Pharmacologic treatments for generalised anxiety disorder: a systematic review and network meta-analysis

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Abstract

Background: Generalised anxiety disorder (GAD) is a disease associated with significant dysfunction. Pharmacologic treatment is often the first choice for clinicians due to the cost and resource constraints of psychological alternatives, but there is a paucity of comparative information for the multiple available drug choices.

Methods: A systematic review and network meta-analysis was performed based on randomised trials in GAD identified from MEDLINE, Web of Science, Cochrane Library, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), Wanfang, Drugs@FDA and commercial pharmaceutical registries. Placebo and active control trials were included. Primary outcomes were efficacy (mean difference [MD] in change in Hamilton Anxiety Scale Score) and acceptability (study discontinuations for any cause). We estimated summary mean treatment differences and odds ratios using network meta-analyses with random effects. This study is registered with PROSPERO, number CRD42018087106.

Findings: This analysis is based on 89 trials, which included 25,441 patients randomly assigned to 22 different active drugs or placebo. Duloxetine (MD: -3·13; 95% credible interval [CrI]: -4·13, -2·13) pregabalin (MD: -2·79; 95% CrI: -3·69, -1·91), venlafaxine (MD: -2·69; 95% CrI: -3·50, -1·89) and escitalopram (MD: -2·45; 95% CrI: -3·27, -1·63) were more efficacious than placebo with relatively good acceptability. Mirtazapine, sertraline, fluoxetine, buspirone and agomelatine were also found to be efficacious and well tolerated but these findings were limited by small samples. Quetiapine (MD: -3·60; 95% CrI: -4·83, -2·39) had the largest impact on HAM-A but it was poorly tolerated (OR: 1·44; 95% CrI: 1·16, 1·80) when compared to placebo. Likewise, paroxetine and benzodiazepine were effective but also poorly tolerated when compared to placebo.

Interpretation: To our knowledge this is the largest contemporary review of pharmacological agents for the treatment of GAD using network analysis. There are several effective treatment choices for GAD across classes of medication. The failure of initial pharmacologic therapy may not be a reason to abandon a pharmacologic treatment strategy.

Funding: No funding was received for this research.

Research in context

Evidence before this study

Meta-analyses on the treatments for generalised anxiety disorder which were available prior to this study did not include all currently available drug. This study includes data from randomised clinical trials in generalised anxiety disorder in adult outpatients published since 1994 in peer-reviewed journals and unpublished data obtained through trial registries and regulatory submissions. Most studies were of adequate quality.

Added value of this study

This analysis is the largest contemporary review of pharmacological agents for the treatment of GAD using network analysis, which allows cross-drug comparisons. This analysis is based on 89 trials, which included 25,441 patients randomly assigned to 22 different active drugs or placebo. In addition, 16 trials conducted in China allowed the inclusion of drugs which have not been studied in other clinical settings.

Implications of all the available evidence

Duloxetine, pregabalin, venlafaxine and escitalopram were more efficacious than placebo with relatively good acceptability. There are several effective treatment choices for GAD across classes of medication.

Introduction

Generalised anxiety disorder (GAD) is a DSM V medical condition associated with significant dysfunction impacting on one's daily physical, psychological and social functioning. GAD is a common condition, with a lifetime prevalence of about 5·7% [1]. The 12 month prevalence has been estimated to be about 1.7% in patients under 65 years, and 3.4% in patients older than 65 years [2]. Clinicians may fail to diagnose GAD since the key symptom of the disease - excessive persistent worry - may be poorly recognised as the problem and articulated by the patient. Patients with GAD may also frequently present with physical symptoms in lieu of worry, including headaches and gastrointestinal complaints [3]. These symptoms can lead to misdiagnosis and delay appropriate treatment. A population study in the United Kingdom found that while 3% of the general population qualified for a diagnosis of GAD based on screening, only 8% of those identified had been formally diagnosed with GAD and were undergoing treatment [4]. Other estimates suggest that, in a primary care setting, GAD is identified and diagnosed correctly in about 34% of patients [5]. In addition, the physical symptoms reported by patients with GAD may have a sound medical explanation as GAD is associated with increased prevalence of migraine headaches, gastrointestinal disease, allergic and respiratory conditions and other chronic illnesses [6]. Depression may be the most common psychological comorbidity. About 62% of patients with GAD also experienced at least one episode of major depressive disorder during their lifetime [7].

Treatments for GAD may include psychological interventions, pharmacological interventions or a combination of these modalities. Pharmacologic therapy is typically the first-line treatment as it is less resource-intensive, and the most comprehensive meta-analysis over all anxiety disorders demonstrated superior effect sizes for pharmacological compared to psychological options [8]. Despite the plethora of pharmacologic options, many patients with GAD do not recover, and in the absence of effective prevention or outright cure for GAD, the objective of management is normally to reduce symptoms and restore function. The highest estimates of the response rate for SSRIs and SNRIs typically ranges from about 60-75% [9]. Thus at the upper end of this range, one in four patients do not achieve anxiety response. A more general review of 50 trials of pharmacologic therapy for any anxiety disorder estimated the probability of a response to first line therapy is 67·7%, and a lower response for second line therapy at about 54·5% [10].

An analysis of 29,131 patients with GAD, which excluded patients with comorbid depression, from the UK clinical research practice datalink found that 46·0% discontinued SSRIs, TCAs or related drugs prescribed as treatments for GAD after a mean of 3·7 months [11]. Even though the reasons for discontinuation are unclear from these data, common problems with SSRIs or SNRIs include sexual dysfunction, weight gain and sleep disturbances [9]. The more recent treatment options for GAD target a reduction of these side effects [12]. These newer compounds include the serotonin modulator and stimulator (SMS) vortioxetine, the melatonergic antidepressant agomelatine, and the serotonergic antidepressant vilazodone.

There is little incentive for pharmaceutical companies to conduct active comparison trials for GAD, and the cost of clinical trials can be prohibitive for academic researchers, governments and other health care payers. Thus, it is difficult to ascertain how these pharmacologic therapies compare to each other in terms of efficacy – reduction of anxiety symptoms – and tolerability. For clinicians choosing among treatment options, it is useful to synthesise available evidence from existing trials in GAD to compare the relative effects of available treatment options. One approach to such a synthesis is a network meta-

analysis, which is a technique that combines direct evidence (comparison of treatments evaluated within the same trials) and indirect evidence (comparisons of treatments across trials with a common comparator) in order to compare multiple treatment options. This study aims to make various comparisons between a range of pharmacological therapies and placebo in the treatment of GAD in adult outpatients using available data from randomised trials in a network meta-analysis approach.

Methods

This study is registered with PROSPERO (registration number CRD42018087106). It is reported as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis [13]. AS, NF and IN developed the rationale and objectives. AS wrote and registered the study protocol. IN, AS and NF developed the inclusion criteria. AS conducted the literature search. AS, PB, YL and ZC reviewed the literature search results and extracted data and performed the assessment of bias. NF and AS developed the statistical analysis methods and AS performed the analysis.

