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Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials

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Abstract

No systematic review or meta-analysis using a hard outcome has been conducted on the role of benzodiazepines for generalized anxiety disorder (GAD). The objective of this study was to assess the effectiveness and efficacy of benzodiazepines in the treatment of GAD based on trial drop-out rates. We used a systematic review of randomized controlled trials that compared any of the three best established benzodiazepines (diazepam, lorazepam and alprazolam) against placebo. Our primary outcome for effectiveness was withdrawal for any reason. Our secondary outcome tapping efficacy was withdrawal due to lack of efficacy, and that tapping side effects was withdrawals due to adverse events.

We included 23 trials. Pooled analysis indicated less risk of treatment discontinuation due to lack of efficacy for benzodiazepines, compared to placebo, relative risk (RR) 0.29 (95% CI 0.18–0.45; $p < 0.00001$). Nevertheless, pooled analysis showed no conclusive results for risk of all-cause patient discontinuation, RR 0.78 (95% CI 0.62–1.00; $p = 0.05$). Meta-regression model showed that 74% of the variation in logRR across the studies was explained by year of publication ($p < 0.001$).

This systematic review did not find convincing evidence of the short-term effectiveness of the benzodiazepines in the treatment of GAD. On the other hand, for the outcome of efficacy, this review found robust evidence in favour of benzodiazepines. Due to the heterogeneity induced by year of publication, three hypotheses are plausible when it comes to being able to account for the differences between efficacy and effectiveness observed in the outcomes (publication bias, quality of the trial literature and a non-differential response to the placebo effect).

Keywords

generalized anxiety disorder, benzodiazepines, systematic review, clinical trial

Introduction

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety sustained over a period of time exceeding 6 months, and leads to severe impairment of different spheres of the subject's life, with great impairment of overall activity (social, occupational and personal) (Struzik *et al*., 2004; Kessler *et al*., 1999). It is estimated that approximately 5% of the population will develop this disorder at some time in their lives (Wittchen *et al*., 1994).

GAD patients often request assistance after having noted the first symptoms over a period of months or even years, by which time the disorder has become chronic and so presents with a worse prognosis. In addition, when patients with GAD request assistance, they frequently report ill-defined and changing symptomatology, thereby hindering correct diagnosis (Kessler *et al*., 2001). Diagnosis is likewise hampered by the coexistence of mood- other anxiety-, and substance-related disorders (Nutt *et al*., 2006; Sareen *et al*., 2006).

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Benzodiazepines are anxiolytic drugs that have traditionally been used in pharmacologic treatment of anxiety conditions and GAD in particular (Mitte *et al*., 2005), though 25–30% of patients do not respond to this treatment. Benzodiazepines act on the benzodiazepine receptors, increasing GABAergic (gamma-aminobutyric acid) activity, at the level of the limbic system (Bordchart, 1999; Sweetman, 2004). The serotoninergic activity in the raphe nuclei that project toward the hippocampus and amygdalae, also affects other monoaminergic, e.g. noradrenergic and dopaminergic, systems.

Due to its active ingredients, this is a drug that can generate a high rate of abuse and physical and psychiatric dependency (Schweizer and Rickels, 1998), and it is therefore contraindicated – or caution is advised – in any patients presenting with addictive problems and all those whose personality traits render them prone to substance addiction (Mahe and Balogh, 2000). Moreover, the use of these substances seems to be associated with sedation, reduced coordination, cognitive impairments (Barker *et al*., 2004), and increased accident proneness (Neutel, 1995; Neutel *et al*., 1996), so that the spread in the use of benzodiazepines has been controversial (Stewart, 2005).

On the basis of data yielded by clinical research, it would appear that reliance on benzodiazepines for treatment of GAD has declined since they were first used, with very positive outcomes being obtained in initial studies followed by an ensuing decrease in effectiveness thereafter. However, no systematic review or meta-analysis has been conducted on the role of benzodiazepines for GAD (Rickels and Rynn, 2002). This is particularly lamentable because 'hard' variables, such as withdrawals of subjects before the conclusion of studies, are seldom taken into consideration (Lieberman *et al*., 2005). This is an easily applicable measure that has important implications in every day clinical practice. Accordingly, this study sought to use a systematic review and meta-analysis to show the real effectiveness of these anxiolytic compounds in the treatment of GAD, especially in the short term, and explain the heterogeneity in the results.

