamide, similarly to topiramate, can cause marked weight loss. It is used off-label for the treatment of obesity and psychotropic-induced weight gain.

Chapter 2

Methods

Criteria considered for studies in this review

Types of studies

The types of studies considered for this review were randomised, placebo controlled, trials of newer anticonvulsants in the treatment of GAD. Randomised controlled trials (RCT's), with both placebo and active comparator arms were considered. However, data from the active comparator arms was not considered in this review. Only short-term RCT's were considered and relapse prevention studies were not included.

Types of Participants

Participants were considered if they suffered from GAD as defined by the criteria set out in the *Diagnostic and Statistical Manual III* (DSM III) (APA, 1980) or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* (*DSM-IV)* (APA, 1994) or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR)* (APA, 2000) or the *International Classification of Diseases-10 (ICD-10) of Mental and Behavioural Disorders* (WHO, 1992). Participants were not restricted according to their age, gender or race.

Types of Intervention

RCT's of anticonvulsants brought to market from 1985 onwards were considered. This included RCT's of felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate or zonisamide. RCT's where the only intervention was a single anticonvulsant compared to a placebo control were included (allowing for the presence of active comparators if necessary). Trials where the anticonvulsant was used as an adjunctive treatment were not included. RCT's which compared different dosages of a single anticonvulsant to a placebo control arm were considered. Data from multicentre trials was also considered.

Types of outcome measures

Studies with dimensional outcome measures were included if they provided symptom severity means and standard deviation data, or allowed the imputation of such data. It was decided on a case-by-case basis whether to include trials where certain established scales used in the study might have undergone minor modifications. Studies with dichotomous outcome measures were included if they provided post medication treatment and placebo response results.

Primary outcomes

Reduction in symptom severity was measured by validated continuous outcome measures specific to GAD. The most widely used instrument in this regard is the Hamilton Anxiety Rating Scale (HAM-A) (HAMILTON 1960). The *Clinical Global Impressions Scale-Improvement item* (CGI-I) (Guy, 1976) is a global outcome measure widely used in clinical trials. It was used to determine treatment response (responders vs. non-responders). Responders on the CGI-I were defined as those having a score of 1 equalling "very much" improved or 2 equalling "much" improved.

Secondary outcome

Medication Acceptability. The total proportion of participants who withdrew from RCT's due to treatment-related adverse events served as a surrogate measure of medication acceptability. If a more direct measurement of medication acceptability was made available by the RCT it was used instead.

Search methods for identification of studies

The search methods as described below were used while conducting the Cochrane Review "*Newer anticonvulsants in the treatment of anxiety disorders*" (Ipser & Stein, 2006). The Cochrane search strategy was designed to provide results which included trials conducted on any of the anxiety disorders. The search results for this review will be obtained by extracting only the trials investigating GAD from the Cochrane search results. The dates in the search strategy below may not refer to the most recent search, as updated searches may be performed during the review process.

Electronic Searches

1. The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR-Studies) was searched with the following search strategy: CCDANCTR-Studies Diagnosis = Anxiety or Anxious or Phobi* or Panic or Obsess* or compulsi* or Post-Traumatic and Intervention = felbamate or gabapentin or lamotrigine or levetiracetam or oxcarbazepine or pregabalin or tiagabine or topiramate or zonisamide CCDANCTR-References
Keyword = Anxiety or Anxious or Phobi* or Panic or Obsess* or compulsi* or Post-Traumatic and Free-Text = felbamate or gabapentin or lamotrigine or levetiracetam or oxcarbazepine or pregabalin or tiagabine or topiramate or zonisamide

2. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2 2006) was searched.

3. Additional searches were carried out on MEDLINE via PubMed (January 1985 to December 2005), and through PsycINFO (1983 to 2005, Part B). The complete MEDLINE search query, as derived from the search strategy developed by Robinson (2002), is provided below:

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) AND (anxiety disorder [mh:noexp] OR "anxiety disorder" [tw] OR phobic disorders [mh:noexp] OR obsessive- compulsive disorder [mh] OR "obsessive-compulsive" [tw] OR stress disorders, post-traumatic [mh:noexp] OR "post-traumatic" [tw]) AND (anti-convulsants [tw] OR anticonvulsants [tw] OR anticonvulsants [mh] OR anti-epileptics [tw] OR antiepileptics [tw] OR felbamate [tw] OR gabapentin [tw] OR lamotrigine [tw] OR levetiracetam [tw] OR oxcarbazepine [tw] OR pregabalin [tw] OR topiramate [tw] OR tiagabine [tw] OR zonisamide [tw]) The PsycINFO search strategy will include the following search query: ("randomisation" OR "randomization") OR "controlled" AND ("anticonvulsants" OR "antiepileptics").

4. Ongoing trials were located using the metaRegister of Controlled Trials database (mRCT) (http://www.controlled-tri- als.com), as well as the National Institute of Health's Computer Retrieval of Information on Scientific Projects (CRISP) service (1972-2005). The search terms "anticonvulsants OR antiepileptics" were entered into the search interface for these databases.

Reference Lists and Correspondence

The bibliographies of all identified trials were scanned for additional studies. Published and unpublished trials were obtained from key researchers if possible, as identified by the frequency with which they were cited in the bibliographies of RCTs and open-label studies. Pharmaceutical companies were contacted if needed. They were identified through the source of funding cited in published RCTs, as well as the companies with which the authors were affiliated.

Data collection and analysis

Study Selection

Two independent raters (AK) and (LA) screened all trial data identified in the first search process. The trials were assessed based on information included in either the abstract or method section. RCTS's were selected if both raters agreed that they satisfied the inclusion criteria as specified in the "Criteria for consideration of studies" section. One rater, (AK) collated the required data from the selected RCT's as specified in the "Data extraction and management" section. Discussion was used to resolve any differences in the assessments made by the independent raters. If agreement could not be reached, differences in assessment were resolved with the advice of a third party (DS).

Data Extraction and Management

Data from each RCT was extracted and recorded in Covidence (Systematic Review Software) (Veritas Health Innovation, n.d.). This is a Web-based systematic review tool officially recommended by the *Cochrane Collaboration* for authors of systematic reviews (Babineau, 2014). It aids in citation screening, data extraction and assessing risk of bias amongst other features. The data collated within Covidence can be directly exported into Review Manager (RevMan) (Cochrane Collaboration, 2011). Covidence populates the necessary sections of a systematic review in RevMan. This includes descriptive information of the trials, risk of bias assessments and summary statistics of the outcome measures. RevMan was used to perform all statistical analyses, to export characteristics of studies, risk of bias assessments, graphs and data tables.

The following specific data was gathered from each RCT: a description of the trials including the primary researcher, publication year and source of funding; the characteristics of the interventions including the number of participants randomised to the treatment and control groups, the total number of dropouts per group, dropouts due to adverse effects, dosages of medication, the time period over which medication was administered and the anticonvulsant used; the characteristics of trial methodology including the diagnostic criteria used, the inclusionary and exclusionary criteria used, the screening instruments used for the primary and comorbid diagnoses and the number of centres involved; the characteristics of participants including: the gender distribution, mean participant age and range, length of time since diagnosis with GAD, previous treatment with medication and baseline severity of GAD.

The primary and secondary outcome measures including: the summary of continuous data with means and standard deviations, summary of dichotomous data reflecting the number of responders, incorporation of intention-to-treat (ITT) with last observation carried forward (LOCF) or completer/observed cases (OC) samples, the least amount of time needed in trial participation to qualify for inclusion in the LOCF sample and use of the mixed effects (ME) model (or another acceptable method) which provided an estimation of a drop-out participant's outcome. Where certain important information was missing from particular studies, attempts were made to obtain it by emailing the investigators.

Assessment of risk of bias of included studies

The *Cochrane Collaboration's* tool for assessing "risk of bias" was used (Higgins & Green, 2011). It assesses risk of bias in each of several key domains. In each domain the risk is classified as either "high", "low" or "unclear" based on information provided in each study. The domains to assess bias across trials include sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias.

Measures of treatment effect

Continuous Data

The following was calculated for continuous data: The mean difference (MD) (the *Cochrane Collaboration* prefer this term to "weighted mean difference") was calculated for continuous data which was measured using the same scale. The standardised mean difference (SMD) was calculated where different scales were used to measure a specific outcome. To calculate the SMD, the differences between the means of the treatment and control groups are standardised in terms of the variability in the trial(Green, 2011).

Dichotomous data

To present dichotomous data, the risk ratio (RR) (the *Cochrane Collaboration* prefer the use of this term to "relative risk") of response to treatment was calculated for the dichotomous outcome of interest (which was CGI-I or related measure). Risk ratios were used in preference to odds ratios as odds ratios are interpreted less easily. When odds ratios are mistakenly interpreted as RR they tend to overestimate the size of treatment effect particularly when the outcome of interest occurs frequently (Higgins & Green, 2011).

The number needed to treat for one additional benefit (NNTb) was determined for measures of treatment response on the CGI- I (or related measure). NNTb was calculated as the inverse of the absolute risk difference due to the medication intervention. NNTb was interpreted as the number of patients that must be treated with medication in relation to a control such that a further patient in the medication group would respond to treatment. A confidence interval for the NNTb could be calculated from the inverted limits of the confidence interval for the absolute risk difference.

When the inverse of the absolute risk difference, or the inverse of the confidence interval limits lead to a negative number, this indicated the direction of effect of the NNT. NNT values are always expressed as a positive whole number. Therefore, if the result obtained is negative the *Cochrane Collaboration* (Higgins & Green, 2011) advises using the term 'number needed to treat for one additional harmful outcome' (NNTh). This is interpreted to indicate a case where an intervention does not lead to an improvement but to a worsening of clinical status on the measure of treatment response.

Unit of Analysis Issues

In the case where more than one fixed dose of an anticonvulsant was compared within a study to the same placebo group, it is necessary to take steps to avoid a unit-of-analysis error. This occurs as the same placebo group is counted more than once during the process of comparison to the different dosage subgroups. This leads to inaccurate results. There are multiple approaches suggested to overcome this problem. In this review, the method currently recommended by the *Cochrane Collaboration* was utilised. Subgroups within a trial are combined using a formula, specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks, Higgins & Altman, 2011), to generate a single, pair-wise outcome for the trial (Green, 2011). By having a single pair-wise outcome allows a trial to be included as part of a meta-analysis. The other options to overcome unit-of-analysis errors include selecting one pair of interventions from the trial and excluding the other subgroups, or undertaking a multiple-treatment meta-analysis (Green, 2011).

Dealing with Missing Data

Most studies use the number of patients randomised to each group at baseline as the intention-to-treat (ITT) sample. As Hoskins (2015) points out, some studies define a modified ITT (MIIT) sample as patients who have received at least one dose of medication and one post baseline assessment. This MIIT sample number might be the only one available and be used in the trial in calculating its outcome data. Dichotomous data was analysed via the ITT sample if it was provided by a trial alternatively the MITT sample was used. Summary statistics for continuous outcome measures were included in order of preference to the method used in their calculation. According to evidence by Verbeke (2009), mixed effect models (ME) are more resistant to bias then analysis by last observation carried forward (LOCF). Based on this, (ME) were included first if possible, then LOCF and lastly observed cases (OC).

Assessment of heterogeneity

The chi-squared test was used to assess heterogeneity. Evidence of heterogeneity was inferred if the chi-square test had a p-value of less then 0.10 as the chi-square statistic has low power when the number of trials is small (Deeks, 2002). The I^2 heterogeneity statistic provided by RevMan was used to determine differences in effect size across trials that cannot be explained by chance alone (Higgins, Thompson, Deeks, *et al.*, 2003; Cochrane Collaboration, 2011). I^2 was interpreted following the guidelines laid out out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks, Higgins & Altman, 2011). I^2 allows the size of the heterogeneity of primary and secondary outcomes and their corresponding importance to be broadly assessed. I^2 was interpreted as follows: 0% - 40% - might not be important; 30%-60% - may represent moderate heterogeneity; 50% -90% - may represent substantial heterogeneity; 75%- 100% - considerable heterogeneity (Deeks, Higgins & Altman, 2011).

Assessment of Reporting Bias

The fact that a study is published does not necessarily imply that it is of high quality. Publication may suggest the possibility of particular biases. (Easterbrook, Berlin, Gopalan, *et al.*, 1991; Dickersin, Min & Meinert, 1992) (Scherer, Dickersin & Langenberg, 1994). A funnel plot of treatment response will be generated and visually assessed for asymmetry. An asymmetrical funnel plot may suggest the possibility of small-sample effects including publication bias.

Data Synthesis

The random effects statistical model was used to get categorical and continuous treatment effects. Within-study sampling error and between-study variation is included in the random effects model. This was used to calculate the precision of the confidence interval around the overall effect size. In comparison the fixed effects model uses only within-study variation. Outcomes were expressed as either an average effect size for each subgroup or by means of 95% confidence intervals.

Ethics

Ethics approval was not, in principal, required for a systematic review such as this. However, there was mandatory documentation, that was required by the University of Cape Town Human Research Ethics Committee, for this minor dissertation. This necessary documentation was handed in accordingly.

Chapter 3

Results

Results of the Search

Three separate searches were made of the *The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register* (CCDANCTR) and *clinicaltrials.gov* website over a three-year period for this review. The last search of the CCDANCTR was up-to-date as of the 31/07/2013 and clinicaltrials.gov as of the 19/08/2013. According to the *Cochrane Collaboration* (Higgins & Green, 2011) a systematic review should be considered for updating approximately two years since the date of the last search. It would be optimal to update the search as it has been more than two years since the last *Cochrane Collaboration* search.