Search strategy and selection criteria

We searched MEDLINE, Web of Science, Cochrane Library, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), Wanfang, Drugs@FDA and registries maintained by Pfizer, Allergan, Eli Lilly, GSK and Astrazeneca for studies published between 1994 (when the current diagnostic criteria for GAD were published in DSM-IV with no material changes in later versions) and August 1, 2017. The criteria for inclusion were: (1) generalised anxiety disorder diagnosed by DSM-IV, IV-TR, V, ICD-10 or CCMD-3, (2) randomised clinical trial, (3) comparison of at least 2 commercially available pharmacologic options or placebo (not including complementary/alternative treatments), (4) conducted in adult outpatients, (5) including at least 10 subjects in each arm, (6) excluding major comorbidities except for depression, (7) excluding relapse prevention or discontinuation designs, (8) excluding GAD refractory to specific drugs or requiring tolerability run-in phases, (9) reporting change from baseline on a scale intended to measure anxiety. Trials of refractory GAD, comorbid conditions and discontinuation designs were excluded to preserve the similarity assumption of the mixed treatment comparison. Journal publications, conference abstracts, sponsor publications such as trial summaries, and documents from regulatory reviews and submissions were considered for inclusion. All publications with an available abstract were considered regardless of language.

Data extraction and quality assessment

A data extraction form was developed to facilitate electronic comparison of entry. Two authors (AS, PB) independently performed extraction for studies published in languages other than Chinese. Two Chinese-speaking authors (YL, ZC) independently performed extraction for studies published in that language. Results were compared between reviewers; discrepancies were reconciled through discussion by the reviewers who extracted the data and, if these remained unresolved, the other authors were involved in arriving at a resolution. The extracted data included study characteristics (duration, blinding), patient characteristics (mean age, gender and race distribution, mean baseline anxiety measure, mean baseline depression measure, criteria used to diagnose GAD), interventions (drug arms and dosages), and outcomes (change in anxiety scale, proportion completing the trial). Risk of bias was assessed using The Cochrane Collaboration's risk of bias assessment tool [14]. The principal summary measures were the difference in change in anxiety scale and the odds ratio for trial discontinuation. Trial

discontinuation was selected as the measure of acceptability because, in contrast to discontinuation due to adverse events, we considered loss to follow-up and withdrawal due to lack of efficacy to be potentially relevant to clinical practice [15, 16].

Data synthesis and statistical analysis

For change in anxiety, the mean change was used as reported. The standard error for change was used when reported, or else derived from the standard deviation, confidence intervals, t and F-statistics or p-values. There were 22 trials (58 treatment arms) that contained baseline, endpoint and change standard deviations for HAM-A. We used these studies to estimate a common correlation coefficient between baseline and endpoint values (r=0.314). For the 14 trials which did not include a measure of the variance of the change, we derived an estimate using the baseline and endpoint standard deviation assuming a correlation of 0.314. When multiple doses of the same drug were used within a trial, a weighted average of the change and pooled estimate of the variance was used to summarise the data. For the binary outcome of trial discontinuation, the number of randomised and withdrawn patients was summed across drug arms. Benzodiazepine anxiolytics were combined into a single treatment arm, which is abbreviated as “benzodiazepines” throughout this text.

The primary analyses were conducted with a Bayesian Markov chain Monte Carlo method and fitted using WinBUGS software (Medical Research Council Biostatistics Unit, Cambridge, UK) [17]. Programming code as described in the NICE DSU Technical Support Document 2 [18] was used with modifications to the priors. Each model was performed by generating 100,000 sample iterations with an initial burn-in period of 100,000 iterations. The model framework, stratified by study, included univariate random effects to allow for apparent heterogeneity between studies in the treatment comparison effects. Diagnostics included examining autocorrelation plots for convergence and examination of Markov traces. We also assessed the results for coherence compared with pairwise meta-analysis results. WINBUGS code and study data are contained in **Appendices 8** and **10**, respectively.

Subgroup analyses were performed for trials above and below the median age, above and below the median proportion of women included, above and below the median baseline anxiety and above and below the median baseline depression scores (based on effect size), and all non-Chinese trials.

There was no external funding source for this study. The corresponding author had full access to all data in the study and takes final responsibility for the decision to submit for publication.

Results

We identified 1,992 records, in which 505 potentially eligible studies were reviewed in full text. Of these studies, 416 were excluded, mostly because they were not primary study reports of randomised trials (n=215), included diagnoses other than GAD based on the DSM VI/V, ICD-9/10 or CCMD-3 diagnostic criteria (n=33), contained < 2 pharmacologic treatment arms (n=17), included patients with comorbidities other than depression (n=11), were designed to study symptom relapse prevention (n=10) or were restricted to patients refractory to specific drugs (n=11). After applying the inclusion criteria, 89 studies were available for inclusion in this analysis (**Figure 1**).

The 89 studies were published between 1998 and 2016 (**Appendices 1-3**). None of the trials deliberately restricted to incident GAD, and most of the studies used the DSM criteria, which requires a 6 month duration of symptoms to complete the diagnosis. These studies ranged in duration of follow up from 4 to 26 weeks (median duration 8 weeks), and all studies included change in Hamilton Anxiety Scale (HAM-A, [19]) as a primary or secondary endpoint. The median baseline HAM-A score was 25. Seven of the studies focused on older patients, with a mean age > 65 years. Sixteen studies contained predominantly Chinese populations, while the remainder tended to include a majority of Caucasian patients (**Appendix 3**). The median percentage of women was 62%, and 75 of the trials required the DSM criteria for GAD. In total, 25,441patients were enrolled in these trials. The direct comparisons are displayed in the network diagram (**Figure 2**). Sixty-three of the trials were placebo-controlled, and 45 included more than one active drug.

Most of the trials were double-blind, and were conducted by pharmaceutical companies as part of a clinical development program (**Appendix 4**). Several of the trials were published prior to the Cochrane collaboration tool, and lacked details about the method of randomisation. Investigator-initiated trials, although more likely to include active controls, were less likely to state a low-risk randomisation strategy and clearly describe an intention-to-treat population. Chinese trials tended to be lower quality; most of these were either open-label or not explicit about blinding (**Appendix 2**).

Treatment efficacy for anxiety reduction and acceptability are shown in **Figures 3a and 3b**. For most treatments, efficacy was demonstrably greater than for placebo and acceptability was similar to placebo. Quetiapine had the largest impact on HAM-A (Mean Difference [MD]: -3·60; 95% credible interval [CrI]: -4·83, -2·39,) among the drugs with large cumulative sample sizes, but patients randomised to quetiapine were less likely to complete trials compared to those in placebo (OR: 1·44; 95% CrI: 1·16, 1·80). Duloxetine (MD: -3·13; 95% CrI: -4·13, -2·13) pregabalin (MD: -2·79; 95% CrI: -3·69, -1·91), venlafaxine (MD: -2·69; 95% CrI: -3·50, -1·89) and escitalopram (MD: -2·45; 95% CrI: -3·27, -1·63) also demonstrated efficacy compared to placebo in large cumulative samples of patients without increased discontinuation. Other drugs like ocinaplon showed encouraging point estimates but with low statistical certainty due to the relatively low number of patients included, resulting in wide credible intervals. Paroxetine and benzodiazepine are both well-studied in GAD, but patients randomised to these drugs were also more likely to discontinue trials compared to placebo. Of the newest agents, only agomelatine showed efficacy compared to placebo in the treatment of GAD, while vilazadone was poorly tolerated.

