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# The Efficacy and Safety of Alprazolam Versus Other Benzodiazepines in the Treatment of Panic Disorder

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**Abstract:** We performed a meta-analysis of all single- or double-blind, randomized controlled trials comparing alprazolam to another benzodiazepine in the treatment of adult patients meeting the *Diagnostic and Statistical Manual of Mental Disorders, Third or Fourth Edition*, criteria for panic disorder or agoraphobia with panic attacks. Eight studies met inclusion criteria, describing a total of at least 631 randomized patients. In the pooled results, there were no significant differences in efficacy between alprazolam and the comparator benzodiazepines on any of the prespecified outcomes: improvement in mean panic attack frequency (between-arm weighted mean difference of 0.6 panic attacks per week; 95% confidence interval [CI], -0.3 to 1.6), improvement in Hamilton Anxiety Rating Scale score (weighted mean difference of 0.8 points; 95% CI, -0.5 to 2.1), and proportion of patients free of panic attacks at the final evaluation (pooled relative risk, 1.1; 95% CI, 0.9–1.4). Statistical heterogeneity on prespecified outcomes was not eliminated by stratification on baseline anxiety level. The available evidence fails to demonstrate alprazolam as superior to other benzodiazepines for the treatment of panic disorder.

**Key Words:** panic disorder, alprazolam, benzodiazepine, meta-analysis  
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When pharmacologic agents are deemed necessary in the management of panic disorder (PD), current guidelines recommend treatment with a selective serotonin reuptake inhibitor (SSRI)<sup>1–3</sup> with tricyclic antidepressants as alternative first-line agents. Benzodiazepines are either no longer recommended<sup>3</sup> or recommended only as a secondary treatment strategy.<sup>1,2</sup>

Alprazolam, a high-potency triazolobenzodiazepine, is supported in the treatment of PD by a number of short-term efficacy studies,<sup>4–10</sup> and by 2 large, randomized, cross-national clinical trials demonstrating short-term efficacy and clinically acceptable tolerability against placebo<sup>11,12</sup> and imipramine.<sup>13</sup> A few longer-term follow-up studies have demonstrated that alprazolam's treatment effect could be sustained for periods greater than 1 year.<sup>14–17</sup>

However, many studies have demonstrated alprazolam's propensity to produce clinically significant withdrawal symptoms and rebound anxiety.<sup>18–21</sup> At a mechanistic level, these symptoms can be conceptualized as a long-term homeostatic adaptation to persistent  $\gamma$ -aminobutyric acid (GABA) agonism, resulting in down-regulation of the GABA-A system and consequent up-regulation of the GABA-mediated level of baseline anxiety.<sup>22</sup> Relative to other benzodiazepines, alprazolam has a short half-life, a high binding affinity to the GABA receptor, and a rapid onset and offset of action, pharmacokinetic properties that are associated with greater risk of dependency and withdrawal.<sup>23</sup> The intensity and prevalence of rebound anxiety with alprazolam accordingly seems greater than with other benzodiazepines.<sup>24,25</sup> Alprazolam is increasingly being used as a drug of abuse<sup>26</sup> and is more toxic than other benzodiazepines in overdose.<sup>27</sup>

Despite this, alprazolam prescribing remains common and continues to rise.<sup>28–30</sup> Alprazolam was the eighth and ninth most prescribed medication in the United States for all causes in 2008 and 2009, respectively,<sup>30</sup> with prescription volume rising by 71% (24.7–42.4 million) between 1998 and 2007.<sup>31</sup> In Australia, where government-sponsored prescription of alprazolam is restricted to secondary treatment of PD, prescriptions rose approximately 100% (0.308–0.616 m) between 1997 and 2007.<sup>32</sup>

Given its increasing use and potential to produce adverse outcomes, the role of alprazolam in PD deserves critical reevaluation. We performed a meta-analysis to determine whether the weight of clinical evidence suggests that alprazolam is superior to other benzodiazepines in the management of PD.