It was not possible to gain access to the *Trials Search Co-ordinator of the Cochrane Depression, Anxiety and Neurosis Group* to perform an updated search. The mini-dissertation was based upon the larger official Cochrane Systematic Review entitled "*Newer anticonvulsants in the treatment of anxiety disorders*" (Ipser & Stein, 2006) which is yet to be completed. By the time the most updated search was performed for this dissertation, the author of this dissertation was no longer planning to work as an author on the official Cochrane Systematic Review and planned to pass it on. Therefore, requesting further searches by the Trials Search Co-ordinator for this dissertation was not considered to be a viable option. Therefore, an independent search was conducted of PubMed on the 16/05/2016 to check for any further studies that may have occurred in this subject area. The following PubMed search query used:

(((((("randomized controlled trial"[Publication Type]) OR "review"[Publication Type]) OR "meta analysis"[Publication Type]) AND anxiety disorders[MeSH Terms]) AND anticonvulsants[MeSH Terms]).

From this search there were no additional citations of RCT's, reviews or meta-analyses identified, of anticonvulsants in the treatment of GAD, after the date of the last official *Cochrane Collaboration* search. Therefore, no new data was added. The systematic review and meta-analysis is considered up-to-date as of the 16/05/2016.

287 citations were generated in the search process. Each citation was screened, using the title and abstract, by two different reviewers (AK) and (LA). 228 citations were removed which included 83 duplicates and 145 trials not meeting inclusion criteria. 59 papers were retrieved for full-text review. 29 were excluded as they did not meet one or more inclusion criteria. Only one record of an unpublished RCT on GAD using anticonvulsants was found. Pfizer conducted this unpublished RCT in 2003 comparing pregabalin, lorazepam and placebo in GAD (Study 1008-025 (Pfizer, data on file)). Attempts were made to obtain this data but were unsuccessful and the trial had to be excluded. All the remaining included trials were published in journals. 30 anxiety disorder full text papers remained. A further 20 full text papers were removed on closer inspection. This consisted of that 17 papers that did not concentrate on GAD and 3 other papers on GAD which did not meet various other inclusion criteria. Ten full text papers on GAD remained. One of the full text papers, Pollack 2008, consisted of 3 independent RCTs. Therefore, there were 12 RCT's from 10 full text papers included in the systematic review and meta-analysis. The flow diagram in **Figure 1** graphically represents the search process which was conducted as recommended by the Cochrane Collaboration's PRISMA statement (Moher, Liberati, Tetzlaff, *et al.*, 2009).

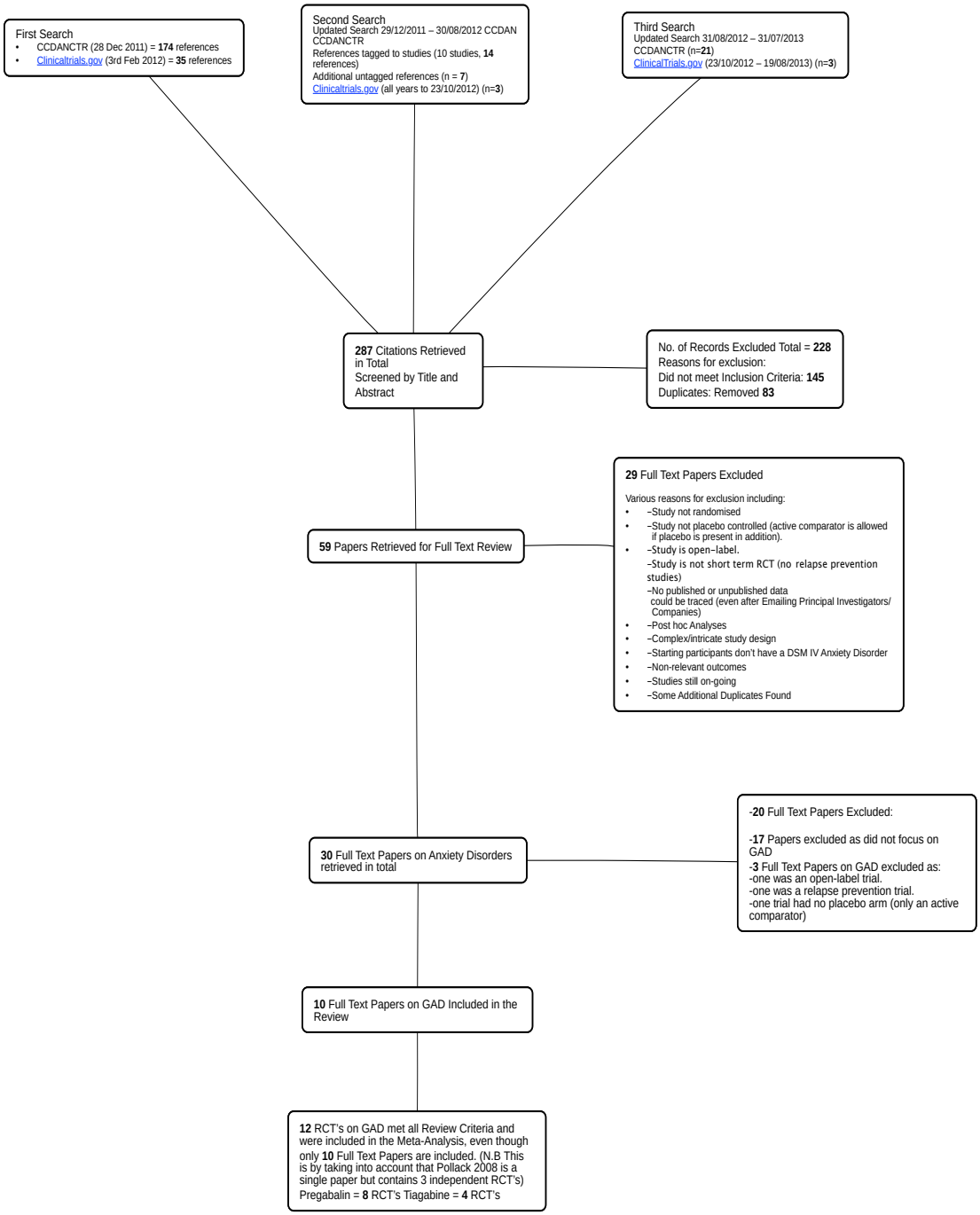

Figure 1. PRISMA Flow Chart of Search

Description of the Studies

Included Studies

Twelve studies were included in the systematic review and meta-analysis. A summary of the baseline demographic, clinical characteristics and study ID of the included studies are presented in **Table 1** below. The included studies will be referred to within the text by their *Study ID* in bold lettering in the format "**Author Year"**.

Study ID and In-Text Citation for the Included Studies

- **Pande 2003** (Pande, Crockatt, Feltner, *et al.*, 2003)
- **Feltner 2003** (Feltner, Crockatt, Dubovsky, *et al.*, 2003)
- **Pohl 2005** (Pohl, Feltner, Fieve, *et al.*, 2005)
- **Pollack 2005** (Pollack, Roy-Byrne, Van Ameringen, *et al.*, 2005)
- **Rickels 2005** (Rickels, Pollack, Feltner, *et al.*, 2005)
- **Montgomery 2006** (Montgomery, Tobias, Zornberg, *et al.*, 2006)
- **Montgomery 2008** (Montgomery, Chatamra, Pauer, *et al.*, 2008)
- **Pollack 2008(a, b and c)** (Pollack, Tiller, Xie, *et al.*, 2008)
- **Kasper 2009** (Kasper, Herman, Nivoli, *et al.*, 2009)
- **Ionescu 2010** (Ionescu, Dehelean, Timofei, *et al.*, 2010)

Design

All twelve studies were RCT's utilising a parallel-group design. **Pollack 2008(a, b and c)** consisted of three independent RCT's described in one publication. All included trials were RCT's with a placebo arm with some containing an additional active comparator arm. The average duration of the trials was 7.2 weeks with the shortest trials lasting 4 weeks and the longest trials 10 weeks.

Setting and Sponsorship Source

Six studies were conducted only in the United States (U.S) and one study had sites in Europe and the U.S. One study was conducted in Romania, and two large studies were conducted across multiple European countries including Belgium, Canada, France, Ireland, the Netherlands, Spain, Sweden, Austria, Germany and the United Kingdom. The average number of sites involved in each study was 35.5. Eleven of the twelve studies were funded by industry. It was unclear who funded the remaining trial **Ionescu 2010**.

Participants

4001 participants are included in the meta-analysis consisting of 2516 participants in the anticonvulsant group and 1485 in the placebo group. These numbers are of ITT or MITT samples as listed in the publications. The total number of participants sometimes differed across summary outcomes within the same trial. This is due to the fact that some trials specified different MITT numbers for different outcomes. Whichever MITT they utilised for the specific outcome was used in the meta-analysis. The average age of participants was 43 years. The average percentage of female participants was 60.4%.

Table 1. Summary of Characteristics of Included Studies

Trial ID	Title
Feltner 2003	A randomized, double-blind, placebo-controlled, fixed-dose, multicentre study of pregabalin in patients with generalized anxiety disorder
Pande 2003	Pregabalin in generalized anxiety disorder: A placebo-controlled trial
Rickels 2005	Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicentre, double-blind, placebo-controlled trial of pregabalin and alprazolam
Pohl 2005	Efficacy of pregabalin in the treatment of generalized anxiety disorder: double-blind, placebo-controlled comparison of BID versus TID dosing
Pollack 2005	The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: Results of a placebo-controlled study
Montgomery 2006	Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: a 6-week, multicentre, randomized, double-blind, placebo-controlled comparison of pregabalin and venlafaxine
Montgomery 2008	Efficacy and safety of pregabalin in elderly people with generalised anxiety disorder
Pollack 2008 (a, b and c)	Tiagabine in adult patients with generalized anxiety disorder: results from 3 randomized, double-blind, placebo-controlled, parallel-group studies
Kasper 2009	Efficacy of pregabalin and venlafaxine-XR in generalized anxiety disorder: Results of a double-blind, placebo-controlled 8-week trial.
Ionescu 2010	The efficacy and the tolerability of pregabalin in the case of adults patients with generalised anxiety disorders

Trial ID	Journal	Industry-Funded
Feltner 2003	Journal of Clinical Psychopharmacology: J. Clin. Psychopharmacol. 2003;23(3):240-249	Yes
Pande 2003	American Journal of Psychiatry: Am. J. Psychiatry 2003;160(3):533-540	Yes
Rickels 2005	Archives of general psychiatry 2005;62(9):1022-1030	Yes
Pohl 2005	Journal of clinical psychopharmacology 2005;25(2):151-158	Yes
Pollack 2005	Journal of clinical psychiatry 2005;66(11):1401-1408	Yes
Montgomery 2006	Journal of clinical psychiatry 2006;67(5):771-782	Yes
Montgomery 2008	British journal of psychiatry 2008;193(5):389-394	Yes
Pollack 2008 (a, b and c)	Journal of clinical psychopharmacology 2008;28(3):308-316	Yes (all 3 studies were industry funded)
Kasper 2009	International clinical psychopharmacology 2009;24(2):87-96.	Yes
Ionescu 2010	Toxicol Lett 2010;196:S87-S87	Unclear

Trial ID	Intervention Sample Size (ITT/MITT)	Placebo Sample Size (ITT/MITT)	Anticonvulsant Used as Intervention	Average Age of Participants
Feltner 2003	204	67	Pregabalin	37,30
Pande 2003	139	69	Pregabalin	36,40
Rickels 2005	270	91	Pregabalin	39,00
Pohl 2005	255	86	Pregabalin	40,00
Pollack 2005	130	130	Tiagabine	37,25
Montgomery 2006	207	101	Pregabalin	43,30
Montgomery 2008	77	96	Pregabalin	72,30
Pollack 2008 (a, b and c)	1057	662	Tiagabine	38,94
Kasper 2009	121	128	Pregabalin	40,35
Ionescu 2010	56	55	Pregabalin	42,50

Trial ID	Females (%)	Duration (Weeks)	Number of Sites	Countries where Study was Conducted
Feltner 2003	51,03%	4	4	U.S
Pande 2003	58,17%	4	5	U.S
Rickels 2005	63,25%	4	29	U.S
Pohl 2005	60,00%	6	19	U.S
Pollack 2005	57,00%	8	32	U.S
Montgomery 2006	60,67%	6	76	Austria, Belgium, Germany, the Netherlands, United Kingdom
Montgomery 2008	77,00%	8	72	13 sites in the U.S and 69 sites in Europe
Pollack 2008 (a, b and c)	60,38%	10	Unclear	U.S
Kasper 2009	62,50%	8	47	Belgium, Canada, France, Ireland, Italy, the Netherlands, Spain, Sweden
Ionescu 2010	54,05%	8	Unclear	Romania

Trial ID	Design	Medication Dosages
Feltner 2003	RCT	Pregabalin 50mg TID & Pregabalin 200mg TID
Pande 2003	RCT	Pregabalin 150mg/day Total (50mg TID) & Pregabalin 600mg/day Total (200mg TID)
Rickels 2005	RCT	Pregabalin 300mg/day Total (Dosed in TID Regimen) & Pregabalin 450mg/day Total (Dosed in TID Regimen) & Pregabalin 600mg/day Total (Dosed in TID Regimen)
Pohl 2005	RCT	Pregabalin 200mg/day Total (100mg BID) & Pregabalin 400mg/day Total (200mg BID) & Pregabalin 450mg/day Total (150 TID)
Pollack 2005	RCT	Tiagabine (2mg-16mg/day Total Dosed in BID Regimen)
Montgomery 2006	RCT	Pregabalin 400mg/day In Total Dosed in BID Regimen & Pregabalin 600mg/day In Total Dosed in Bid Regimen
Montgomery 2008	RCT	Pregabalin (150- 600mg) Flexibly Dosed
Pollack 2008 (a, b and c)	RCT	Tiagabine 12mg/Day Total (Fixed Dosage in BID Regimen), Tiagabine 8mg/Day Total (Fixed Dosage in BID Regimen) & Tiagabine 4mg/Day Total (Fixed Dosage in BID Regimen) in Study "*a*". Tiagabine (4mg-16mg Total Flexibly Dosed in BID Regimen) in Study "*b*". Tiagabine (4mg-16mg Total Flexibly Dosed in BID Regimen) in Study *c*.
Kasper 2009	RCT	Pregabalin (300 -600mg/day Flexibly Dosed in BID Regimen)
Ionescu 2010	RCT	Pregabalin (150mg/day to 600mg/day Flexibly Dosed)

Inclusion Criteria

The inclusion criteria varied across the studies, with some studies more stringent than others. The permitted age of participants was 18 years or older with some studies setting an upper limit of 65 years old and one study requiring patients only older then 65 years. Participants had to meet DSM-IV (APA, 1994) or DSM-IV-TR (APA, 2000) criteria for GAD with most studies using the Mini-International Neuropsychiatric Interview (Sheehan, Lecrubier, Sheehan, *et al.,* 1998) to confirm the diagnosis. Across most studies, patients had to have a HAM-A total score >= 20 at screening and baseline visits.