Among comparisons across active drugs (**Table 1**), performance differences in HAM-A were generally in the comparison of a very effective drug to an ineffective drug. Quetiapine (MD: -2·8, 95% CrI: = -4·7, -0·98), duloxetine (MD: -2·4; 95% CrI: -4·1, -0·64) and bupropion (MD: -4·5; 95% CrI: -8·1, -0·95) each showed better anxiety reduction than tiagabine by more than half a point (i.e. 95% CrI excludes 0·5), and quetiapine showed greater improvement compared to vortioxetine by more than half a point (MD: -2·5; 95% CrI: -4·3, -0·67). Effective drugs with the largest cumulative samples were more likely to show differences compared to active therapies. Similarly, differences in acceptability across active comparisons largely involved drugs with acceptability profiles worse than placebo. Pairwise comparisons were consistent with these findings (**Appendix 7**).

Subgroups

There were no material differences across subgroups. Of note, the exclusion of the Chinese trials had almost no impact on the results (**Appendices 5 & 6**). Maprotiline and mirtazapine were only studied in China, so estimates restricted to other trials are not available.

Discussion

This analysis is based on 89 trials, which included 25,441 patients randomly assigned to active drugs or placebo. To our knowledge this is the largest contemporary review of pharmacological agents for the treatment of GAD using network analysis. Duloxetine, pregabalin, venlafaxine and escitalopram were more efficacious than placebo with relatively good acceptability. Mirtazapine, sertraline, fluoxetine buspirone and agomelatine were also found to be efficacious and well tolerated but these findings were limited by small samples. Quetiapine had the largest impact on HAM-A but it was poorly tolerated when compared to placebo. Likewise, paroxetine and benzodiazepine were effective but also poorly tolerated when compared to placebo. Among the active comparisons quetiapine, duloxetine and bupropion each showed better anxiety reduction than tiagabine by more than half a point on HAM-A and quetiapine showed greater improvement compared to vortioxetine by more than half a point.

Over the years of the various pharmacological options, benzodiazepines were the first line of treatment in clinical practice for anxiety. Their effect on reducing symptoms in this network analysis is good. However, the potentially fatal interactions with alcohol and opioids and the potential for addiction together with poor acceptability as suggested in this network analysis limits their use in practice. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) are quite widely used as the first-line pharmacologic therapy for generalised anxiety, but until now the evidence base for their use remained incomplete [20]. This together with the NICE recommendation of using sertraline as the first choice treatment based on three trials of 375 patients randomised to sertraline make our network meta-analysis unique in terms of strengthening the evidence base for the management of anxiety disorders in clinical practice. The evidence emerging from this paper strongly supports the use of escitalopram, duloxetine and venlafaxine for the management of anxiety. Sertraline, fluoxetine and mirtazapine are also treatment options to consider but larger studies are needed to confirm these findings. Low-dose amitriptyline is still frequently used in the elderly [21] despite concerns about whether it is appropriate for this population [22]. There were no studies in this review on the use of amitriptyline.

Quetiapine showed the largest reduction in anxiety symptoms, but the trade-off was worse acceptability compared to other options. This finding is consistent with the work of Maneeton and colleagues [23], who found that higher doses of quetiapine showed higher rates of response in HAM-A, but also that discontinuation due to adverse events was greater with quetiapine compared to placebo. Pregabalin had a large impact on anxiety symptoms compared to placebo with no clinically important difference in acceptability, which is consistent with recent meta-analyses in GAD [24]. In fact, the acceptability of pregabalin surpassed many other active agents. Agomelatine (based on our small cumulative samples) was the only drug with established effectiveness among the new pharmacologic options to treat GAD, and showed improved acceptability compared to active drugs including benzodiazepine, quetiapine and paroxetine. In practice however, agomelatine may have limited use on account of concerns about liver toxicity [25].

The most comprehensive network meta-analysis for GAD prior to this analysis [26] included 27 randomised trials of 9 active drugs (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine,

pregabalin, sertraline, tiagabine, and venlafaxine) and examined HAM-A response rate (defined as a > 50% reduction from baseline score). While it is unclear that this previous analysis would be comparable to ours due to differences in trials and drugs compared, it is reassuring that there are similarities. Baldwin found that tigabine had the poorest response rate among all active drugs, which is consistent with our results. Lorazepam had the second-best response rate but the poorest acceptability as measured by trial withdrawal due to adverse events, and our efficacy and acceptability findings for benzodiazepines are consistent with this result. Pregabalin was ranked first for acceptability in keeping with our finding where it was better tolerated than several other active agents. The main difference was that we found convincing effectiveness for venlafaxine, which was previously identified among the poorest for HAM-A response.

This analysis synthesises available evidence and improves the ability to compare the efficacy and acceptability of active pharmacologic treatments for GAD. Newer agents for GAD have few studies against active agents, and are unlikely to be tested against older agents such as benzodiazepine, buspirone and hydroxyzine. By pooling direct and indirect evidence in our mixed treatment comparison, this study is able to provide the best available evidence to clinicians about where newer agents may fit into the existing hierarchy of options. The use of a consistent measurement for efficacy and acceptability (change in HAM-A and study discontinuation) are also strengths, as differences in outcomes can lead to erroneous conclusions.

There are also several important limitations to this study. First, the trials were conducted across a broad range of settings. While active comparison trials were more likely in non-industry settings, industry trials appear to have adopted modern reporting standards (e.g. CONSORT) sooner. However, it is essential to include all eligible studies in mixed treatment comparisons to reduce the potential for biased results. The addition of 16 trials conducted in China and published in Chinese provided direct evidence for several comparisons which were not otherwise available. A limitation of the mixed treatment method is the reliance on the assumption that the trials are similar (exchangeable). However, the subgroup analyses over clinical and demographic subgroups provided no contradiction to this assumption. Exclusion of the Chinese trials made little difference to the estimates, which suggests that the low quality of these trials may be due to poor reporting and not to poor execution. Publication bias is always a concern, and we went to considerable lengths to identify trials relevant to the review including through direct contact with FDA and the inclusion of non-English language trials. Our analysis includes several unpublished studies. Registries such as clinicaltrials.gov and access to regulatory submissions were used to try to identify all conducted studies, and these tools were crucial to the completeness of our network. This network contains a small number of open loops, which may reduce the accuracy of estimates for those treatments. Hopefully future active-controlled trials can alleviate this deficiency in the future. Finally, this study only compared pharmacologic treatments of generalized anxiety disorder, but did not include non-pharmacologic treatments such as cognitive behaviour therapy, which may also be appropriate for some patients.

This study substantially strengthens the clinical basis for the use of venlafaxine, pregabalin, escitalopram and duloxetine as first-line choices for GAD. Sertraline, fluoxetine and buspirone are also possible first line alternatives but the evidence for their use is limited by small samples studied to date. For patients who have failed first-line choices, agomelatine may be considered based on the limited data emerging from our review. Vortioxetine and vilazodone do not appear effective and do not support premium pricing in treatment of GAD. Mirtazapine has only been studied in China for treatment of GAD, and the

safety profile is unclear from the 10 short-term trials with low event-rates for drop-outs. A recent network meta-analysis for major depressive disorder showed that treatment discontinuation for mirtazapine is similar to placebo [15], which is encouraging. Buspirone and hydroxyzine are faster-acting than most of the other drugs in this analysis, and showed reasonable efficacy. These drugs may be suitable alternatives to benzodiazepines for patients with acute exacerbations, and may be generally under-utilised in clinical practice. The next iteration of the NICE guidelines for generalised anxiety could consider the evidence from our analysis to provide drug therapy recommendations.

