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Meta-analysis of the comparative efficacy of benzodiazepines and antidepressants for psychic versus somatic symptoms of generalized anxiety disorder

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ABSTRACT

Background: Benzodiazepines and antidepressants are effective agents for the treatment of generalized anxiety disorder (GAD), with the HAM-A frequently used as a primary outcome measure. The GAD literature is inconsistent regarding which medications are more effective for somatic versus psychic symptoms of GAD, and treatment guidelines do not advocate for prescribing based on subtype. This meta-analysis aimed to determine whether benzodiazepines and antidepressants have a differential impact on the somatic versus psychic subscales of the HAM-A in GAD.

Methods: An electronic search was undertaken for randomized controlled trials of either benzodiazepines or antidepressants for GAD that reported treatment response using the HAM-A subscales. Data were extracted by independent reviewers. A random effects assessment of weighted mean difference with 95% confidence intervals and subgroup difference was applied. All analysis was done on SPSS 26. An assessment of bias, and of quality of evidence was performed.

Results: 24 randomized controlled trials met the inclusion criteria: 18 antidepressant trials, 5 benzodiazepine trials and 1 of both. 14 studies were assessed as having between some and high risk of bias, while 10 were assessed as having low risk of bias. Benzodiazepines (WMD of 1.81 [CI 1.03, 2.58]) were significantly more effective than antidepressants (WMD of 0.83 [CI 0.64, 1.02]) for reducing somatic symptoms of GAD ($Chi^2 = 5.81$, $p = 0.02$), and were also more effective (WMD of 2.46 [CI 1.83, 3.09]) in reducing psychic symptoms than antidepressants (WMD of 1.83 [CI 1.55, 2.10]), although this comparison did not reach statistical significance ($Chi^2 = 3.31$, $p = 0.07$).

Conclusion: The finding that benzodiazepines were significantly more effective than antidepressants for somatic symptoms needs to be weighed up against potential benefits of antidepressants over benzodiazepines. It may be useful for future treatment guidelines for GAD to explicitly consider symptom subtype.

1. Background

Generalized anxiety disorder (GAD) is a chronic and disabling disorder with a combined lifetime prevalence of 3.7%, 12-month prevalence of 1.8%, and 30-day prevalence of 0.8% [1,2,3,4]. Benzodiazepines and antidepressants are effective agents for the treatment of GAD [5]. The Hamilton Anxiety scale (HAM-A) is frequently used as a primary outcome measure to assess GAD, and has a psychic and somatic symptom sub-subscale [6,7]. The psychic subscale captures excessive anxiety, inability to control worries, difficulty concentrating and feeling on edge; while the somatic subscale includes fatigue, restlessness, muscle tension, nausea and diarrhea, palpitations and sweating [8].

Benzodiazepines enhance the transmission of the neurotransmitter GABA; while antidepressants, such as tricyclic antidepressant (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) affect the neurotransmission of monoamines. There is inconsistency in the literature regarding the

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efficacy of benzodiazepines and antidepressants on the psychic versus somatic symptoms of GAD. Some work has shown benzodiazepines to be more effective in treating somatic symptoms [9,10,11], while other work has found benzodiazepines to be equivalent for psychic and somatic symptoms of GAD [12,13,14]. In contrast, some work has found antidepressants to be more effective in treating psychic symptoms [15,16,17,18,19,10,20,21,22,23], while other work has found antidepressants to be equivalent for psychic and somatic symptoms of GAD [24,25,12,26,27,28,29,30,31].

Most treatment guidelines, including the World Federation of Societies of Biological Psychiatry (WFSBP), the Canadian, and the Australian/New Zealand, suggest that SSRI/SNIRs are a first line treatment of choice, with benzodiazepines reserved for more refractory individuals given the important adverse effects associated with these agents [32,33,34]. The British Association for Psychopharmacology recommends the use of various antidepressant medications, pregabalin, and certain benzodiazepines as first-line treatments for GAD [35]. Despite the findings noted earlier that some classes of medication may act more specifically on particular symptoms of GAD, none of the guidelines bases choice of medication on GAD subtyping.