Methods

Identification of studies

We searched Medline (1966–January 2005), Embase (1974–January 2005), and the Cochrane Controlled Trials Register (CENTRAL) (January 2005), for papers in all languages, using the following search terms: benzodiazepine*, diazepam*, lorazepam*, alprazolam*. In addition, a manual search was made of references cited in the papers retrieved and the Internet.

Inclusion criteria

Studies included in this systematic review were all those that met the definition of being double-blind, randomized placebo-controlled trials that compared any of the three best established benzodiazepines (diazepam, lorazepam and alprazolam) against placebo for the treatment of GAD.

Selection procedure, data extraction and quality assessment

Studies that fulfilled the inclusion criteria were selected for comprehensive analysis, quantitative as well as qualitative. The quality of the randomized clinical studies was evaluated by reference to their clinical relevance and methodologic quality.

Outcome measures

We chose withdrawals from trials for any reason as the principal outcome measure in this review, as was done in the recently published large trial in schizophrenia called CATIE (Lieberman *et al*., 2005). We argue that withdrawal for any reason represents the most comprehensible and comprehensive overall index of effectiveness of any intervention. The principal outcome measure for ascertaining the safety of the treatment was study withdrawals due to adverse event. Withdrawals due to lack of efficacy will be used as a secondary measure tapping efficacy, as opposed to effectiveness, of an intervention in question.

Data synthesis

All studies were examined in detail, with data on withdrawals being collected and the complete intervention being reviewed in each instance. The joint relative risk (RR) was calculated with the aid of Mantel-Haenszel's fixed effects model (Mantel and Haenszel, 1959; Deeks and Altman, 2001), and in those cases where moderate heterogeneity was in evidence, DerSimonian and Laird's (1986) random effects model and its 95% CI was used. Chi-squared tests were run, I-squared statistic (the percentage of total variation across studies due to heterogeneity) computed (Higgins *et al*., 2003) and figures inspected to detect any possible statistical heterogeneity among the trial outcomes. $p < 0.05$ according to chi-squared test and I-squared $>50\%$ will be considered indicative of heterogeneity. The former is dependent on sample size while the latter is not. To explain heterogeneity by reference to a continuous measure, a meta-regression was performed on the basis of the above assumptions, using year of publication of all studies included in the meta-analysis as the explanatory variable of heterogeneity. To study a possible publication bias a Begg's funnel plot with pseudo 95% confidence limits was used. All analyses were performed with RevMan 4.2 and STATA/SE 8.0 user for Meta-analysis (Sharp and Sterne, 1997; The Cochrane Collaboration, 2003).

Results

The search strategies implemented yielded a total of 1217 references that, in some way, linked generalized anxiety disorder to one or more of the medical drugs targeted for evaluation in this review. Following a critical perusal of the Abstracts, a total of 137 studies could then be identified as potentially eligible for inclusion and a total of 1080 Abstracts directly excluded. Most of these references were excluded due to their research designs: no control groups; narrative reviews; before and after designs; or quasi random allocation.

After this initial screening, a comprehensive analysis based on the complete paper, was made of those studies with potential inclusion criterion. This led to a total of 114 studies being excluded for different reasons, chief among which were lack of data on: the outcome measure required for review purposes; the intervention; and the diagnostic criteria. Accordingly, a total of 23 studies were finally deemed to have been included for statistical analysis (Fig. 1).

Study populations

Participants in the clinical trials included in this review were aged from 17 to 70 years, and sample sizes ranged from 20 to 213 participants per trial. In 18 studies the population selected was outpatient, with five studies omitting to report on this aspect. Of the 23 studies included, only four met GAD diagnostic criteria as per the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV), while the remaining studies met GAD diagnostic criteria as per the DSM-III and DSM-III-R. The most frequent exclusion criteria in the initial screening of the clinical trials analysed pertained to concomitant psychiatric disorders, evaluated by means of standardized diagnostic assessment scales. Similarly, participants whose clinical histories showed them to be consuming or dependent on substances of abuse or registering other medical problems, were also excluded. Although trial duration ranged from 2 through 24 weeks, it should be noted that the most frequent intervention – as reported by 14 of the 23 studies analysed – lasted 4 weeks. Indeed, only one study involving more than 8 weeks of treatment was included. The type of dose administered during the studies was fixed in 13, and flexible in 10 trials. The most frequent intervention was diazepam versus placebo used in 12 studies, followed by lorazepam versus placebo in seven studies and, lastly, alprazolam versus placebo in four studies.