There are important research implications emerging from this analysis. First and foremost, newer sources of clinical trial information such as clinicaltrials.gov and clinical trial reports maintained in pharmaceutical trial registries allow the inclusion of unpublished and earlier-phase trials, which would otherwise be commercial in confidence and thus inaccessible. The choice of what and where to publish may be influenced by corporate development strategy, especially prior to regulatory approval. The inclusion of previously unpublished studies allows a more complete analysis and comparison of these agents. Second, international research databases such as the Chinese National Knowledge Infrastructure (CNKI) and Wanfang increased the number of trials available. It is also interesting that the trials from China tend to include active comparators, which suggests that the motivation for these studies is different from that of the rest of the world. These active comparison trials may offer a better opportunity to compare direct and indirect evidence, particularly when they are conducted with true equipoise between alternative therapies.

In summary, our findings suggest that there are several viable options for the treatment of GAD. There are differences in the efficacy and acceptability profiles across these options, and the best choice may not be uniform across patients. We hope that this analysis contributes a helpful perspective to aid in these decisions.

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Figure 1: Study selection process.

*RCTs=randomised controlled trials. *Industry websites and trial registries.*

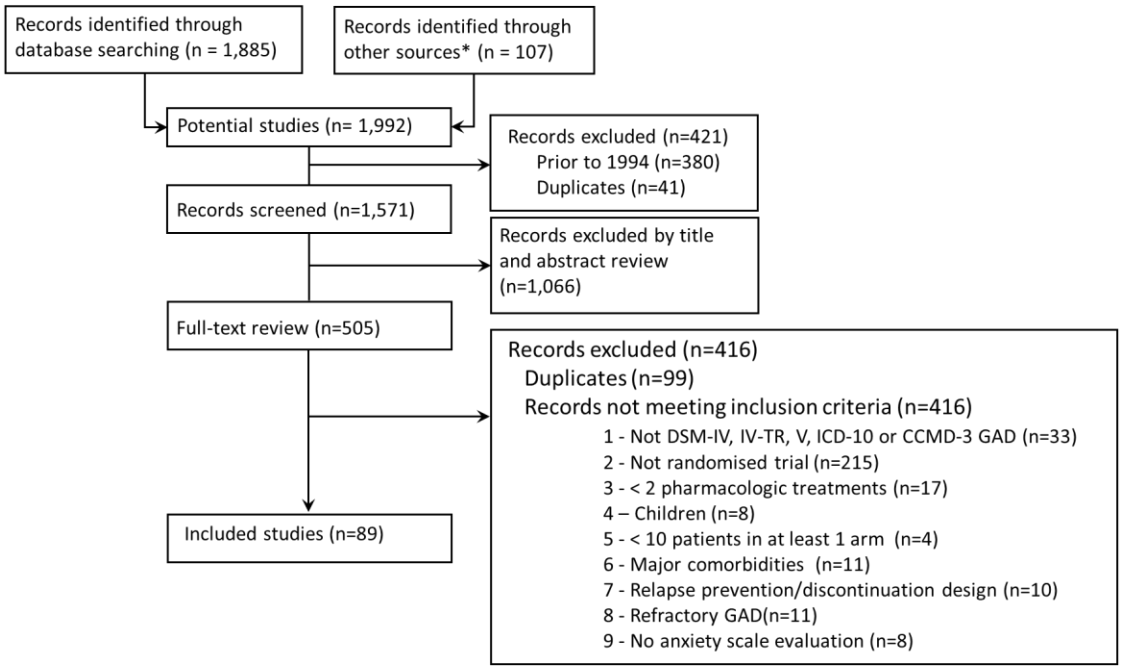

Figure 2: Network meta-analysis of available comparisons.

Line width is proportional to the number of trials including every pair of treatments (direct comparisons). Circle size is proportional to the total number of patients for each treatment in the network.

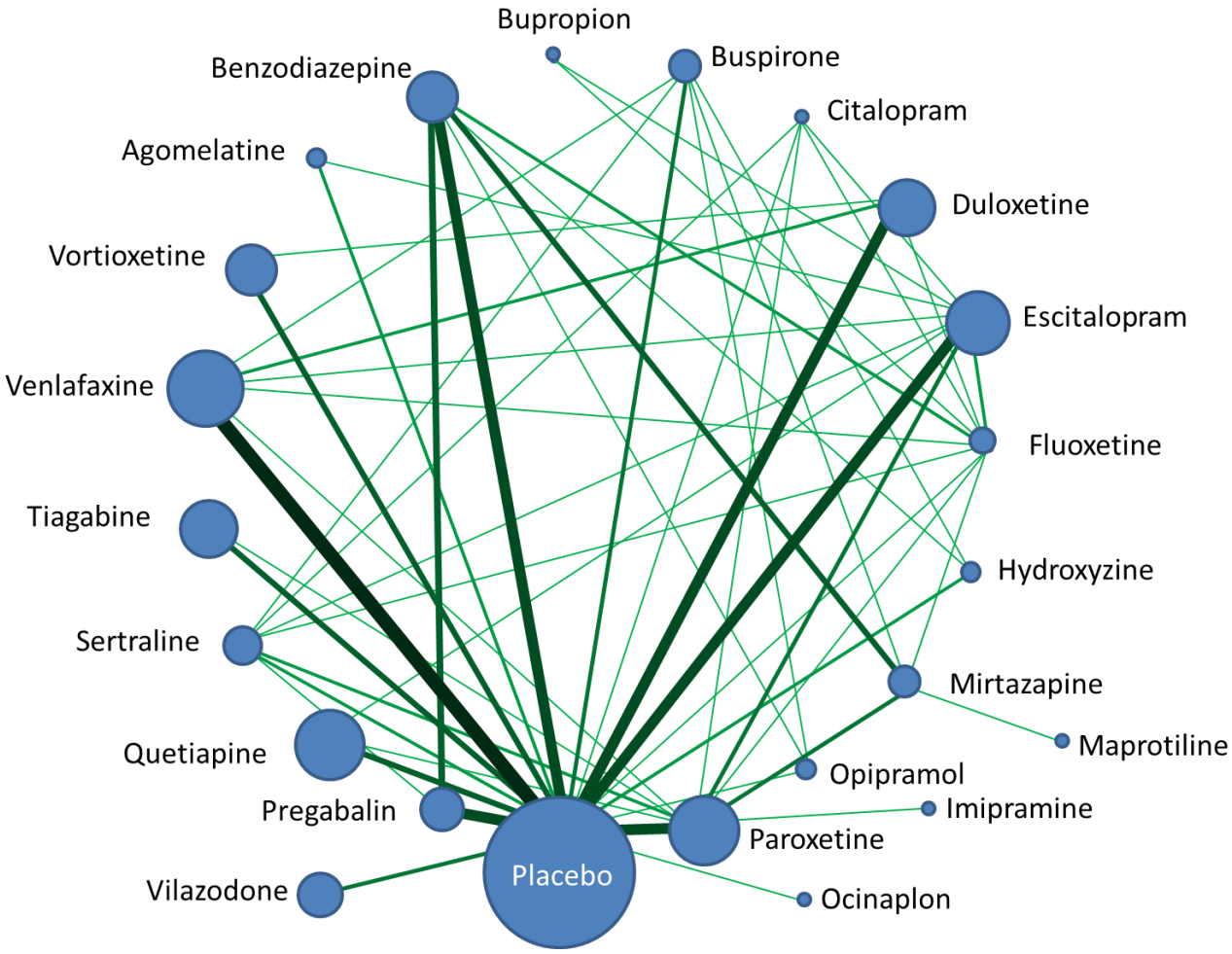

Figure 3A: Forest plot of network meta-analysis of all trials for efficacy (mean difference in change in HAM-A from baseline).