Although a number of systematic reviews of GAD pharmacotherapy are available, including those undertaken as part of a treatment guideline, few have focused on the question of whether somatic vs psychic symptoms of GAD respond differently to different medication classes. We therefore undertook a systematic review and meta-analysis of the literature to determine whether antidepressants and benzodiazepines have a differential impact on somatic versus psychic symptoms of GAD.

2. Methods

2.1. HAM-A

The Hamilton Anxiety Rating Scale (HAM-A) is a widely used and validated tool for assessing the severity of a patient's anxiety. It measures both psychic (mental) and somatic (physical) symptoms associated with anxiety. The HAM-A consists of 14 items, each defined by a series of symptoms, and measures the severity of anxiety symptoms on a scale from 0 (not present) to 4 (severe).

In comparison to other tools in the assessment of GAD, HAM-A covers a broad range of anxiety symptoms, including both psychic and somatic subsets. This makes it particularly useful in clinical settings for assessing the overall severity of anxiety and monitoring treatment outcomes, and ideal for our research question. The Generalized Anxiety Disorder-7 (GAD-7) is a self-report questionnaire that is quicker to administer, highly effective for screening purposes with good psychometric properties but does not capture the full range of anxiety symptoms [36]. The Beck Anxiety Inventory (BAI) focuses more on the physiological aspects of anxiety than HAM-A [37]. It's useful for distinguishing anxiety from depression but does not fully capture the psychic symptoms of anxiety. For these reasons the HAM-A was selected.

2.2. Search strategy for identification of studies

Two reviewers (CB and CC) searched the electronic databases of PubMed, Embase, Web of Science; as well as the Cochrane Center Register of Controlled Trials (CENTRAL), and the ClinicalTrials registry from inception until January 12, 2023, for relevant studies using search terms curated for each database, covering generalized anxiety disorder, antidepressants and benzodiazepines.

The search was limited to randomized controlled trials. No language restrictions were applied. The references of appropriate papers and previous meta-analyses were also searched for citations of further relevant published and unpublished research.

2.3. Selection of studies

The titles and abstracts of studies obtained by this search strategy were examined by two reviewers (CB and CC) to determine inclusion in this meta-analysis. Any discrepancies were resolved by consensus, or discussion with a third reviewer (DJS). For inclusion of studies in this review, they needed to (1) be randomized, (2) double-blind, (3) placebo-controlled, (4) of either benzodiazepines or antidepressants, (5) targeting patients with generalized anxiety disorder, as defined by DSM diagnostic criteria or International Classification of Diseases (ICD) diagnostic guidelines, (5) and include psychic and somatic subscales of the HAM-A group data.

Studies were restricted to adults (18–65 years old), in this way we excluded studies focused on paediatric or geriatric populations. Discontinuation studies or studies which involved duplication of data from prior reported research included in this review were excluded. Head-to-head and crossover trials studies without a placebo control were also excluded. Any studies requiring concomitant medications were excluded.

2.4. Data extraction and management

Data were extracted by independent reviewers (CB and CC) on specially designed Microsoft Excel spreadsheets. HAM-A psychic and somatic subscale scores at baseline were recorded in medication and placebo groups. We also gathered data on trial medication, trial design, maximum daily medication dose, number of participants in active group, and number of participants in placebo group. Any disagreement among reviewers was resolved through discussion and the procurement of more information from the study investigators if possible. If contacting the corresponding author was ineffective, we also searched pharmaceutical company databases for the data.

2.5. Assessment of risk of bias

Two review authors (CB and CC) independently assessed the risk of bias of included trials using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). This tool examines five domains including: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (effect of assignment to intervention and effect of adhering to intervention), missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result. Risk of bias was categorized as low, high, or some concerns. Disagreements about risk of bias were resolved by discussion with a third review author (DJS) until consensus was reached.