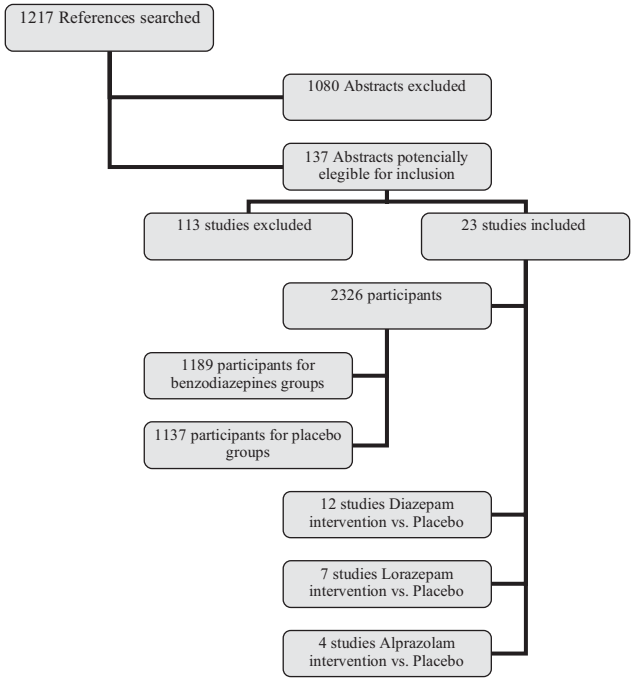

Figure 1 Flowchart showing selection of trails.

Quality of included studies

The main methodologic problem of the studies covered by this review resided in the fact that there was no clear report of the allocation concealment procedure adopted during the randomization process (e.g. a central randomization that is administrated by someone who is not responsible for recruiting subjects). Trial reports should provide information confirming that allocation to groups remained unknown, at least until the time of such allocation (Giacinti *et al*., 2006; Jüni *et al*., 2001). Accordingly, when a study furnishes no type of information on the randomization process, a high risk of selection bias must be assumed to be present. On the other hand most of the trials found were conducted many years ago in accordance with their current scientific and local ethics approval.

One indispensable inclusion criterion in this review was the need for double-blinding in the design of each study. Nonetheless, one of the main limitations of medical drug comparisons resides in the practical impossibility of blinding subjects, since each intervention has adverse effects that are, to a greater or lesser degree, characteristic.

Withdrawals for any reason Benzodiazepines versus placebo. This analysis comprised 23 studies, with a combined sample of 2326 subjects, 1189 of whom belonged to the benzodiazepine group and 1137 to the placebo group. In conjunction, the 23 studies analyzed displayed statistical heterogeneity (chi-squared test: 41.80; $p = 0.007$; $I^2 = 47.4\%$). The magnitude of the relative risk of withdrawal for any reason, using a random effects model was 0.78 (95% CI 0.62–1; $p = 0.05$), practically on the limit of statistical significance in favour of benzodiazepines (Fig. 2).

Withdrawals due to lack of efficacy Benzodiazepines versus placebo. This analysis comprised 20 studies, with a combined sample of 2061 subjects, 1036 of whom belonged to the benzodiazepine group and 1025 to the placebo group. Taken together, the 20 studies analysed displayed no statistical heterogeneity (chi-squared test: 8.17 $p = 0.88$; $I^2 = 0\%$). The magnitude of the relative risk of withdrawal due to lack of efficacy, using a fixed effects model, was 0.29 (95% CI 0.18–0.45; $p < 0.00001$) in favour of benzodiazepines (Fig. 3).

Withdrawals due to adverse event Benzodiazepines versus placebo. This analysis comprised 19 studies, with a combined sample of 1950 subjects, 980 of whom belonged to the benzodiazepine group and 970 to the placebo group. As a whole, the 19 studies analysed displayed statistical homogeneity (chi-squared test: 20.49; $p = 0.15$; $I^2 = 26.8\%$). The magnitude of the relative risk of withdrawal due to adverse event, using a fixed effects model, was 1.54 (95% CI 1.17–2.03; $p = 0.002$), i.e. a risk of over 50% for the benzodiazepine group.