## METHODS

For a full description of methods please refer to the Supplemental Material (Supplemental Digital Content 1, <http://links.lww.com/JCP/A76>). A systematic search on major electronic databases (Cochrane Controlled Trials Register, PubMed, Embase, and PsycINFO) using a Boolean Search Strategy with key words “panic disorder” AND (“alprazolam” OR “Xanax”) was conducted on April 13, 2010. Inclusion criteria required studies to be single- or double-blind, randomized controlled trials comparing 2 or more doses of alprazolam with any alternative benzodiazepine for the treatment of patients 18 years or older with a diagnosis of PD (or agoraphobia with panic attacks) according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition or Fourth Edition, Text Revision*, criteria. One or more of the following outcomes also had to be reported: change in panic attack frequency (PAF; primary meta-analysis outcome), change in Hamilton Anxiety Scale (HAM-A) score, proportion of patients free of panic attacks at study conclusion, self- or clinician-rated global improvement measures, or a measure of anxiety or depressive symptoms at study conclusion. Two authors independently reviewed the titles and abstracts of 548 articles initially identified by our search strategy and retrieved 30 articles for further evaluation. Sixteen of these articles had potentially relevant data and were reviewed by all authors. Each

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author independently concluded that only 8 of these studies met inclusion criteria. Using a standardized data extraction work sheet, 2 authors independently extracted study design, patient population, number of patients enrolled and randomized, comparator benzodiazepine, the prespecified meta-analysis outcomes, and data on adverse effects from each of the 8 studies. Disagreements were resolved by discussion after rereview of the articles. Quality assessment was undertaken in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.<sup>33</sup> Meta-analysis for each outcome was conducted using a random effects model by the method of DerSimonian and Liard.<sup>34</sup> Sensitivity analyses were performed as described in the supplementary material (Supplemental Digital Content 1). Data synthesis and all statistical analyses were completed using STATA version 11,<sup>35</sup> using 2-sided tests at a significance level of 0.05.

## RESULTS

### Search Results and Description of Studies

Eight studies met inclusion criteria,<sup>6,36–42</sup> and basic descriptors of each study are summarized in Table 1. Summing across all studies, at least 631 patients were randomized to either alprazolam or comparator benzodiazepine arms. This underestimates the true number of enrolled subjects because 1 article reported the number of patients completing the trial but not the number of patients initially randomized.<sup>37</sup>

### Quality Assessment

None of the included studies specified their method of randomization. Five studies<sup>36,38,39,41,42</sup> clearly described an adequate blinding process, and in 3 studies,<sup>6,37,40</sup> the blinding process was unclear. Three studies<sup>38,41,42</sup> performed intention-to-treat (ITT) analyses for all outcomes, 3 studies<sup>36,39,40</sup> reported ITT analyses for some outcomes, and 2 studies<sup>6,37</sup> reported results only on those patients completing the trial.

### Outcomes

#### Panic Attack Frequency

Five studies reported the mean (SD) for PAF in each arm at both baseline and final assessment and could be used in the pooled analysis of this outcome.<sup>6,38,40–42</sup> The change in mean PAF from baseline to final evaluation ( $\Delta$ PAF) was summarized for alprazolam and comparator arms in each trial. A trial-level summary measure was obtained by subtracting the alprazolam arm  $\Delta$ PAF from the comparator arm  $\Delta$ PAF to obtain a “difference in  $\Delta$ PAF.” In the pooled analysis, there was no significant difference in mean PAF improvement between the alprazolam and comparator arms (weighted mean difference in  $\Delta$ PAF of 0.6 panic attacks per week, 95% confidence interval [CI],  $-0.3$  to  $1.6$ ; Fig. 1: PAF Forest Plot). Significant between-study heterogeneity prompted post hoc removal of a study with a particularly low mean weighted baseline PAF, but reanalysis of the remaining studies neither changed the conclusion of the original analysis nor improved the between-study heterogeneity (see Supplemental Material, Supplemental Digital Content 1).

#### Hamilton Anxiety Scale

Six studies reported mean HAM-A scores with SDs at both baseline and final evaluation.<sup>6,36–38,40,42</sup> A trial-level summary measure, the “difference in  $\Delta$ HAM-A,” was obtained by a method analogous to that described for the “difference in  $\Delta$ PAF.” The pooled analysis demonstrated no difference in mean HAM-A improvement between alprazolam and comparator benzodiazepine

(between-arm weighted mean difference of 0.8 points; 95% CI,  $-0.5$  to  $2.1$ ; See Supplementary Figure S3 [Supplemental Digital Content 2]: HAM-A Forest Plot, <http://links.lww.com/JCP/A80>). Significant between-study heterogeneity was not eliminated by a post hoc exploratory stratification on baseline HAM-A score (see Supplemental Material, Supplemental Digital Content 1).