2.6. Assessment of quality of evidence

Two review authors (CB and CC) independently assessed the quality of evidence of the meta-analysis using GRADE (Grading of Recommendations, Assessment, Development, and Evaluations). The GRADE approach results in an assessment of the quality of a body of evidence as high (very confident that the true effect lies close to that of the estimate of the effect), moderate (moderately confident in the effect estimate, the true effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different), low (confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect), or very low (very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect. Disagreements about quality of evidence were resolved by discussion with a third review author (DJS) until consensus was reached.

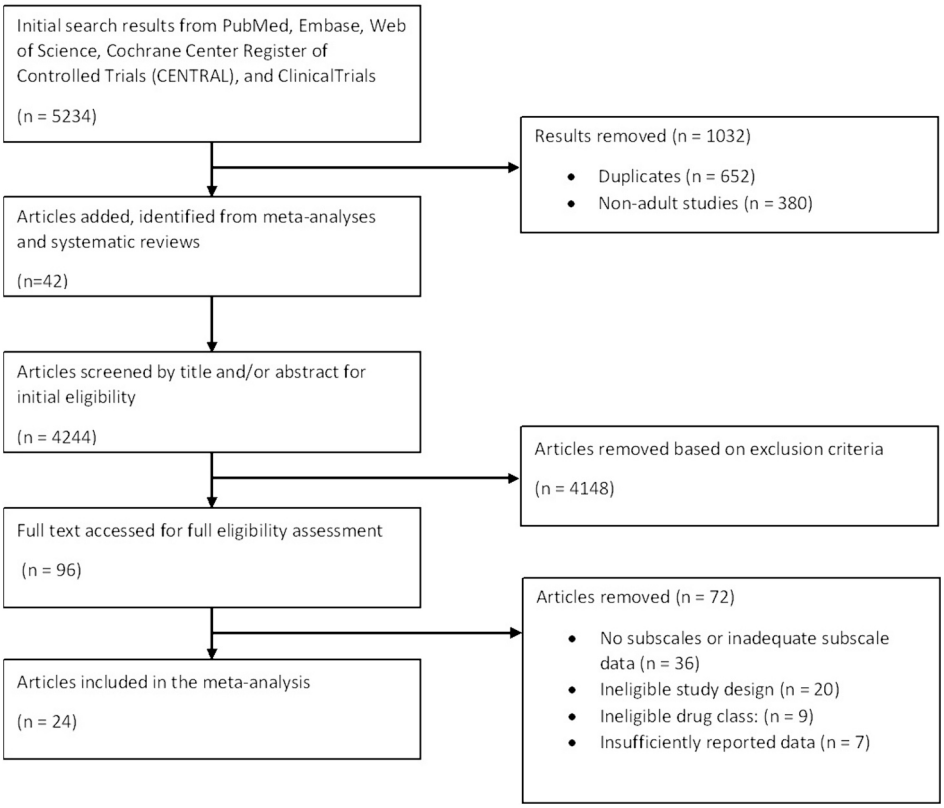

Fig. 1. PRISMA.
A PRISMA diagram showing the process of the search for, and subsequently included articles in the meta-analysis.

2.7. Statistical analysis

Statistical analysis was performed using Review Manager 5.3 (Cochrane Collaboration, London, UK). Where possible, all analyses were conducted using the intent-to-treat (ITT) populations. Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for the somatic and psychic subscales of the HAM-A. The chi-squared test ($P < 0.05$) and the inconsistency index (I^2) were used to assess heterogeneity, we further interpreted heterogeneity as 0% to 40%: may not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity, with the overlap depending on magnitude and direction of effects, as well as strength of evidence for heterogeneity. A random-effects model was used to pool studies with substantial heterogeneity. Publication bias was assessed by plotting the effect size against standard error for each included trial (i.e., funnel plot) and if asymmetry was found, the Egger's test was applied. The significance of the pooled estimates was determined by the Z statistic; statistical significance was set at $P < 0.05$.