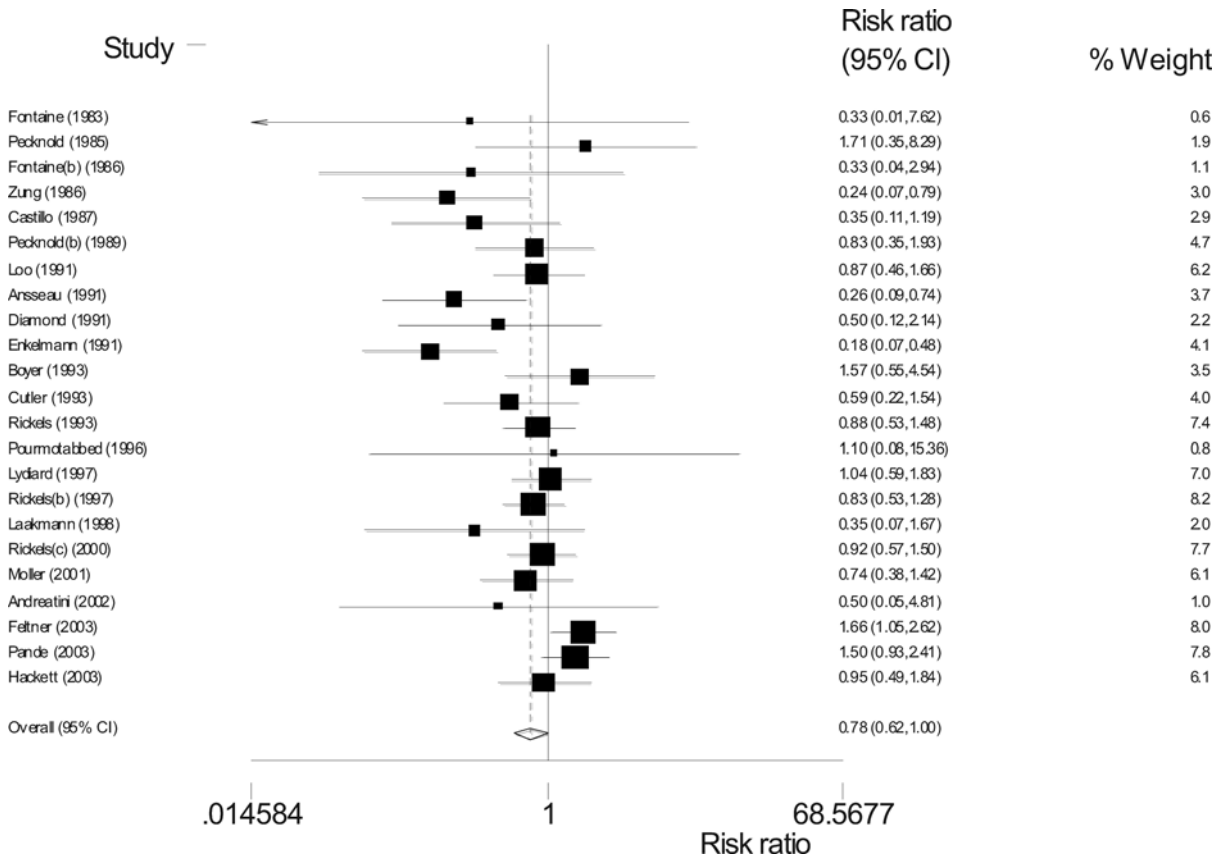

Figure 2 Effectiveness: Withdrawals for any reason on benzodiazepines vs. placebo.

Explanation of quantitative results

The above comparisons highlight the great difference that exists between results in terms of efficacy (withdrawal due to lack of efficacy) and those in terms of effectiveness (withdrawal for any reason). Furthermore, there is considerable heterogeneity among the outcomes of the respective trials in terms of effectiveness, or what amounts to the same thing, the differences observed in the results are not due to chance, thus making it essential to ascertain precisely which variables are exerting influence.

Explanation for the heterogeneity in the effectiveness-related results

As an explanation for the heterogeneity observed, different approaches were made, based on a detailed study of these results taken individually.

First, diagnostic criterion: This meta-analysis was performed by grouping studies according to the diagnostic criterion used. This analysis enabled us to ascertain whether or not the diagnostic criterion used was a source of heterogeneity in the results observed.

Withdrawal for any reason (only studies using DSM-III) Overall, the 11 studies analysed displayed statistical homogeneity ($p = 0.09$; $I^2 = 38.6\%$). The magnitude of the relative risk of withdrawal for any reason was 0.57 (0.39–0.83; $p = 0.004$), with this being statistically significant in favour of benzodiazepines (Fig. 4A).

Withdrawal for any reason (only studies using DSM-III-R) Taken together, the eight studies analysed displayed statistical homogeneity ($p = 0.36$; $I^2 = 9.0\%$). The magnitude of the relative risk of withdrawal for any reason was 0.85 (0.62–1.16; $p = 0.31$), with no statistically significant differences in evidence (Fig. 4A).