In patients with comorbid psychiatric disorders, GAD was required to be the primary psychiatric disorder as judged by the investigator. In some studies patients were required to have a Covi Anxiety Scale (Lipman, 1982) score of >=9 and a Raskin Depression Scale (Raskin, Schulterbrandt, Reatig, *et al.*, 1969) score of <= 7 to confirm that anxiety symptoms outweighed depression symptoms. The majority of studies required patients to be free of psychotropic medication for two weeks prior to enrolment or five weeks in the case of fluoxetine. Most trials permitted no psychotropic medications during the trials although some trials allowed zolpidem 5mg less than two nights per week and not the night before a clinic visit.

Exclusion Criteria

Exclusion criteria were numerous and varied across the trials. Patients were excluded if they: were diagnosed with from additional Axis I pathology excepting dysthymia, simple phobia, social phobia, somatization disorder or previous episodes of major depression disorder; were suffering from a current episode of major depression; had severe personality disorders such as antisocial or borderline; suffered from substance abuse or dependence, with an episode occurring in the previous six months (some studies included a urine drug screen); were considered a suicide risk judged on history and examination or scored greater than or equal to two on item three (which reflects level of suicidal ideation) of the HAM-D (Hamilton, 1960).

Some studies specifically stated that patients with a diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorders or bipolar disorders were excluded. Particular studies stated additional physical conditions as exclusionary criteria including: any serious haematological, autoimmune, endocrine, cardiovascular, renal, hepatic, gastrointestinal or neurological disorder including any history of a seizures. All studies excluded women who were pregnant or lactating. Most studies specified that women in their childbearing years had to be on some form of reliable contraception.

Interventions

Pregabalin was used as the intervention in eight of the studies and tiagabine in the remaining four studies. Various dosage regimes were used which appear in **Table 1**. Five pregabalin studies placed the participants randomly into separate fixed-dosage groups with differing dosage regimes. The remaining three pregabalin studies allowed a flexible dosing regime which ranged from 150mg/day to 600mg/day. There were three flexibly dosed trials of tiagabine and one fixed dosage regimen trial. The dosage of tiagabine ranged from 2mg/day up to 16mg/day. The fixed dosage study specifically had groups assigned to 4mg, 8mg and 12mg/day. For studies with multiple treatment dosage arms, the subgroups were combined to form one intervention arm using the method described above under **Unit of Analysis Issues**.

Outcomes

All the studies used the Hamilton Anxiety Rating Scale (HAM-A) (HAMILTON, 1960) for the primary continuous outcome. This allowed for the mean difference (MD) as opposed to the SMD to be used in the meta-analysis. All the trials, with the exception of **Pande 2003** and **Ionescu 2010** provided complete data to allow calculation of the dichotomous outcome of treatment response utilising the CGI-I. **Pande 2003** provided unclear information on the number of responders in the 150mg pregabalin group, but provided clear data for its other groups. **Ionescu 2010** was the only trial which provided no data to allow the calculation of treatment response. All the trials provided the necessary data to allow for calculation of treatment acceptability by using the RR of drop-outs due to treatment-adverse effects. The number needed to treat for an additional beneficial outcome (NNTb) could be calculated for the anticonvulsants as a group, as well as for pregabalin and tiagabine alone.

There was sufficient data to allow a meta-analysis to be undertaken for the two primary outcomes and the single secondary outcome. The summary statistics that were obtained for all outcomes in the meta-analysis were expressed as an effect estimate with a 95% confidence interval. Forest plots were generated for the primary outcomes and the secondary outcome of the anticonvulsants as a group, pregabalin considered alone and tiagabine considered alone. All the forest plots are displayed below in the main body of the text. The full data tables, are displayed in the **Appendices**. The data tables contain all the outcome data generated in the meta-analysis for each individual study and the pooled effect estimates.

Excluded Studies

Excluded Studies mainly consisted of trials not assessing GAD using the criteria sets as specified “Methods” section. Other studies were excluded for not using the specified anticonvulsants as interventions. Many studies were excluded for not being randomised or not having a placebo control arm. Other finer details excluded studies. For example, three studies in particular were excluded and are presented below in **Table 2**. Rosenthal (2003) was excluded for possessing no placebo arm. Feltner (2008) was excluded as it was a long-term relapse prevention study. Rickels (2012) was excluded as it used an anticonvulsant as adjunctive treatment. There were no ongoing studies or studies awaiting classification that were apparent at the time of the last search.

Table 2 Excluded Studies

Rosenthal 2003 (Rosenthal, 2003)

Reason for exclusion	Open Label Study (No placebo Arm only Active Comparator)

Feltner 2008 (Feltner, Wittchen, Kavoussi, *et al.*, 2008)

Reason for exclusion	Not Short Term (relapse prevention study)

Rickels 2012 (Rickels, Shiovitz, Ramey, et al., 2012)

Reason for exclusion	Adjunctive therapy

Risk of Bias in Included Studies

The 'risk of bias' (methodological quality) was assessed in the included studies. This was done according to the 'Risk of Bias tool' specified by the *Cochrane Collaboration* (Higgins & Green, 2011). Bias was assessed across the recommended domains: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. Bias was rated as unclear, low or high risk in each domain. Displayed below in **Figure 2** is a *Risk of Bias Graph* which presents judgements about each risk of bias domain expressed as percentages across all the included studies**. Figure 3** displays the *Risk of Bias Summary* which presents judgements on each risk of bias item for each of the included studies. A brief commentary on the *'Risk of Bias'* for each study follows.

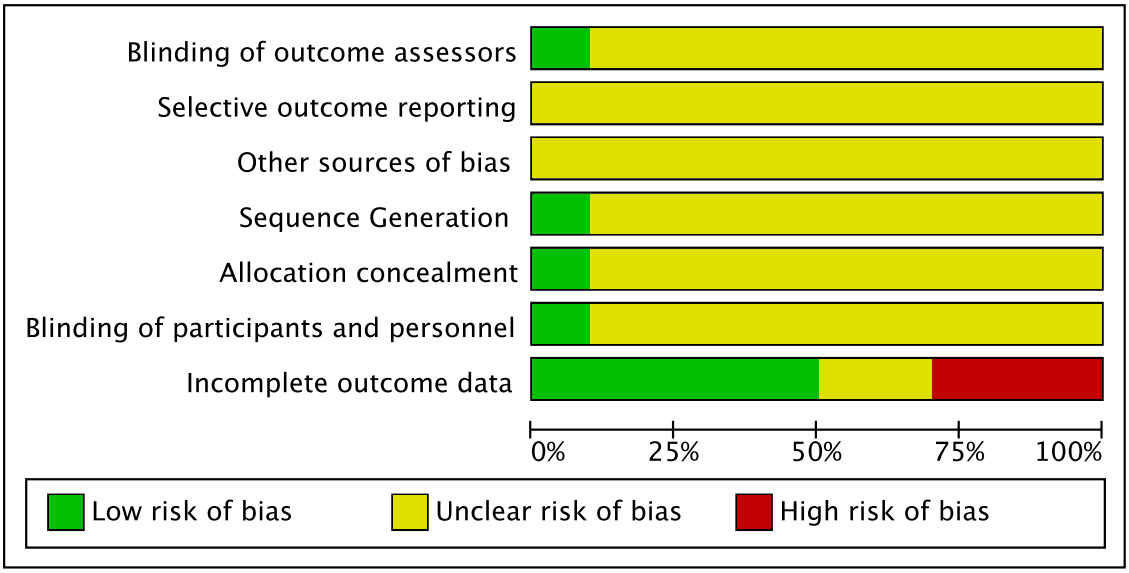

Figure 2: *Risk of Bias Graph*, displays judgements about each risk of bias domain expressed as percentages across all the included studies.

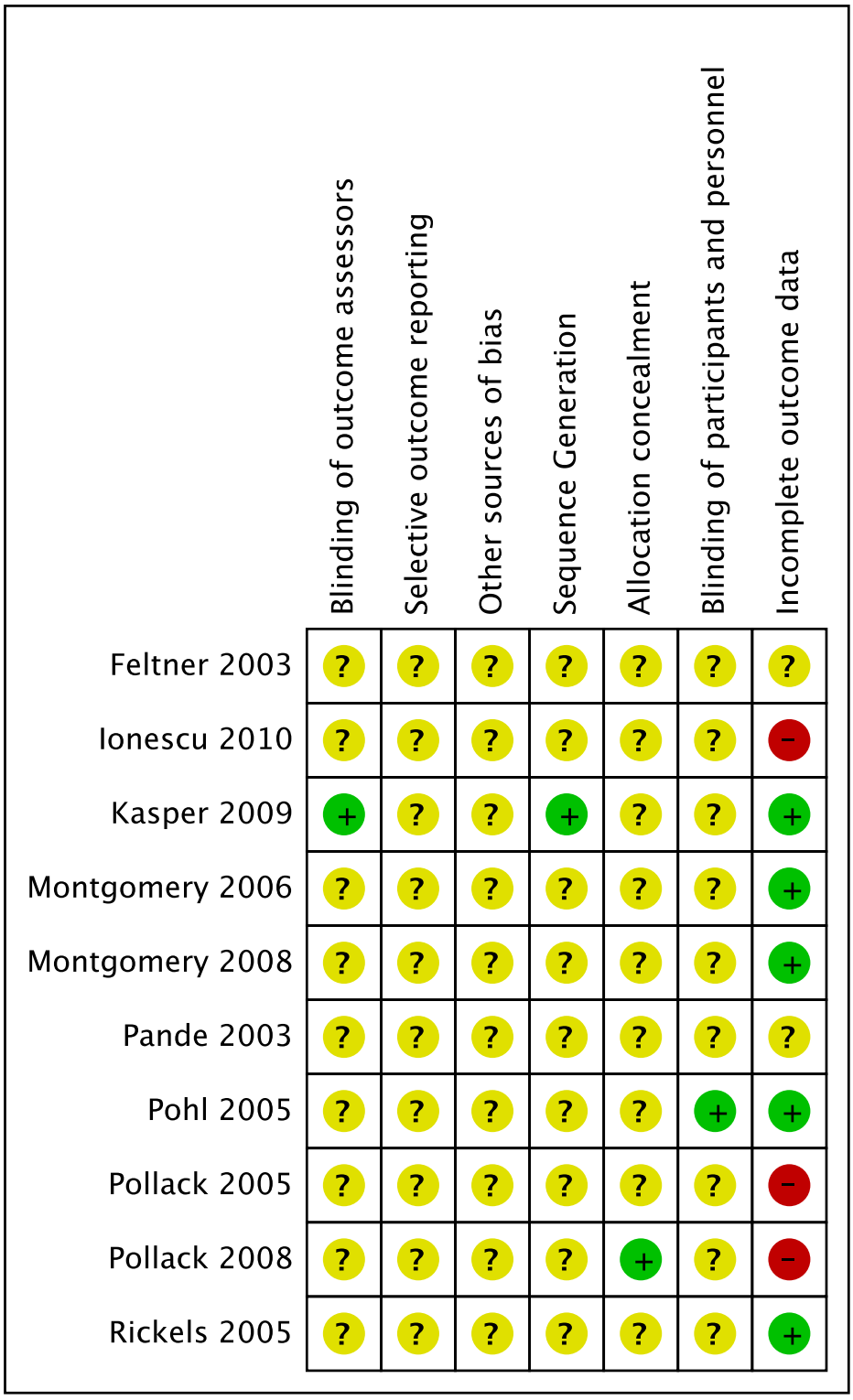

Figure 3: *Risk of Bias Summary*, displays judgements on each risk of bias item for each of the included studies. Key: Yellow circle containing '?' = unclear risk of bias; Green circle containing '+' = low risk of bias; Red circle containing '-'= high risk of bias;

Allocation

Random sequence generation (Selection Bias)

Feltner 2003, **Pande 2003**, **Pohl 2005**, **Pollack 2005**, **Rickels 2005**, **Montgomery 2006**, **Montgomery 2008**, **Pollack 2008(a, b and c)** and **Ionescu 2010** did not make it clear in their texts' how a randomised sequence was generated in the trials. Therefore, the risk of selection bias in all the the above trials was judged to be unclear. Only **Kasper 2009** made it clear how sequence generation was performed in the trial stating that a computer-generated sequence was utilised for the randomisation process. Therefore, **Kasper 2009** was the only trial to receive a rating of low in regards to the risk of selection bias from sequence generation.