3. Results

3.1. Search strategy

The search strategy is summarized in Fig. 1, and yielded 5234 articles from PubMed, Embase, Web of Science, Cochrane Center Register of Controlled Trials (CENTRAL), and ClinicalTrials. Prior to assessment of eligibility 1032 studies were removed, as 652 were duplicates, and 380 were non-adult studies. 42 additional articles were added from other meta-analyses and systematic reviews. This left 4244 articles to be screened by title, and where necessary, abstract, for initial eligibility. 4148 articles were removed based on exclusion criteria. Subsequently, 96 articles underwent full text eligibility assessment. 72 articles were removed, 36 due to the lack of, or poor reporting of, HAM-A subscales, 20 due to ineligible study design, 9 due to ineligible drug class, and 7 due to insufficiently reported data.

3.2. Description of included studies

This process yielded 24 randomized controlled trials for inclusion in the meta-analysis: 18 antidepressant studies, 5 benzodiazepine studies, and 1 study that incorporated both [15,24,16,9,17,18,25,38,26,12,28,19,20,21,39,13,14,29,30,11,22,23,31,40]. As some studies trialed multiple medications, we included a total of 27 data sets in the meta-analysis. Fig. 1 shows a PRISMA diagram of the search strategy results. There were 5 duloxetine, 4 escitalopram, 4 venlafaxine, 3 paroxetine, 3 vilazodone, 2 sertraline, 2 alprazolam, 2 diazepam, and 2 lorazepam data sets.

3.3. Assessment of bias

Four studies were assessed as being at high risk of bias, 11 were assessed as having some concerns of bias, and 9 were assessed as being at low risk of bias. Of the antidepressant data sets, 28.57% were assessed as low risk, 47.62% as having some concerns, and 23.81% as high risk. Of the benzodiazepine data sets, 50% were assessed as low risk, 33.33% as having some concerns, and 16.67% as high risk.

Fig. 2 shows a summary of the assessment of bias.

3.4. Assessment of quality of evidence

Using GRADE, we assessed the quality of the meta-analysis of

Study ID	Randomization	Deviations	Missing data	Measurement	Selection	Overall
Allugander_2004	Low	Low	Low	Low	Low	Low
Allugander_2007	Low	Some concerns	Low	Low	Low	Some concerns
Bandelow_2010	Low	Low	Low	Low	Low	Low
Boyer_1993	Low	Low	Low	Low	Some concerns	Some concerns
Cohn_1989	Low	Low	Low	Low	Low	Low
Coric_2010	Some concerns	Some concerns	Low	Low	Low	Some concerns
Dahl_2005	Some concerns	Low	Low	Some concerns	Low	Some concerns
Davidson_2004	Low	Some concerns	High	Low	Low	High
Durgham_2016	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Feltner_2009	Low	Low	High	Low	High	High
Gommoll_2015a	Some concerns	Low	Low	Low	Low	Some concerns
Gommoll_2015b	Some concerns	Low	Some concerns	Low	Low	Some concerns
Hartford_2007	Low	Some concerns	High	Low	Low	High
Kasper_2009	Low	Low	Low	Low	Low	Low
Kasper_2014	Some concerns	Low	Low	Low	Low	Some concerns
Merideth_2012	Low	Low	Low	Low	Low	Some concerns
Moller_2001	Low	Low	Low	Low	Low	Low
Nicolini_2009	Low	Low	Some concerns	Low	Low	Some concerns
Pande_2003	Some concerns	Low	Low	Low	Low	Some concerns
Rickels_2000	Low	Low	Low	Low	Low	Low
Rickels_2005	Low	Low	Low	Low	Low	Low
Rynn_2008	Low	Low	Low	Low	Low	Low
Stein_2014	Low	Low	Low	Low	Low	Low
Wu_2011	Low	High	High	Low	Low	High

Antidepressant
Benzodiazepine

Fig. 2. Assessment of bias summary.
A table showing the assessment of bias for the included randomized-controlled trials, using ROB 2: A revised Cochrane risk-of-bias tool.

response of somatic and psychic symptoms to antidepressants and benzodiazepines as moderate. In this way we are moderately confident in the effect estimate, the true effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different). The factors that reduced the rating were individual study variations (given the assessment of bias), inconsistency of results (heterogeneity within the meta-analysis, particularly from the benzodiazepine data). The factor that increased the rating was the large magnitude of effect. The factors that had no effect on the rating were indirectness of evidence, imprecision, publication bias (symmetrical funnel plot, Egger's test inappropriate), dose-response gradient, and confounding.