Withdrawal for any reason (only studies using DSM-IV) As a whole, the three studies analysed displayed statistical homogeneity ($p = 0.38$; $I^2 = 0\%$). The magnitude of the relative risk of withdrawal for any reason was 1.43 (1.06–1.92; $p = 0.02$), with statistically significant differences in favour of the placebo group (Fig. 4A).

Second, Individual outcomes: this meta-analysis was performed by separately analysing the different medical drugs assessed, with the aim, as in the previous approaches, of reducing heterogeneity.

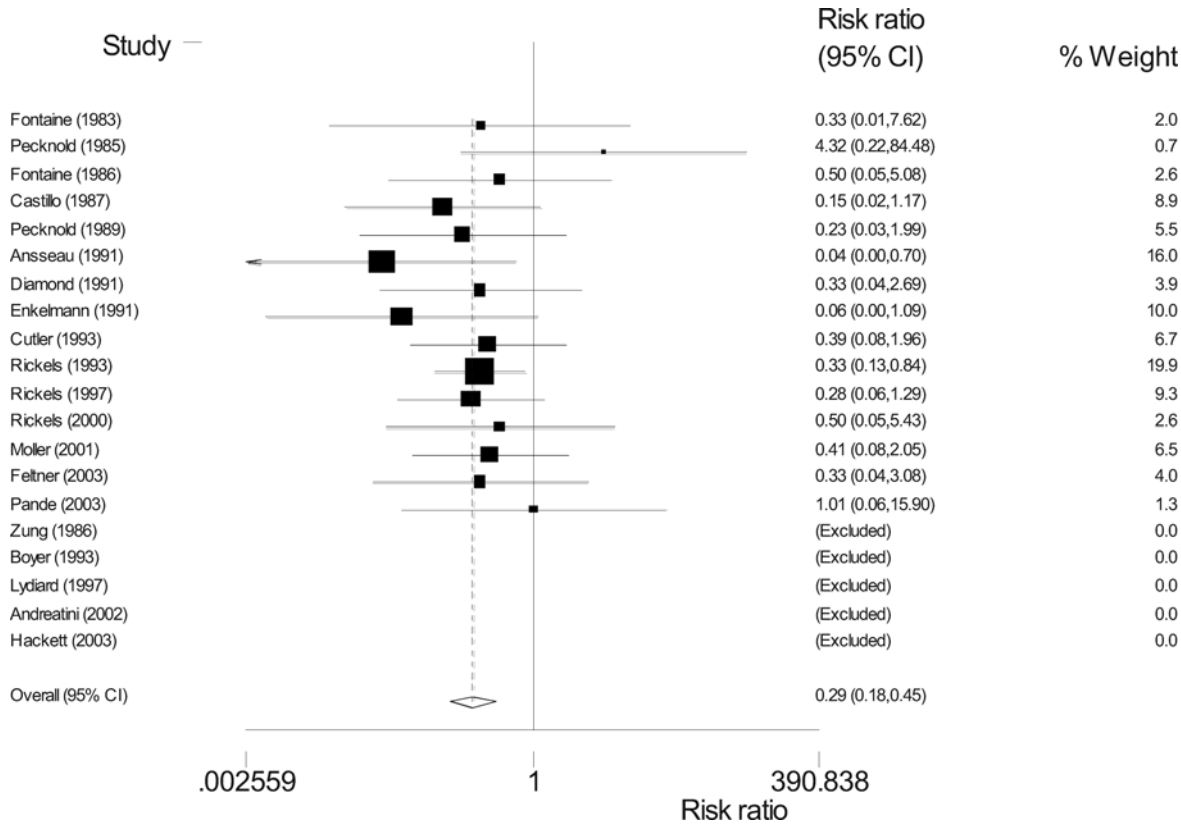

Figure 3 Efficacy: Withdrawls due to lack of efficacy on benzodiazepines vs. placebo.

Withdrawal for any reason (studies with diazepam) Overall, the 12 studies analysed displayed statistical homogeneity ($p = 0.35$; $I^2 = 9.6\%$). The magnitude of the relative risk of withdrawal for any reason was 0.80 (0.64–0.99; $p = 0.04$), with statistically significant differences in favour of diazepam (Fig. 4B).

Withdrawal for any reason (studies with lorazepam) As a whole, the seven studies analysed displayed statistical heterogeneity ($p = 0.04$; $I^2 = 54.0\%$). The magnitude of the relative risk of withdrawal for any reason was 1.12 (95% CI 0.86–1.46; $p = 0.41$), with no statistically significant differences in evidence (Fig. 4B).