Drugs compared with placebo, which was the reference compound. CrI=credible interval, T=number of trials, P=total number of patients.

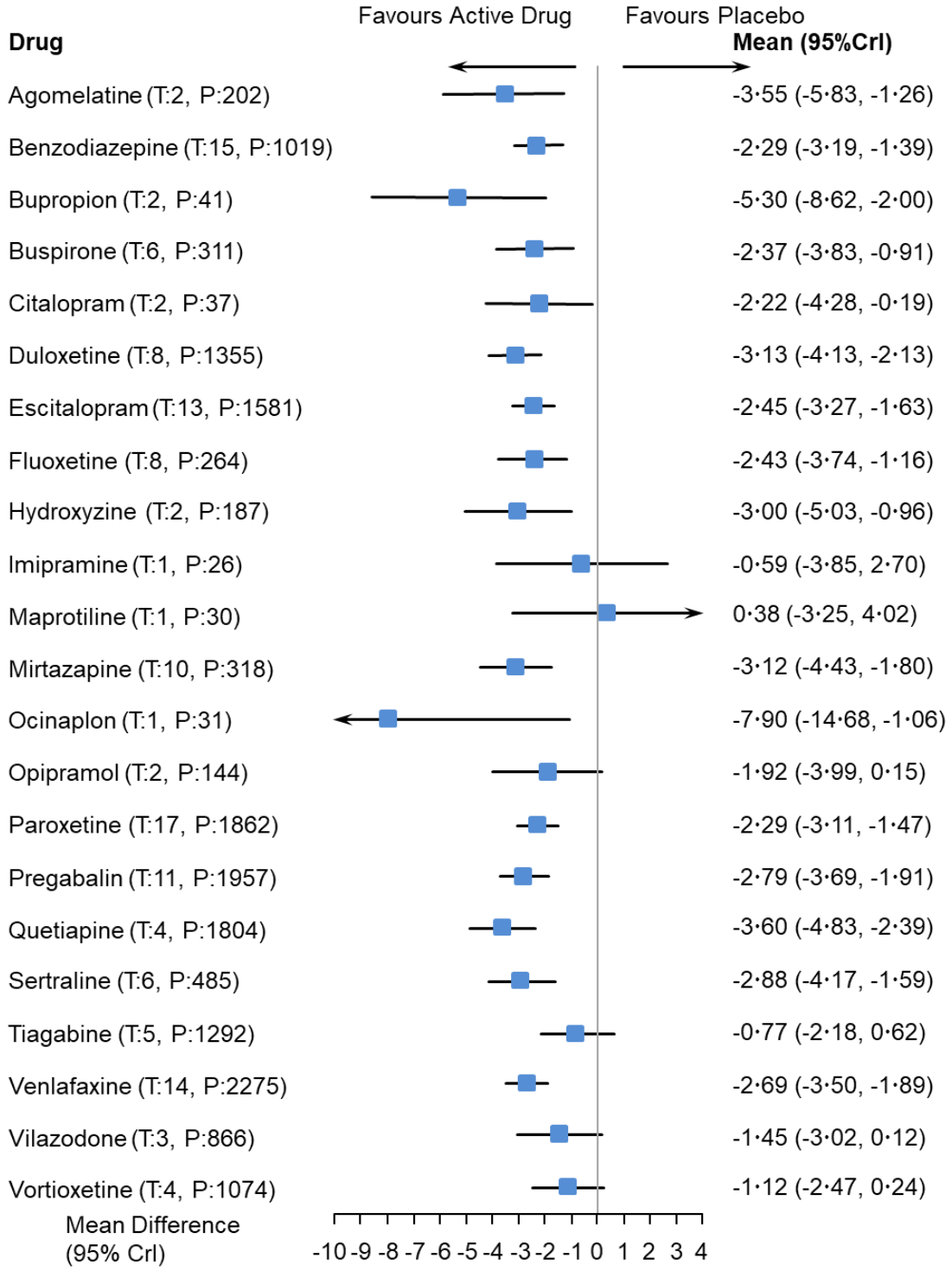

Figure 3B: Forest plot of network meta-analysis of all trials for acceptability (odds ratio for failure to complete study).

Drugs compared with placebo, which was the reference compound. CrI=credible interval, OR=odds ratio, T=number of trials, P=total number of patients.