3.5. HAM-A psychic subscale

In the treatment of psychic anxiety symptoms as measured by the HAM-A psychic subscale, a combination of all antidepressant (3131 patients) and benzodiazepine (298 patients) studies showed a weighted mean difference (WMD) of 1.96 [Confidence Interval (CI) 1.69, 2.22]. There was moderate heterogeneity with $Tau^2 = 0.18$; $Chi^2 = 42.42$, df = 26 ($p = 0.02$); $I^2 = 40\%$. The test for overall effect showed Z = 14.48 ($P < 0.00001$). Fig. 3a shows a Forest plot of the HAM-A Psychic data sets. An Egger's test was not performed as the funnel plot was symmetrical.

In the treatment of psychic anxiety symptoms, antidepressants showed an WMD of 1.83 [CI 1.55, 2.10] from placebo. There were low degrees of heterogeneity with $Tau^2 = 0.11$; $Chi^2 = 27.93$, df = 20 ($P = 0.11$); $I^2 = 28\%$. The test for overall effect was significant (Z = 13.15, $P < 0.00001$).

In the treatment of psychic anxiety symptoms, SSRI's showed an WMD of 1.91 [CI 1.55, 2.26], with the test for overall effect of Z = 10.55 ($P < 0.00001$); while SNRI's showed an WMD of 1.96 [CI 1.47, 2.46], with the test for overall effect of Z = 7.77 ($P < 0.00001$). The test for subgroup difference between SSRIs and SNRIs did not reach statistical significance ($Chi^2 = 0.03$, df = 1, $P = 0.86$, $I^2 = 0\%$).

In the treatment of psychic anxiety symptoms, benzodiazepines showed a WMD of 2.46 [CI 1.83, 3.09]. There was moderate heterogeneity with $Tau^2 = 0.27$; $Chi^2 = 8.91$, df = 5 ($P = 0.11$); $I^2 = 44\%$. The test for overall effect was significant (Z = 7.68, $P < 0.00001$).

The test for subgroup differences between antidepressants and benzodiazepines showed a trend towards statistical significance ($Chi^2 = 3.31$, df = 1, $P = 0.07$, $I^2 = 69.7\%$).

3.6. HAM-A somatic subscale

In the treatment of somatic anxiety symptoms, a combination of all antidepressant (3131 patients) and benzodiazepine (298 patients) studies showed a WMD of 1.05 [CI 0.78, 1.31]. There was substantial heterogeneity ($Tau^2 = 0.27$; $Chi^2 = 59.52$, df = 26, $P = 0.0002$, $I^2 = 56\%$). The test for overall effect was significant (Z = 7.76, $P < 0.00001$). Fig. 4a shows a Forest plot of the HAM-A somatic data sets, an Egger's test was inappropriate as the funnel plot was symmetrical.

In the treatment of somatic anxiety symptoms, antidepressants showed a WMD of 0.83 [CI 0.64, 1.02]. There was very low heterogeneity ($Tau^2 < 0.001$; $Chi^2 = 18.28$, df = 20, $P = 0.57$, $I^2 = 0\%$). The test for overall effect was significant (Z = 8.50, $P < 0.00001$).