Allocation Concealment (Selection Bias)

Feltner 2003, **Pande 2003**, **Pohl 2005**, **Pollack 2005**, **Rickels 2005**, **Montgomery 2006**, **Montgomery 2008**, **Kasper 2009** and **Ionescu 2010** made no comment in their texts, on any procedures used to conceal allocation. Therefore, all the above trials received a rating of unclear regarding the risk of selection bias from allocation concealment. Only **Pollack 2008(a, b and c)** made it clear how allocation concealment was performed in all three trials, stating that the sponsors generated the randomization sequence for the allocation and then distributed a code to the study personnel. Therefore, **Pollack 2008(a, b and c)** were the only trials to receive a rating of low for the risk of selection bias from allocation concealment.

Blinding

Blinding of outcome assessment (Detection Bias)

Feltner 2003, **Pande 2003**, **Pohl 2005**, **Pollack 2005**, **Rickels 2005**, **Montgomery 2006**, **Montgomery 2008**, **Pollack 2008(a, b and c)** all describe their study design as "double-blinded". However, none of these trials describe in necessary detail what procedures, if any, were used to ensure the blinding of the outcome assessors. This makes the risk of detection bias in these trials unclear. Regarding blinding of outcome assessors in **Kasper 2009**, it is specifically stated that *"investigators"* assessed the outcomes during *"double-blind treatment"*. Given the more definite assurance and the way it is unambiguously stated in the manuscript, the risk of detection bias in **Kasper 2009** was judged to probably be low.

With regards to the blinding of outcome assessors, **Ionescu 2010** does not actually state, in the text, if the trial was single or double-blinded. The protocol of **Ionescu 2010** was not accessible and the authors were not contactable. For the purpose of this review, it was assumed, because **Ionescu 2010** has a placebo arm, that by implication the participants were blinded somehow, and hence, the study is at least single-blinded. However, it is not clear from the text, who the outcome assessors were and if they were blinded. The risk of detection bias would only be valid to comment on if **Ionescu 2010** was a double-blinded study. Nevertheless, if it is assumed the outcome assessors were indeed blinded, from the text available, the risk of detection bias in **Ionescu 2010** would be judged as unclear.

Blinding of participants and personnel (Performance Bias)

Feltner 2003, **Pande 2003**, **Pollack 2005**, **Rickels 2005**, **Montgomery 2006**, **Montgomery 2008**, **Pollack 2008 (a, b and c)**, **Kasper 2009** and **Ionescu 2010** were all judged to have an unclear risk of performance bias. None of these trials described in sufficient detail, or were clear and definitive enough in describing, how participants and personnel were blinded. Only **Pohl 2005** described, in sufficient detail, methods used to ensure the blinding of participants and personnel. It specified that all medication was blister packed and provided in a TID regimen. Therefore, **Pohl 2005** received a rating of low for the risk of performance bias.

Incomplete Outcome Data (Attrition Bias)

Table 3 briefly overviews the factors involved in the assessment of *Incomplete Outcome Data* which allows the risk of attrition bias in the included studies to be judged. One feature to note is that a comparison of the characteristics of drop-outs compared to study completers is important for studies to perform. Such a comparison allows the extent to which attrition bias could affect study outcomes to be assessed. Only one of the included studies, **Montgomery 2006**, mentioned this in their text.

Table 3 Assessment of Incomplete Outcome Data (Attrition Bias)

Study ID	Average Attrition Rate	Attrition Rate in Intervention and Placebo Group Compare Favourably	Completeness of Outcome Data	Comparison of Drop-outs to Study Completers	Risk of Attrition Bias Judgement
Feltner 2003	27.7%	Yes	Fair	No	Unclear
Pande 2003	22.1%	Yes	Fair	No	Unclear
Pohl 2005	27.8%	Yes	Good	No	Low
Pollack 2005	27.5%	Yes	Poor	No	High
Rickels 2005	21.5%	Yes	Good	No	Low
Montgomery 2006	21.7%	No –But attrition rates are fairly low overall	Good	Yes –found no “notable differences” between groups	Low
Montgomery 2008	26.5%	Yes	Good	No	Low
Pollack 2008(a, b and c)	34.3%	No	Fair	No	High
Kasper 2009	27.3%	Yes	Good	No	Low
Ionescu 2010	Unclear	No	Very Poor	No	High

Selective Reporting (Reporting Bias)

With regards to selective outcome reporting, we did not have access to the protocol of any of the included studies. Therefore, we could not comment with certainty on potential selective reporting in the published manuscripts. Hence, the risk of reporting bias in all the included studies was judged to be unclear.

Other Potential Sources of Bias

No other potential sources of bias were thought to be present in the publications of all the included studies. However, without more information or data to confirm this, it is not certain that other sources of bias do not actually exist in each trial. Therefore, the risk of other potential sources of bias in all the included studies was judged to be unclear.

Effects of Interventions

For the primary and secondary outcome comparisons, in all cases, the component trials (a, b and c) of Pollack 2008 were assessed as three separate trials

Primary Outcomes: Continuous Outcome

The following information applies to all the continuous primary outcome comparisons: a random effects meta analysis was generated using the mean difference (MD) as an effect measure expressed as an effect estimate with a 95% confidence interval (CI); the mean change in HAM-A total score at study end-point was used to reflect the reduction in symptom severity in GAD; the MD of the mean change in HAM-A scores between intervention and placebo groups was utilised as the effect measure and a negative MD favoured the intervention group relative to the placebo group.

The Anticonvulsant Group (pregabalin and tiagabine combined) compared to Placebo in Treating GAD

A meta-analysis comparing the anticonvulsant group to placebo, was performed on twelve studies containing 3986 participants. **Figure 4** displays the related forest plot. The overall effect estimate was significant and in favour of the anticonvulsant group with an MD of -2.10 [-2.83, -1.36] (95% CI) compared to placebo. There was evidence of moderate heterogeneity in the overall results (Chi^2 p-value = 0.03 and I^2 = 48%).

Pregabalin compared to Placebo in Treating GAD

A meta-analysis comparing pregabalin to placebo was performed on eight studies containing 2007 participants. **Figure 7** displays the related forest plot. The overall effect estimate was significant and in favour of the pregabalin group with a MD of -2.86 [-3.52, -2.21] (95% CI) compared to placebo. There was no evidence of heterogeneity across the studies (Chi^2 p-value = 1.00 and I^2 = 0%).

Tiagabine compared to Placebo in Treating GAD

A meta-analysis comparing tiagabine to placebo was performed on four studies containing 1979 participants. **Figure 10** displays the related forest plot. The overall effect estimate was not statistically significant with a MD of -0.58[-1.41, 0.25] (95% CI) of tiagabine compared to placebo. There was no evidence of heterogeneity in the overall results (Chi^2 p-value = 0.54 and I^2 = 0%).

Primary Outcomes: Dichotomous Outcome

The following information applies to all the dichotomous primary outcome comparisons: a random effects meta-analysis was generated using risk ratio (RR) as an effect measure expressed as an effect estimate with a 95% confidence interval (CI); treatment response (responders versus non-responders) in the intervention and placebo groups was calculated using the CGI-I by defining a responder as those having a CGI-I score of 1 equalling "very much" improved or 2 equalling "much" improved; RR >1 of treatment response favoured the intervention group relative to the placebo group; NNTb was calculated expressed for each comparison as a positive whole number with a 95% CI; NNTh was if used to indicate that a negative number was generated during the NNT calculation and **Ionescu 2010** was not estimable as it provided no outcome data for treatment response.

The Anticonvulsant Group compared to Placebo in Treating GAD

A meta-analysis comparing the anticonvulsant group to placebo was performed on eleven studies containing 4000 participants. **Figure 5** displays the related forest plot. The overall effect estimate of treatment response was significant and in favour of the anticonvulsant group (RR 1.23 [1.12, 1.35] 95% CI) relative to placebo.

Heterogeneity was not suggested by the Chi^2 test which had a p-value of 0.17. The I^2 statistic was 29% reflecting a magnitude of heterogeneity which might not be important. NNTb was calculated to be 11 [16,8] 95% CI.

Pregabalin compared to Placebo in Treating GAD

A meta-analysis comparing pregabalin to placebo was performed on seven studies containing 2021 participants. **Figure 8** displays the relevant forest plot. The overall effect estimate of treatment response was significant and in favour of pregabalin (RR 1.35 [1.21, 1.50] 95% CI) relative to placebo. There was no indication of heterogeneity across trials (Chi^2 test ($p = 0.42$); $I^2 = 0\%$). NNTb was calculated to be 7 [10,5] 95% CI.

Tiagabine compared to Placebo in Treating GAD

A meta-analysis comparing tiagabine to placebo was performed on four studies containing 1979 participants. **Figure 11** displays the related forest plot. The overall effect estimate of treatment response of tiagabine compared to placebo was not statistically significant (RR 1.09 [0.98, 1.22] 95% CI). There was no indication of heterogeneity across the trials (Chi^2 test p-value = 0.75); I^2 = 0%). NNTb was calculated to be 25 [227(NNTh), 12(NNTb)] 95% CI.

Secondary Outcome: Dichotomous Outcome

The following information applies to all the dichotomous secondary outcome comparisons: a random effects meta-analysis was generated using risk ratio (RR) as an effect measure expressed as an effect estimate with a 95% confidence interval (CI); treatment acceptability was assessed using the total proportion of participants who withdrew from the trial due to treatment-related adverse events in the intervention and placebo groups respectively and a RR >1 of treatment acceptability favoured the placebo group relative to the intervention group.

Treatment Acceptability of the Anticonvulsant Group Compared to Placebo in GAD

A meta-analysis comparing the anticonvulsant group to placebo was performed on twelve studies containing 4110 participants. **Figure 6** displays the related forest plot. The overall effect estimate of treatment acceptability was significant and was not in favour of the anticonvulsant group compared to placebo (RR 1.49 [1.18, 1.88] 95% CI). Heterogeneity was not suggested by the Chi^2 test which had a p-value of 0.31. The I^2 statistic was 14% which is in keeping with a level of heterogeneity which might not be important.

Treatment Acceptability of Pregabalin Compared to Placebo in GAD

A meta-analysis comparing pregabalin to placebo was performed on eight studies containing 2054 participants. **Figure 9** displays the related forest plot. The overall effect estimate of treatment acceptability of pregabalin relative to placebo was not statistically significant (RR 1.23 [0.92, 1.65] 95% CI). There was no detectable evidence of heterogeneity across the studies (Chi^2 (p=0.68), I^2 =0).

Treatment Acceptability of Tiagabine Compared to Placebo in GAD

A meta-analysis comparing tiagabine to placebo was performed on 4 studies which included 2056 participants. **Figure 12** displays the related forest plot. The overall effect estimate of treatment acceptability was significant and not in favour of tiagabine relative to placebo (RR 1.95 [1.29, 2.93] 95% CI). There was no evidence of heterogeneity inferred from the Chi^2 statistic with the p-value = 0.2. However, I^2 = 36%, suggesting a level of heterogeneity that may be moderately important or might not be important.

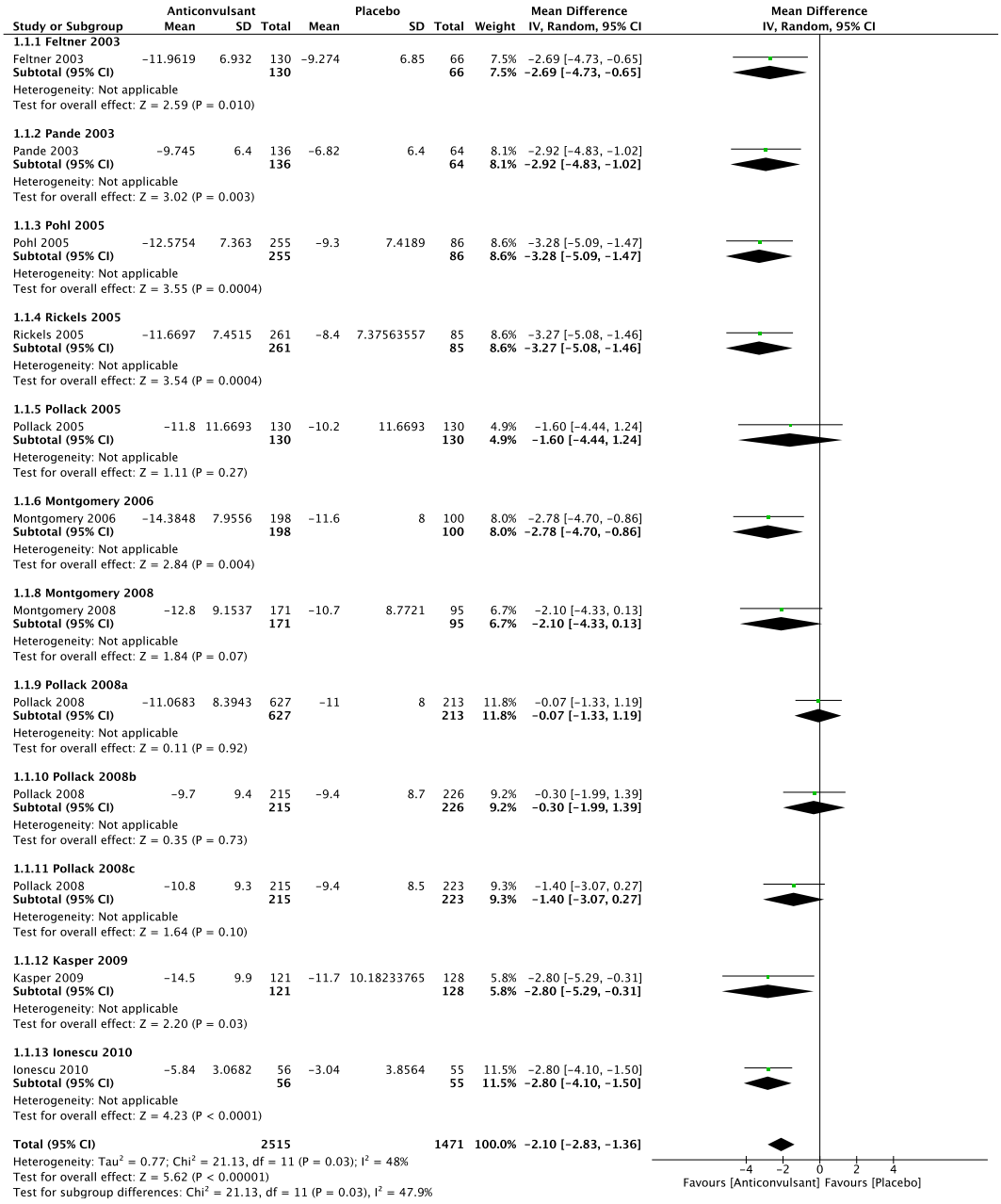

Figure 4: Forest plot of Comparison of the Anticonvulsant Group Compared to Placebo in Treating GAD. Outcome: Reduction in Symptom Severity as Measured by Mean Change in HAM-A Total Score in The Anticonvulsant Compared to Placebo Group.