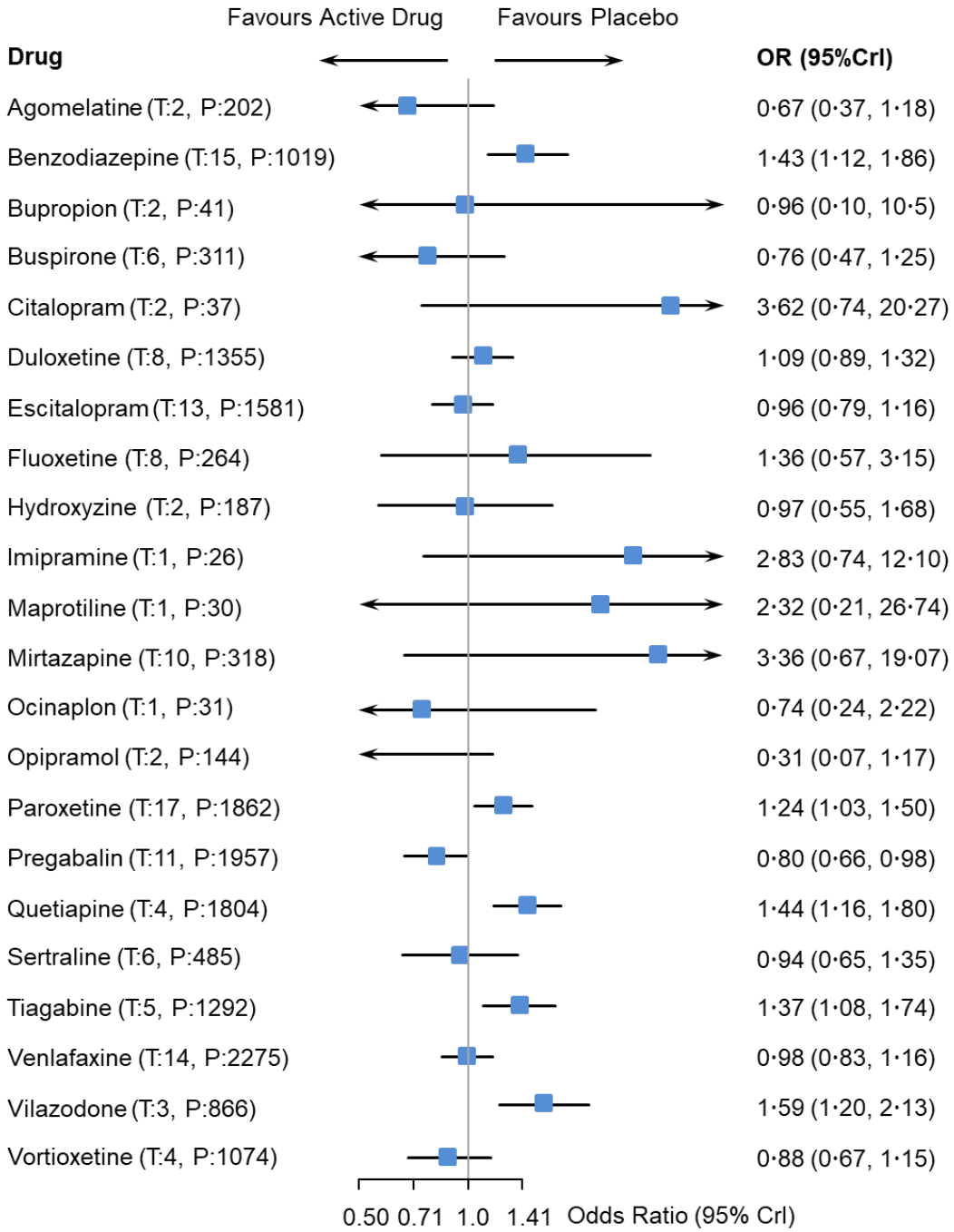

Table 1: Active comparisons for efficacy and acceptability.

*Numbers above the diagonal show mean differences in efficacy (i.e., difference in change in HAM-A) and 95% CrI. Means < 0 indicate that the row drug reduces anxiety better than the column drug, and + with blue font indicates that the 95% CrI does not include 0. Means > 0 indicate that the column drug reduces anxiety better than the row drug, and * with blue font indicates that the 95% CrI does not include 0. Numbers below the diagonal show odds ratios for acceptability (i.e., comparing the odds of premature trial discontinuation) and 95% CrI. Odds ratios > 1 indicate that the column drug is more tolerable than the row drug, and * with blue font indicates that the 95% CrI does not include 1. Odds ratios < 1 indicate that the row drug is more tolerable than the column drug, and + with blue font indicates that the 95% CrI does not include 1*.