### Proportion of Panic Attack-Free Patients

Six trials reported data on the proportion of subjects in each arm who were “panic attack-free” at trial conclusion, defined as either no reported panic attacks for 1 week<sup>38–40,42</sup> or 2 weeks<sup>36,41</sup> before the final assessment. Only 3 studies clearly describe performing an ITT analysis<sup>38,41,42</sup> and the remainder report outcome data only for subjects that completed the trial. The main analysis for this end point was therefore performed using data from all trials for “completers” only. The pooled results for this analysis demonstrated no significant difference between alprazolam and comparator benzodiazepines (pooled relative risk,  $1.1$ ; 95% CI,  $0.9$ – $1.4$ ; Supplementary Figure S4 [Supplemental Digital Content 3]: Forest Plot for PA-Free, <http://links.lww.com/JCP/A81>), with no significant between-study heterogeneity ( $I^2 = 0.36$ , heterogeneity  $\chi^2 P = 0.17$ ). As described further in the supplementary methods and results, “conservative ITT” and “pharmaceutical optimists’ ITT” sensitivity analyses were then performed to explore the robustness of this result, and the conclusions of these sensitivity analyses did not differ from those of the main analysis.

One additional sensitivity analysis was performed after removing the only study with a crossover design.<sup>39</sup> This had no substantial effect on the point estimate, CI, or conclusion of the analysis among completers (pooled relative risk,  $1.1$ ; 95% CI,  $0.9$ – $1.4$ ) or of the accompanying sensitivity analyses.

### Other Prespecified Outcome Measures

For self- and clinician-rated global improvement measures and measures of anxiety or depressive symptoms at study conclusion, 2 or fewer studies reported results on common outcome measurement scales. Because this would impair both the validity and interpretability of quantitative data synthesis, a meta-analysis on these outcomes was not performed.

### Adverse Effects

Definitions of adverse effects were inconsistent across the 8 studies. Moreover, all authors felt that the adverse effect surveillance and reporting in all studies were of poor quality. As such, the authors agreed a quantitative synthesis of adverse effect data was not appropriate. The most commonly reported adverse effect was sedation, reported in 6 studies.<sup>37–42</sup> Participant dropout rates due to adverse effects were reported in 6 studies,<sup>36,38–42</sup> and this did not differ between the alprazolam and comparator arms. No study reported a clinically significant difference in tolerability between alprazolam and comparative benzodiazepine. No study reported data on tolerance or dependence to administered agents.

### Examining for Small Study Effects and Potential Publication Bias

We examined for small study effects (for which publication bias is 1 explanation) using the “difference in  $\Delta$ PAF” outcome. The Egger test for small study effects suggested no such effects were present ( $P = 0.12$ ; see Supplementary Figure S7 [Supplemental Digital Content 4]: Egger Plot for Small Study Effects, <http://links.lww.com/JCP/A82>). However, the funnel plot demonstrated obvious asymmetry, suggesting published small studies