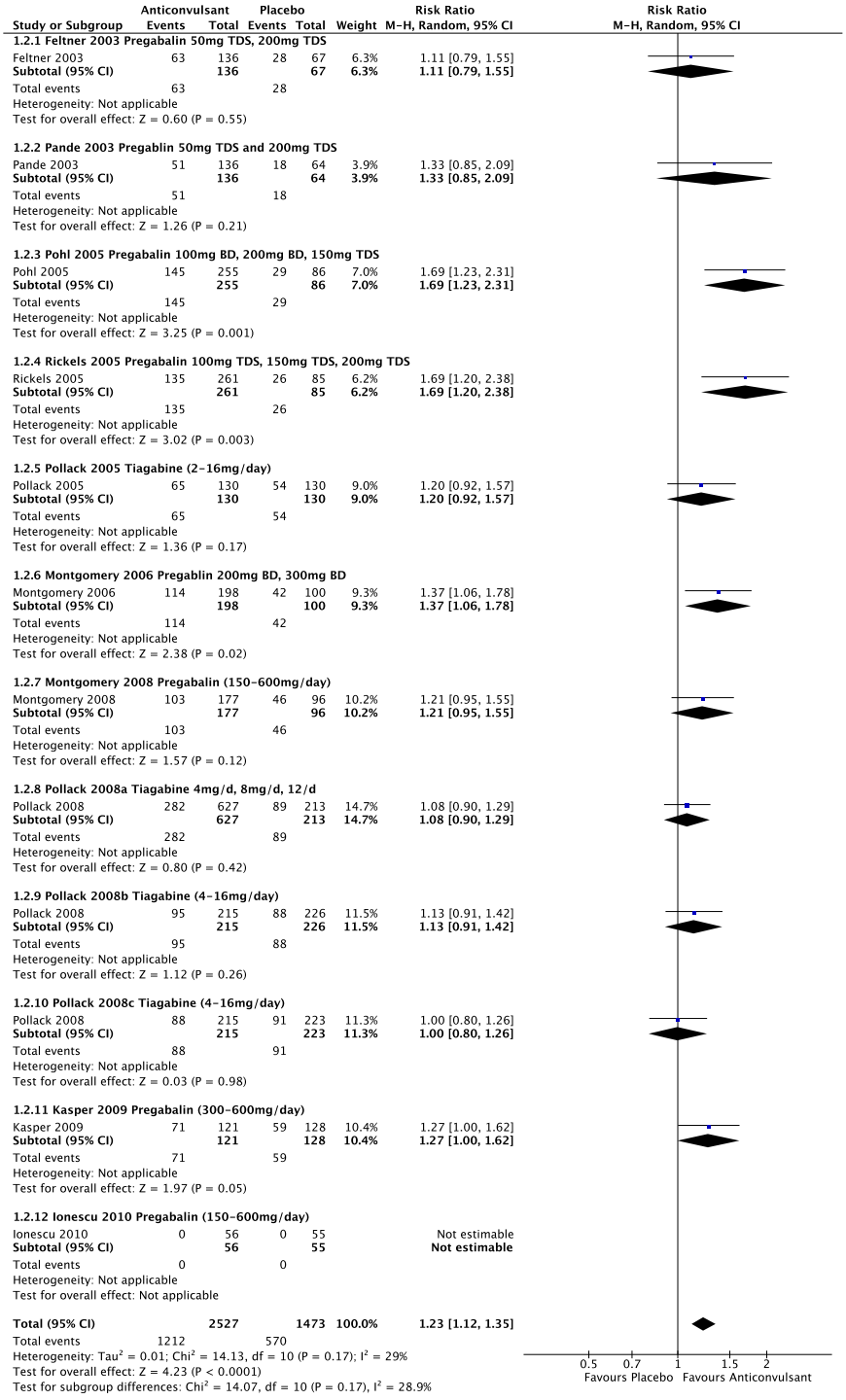

Figure 5: Forest plot of the Anticonvulsant Group Compared to Placebo in Treating GAD. Outcome: Risk Ratio of Treatment Response (Responders vs Non-Responders on CGI-I Score) of the Anticonvulsant Group Compared to Placebo.

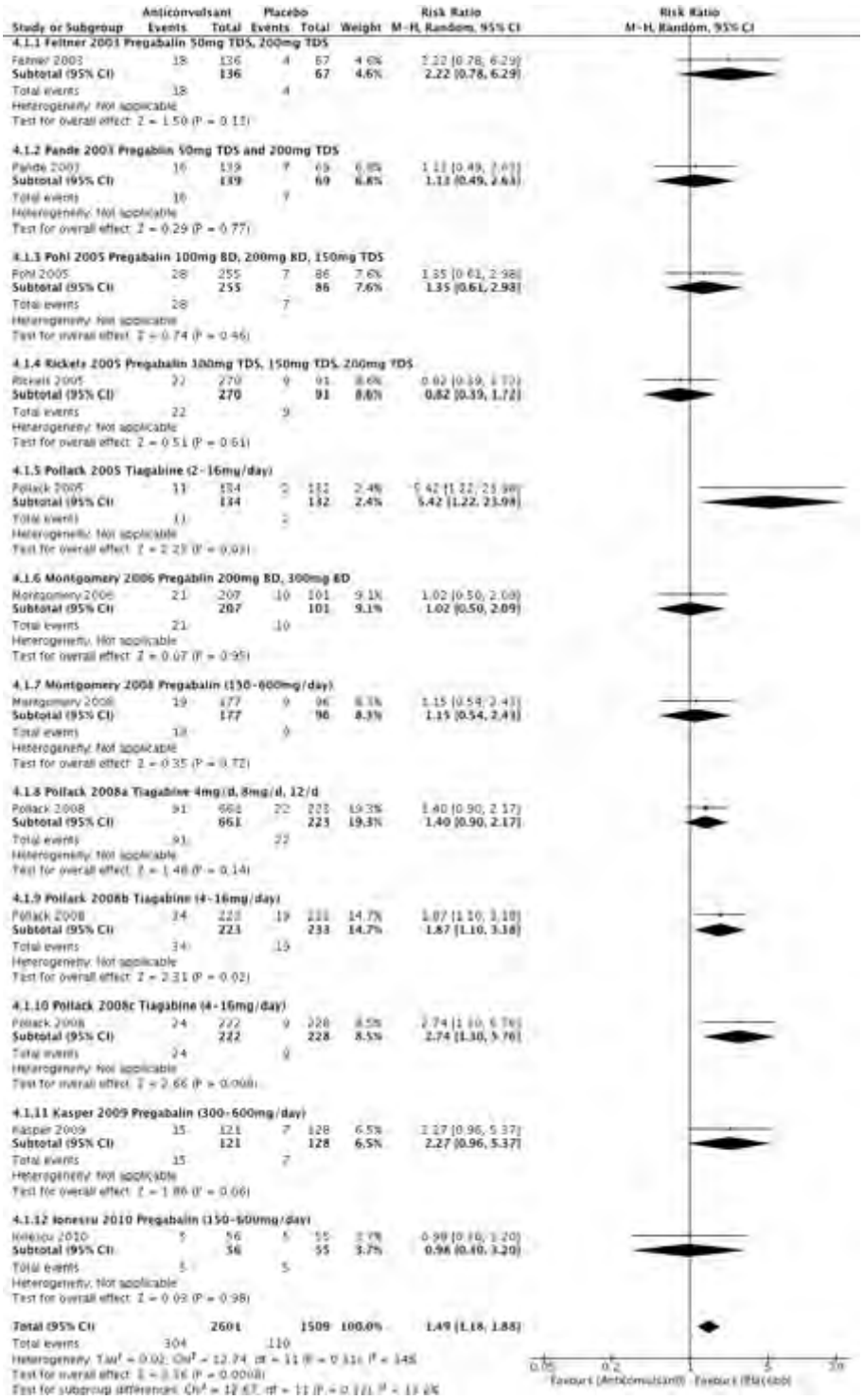

Figure 6: Forest plot of Treatment Acceptability of the Anticonvulsant Group Compared to Placebo in Treating GAD. Outcome: Risk Ratio of Drop-Outs Due to Treatment-Adverse Effects in Anticonvulsant Compared to Placebo Group.

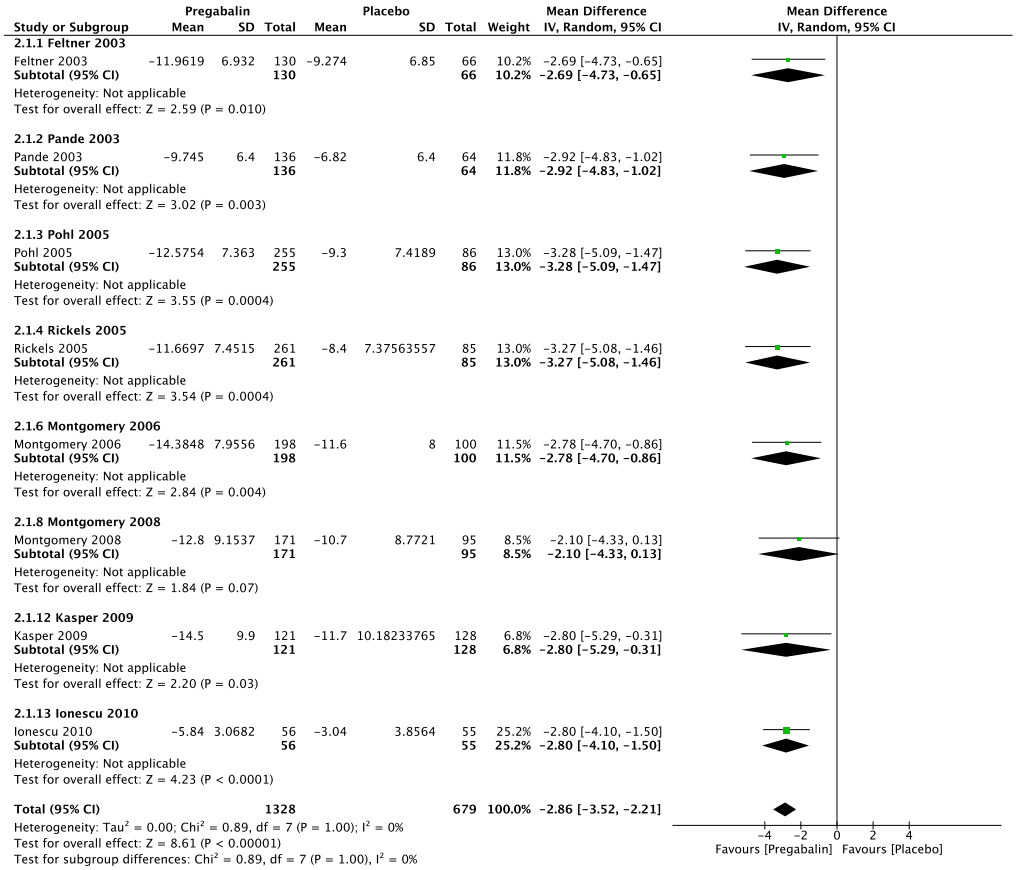

Figure 7: Forest plot of Comparison of Pregabalin Compared to Placebo in Treating GAD. Outcome: Reduction in Symptom Severity as Measured by Mean Change in HAM-A Total Score in The Pregabalin Compared to Placebo Group.