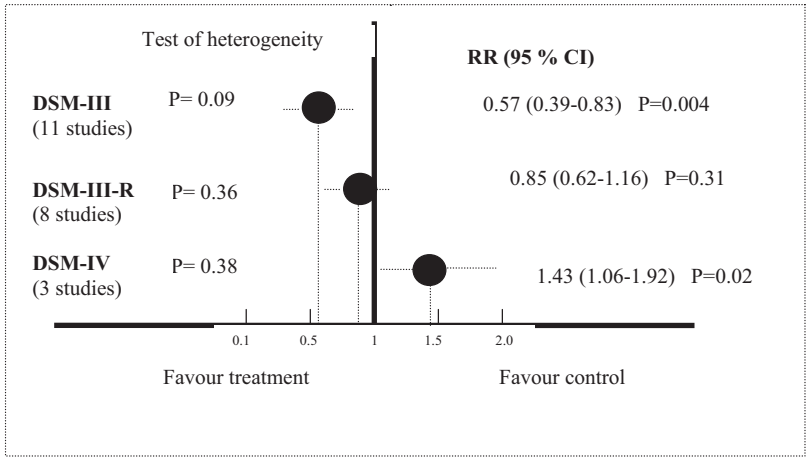

Figure 4A Withdrawls for any reason. Pooled analysis for: DSM-III; DSM-III-R and DSM-IV.

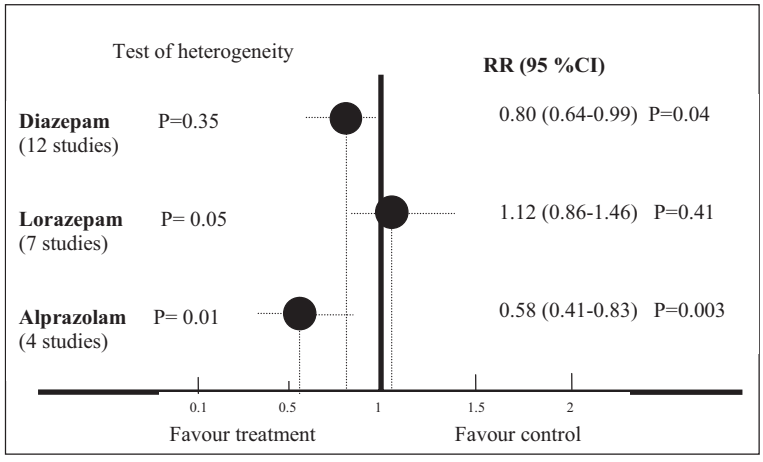

Figure 4B Withdrawls for any reason. Pooled analysis for: Diazepan; lorazepam and alprazolam.

Withdrawal for any reason (studies with alprazolam) In conjunction, the four studies analysed displayed statistical heterogeneity ($p = 0.01$; $I^2 = 72.4\%$). The magnitude of the relative risk of withdrawal for any reason was 0.58 (95% CI 0.41–0.83; $p = 0.003$), with statistically significant differences in favor of alprazolam (Fig. 4B).

Meta-regression

After a detailed analysis of the results of the two previous approaches, along with close observation of the initial forest plot (Fig. 2), we decided to ascertain what heterogeneity was contributed to outcomes by year of publication of the trials. This variable also seems to mediate in the two previous approaches. We therefore performed a post-hoc meta-regression, using the year of publication of all studies included in the meta-analysis as the explanatory variable, and the relative risk (RR) of therapeutic efficacy in each study as the dependent variable. The meta-regression model showed that 74% of the variation in logRR across the studies was explained by year of publication ($p < 0.001$) (Fig. 5).

Publication bias

Lastly, when an analysis was performed to ascertain the risk of publication bias in the results, a possible publication bias was also observed. Begg's test: $p < 0.012$ (Fig. 6).