In the treatment of somatic anxiety symptoms, SSRI's showed a WMD of 0.80 [CI 0.51, 1.09], with the test for overall effect significant (Z = 10.86, P < 0.00001); while SNRI's showed a WMD of 0.88 [CI 0.54, 1.22], with the test for overall effect again significant (Z = 5.05, P < 0.00001). The test for subgroup difference between SSRIs and SNRIs did not reach statistical significance ($Chi^2 < 0.001$, df = 1 ($P = 0.96$, $I^2 = 0\%$).

In the treatment of somatic anxiety symptoms, benzodiazepines showed a WMD of 1.81 [CI 1.03, 2.58]. There was substantial heterogeneity ($Tau^2 = 0.69$; $Chi^2 = 19.28$, df = 5, $P = 0.002$, $I^2 = 74\%$). The test for overall effect was significant (Z = 4.58, $P < 0.00001$). The test for subgroup differences between antidepressants and benzodiazepines reached statistical significance ($Chi^2 = 5.81$, df = 1, $P = 0.02$, $I^2 = 82.8\%$), with benzodiazepines more effective than antidepressants.

4. Discussion

This review and meta-analysis investigated the comparative efficacy of benzodiazepines and antidepressants in treating psychic versus somatic symptoms of GAD. Based on moderate quality evidence, benzodiazepines were more effective than antidepressants in reducing both somatic and psychic symptoms, with the difference in somatic symptoms