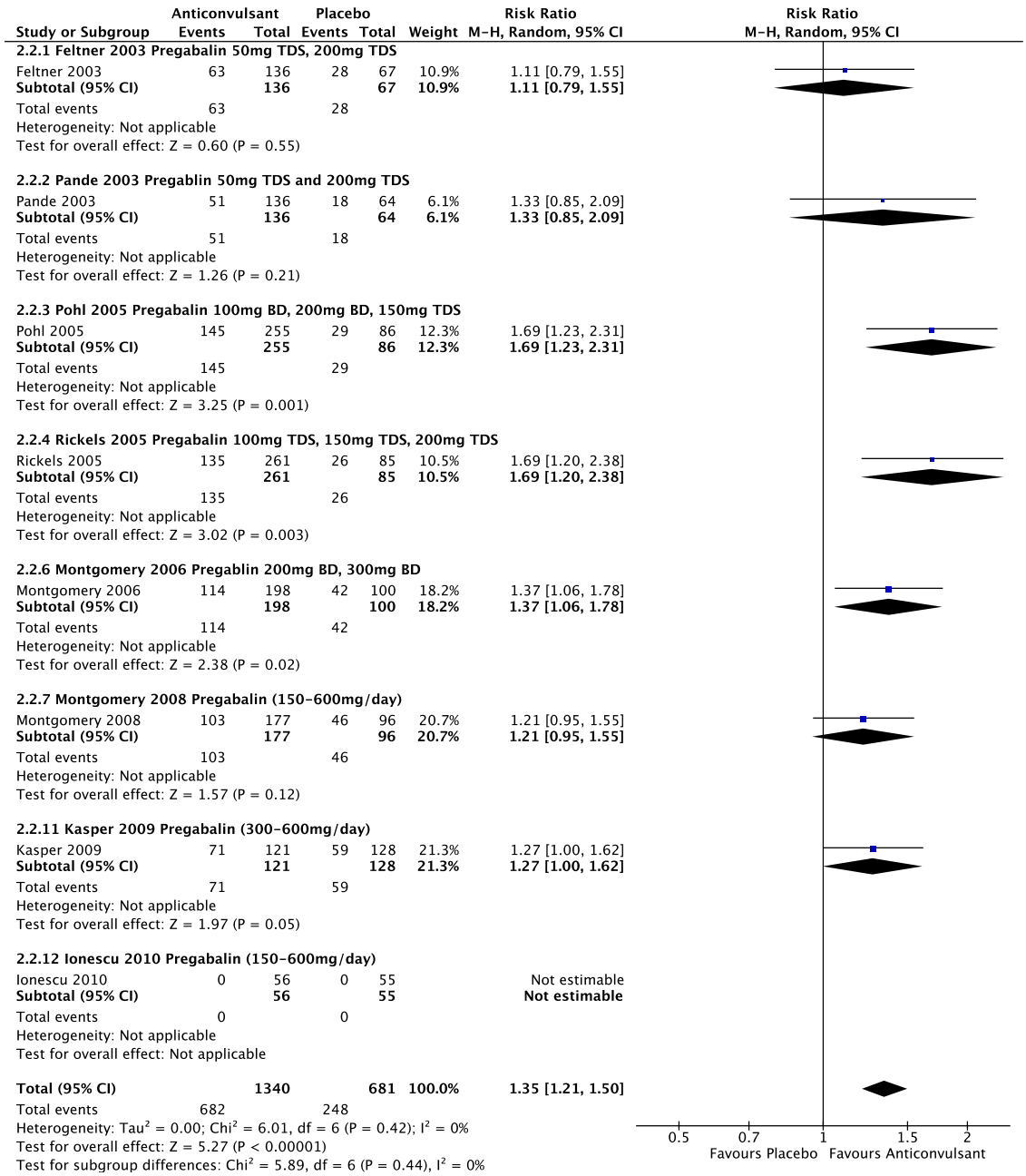

Figure 8: Forest plot of Pregabalin Compared to Placebo in Treating GAD. Outcome: Relative Risk (Risk Ratio) of Treatment Response (Responders vs Non-Responders on CGI-I Score) of Pregabalin Compared to Placebo.

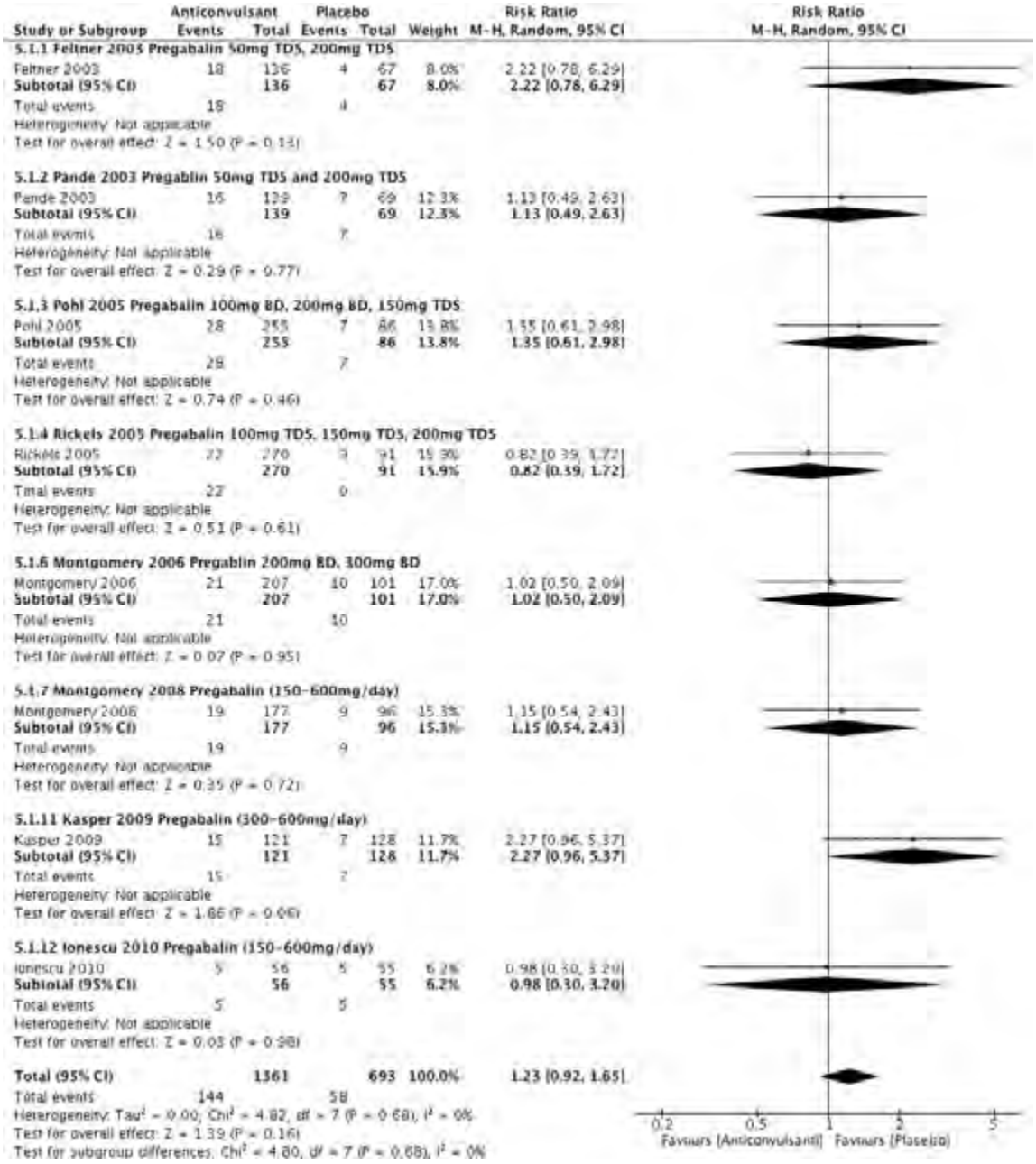

Figure 9: Forest plot of Treatment Acceptability of Pregabalin Compared to Placebo in Treating GAD. Outcome: Relative Risk (Risk Ratio) of Drop-Outs Due to Treatment-Adverse Effects in Pregabalin Compared to Placebo Group.

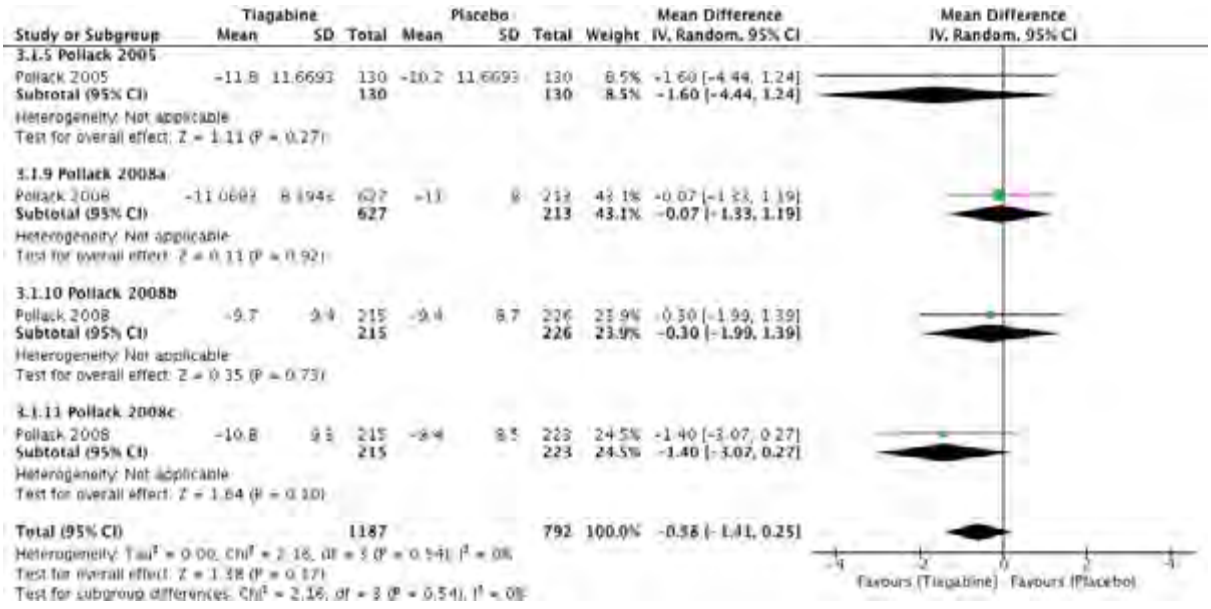

Figure 10: Forest plot of Comparison of Tiagabine Compared to Placebo in Treating GAD. Outcome: Reduction in Symptom Severity as Measured by Mean Change in HAM-A Total Score in The Tiagabine Compared to Placebo Group.

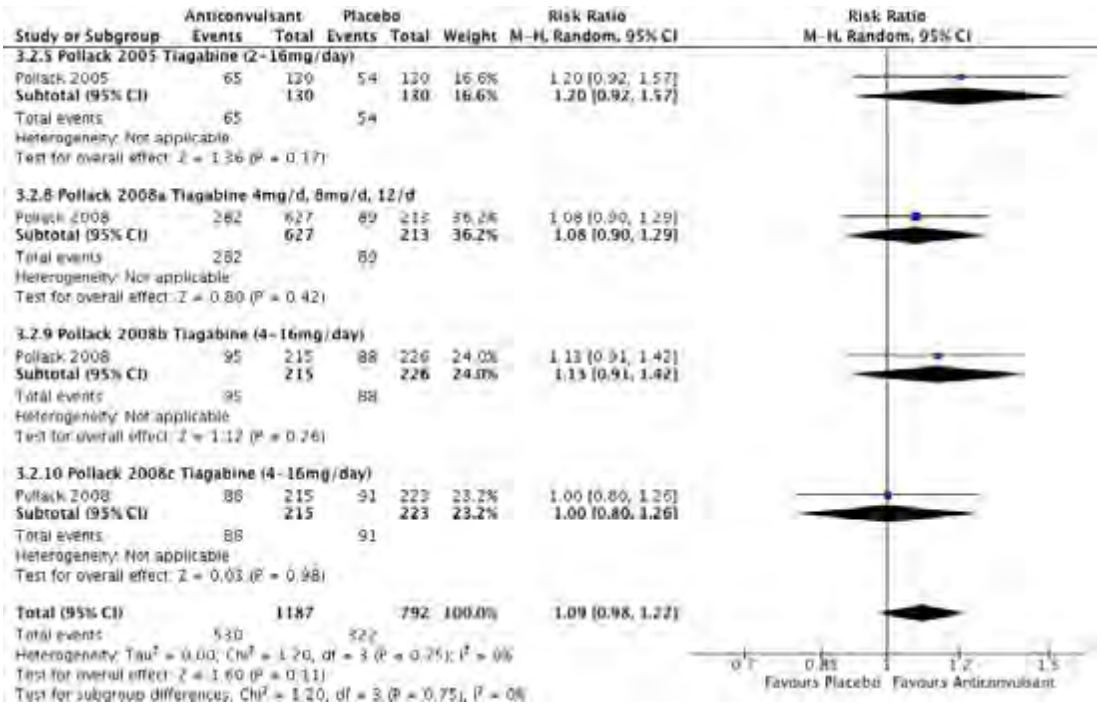

Figure 11: Forest plot of Tiagabine Compared to Placebo in Treating GAD. Outcome: Relative Risk (Risk Ratio) of Treatment Response (Responders vs Non-Responders on CGI-I Score) of Tiagabine Compared to Placebo.

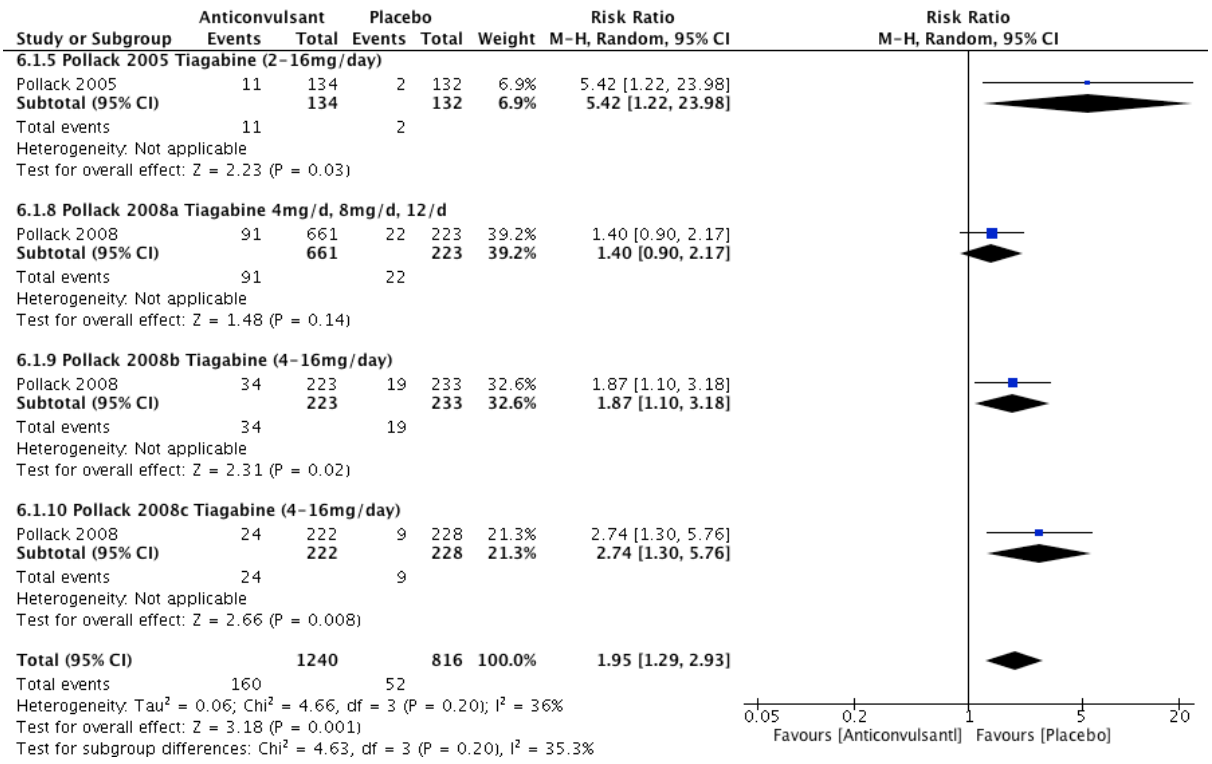

Figure 12: Forest plot of Treatment Acceptability of Tiagabine Compared to Placebo in Treating GAD. Outcome: Relative Risk (Risk Ratio) of Drop-Outs Due to Treatment-Adverse Effects in Tiagabine Compared to Placebo Group.