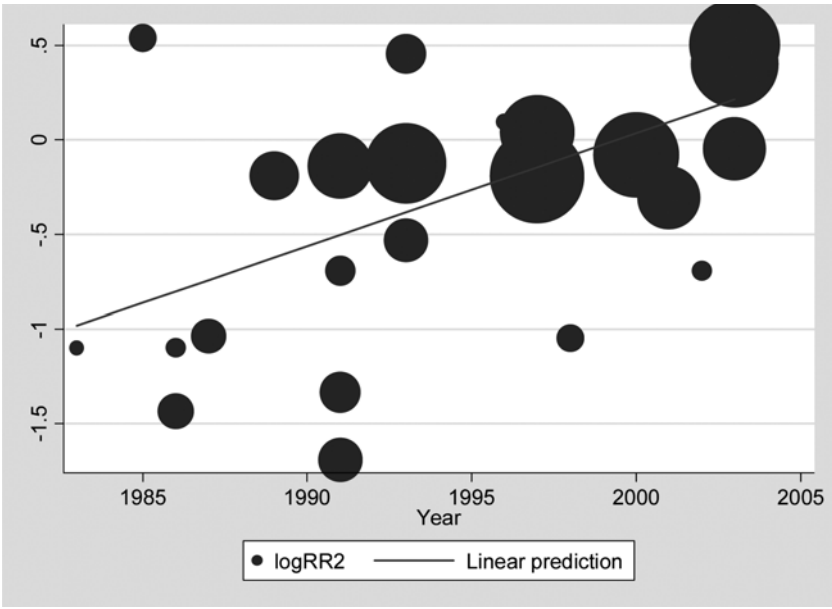

Figure 5 Meta-region model using the year of publication as explicative variable and the logRR for treatment discontinuation as dependent variable.

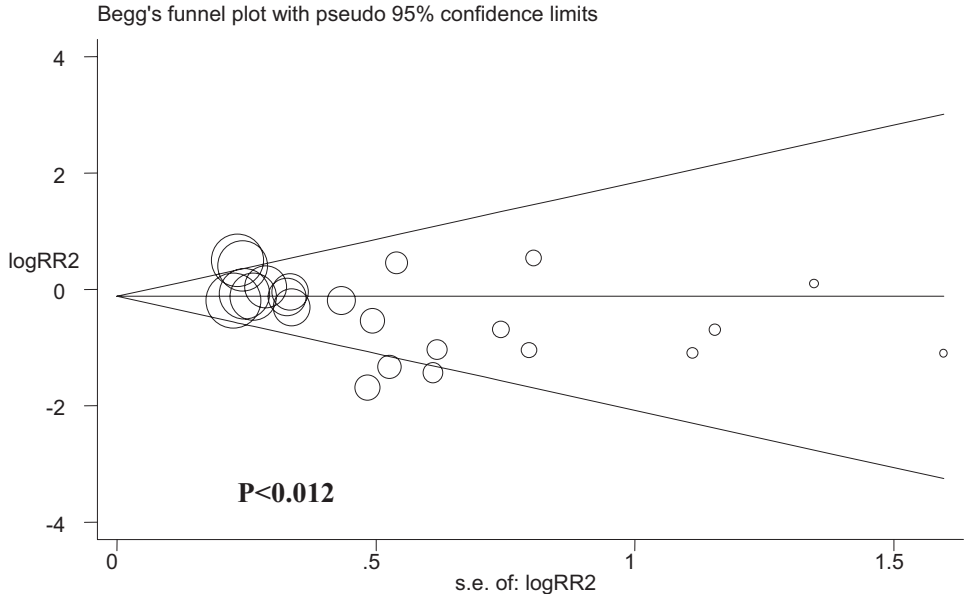

Figure 6 Study of publication bias.

Discussion

This is the first rigorous systematic review of benzodiazepines for generalized anxiety disorder.

First, this systematic review failed to find convincing evidence of the short-term effectiveness of the benzodiazepines in the treatment of generalized anxiety disorder based on withdrawal rates. However, an index of efficacy based on early withdrawals from studies due to lack of efficacy indicated that benzodiazepines (alprazolam, diazepam and lorazepam) are efficacious as against placebo in short-term treatment of generalized anxiety disorder. In other words, the studies assessed have a short-term rate of withdrawals for any reason which, though not due to the efficacy of benzodiazepinic drugs, is statistically comparable to the rate of withdrawals generated in the groups that received a placebo. This study withdrawal rate is particularly important in view of the fact that the trials were conducted in the very short term, with most lasting just 4 weeks. In clinical practice, this could well imply appreciable withdrawal rates in both short- and long-term treatments (Allgulander *et al*., 2003).

Second, we encountered substantial heterogeneity in our meta-analytic results. Practically all the previous approaches reduce the initially observed degree of heterogeneity. Yet these approaches also display a common feature that may, in itself, account for such heterogeneity, the feature that was analysed in the meta-regression section, namely, year of publication. In this case, up to 74% of the inter-study heterogeneity is explained. The conclusion to be drawn from this analysis is that the more recent the study, the smaller the positive effect seemingly found in favour of benzodiazepines: in contrast, the longer ago the publication of the study, the greater the effect in favor of benzodiazepines (lower study withdrawal rates).