Drug	Ago	Benzo	Buprop	Busp	Cital	Dulox	Escit	Fluox	Hydrox	Imipra	Mapro
Ago		-1.3 (-3.7, 1.21)	1.75 (-2.2, 5.74)	-1.2 (-3.9, 1.53)	-1.3 (-4.3, 1.71)	-.41 (-2.9, 2.08)	-1.1 (-3.4, 1.22)	-1.1 (-3.7, 1.48)	-.54 (-3.6, 2.51)	-3.0 (-6.9, 0.97)	-3.9 (-8.2, 0.36)
Benzo	**0.47 (0.25, 0.87)+**		3.01 (-.37, 6.40)	0.08 (-1.6, 1.73)	-.06 (-2.3, 2.14)	0.85 (-.49, 2.17)	0.17 (-1.0, 1.35)	0.14 (-1.2, 1.57)	0.71 (-1.5, 2.85)	-1.7 (-5.1, 1.67)	-2.7 (-6.3, 0.99)
Buprop	0.69 (0.06, 7.07)	1.50 (0.14, 15.4)		-2.9 (-6.5, 0.66)	-3.1 (-6.9, 0.73)	-2.2 (-5.6, 1.23)	-2.8 (-6.1, 0.43)	-2.9 (-6.2, 0.41)	-2.3 (-6.2, 1.58)	**-4.7 (-9.4, -.13)+**	**-5.7 (-11, -.80)+**
Busp	0.87 (0.41, 1.87)	**1.87 (1.09, 3.23)***	1.27 (0.12, 13.9)		-.15 (-2.6, 2.36)	0.76 (-.99, 2.53)	0.08 (-1.6, 1.75)	0.06 (-1.8, 1.99)	0.63 (-1.7, 2.90)	-1.8 (-5.4, 1.78)	-2.7 (-6.6, 1.13)
Cital	**0.18 (0.03, 0.98)+**	0.40 (0.07, 1.97)	0.26 (0.02, 5.00)	0.21 (0.04, 1.09)		0.91 (-1.4, 3.16)	0.23 (-1.9, 2.34)	0.21 (-2.0, 2.46)	0.78 (-2.1, 3.63)	-1.6 (-5.4, 2.16)	-2.6 (-6.8, 1.52)
Dulox	0.61 (0.33, 1.13)	1.32 (0.96, 1.82)	0.88 (0.09, 9.84)	0.70 (0.42, 1.18)	3.32 (0.66, 18.9)		-.68 (-1.9, 0.59)	-.70 (-2.2, 0.84)	-.13 (-2.4, 2.14)	-2.5 (-6.0, 0.85)	-3.5 (-7.3, 0.23)
Escit	0.70 (0.38, 1.24)	**1.50 (1.09, 2.07)***	1.00 (0.10, 11.0)	0.80 (0.47, 1.35)	3.78 (0.77, 21.1)	1.14 (0.86, 1.50)		-.02 (-1.4, 1.38)	0.56 (-1.7, 2.73)	-1.9 (-5.2, 1.46)	-2.8 (-6.6, 0.88)
Fluox	0.49 (0.17, 1.42)	1.06 (0.44, 2.60)	0.70 (0.07, 9.40)	0.56 (0.21, 1.51)	2.69 (0.48, 18.0)	0.80 (0.34, 1.96)	0.70 (0.30, 1.72)		0.57 (-1.8, 2.94)	-1.8 (-5.3, 1.58)	-2.8 (-6.6, 0.95)
Hydrox	0.69 (0.31, 1.53)	1.48 (0.83, 2.66)	0.99 (0.09, 11.6)	0.79 (0.40, 1.56)	3.74 (0.69, 23.1)	1.12 (0.63, 2.03)	0.98 (0.55, 1.78)	1.40 (0.50, 3.73)		-2.4 (-6.3, 1.45)	-3.4 (-7.6, 0.79)
Imipra	0.23 (0.05, 1.00)	0.51 (0.12, 1.99)	0.34 (0.02, 5.17)	0.27 (0.06, 1.16)	1.30 (0.13, 12.1)	0.38 (0.09, 1.49)	0.34 (0.08, 1.32)	0.48 (0.09, 2.34)	0.34 (0.07, 1.47)		-.96 (-5.8, 3.86)
Mapro	0.29 (0.02, 3.39)	0.62 (0.05, 6.74)	0.42 (0.01, 13.7)	0.33 (0.03, 3.90)	1.60 (0.08, 35.4)	0.47 (0.04, 5.24)	0.41 (0.04, 4.65)	0.59 (0.04, 7.13)	0.42 (0.04, 4.89)	1.22 (0.08, 18.8)	
Mirtaz	0.20 (0.03, 1.08)	0.43 (0.08, 2.16)	0.29 (0.01, 5.86)	0.22 (0.04, 1.28)	1.07 (0.10, 13.8)	0.32 (0.06, 1.68)	0.28 (0.05, 1.46)	0.41 (0.06, 2.46)	0.29 (0.05, 1.61)	0.84 (0.10, 7.22)	0.69 (0.11, 3.81)
Ocin	0.90 (0.26, 3.21)	1.93 (0.63, 6.20)	1.31 (0.10, 17.9)	1.03 (0.31, 3.50)	5.00 (0.70, 39.6)	1.47 (0.48, 4.66)	1.29 (0.43, 4.13)	1.83 (0.45, 7.82)	1.31 (0.38, 4.61)	3.81 (0.67, 25.1)	3.12 (0.22, 47.8)
Opip	2.15 (0.51, 10.7)	**4.63 (1.23, 22.0)***	3.15 (0.25, 52.4)	2.46 (0.63, 11.3)	**11.9 (1.61, 106)***	3.51 (0.93, 16.3)	3.08 (0.81, 14.4)	4.37 (0.89, 25.1)	3.14 (0.76, 15.5)	**9.56 (1.41, 67.5)***	7.82 (0.45, 137)
Parox	**0.54 (0.29, 0.97)+**	1.16 (0.85, 1.60)	0.78 (0.08, 8.59)	0.62 (0.37, 1.05)	2.93 (0.59, 16.5)	0.88 (0.67, 1.15)	**0.77 (0.60, 1.00)+**	1.10 (0.45, 2.62)	0.78 (0.43, 1.41)	2.29 (0.60, 9.70)	1.87 (0.17, 21.7)
Pregab	0.83 (0.45, 1.52)	**1.78 (1.39, 2.31)***	1.19 (0.12, 13.0)	0.95 (0.57, 1.61)	4.45 (0.90, 25.3)	**1.35 (1.02, 1.79)***	1.19 (0.90, 1.58)	1.70 (0.69, 4.01)	1.21 (0.67, 2.16)	3.53 (0.90, 15.2)	2.88 (0.26, 33.6)
Quet	**0.46 (0.25, 0.85)+**	1.00 (0.71, 1.39)	0.67 (0.07, 7.37)	**0.53 (0.31, 0.91)+**	2.51 (0.50, 14.2)	0.76 (0.56, 1.01)	**0.66 (0.50, 0.88)+**	0.94 (0.38, 2.24)	0.67 (0.37, 1.22)	1.96 (0.50, 8.54)	1.61 (0.14, 18.7)
Sert	0.71 (0.36, 1.40)	1.53 (0.98, 2.39)	1.04 (0.10, 11.7)	0.82 (0.44, 1.50)	3.85 (0.75, 22.4)	1.16 (0.77, 1.77)	1.02 (0.67, 1.56)	1.45 (0.55, 3.67)	1.04 (0.53, 2.00)	3.02 (0.75, 13.7)	2.48 (0.22, 30.8)
Tiag	**0.49 (0.26, 0.90)+**	1.05 (0.74, 1.48)	0.70 (0.07, 7.74)	**0.56 (0.33, 0.97)+**	2.66 (0.54, 15.2)	0.79 (0.58, 1.08)	**0.70 (0.51, 0.95)+**	0.99 (0.40, 2.38)	0.71 (0.39, 1.29)	2.07 (0.53, 8.94)	1.69 (0.15, 19.6)
Venla	0.68 (0.37, 1.23)	**1.46 (1.09, 1.98)***	0.98 (0.10, 10.9)	0.78 (0.48, 1.28)	3.68 (0.75, 20.7)	1.11 (0.87, 1.41)	0.97 (0.76, 1.25)	1.39 (0.58, 3.25)	0.99 (0.55, 1.75)	2.89 (0.74, 12.4)	2.36 (0.21, 27.4)
Vilaz	**0.42 (0.22, 0.79)+**	0.90 (0.62, 1.33)	0.60 (0.06, 6.70)	**0.48 (0.27, 0.85)+**	2.29 (0.44, 12.9)	**0.68 (0.48, 0.97)+**	**0.60 (0.42, 0.85)+**	0.86 (0.34, 2.04)	0.61 (0.33, 1.13)	1.78 (0.45, 7.84)	1.45 (0.13, 17.0)
Vortiox	0.76 (0.40, 1.42)	**1.64 (1.14, 2.37)***	1.09 (0.11, 12.1)	0.87 (0.50, 1.52)	4.14 (0.81, 23.6)	1.24 (0.90, 1.70)	1.09 (0.78, 1.52)	1.55 (0.62, 3.76)	1.11 (0.60, 2.03)	3.23 (0.82, 14.1)	2.66 (0.23, 30.9)