Assessment of Reporting Bias (Publication Bias)

It is recommended by the *Cochrane Collaboration* (Higgins & Green, 2011) that a funnel plot should only be used in meta-analysis with ten or more studies as fewer studies could lead to misleading results. This meta-analysis contained twelve studies and therefore a funnel plot was generated. The funnel plot displayed below in **Figure 13** is generated from the risk ratio of treatment response of anticonvulsants compared to placebo. It was visually assessed to detect any small-trial (small-sample) effects which may include publication bias.

It appears some asymmetry may be present when comparing the lower left corner to the lower right corner. However, it has been pointed out by Simmonds (2015) that visually assessing a funnel plot is a purely subjective process and can easily be misinterpreted

mainly when the number of studies is low. No inferences regarding possible publication bias will be made from the visual assessment of this funnel plot taking into account the relatively low number of trials and the above limitations associated with visual assessment. Formal statistical tests of asymmetry were not performed in this review.

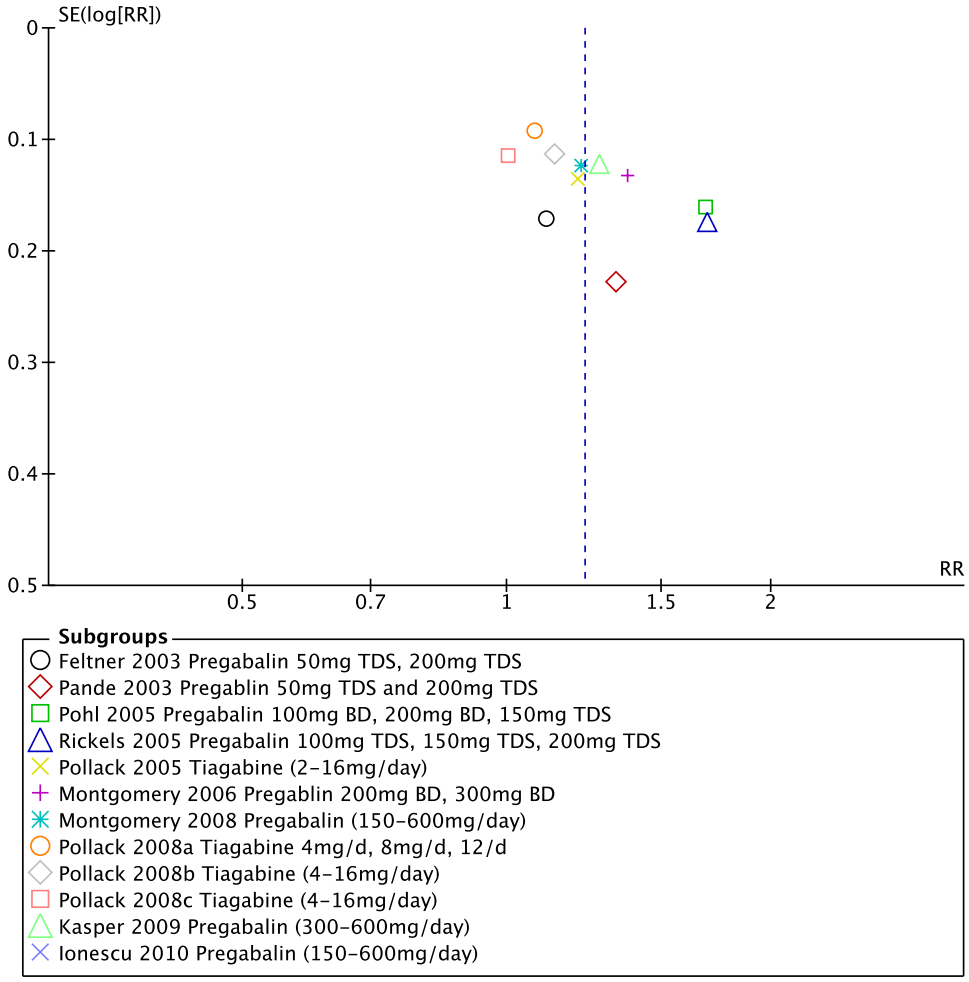

Figure 13: Funnel plot of Treatment Response of the Anticonvulsant Group Compared to Placebo in Treating GAD Visually Assessed to Detect Any Small-Trial Effects Including Publication Bias. Analysis Method: Risk Ratio Effect Measure, Random Effects Analysis Model.

Chapter 4

Discussion

Summary of Main Results

This systematic review and meta-analysis investigated the use of the newer anticonvulsants in generalised anxiety disorder and involved twelve short term randomised placebo controlled trials. Eight RCT's involved pregabalin and four involved tiagabine. The main result in the meta-analysis was that pregabalin demonstrated significant efficacy relative to placebo in reducing symptom severity and treatment response rates in GAD. In contrast, tiagabine failed to show significant efficacy in the primary outcomes and displayed significantly poor treatment acceptability. The two agents, when considered together, did display significant efficacy in both primary outcomes. However, the superior efficacy of pregabalin most likely compensated for the somewhat poorer efficacy of tiagabine.

The anticonvulsant group (comprising pregabalin and tiagabine) was found to be superior to placebo when using reduction of HAM-A scores as a continuous outcome with an overall MD of -2.10 [-2.83, -1.36] (95% CI) compared to placebo. The anticonvulsant group demonstrated significant superiority to placebo in treatment response utilising the CGI-I to create this dichotomous outcome. The overall risk ratio of treatment response was 1.23 [1.12, 1.35] (95% CI), with a RR > 1 favouring the anticonvulsant group. The NNTb for the anticonvulsant group versus placebo was calculated to be 11 [16,8] 95% CI. The treatment acceptability of the anticonvulsant group was found to be significantly inferior to placebo with an overall risk ratio of 1.49 ([1.18, 1.88] 95% CI), where in this case a RR >1 did not favour the anticonvulsants.

Pregabalin was found to have significant results showing it to be more efficacious than placebo in terms of reduction of symptom severity (MD -2.86 [-3.52, -2.21] (95% CI) and in terms of treatment response (RR 1.35 [1.21, 1.50] 95% CI). The NNTb for pregabalin was calculated to be 7 [10,5] 95% CI. In terms of treatment acceptability, pregabalin produced a non-significant result compared to placebo (RR 1.23 [0.92, 1.65] 95% CI). Therefore, the treatment acceptability of pregabalin could not be shown, with statistical significance, to be inferior to placebo.

Tiagabine did not demonstrate statistically significant efficacy compared to placebo in terms of reduction of symptom severity (MD of -0.58[-1.41, 0.25] 95% CI) and in treatment response (RR 1.09 [0.98, 1.22] 95% CI). NNTb for tiagabine was calculated to be 25 [227(NNTh), 12(NNTb)] (95% CI). Tiagabine had a statistically significant unfavourable result of treatment acceptability relative to placebo (RR 1.95 [1.29, 2.93] 95% CI).

Consistencies and Inconsistencies with Other Studies or Reviews

This study is consistent with the findings in the review by Mula (2011) which mentions only pregabalin and tiagabine as agents that have been investigated to a reasonable extent in GAD. The review also remarks on the good evidence base regarding the use of pregabalin in GAD, that the findings in tiagabine studies were generally unfavourable, and that there is little data on the other anticonvulsants in GAD. There was no meta-analysis or quantitative data presented by Mula (2011). The same conclusions were reached in an earlier review by Mula (2007).

Kinrys (2005) describe similar findings in their review concluding that there appears to be good early data from RCT's demonstrating efficacy of pregabalin and that there are poorer quality studies of tiagabine with inconsistent results. The review also mentions two case reports of gabapentin and one of levetiracetam that showed potential in treating GAD but no randomised controlled trials. Kinrys (2005) did not present any quantitative meta-analytic data.

The two reviews of anticonvulsant use in GAD by Van Ameringen (2008; Van Ameringen, Mancini, Pipe, et al., 2004a) are also consistent with the results of this dissertation. The findings note that pregabalin is already showing good evidence, tiagabine is showing mixed results but justifying further investigation and minimal evidence in the form of case reports for gabapentin and levetiracetam exists. There was no meta-analytic data in either review by Van Ameringen (2008; Van Ameringen, Mancini, Pipe, et al., 2004a). Huh (2011) published a review on alternatives to antidepressants in treating GAD and pregabalin was the only anticonvulsant that was recommended. This finding also supports the results of this dissertation.

Pregabalin, particularly, and its role in GAD has been quite comprehensively reviewed over the past few years. Most recently Baldwin (2015) published an extensive review of the existing literature regarding the efficacy and safety of pregabalin GAD. In his review, which is not a meta-analysis with any quantitative data, Baldwin (2015) examined the findings from 11 randomised double-blind trials and two open-label studies. The conclusions of Baldwin (2015) are largely consistent with the results of the systematic review conducted in this dissertation. Baldwin (2015) notes that pregabalin has consistently demonstrated to be an effective treatment in GAD, with a relatively benign side effect profile that is well-tolerated by patients and it has a unique mechanism of action in comparison to other medications used in GAD which makes it a valuable treatment option. In contrast to this dissertation, Baldwin (2015) does not note that the bulk of the high quality RCT data on pregabalin comes from studies funded by the manufacturer

Boschen (2011) performed a meta-analysis of pregabalin in the treatment of GAD in which seven published placebo controlled trials were considered. It is not straightforward to compare the results of Boschen (2011) to the results obtained in the meta-analysis of this dissertation due to differences in methodology. This dissertation used: a mean difference (MD) in HAM-A total score points as an effect estimate of symptom reduction; a random effects statistical model; a different mechanism of dealing with unit-of-analysis issues and provided dichotomous outcome data for calculating treatment response. In contrast, the meta-analysis by Boschen (2011): used Hedges' g to calculate an overall effect size; used a fixed effects statistical model; utilised only the highest dosage of pregabalin in each trial as a method to overcome unit-of-analysis errors and did not provide a dichotomous outcome of treatment response.

The effect size using Hedges' g is equivalent to the standardised mean difference (SMD) which is the term preferred by the *Cochrane Collaboration* (Higgins & Green, 2011). Boschen (2011) determined the overall effect size of pregabalin using Hedges' g to be 0.364 ([0.256 to 0.551] (95% CI) P <0.001, Z= 6.06). The basic rules of thumb for interpreting SMD's suggested by the *Cochrane Collaboration* includes: 0.2 = a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen, 1988); an alternative interpretation suggested is: < 0.40 = small, 0.40 to 0.70 = moderate, > 0.70 = large (Higgins & Green, 2011). Based on these rules of thumb, the SMD of 0.364 ([0.256 to 0.551] (95% CI)) reported by Boschen (2011) could be considered to represent a significant small to moderate effect of pregabalin in treating GAD. The MD in HAM-A points, obtained in this dissertation's meta-analysis for pregabalin was -2.86 [-3.52, -2.21] (95% CI) and was statistically significant. These results both indicate a significant effect of pregabalin in treating GAD. However, the methodological differences between the two meta-analyses are probably too large to allow any firm conclusions to be drawn from their direct comparison.

Limitations of This Study

Among the many limitations of this study, the following were thought to be important. Although this systematic review is considered up-to-date as of May 2016, the last official search performed by the CCDANCTR was in August 2013. An updated, independent search of PubMed was conducted on the 16th of May 2016. It could be considered a limitation that an updated official search could not be performed by the CCDANCTR. Their resources could have allowed for a potentially more powerful and thorough search process.

It could be considered a limitation that a multiple-treatment meta-analysis was not performed to deal with unit-of-analysis errors. The method used in this dissertation, although currently recommended by the *Cochrane Collaboration* (Higgins & Green, 2011), potentially could produce less accurate results than a multiple-treatment meta-analysis.

This review did not take into account the possibility of a dose-response relationship of an anticonvulsant due to the methodology employed. There appears to be conflicting evidence over whether pregabalin has a dose-response effect in GAD treatment (Boschen, 2012; Baldwin, Boer, Lyndon, *et al.*, 2015). Despite this, not accounting for dose-response relationships might still be considered a limiting factor.