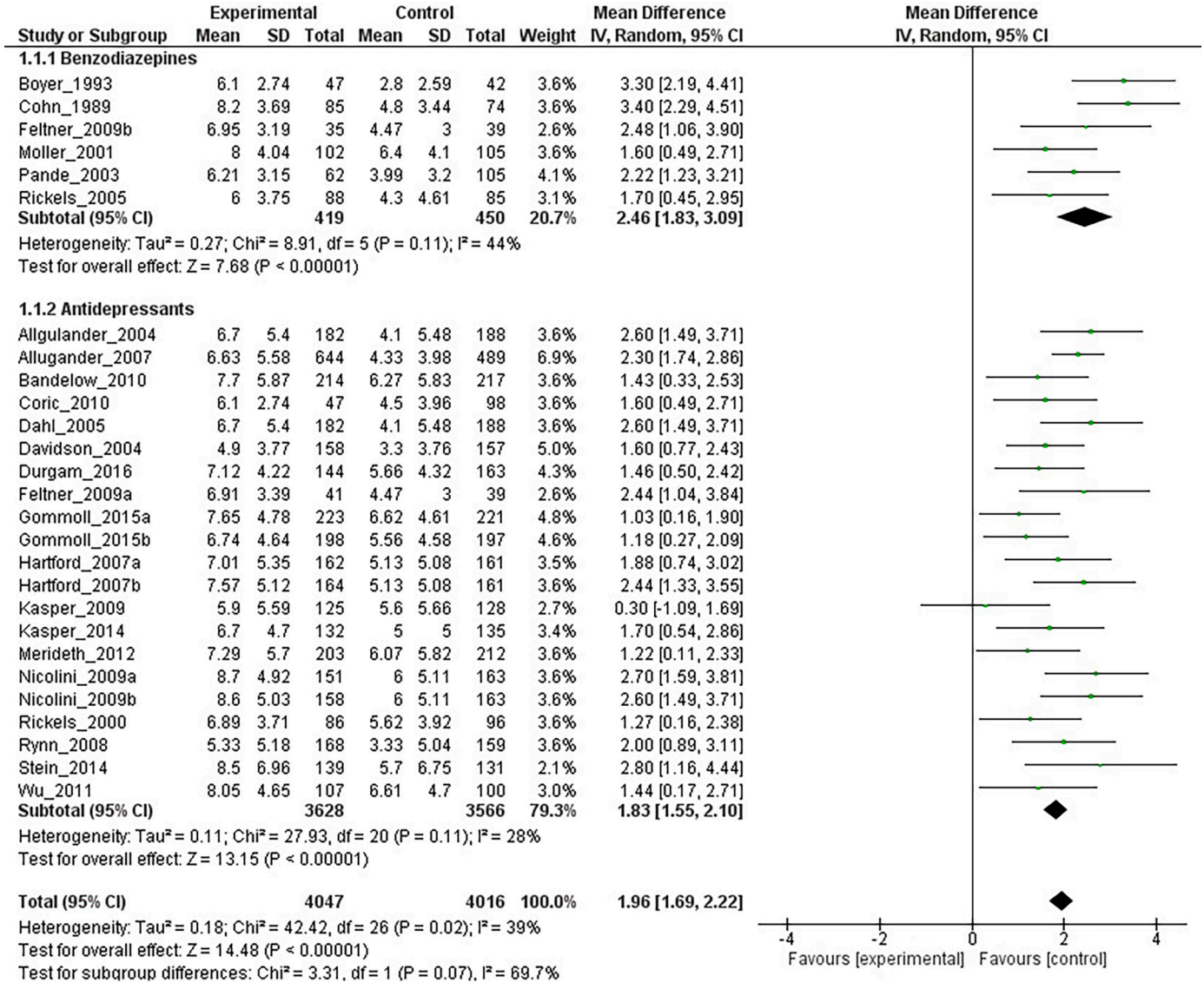

Fig. 3. HAM-A Psychic - Forest plot.
A forest plot demonstrating overall results for the HAM-A Psychic subscale, including the results of the included randomized-controlled trials, with relevant subtotals for benzodiazepine and antidepressant subgroups. Assessment of heterogeneity, overall effect and subgroup difference is included.

reaching statistical significance and the difference in psychic symptoms trending towards statistical significance. These findings are consistent with some previous work [41,42] that reported greater efficacy of benzodiazepines than SSRIs in the treatment of somatic symptoms of GAD. However, the findings are inconsistent with some previous work which suggested that SSRIs are more effective than benzodiazepines for psychic symptoms of GAD [27,10,43,22,44,45].

The finding that benzodiazepines were significantly more effective than antidepressants for somatic symptoms needs to be weighed up against potential benefits of antidepressants over benzodiazepines. Treatment guidelines have, for example, highlighted the benefit of antidepressants for some comorbid conditions, and the potential of benzodiazepines for tolerance, dependence, and other adverse effects [32,33,34]. Indeed, in clinical practice a range of considerations should be employed when selecting a medication for the treatment of GAD [46].

Several limitations deserve emphasis. First, there was moderate heterogeneity within the benzodiazepine subgroup, which makes the validity of treatment effect estimates for this class of medication uncertain. The heterogeneity may be due to differences in study design, patient populations, drug dosages, or other factors that were not accounted for in our analysis. Second, the majority of studies included in our analysis used SSRIs, SNRIs and benzodiazepines, which limits the generalizability of our findings to other classes of antidepressants or anxiolytics. Third, the studies included in our analysis had varying methodological quality and risk of bias, which could have influenced the results. Finally, the meta-analysis was not pre-registered.

5. Conclusion

Our meta-analysis found that benzodiazepines were significantly more effective than antidepressants for somatic symptoms of GAD, and non-significantly more effective than antidepressants for psychic symptoms of GAD. These findings need to be weighed up against potential benefits of antidepressants over benzodiazepines; these are often emphasized in current treatment guidelines. Certainly, a balanced and individualized approach to medication selection in GAD is important,