Due to the heterogeneity induced by year of publication, three hypotheses are plausible when it comes to being able to account for the differences between efficacy and effectiveness observed in the outcomes. The first hypothesis turns on the well-known publication bias (Rothstein *et al*., 2005), that is to say, clinical trials with negative outcomes tend to be published in lower numbers than those with positive outcomes (Dubben and Beck-Bornholdt, 2005). After observing the meta-analysis of withdrawals for any reason, together with the analysis specifically performed to ascertain the overall risk of such bias in the meta-analysis, it will be seen that the oldest studies, albeit rather imprecise (small sample sizes), mainly tend to report positive outcomes (Copas and Shi, 2000). This could have boosted clinical research in this field of study, subsequently leading to observation of less positive results based on more precise studies (larger sample sizes) (Toma *et al*., 2006). At a clinical level, these initial positive results (since negative results were not published) could well have heightened the perception of the effectiveness of benzodiazepines in the treatment of this disorder.

The second hypothesis is based on the quality of the trial literature. Quality in the reporting of data of a clinical trial is known to be directly related to the outcomes observed by such a trial (Schulz *et al*., 1995), or what comes to the same, the better the quality of the data-reporting, the less pronounced the effect observed in favor of experimental intervention. The reason for this fact is that the biases created by poor quality in study design usually tend to overestimate the effect of the intervention being assessed (Moher *et al*., 2004). Logically, this fact is also connected with the year of publication, since in recent years journals have demanded higher quality in the reporting of clinical studies (Moher *et al*., 2001). This is why the oldest studies could be showing more pronounced effects in favour of benzodiazepines due to a higher risk of bias.

Yet, on demanding higher quality, the most recent studies would, in contrast, display less pronounced effects in favour of benzodiazepines.

Lastly, the third hypothesis postulates that the observed heterogeneity in the outcomes could be caused by a non-differential response to the placebo effect for intervention and control groups. The protocols required of clinical trials are ever stricter insofar as patient inclusion is concerned. This means that the samples of subjects used in clinical trials are becoming further and further removed from subjects treated in daily clinical practice. Subjects without multimedication or co-interventions, with very well-defined symptomatology and no associated comorbidity would not seem to be the standard profile of the patient that seeks psychiatric help. Hence, a subject in a clinical trial (ideal patient) will have a better response to any intervention, including a placebo (Walach *et al*., 2005), and the results in both groups (intervention and control) tend to be similar.

Clinical implications

At a clinical level, benzodiazepines, as a treatment for GAD have, until very recently, been the most widely used anxiolytic drugs (Gorman, 2003). The earlier trial results, described above, coupled with these drugs' very short-term effects on anxiety (Struzik *et al*., 2004) and acceptable initial tolerance, converted benzodiazepines into the gold standard (Rynn and Brawman-Mintzer, 2004). Subsequently, and due mainly to the adverse effects generated by these compounds – such as dependency, low long-term tolerance, or cognitive and motor disorders, including work and traffic accidents (Rudolph, 2001) – research into the treatment of this disorder shifted towards safer and more effective compounds, such as buspirone or selective serotonin reuptake inhibitor antidepressants (Goodman, 2004). Yet benzodiazepine compounds remained the gold standard in controlled clinical studies (Rickels and Rynn, 2002).

In contrast to the results of earlier reviews (Davidson, 2001), however, the outcomes observed in this review seem to show that, based on total withdrawals from clinical studies, benzodiazepines do not even prove definitively superior to placebo in the short term. In a clinical (though not experimental) setting, subjects could withdraw from treatment a few weeks after the start in the same proportions as subjects who receive a placebo in a clinical trial, indicating that benzodiazepines are not an effective treatment for GAD. One possible reason for the contradictory results yielded by the different reviews could reside in their respective search dates as well as comprehensiveness of their data searches. In other words, whereas the initial reviews would have only encountered saliently positive results, due in part to the above-mentioned risk of publication bias, as research gradually progressed and gained in precision with larger-sized samples, outcomes have tended to display less positive effects. Furthermore, special mention should also be made of the outcome measure used in this review, since it differed from other more psychometric measures, such as the rating scales used as the principal variable of effectiveness in other reviews (Pollack *et al*., 2003). In our case, we endeavoured to obtain a composite measure close to clinical reality and, thus easily interpretable by clinicians and consumers alike.

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