The various definitions of intention-to-treat (ITT) employed in the different trials has lead to the notion, as described above, of a modified-intention-to-treat (MIIT) sample number provided by each trial. The inconsistency in what constitutes a MIIT sample has been noted already by other researchers, as it could lead to inaccurate or misleading results (Hoskins, Pearce, Bethell, *et al.*, 2015). This review used the MIIT provided by each relevant study, as on many occasions, each trial only had outcome data based on this MIIT. The results of the review should be interpreted with this in mind as potential limitation.

The scope of the conclusions of this dissertation could potentially be limited for the following reasons: only short-term RCT's were evaluated and data from relapse prevention trials were omitted; consideration was only given to trials where a single anticonvulsant was compared to placebo; data from comparisons with active comparators was omitted and trials using anticonvulsants as adjunctive treatment in GAD were not considered. Conclusions could be further limited as outcome data from the RCTs was frequently in the incorrect format, only partially presented or, in some instances, missing completely. In the majority of cases it was possible to impute missing, or incomplete data using the statistical software within RevMan (Cochrane Collaboration, 2011). However, imputing data is not ideal as there is a potential risk that errors can be made during imputation which could lead to inaccurate results. In the case of **Ionescu 2010** it was not possible to obtain any data to calculate treatment response and the trial had to be entirely omitted from the meta-analysis of treatment response. This will have certainly impacted the pooled effect estimate of treatment response in this meta-analysis. However, it is difficult to be certain as to size and manner of the effect this would have had on the overall estimate.

The RCT's included in this systematic review were all conducted in the United States and Europe. Also, almost all the trials had fairly strict exclusion criteria, especially regarding other psychiatric comorbidities and use of other psychotropic medications. Therefore, this can raise questions over the generalisabilty of these results. This would affect not only the generalisabilty to psychiatric practice overall, where comorbidity and polypharmacy in patients is the norm, but also in particular to low and middle income populations.

It must also be borne in mind that eleven of the twelve RCTs were funded by the company that manufactured the medication used as the intervention in the study. Although there were only a few occasions in the review process when it was necessary, attempts to obtain unpublished trial data from pharmaceutical companies were unsuccessful. Any missing unpublished data is a limiting factor and potentially could affect the results of a systematic review significantly.

Conclusion

In conclusion, pregabalin and tiagabine were the only agents, among the multiple newer anticonvulsants considered, that were found to be appropriate for inclusion in this systematic review and meta-analysis of GAD. The results demonstrated significant efficacy of pregabalin in symptom severity reduction and treatment response in GAD. Tiagabine, however, failed to show significant efficacy in the primary outcomes and displayed significantly unfavourable treatment acceptability.

Implications for Clinical Practice

Pregabalin proved to be significantly efficacious in treating GAD with a reasonably good level of treatment acceptability. The dosages used ranged from 150mg/day up to 600mg/day within the different pregabalin trials. However, due to methodological limitations, it is not possible based on this review, to make a recommendation on the optimal dosage of pregabalin to use to achieve a clinical response. Similarly, because only short term studies of pregabalin were considered, ranging from 4 weeks to 8 weeks, recommendations cannot be made on outcome variables beyond this duration including how long treatment should continue. Apart from pregabalin, there is no evidence from this systematic review to suggest that any of the other newer anticonvulsants considered, display efficacy in GAD over the time periods considered and the dosages used.

Implications for Future Research

This review suggests that further work is needed to clarify the place of the newer anticonvulsants in the treatment armamentarium of GAD. In particular, it would be useful for further work to establish consensus on the position pregabalin should occupy in recognised treatment guidelines for GAD. It would useful in further work to determine the optimal dosage and duration of treatment that should be recommended in the use of pregabalin in treating GAD.

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Appendices

Table 4. The Data Tables

1 Anticonvulsants Compared to Placebo in Treating GAD

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Reduction in Symptom Severity as Measured by Mean Change in HAM-A Total Score in The Anticonvulsant Compared to Placebo Group	10	3986	Mean Difference (IV, Random, 95% CI)	-2.10 [-2.83, -1.36]
1.1.1 Feltner 2003	1	196	Mean Difference (IV, Random, 95% CI)	-2.69 [-4.73, -0.65]
1.1.2 Pande 2003	1	200	Mean Difference (IV, Random, 95% CI)	-2.92 [-4.83, -1.02]
1.1.3 Pohl 2005	1	341	Mean Difference (IV, Random, 95% CI)	-3.28 [-5.09, -1.47]
1.1.4 Rickels 2005	1	346	Mean Difference (IV, Random, 95% CI)	-3.27 [-5.08, -1.46]
1.1.5 Pollack 2005	1	260	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.44, 1.24]

1.1.6 Montgomery 2006	1	298	Mean Difference (IV, Random, 95% CI)	-2.78 [-4.70, -0.86]
1.1.8 Montgomery 2008	1	266	Mean Difference (IV, Random, 95% CI)	-2.10 [-4.33, 0.13]
1.1.9 Pollack 2008a	1	840	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.33, 1.19]
1.1.10 Pollack 2008b	1	441	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.99, 1.39]
1.1.11 Pollack 2008c	1	438	Mean Difference (IV, Random, 95% CI)	-1.40 [-3.07, 0.27]
1.1.12 Kasper 2009	1	249	Mean Difference (IV, Random, 95% CI)	-2.80 [-5.29, -0.31]
1.1.13 Ionescu 2010	1	111	Mean Difference (IV, Random, 95% CI)	-2.80 [-4.10, -1.50]
1.2 Treatment Response (Responders vs Non-Responders on CGI-I Score) of Anticonvulsants compared to Placebo	10	4000	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.12, 1.35]
1.2.1 Feltner 2003	1	203	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.55]

Pregabalin 50mg TDS, 200mg TDS				
1.2.2 Pande 2003 Pregabalin 50mg TDS and 200mg TDS	1	200	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.85, 2.09]
1.2.3 Pohl 2005 Pregabalin 100mg BD, 200mg BD, 150mg TDS	1	341	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.23, 2.31]
1.2.4 Rickels 2005 Pregabalin 100mg TDS, 150mg TDS, 200mg TDS	1	346	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.20, 2.38]
1.2.5 Pollack 2005 Tiagabine (2-16mg/day)	1	260	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.92, 1.57]
1.2.6 Montgomery 2006 Pregabalin 200mg BD, 300mg BD	1	298	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.06, 1.78]
1.2.7 Montgomery 2008	1	273	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.95, 1.55]

Pregabalin (150-600mg/day)				
1.2.8 Pollack 2008a Tiagabine 4mg/d, 8mg/d, 12/d	1	840	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.90, 1.29]
1.2.9 Pollack 2008b Tiagabine (4-16mg/day)	1	441	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.42]
1.2.10 Pollack 2008c Tiagabine (4-16mg/day)	1	438	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.80, 1.26]
1.2.11 Kasper 2009 Pregabalin (300-600mg/day)	1	249	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.00, 1.62]
1.2.12 Ionescu 2010 Pregabalin (150-600mg/day)	1	111	Risk Ratio (M-H, Random, 95% CI)	Not estimable

2 Pregabalin Compared to Placebo in Treating GAD

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

2.1 Mean Change from Baseline in HAM-A Total Score	8	2007	Mean Difference (IV, Random, 95% CI)	-2.86 [-3.52, -2.21]
2.1.1 Feltner 2003	1	196	Mean Difference (IV, Random, 95% CI)	-2.69 [-4.73, -0.65]
2.1.2 Pande 2003	1	200	Mean Difference (IV, Random, 95% CI)	-2.92 [-4.83, -1.02]
2.1.3 Pohl 2005	1	341	Mean Difference (IV, Random, 95% CI)	-3.28 [-5.09, -1.47]
2.1.4 Rickels 2005	1	346	Mean Difference (IV, Random, 95% CI)	-3.27 [-5.08, -1.46]
2.1.6 Montgomery 2006	1	298	Mean Difference (IV, Random, 95% CI)	-2.78 [-4.70, -0.86]
2.1.8 Montgomery 2008	1	266	Mean Difference (IV, Random, 95% CI)	-2.10 [-4.33, 0.13]
2.1.12 Kasper 2009	1	249	Mean Difference (IV, Random, 95% CI)	-2.80 [-5.29, -0.31]
2.1.13 Ionescu 2010	1	111	Mean Difference (IV, Random, 95% CI)	-2.80 [-4.10, -1.50]
2.2 Treatment Response to Pregabalin	8	2021	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.21, 1.50]

compared to Placebo				
2.2.1 Feltner 2003 Pregabalin 50mg TDS, 200mg TDS	1	203	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.55]
2.2.2 Pande 2003 Pregabalin 50mg TDS and 200mg TDS	1	200	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.85, 2.09]
2.2.3 Pohl 2005 Pregabalin 100mg BD, 200mg BD, 150mg TDS	1	341	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.23, 2.31]
2.2.4 Rickels 2005 Pregabalin 100mg TDS, 150mg TDS, 200mg TDS	1	346	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.20, 2.38]
2.2.6 Montgomery 2006 Pregabalin 200mg BD, 300mg BD	1	298	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.06, 1.78]
2.2.7 Montgomery 2008	1	273	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.95, 1.55]

Pregabalin (150-600mg/day)				
2.2.11 Kasper 2009 Pregabalin (300-600mg/day)	1	249	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.00, 1.62]
2.2.12 Ionescu 2010 Pregabalin (150-600mg/day)	1	111	Risk Ratio (M-H, Random, 95% CI)	Not estimable

3 Tiagabine Compared to Placebo in Treating GAD

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Mean Change from Baseline in HAM-A Total Score	2	1979	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.41, 0.25]
3.1.5 Pollack 2005	1	260	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.44, 1.24]
3.1.9 Pollack 2008a	1	840	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.33, 1.19]
3.1.10 Pollack 2008b	1	441	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.99, 1.39]

3.1.11 Pollack 2008c	1	438	Mean Difference (IV, Random, 95% CI)	-1.40 [-3.07, 0.27]
3.2 Treatment Response to Tiagabine compared to Placebo	2	1979	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.98, 1.22]
3.2.5 Pollack 2005 Tiagabine (2-16mg/day)	1	260	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.92, 1.57]
3.2.8 Pollack 2008a Tiagabine 4mg/d, 8mg/d, 12/d	1	840	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.90, 1.29]
3.2.9 Pollack 2008b Tiagabine (4-16mg/day)	1	441	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.42]
3.2.10 Pollack 2008c Tiagabine (4-16mg/day)	1	438	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.80, 1.26]

4 Treatment Acceptability of Anticonvulsants Compared to Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

4.1 Relative Risk of Adverse Event in Anticonvulsant compared to Placebo Group	10	4110	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.18, 1.88]
4.1.1 Feltner 2003 Pregabalin 50mg TDS, 200mg TDS	1	203	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.78, 6.29]
4.1.2 Pande 2003 Pregabalin 50mg TDS and 200mg TDS	1	208	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.49, 2.63]
4.1.3 Pohl 2005 Pregabalin 100mg BD, 200mg BD, 150mg TDS	1	341	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.61, 2.98]
4.1.4 Rickels 2005 Pregabalin 100mg TDS, 150mg TDS, 200mg TDS	1	361	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.39, 1.72]
4.1.5 Pollack 2005 Tiagabine (2-16mg/day)	1	266	Risk Ratio (M-H, Random, 95% CI)	5.42 [1.22, 23.98]
4.1.6 Montgomery 2006 Pregabalin 200mg BD, 300mg BD	1	308	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.50, 2.09]

4.1.7 Montgomery 2008 Pregabalin (150-600mg/day)	1	273	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.54, 2.43]
4.1.8 Pollack 2008a Tiagabine 4mg/d, 8mg/d, 12/d	1	884	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.90, 2.17]
4.1.9 Pollack 2008b Tiagabine (4-16mg/day)	1	456	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.10, 3.18]
4.1.10 Pollack 2008c Tiagabine (4-16mg/day)	1	450	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.30, 5.76]
4.1.11 Kasper 2009 Pregabalin (300-600mg/day)	1	249	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.96, 5.37]
4.1.12 Ionescu 2010 Pregabalin (150-600mg/day)	1	111	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.20]

5 Treatment Acceptability of Pregabalin Compared to Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Relative Risk of Adverse Event in Pregabalin compared to Placebo Group	8	2054	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.92, 1.65]

5.1.1 Feltner 2003 Pregabalin 50mg TDS, 200mg TDS	1	203	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.78, 6.29]
5.1.2 Pande 2003 Pregabalin 50mg TDS and 200mg TDS	1	208	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.49, 2.63]
5.1.3 Pohl 2005 Pregabalin 100mg BD, 200mg BD, 150mg TDS	1	341	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.61, 2.98]
5.1.4 Rickels 2005 Pregabalin 100mg TDS, 150mg TDS, 200mg TDS	1	361	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.39, 1.72]
5.1.6 Montgomery 2006 Pregabalin 200mg BD, 300mg BD	1	308	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.50, 2.09]
5.1.7 Montgomery 2008 Pregabalin (150-600mg/day)	1	273	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.54, 2.43]
5.1.11 Kasper 2009 Pregabalin (300-600mg/day)	1	249	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.96, 5.37]

5.1.12 Ionescu 2010 Pregabalin (150-600mg/day)	1	111	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.20]

6 Treatment Acceptability of Tiagabine Compared to Placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Relative Risk of Adverse Event in Tiagabine compared to Placebo Group	2	2056	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.29, 2.93]
6.1.5 Pollack 2005 Tiagabine (2-16mg/day)	1	266	Risk Ratio (M-H, Random, 95% CI)	5.42 [1.22, 23.98]
6.1.8 Pollack 2008a Tiagabine 4mg/d, 8mg/d, 12/d	1	884	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.90, 2.17]
6.1.9 Pollack 2008b Tiagabine (4-16mg/day)	1	456	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.10, 3.18]
6.1.10 Pollack 2008c Tiagabine (4-16mg/day)	1	450	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.30, 5.76]