Drug	Mirtaz	Ocin	Opip	Parox	Pregab	Quet	Sert	Tiag	Venla	Vilaz	Vortiox
Ago	-.43 (-3.1, 2.19)	4.36 (-2.8, 11.5)	-1.6 (-4.7, 1.46)	-1.3 (-3.7, 1.15)	-.76 (-3.2, 1.70)	0.06 (-2.5, 2.63)	-.66 (-3.2, 1.93)	**-2.8 (-5.5, -.10)+**	-.85 (-3.3, 1.58)	-2.1 (-4.9, 0.68)	-2.4 (-5.1, 0.24)
Benzo	0.83 (-.54, 2.19)	5.61 (-1.3, 12.5)	-.37 (-2.5, 1.76)	0.00 (-1.1, 1.14)	0.50 (-.54, 1.53)	1.32 (-.18, 2.82)	0.59 (-.92, 2.11)	-1.5 (-3.2, 0.15)	0.41 (-.78, 1.59)	-.83 (-2.6, 0.97)	-1.2 (-2.8, 0.45)
Buprop	-2.2 (-5.7, 1.29)	2.60 (-5.0, 10.1)	-3.4 (-7.3, 0.51)	-3.0 (-6.4, 0.35)	-2.5 (-5.9, 0.89)	-1.7 (-5.2, 1.81)	-2.4 (-5.9, 1.07)	**-4.5 (-8.1, -.95)+**	-2.6 (-6.0, 0.78)	**-3.8 (-7.5, -.19)+**	**-4.2 (-7.8, -.65)+**
Busp	0.74 (-1.1, 2.63)	5.53 (-1.5, 12.5)	-.46 (-2.7, 1.87)	-.09 (-1.7, 1.56)	0.41 (-1.3, 2.11)	1.23 (-.66, 3.13)	0.51 (-1.3, 2.37)	-1.6 (-3.6, 0.42)	0.32 (-1.3, 1.93)	-.92 (-3.0, 1.24)	-1.3 (-3.2, 0.75)
Cital	0.89 (-1.5, 3.25)	5.67 (-1.4, 12.8)	-.30 (-3.2, 2.59)	0.07 (-2.1, 2.16)	0.56 (-1.7, 2.77)	1.38 (-.98, 3.74)	0.66 (-1.6, 2.92)	-1.5 (-3.9, 1.02)	0.47 (-1.7, 2.64)	-.77 (-3.4, 1.79)	-1.1 (-3.5, 1.32)
Dulox	-.01 (-1.6, 1.60)	4.77 (-2.1, 11.7)	-1.2 (-3.5, 1.08)	-.84 (-2.1, 0.43)	-.35 (-1.7, 1.00)	0.47 (-1.1, 2.05)	-.25 (-1.9, 1.37)	**-2.4 (-4.1, -.64)+**	-.44 (-1.6, 0.76)	-1.7 (-3.5, 0.17)	**-2.0 (-3.6, -.43)+**
Escit	0.67 (-.81, 2.13)	5.45 (-1.4, 12.3)	-.53 (-2.8, 1.70)	-.16 (-1.2, 0.87)	0.34 (-.84, 1.53)	1.15 (-.23, 2.53)	0.43 (-1.0, 1.88)	**-1.7 (-3.3, -.06)+**	0.24 (-.86, 1.34)	-1.0 (-2.8, 0.76)	-1.3 (-2.9, 0.23)
Fluox	0.69 (-.92, 2.26)	5.46 (-1.5, 12.4)	-.51 (-2.9, 1.89)	-.14 (-1.6, 1.25)	0.36 (-1.2, 1.84)	1.18 (-.58, 2.89)	0.45 (-1.3, 2.13)	-1.7 (-3.6, 0.22)	0.27 (-1.2, 1.72)	-.97 (-3.0, 1.03)	-1.3 (-3.2, 0.53)
Hydrox	0.12 (-2.3, 2.51)	4.90 (-2.2, 12.0)	-1.1 (-3.9, 1.77)	-.72 (-2.9, 1.48)	-.21 (-2.4, 1.99)	0.60 (-1.8, 3.00)	-.12 (-2.5, 2.28)	-2.2 (-4.7, 0.25)	-.31 (-2.5, 1.88)	-1.5 (-4.1, 1.03)	-1.9 (-4.3, 0.58)
Imipra	2.54 (-.90, 5.96)	7.32 (-.33, 14.9)	1.33 (-2.5, 5.22)	1.70 (-1.5, 4.89)	2.20 (-1.1, 5.58)	3.02 (-.43, 6.49)	2.30 (-1.2, 5.79)	0.19 (-3.3, 3.77)	2.11 (-1.2, 5.48)	0.87 (-2.8, 4.51)	0.54 (-3.0, 4.07)
Mapro	**3.50 (0.10, 6.90)***	**8.29 (0.58, 16.1)***	2.29 (-1.8, 6.45)	2.67 (-.97, 6.31)	3.17 (-.54, 6.90)	**3.98 (0.17, 7.83)***	3.26 (-.58, 7.11)	1.15 (-2.7, 5.06)	3.08 (-.63, 6.80)	1.83 (-2.1, 5.81)	1.49 (-2.4, 5.38)
Mirtaz		4.79 (-2.2, 11.7)	-1.2 (-3.6, 1.19)	-.83 (-2.1, 0.45)	-.33 (-1.8, 1.18)	0.48 (-1.3, 2.25)	-.24 (-2.0, 1.53)	**-2.3 (-4.3, -.44)+**	-.43 (-1.9, 1.08)	-1.7 (-3.7, 0.38)	**-2.0 (-3.9, -.13)+**
Ocin	4.58 (0.70, 36.6)		-6.0 (-13, 1.18)	-5.6 (-12, 1.27)	-5.1 (-12, 1.80)	-4.3 (-11, 2.66)	-5.0 (-12, 1.94)	**-7.1 (-14, -.13)+**	-5.2 (-12, 1.68)	-6.4 (-13, 0.58)	-6.8 (-14, 0.18)
Opip	**11.0 (1.21, 111)***	2.42 (0.43, 15.4)		0.37 (-1.8, 2.60)	0.87 (-1.3, 3.08)	1.69 (-.72, 4.10)	0.96 (-1.4, 3.37)	-1.1 (-3.6, 1.37)	0.78 (-1.4, 2.99)	-.47 (-3.1, 2.15)	-.80 (-3.3, 1.66)
Parox	2.72 (0.53, 15.7)	0.60 (0.19, 1.82)	**0.25 (0.05, 0.97)+**		0.50 (-.66, 1.68)	1.32 (-.06, 2.70)	0.60 (-.83, 2.01)	-1.5 (-3.1, 0.08)	0.41 (-.69, 1.51)	-.84 (-2.6, 0.93)	-1.2 (-2.7, 0.39)
Pregab	4.21 (0.82, 23.7)	0.92 (0.29, 2.83)	0.38 (0.08, 1.46)	**1.54 (1.17, 2.03)***		0.82 (-.69, 2.32)	0.09 (-1.4, 1.55)	**-2.0 (-3.7, -.36)+**	-.10 (-1.2, 1.04)	-1.3 (-3.2, 0.45)	**-1.7 (-3.3, -.06)+**
Quet	2.33 (0.45, 13.3)	0.51 (0.16, 1.58)	**0.22 (0.05, 0.82)+**	0.86 (0.65, 1.14)	**0.56 (0.41, 0.75)+**		-.72 (-2.5, 1.03)	**-2.8 (-4.7, -.98)+**	-.91 (-2.4, 0.54)	**-2.1 (-4.1, -.17)+**	**-2.5 (-4.3, -.67)+**
Sert	3.64 (0.70, 21.3)	0.79 (0.24, 2.51)	0.33 (0.07, 1.30)	1.32 (0.88, 2.00)	0.86 (0.57, 1.30)	**1.54 (1.01, 2.36)***		**-2.1 (-4.0, -.20)+**	-.19 (-1.7, 1.31)	-1.4 (-3.5, 0.60)	-1.8 (-3.6, 0.09)
Tiag	2.46 (0.47, 14.0)	0.54 (0.17, 1.66)	**0.23 (0.05, 0.86)+**	0.90 (0.67, 1.22)	**0.59 (0.43, 0.80)+**	1.05 (0.76, 1.45)	0.68 (0.44, 1.07)		**1.92 (0.30, 3.54)***	0.68 (-1.4, 2.78)	0.34 (-1.6, 2.29)
Venla	3.42 (0.68, 19.7)	0.76 (0.24, 2.29)	0.32 (0.07, 1.19)	1.26 (0.98, 1.62)	0.82 (0.64, 1.05)	**1.47 (1.12, 1.93)***	0.96 (0.64, 1.43)	**1.40 (1.05, 1.86)***		-1.2 (-3.0, 0.51)	**-1.6 (-3.1, -.02)+**
Vilaz	2.12 (0.41, 12.0)	0.47 (0.14, 1.44)	**0.19 (0.04, 0.76)+**	0.78 (0.55, 1.09)	**0.51 (0.35, 0.72)+**	0.91 (0.63, 1.30)	**0.59 (0.37, 0.94)+**	0.86 (0.59, 1.25)	**0.62 (0.44, 0.86)+**		-.33 (-2.4, 1.72)
Vortiox	3.84 (0.74, 22.0)	0.85 (0.26, 2.63)	0.35 (0.08, 1.37)	**1.41 (1.02, 1.96)***	0.92 (0.66, 1.28)	**1.64 (1.16, 2.33)***	1.07 (0.68, 1.69)	**1.56 (1.10, 2.23)***	1.12 (0.82, 1.54)	**1.82 (1.23, 2.70)***	