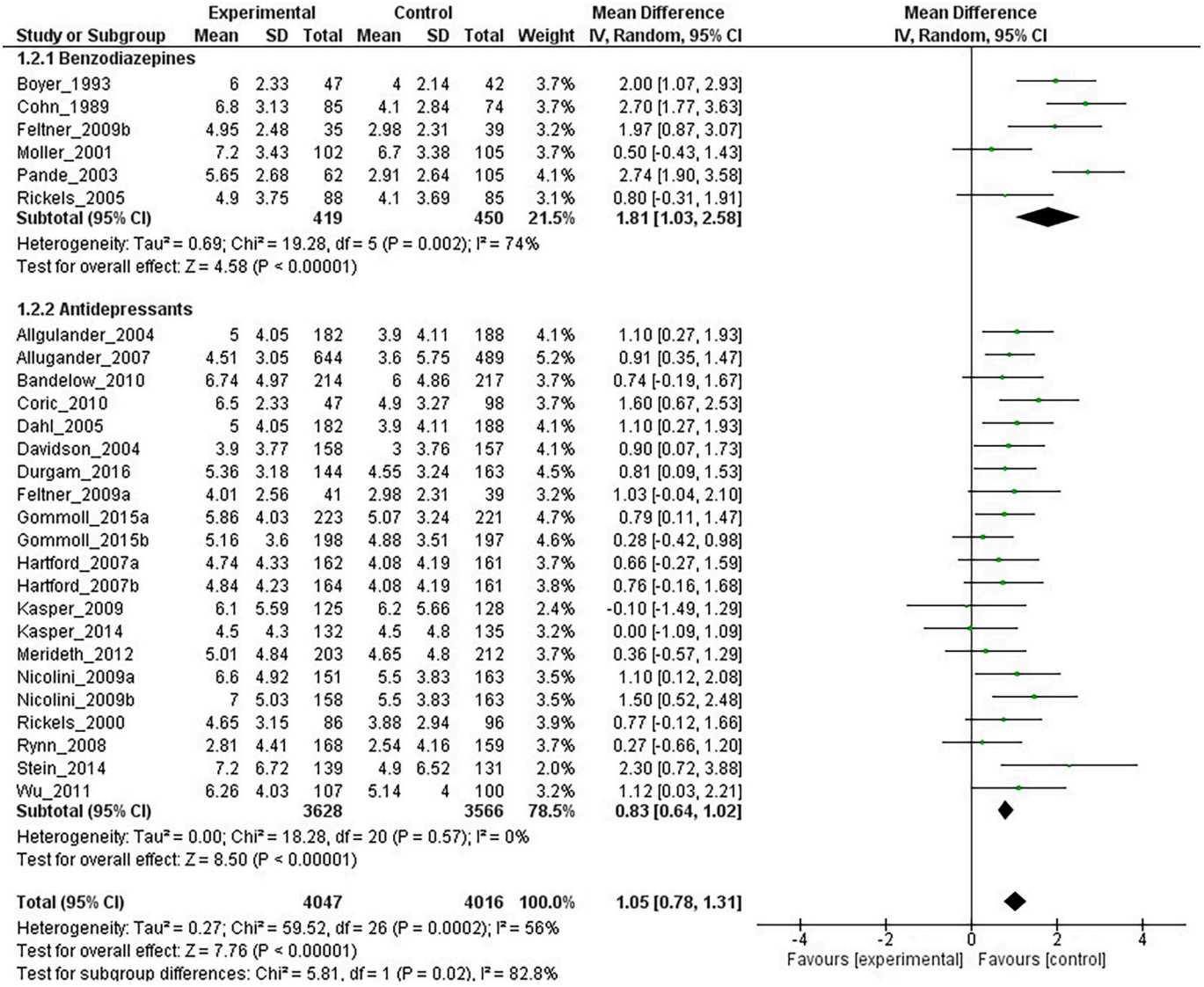

Fig. 4. HAM-A Somatic - Forest plot.
A forest plot demonstrating overall results for the HAM-A Somatic subscale, including the results of the included randomized-controlled trials, with relevant subtotals for benzodiazepine and antidepressant subgroups. Assessment of heterogeneity, overall effect and subgroup difference is included.

with careful consideration given to the risks and benefits associated with different medication classes. The employment of standardized assessments encompassing both psychic and somatic symptoms of GAD may be valuable in the clinic, as well as in future research. It may also be useful for future treatment guidelines for GAD to explicitly consider symptom subtype.

Credit authorship contribution statement

Chad Beyer: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christopher B. Currin:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Taryn Williams:** Writing – review & editing, Writing – original draft. **Dan J. Stein:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

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