TABLE 1. Identified Studies Meeting Inclusion Criteria

	Comparator BZD	Study Design	Subjects (Alprazolam/Comparator BZD), n	Definition of PD	Active Treatment Study Duration	ITT	Outcome Measures
Dunner et al <sup>6</sup>	Diazepam	DBRCT with a third placebo arm	16/16	DSM-III PD plus DSM-III GAD with >1 panic attack/wk	6–9 wk with taper	No	HAM-A, PAF
Charney and Woods <sup>36</sup>	Lorazepam	DBRCT/longitudinal intervention	27/21	DSM-III PD with limited or extensive phobic avoidance	6 wk	Partial	HAM-A, Global Impression Scale (physician and patient rated)
Meco et al <sup>37</sup>	Etizolam	DBRCT	15/15	DSM-III PD or agoraphobia with panic attacks	6 wk	No	HAM-A, PAF, Global Improvement (patient rated)
Pyke and Greenberg <sup>39</sup>	Adinazolam	Crossover, DB	14 (crossover)	DSM-III PD or agoraphobia with panic attacks	8 wk	8 wk	Sheehan Anxiety Scale, Global Improvement Scale (physician rated), self-report symptom inventory
Schweizer et al <sup>40</sup>	Lorazepam	DBRCT efficacy analysis	30/30	DSM-III PD or agoraphobia with panic attacks	6 wk	Partial	PAF, HAM-A, Global Impression Scale (physician and patient rated), Phobic Avoidance Scale
Tesar et al <sup>41</sup>	Clonazepam	DBRCT with a third placebo arm	24/26	DSM-III PD or agoraphobia with panic attacks	6 wk	Yes	Global Impression Scale (physician and patient rated)
Pecknold et al <sup>42</sup>	Alprazolam XR	DBRCT with a third placebo arm	69/70	DSM-III PD or agoraphobia with panic attack	6 wk	Yes	Global Impression Scale (physician rated)
Noyes et al <sup>38</sup>	Diazepam	DBRCT with a third placebo arm	78/81	DSM-III PD or agoraphobia with panic attacks	8 wk	Yes	Global Impression Scale (patient rated), Sheehan Anxiety Scale, HAM-A

BZD indicates benzodiazepine; DB, double-blinded; DBRCT, double-blinded randomized controlled trial; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, Third Edition; GAD, generalized anxiety disorder; XR, extended release.

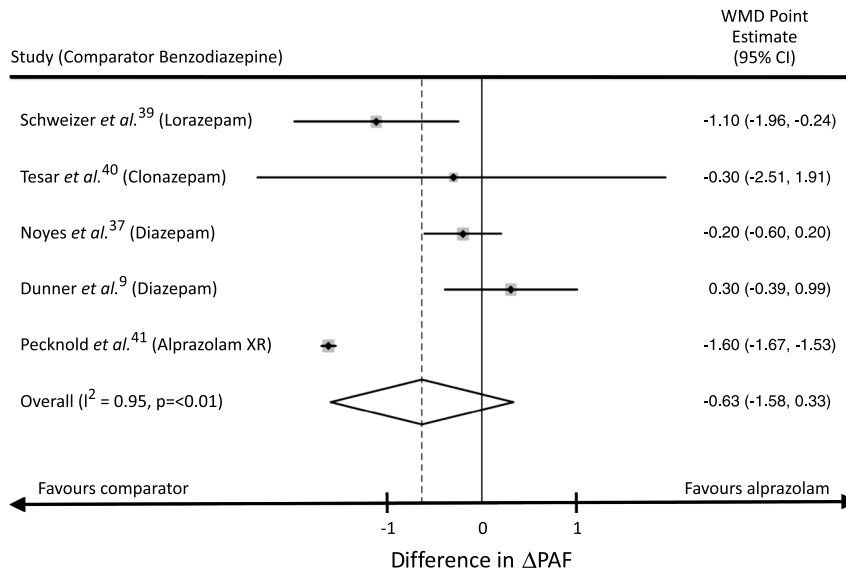


FIGURE 1. Forest plot for between-arm difference in PAF, improvement from baseline to final evaluation.

tend to favor alprazolam (see Supplemental Figure S8 [Supplemental Digital Content 5]; Begg Funnel Plot for Small Study Effects, <http://links.lww.com/JCP/A83>). Because the appearance and validity of these statistical tests can be affected by the choice of outcome measure, by the choice of study weight on the y axis, and particularly by the small number of studies and significant between-study heterogeneity in this meta-analysis, interpretation of these results is difficult.

**DISCUSSION**

This quantitative meta-analysis of all relevant single- or double-blind, randomized controlled trials did not demonstrate an advantage of alprazolam over other benzodiazepines in the management of adult patients with PD or agoraphobia with panic attacks.

Our meta-analysis has several features that may introduce bias and limit the strength of its conclusions. There were only a small number of relevant studies. There was significant between-study heterogeneity in study design, comparator benzodiazepine choice, and in outcome measures reported. None of the studies specified their method of randomization. Three studies<sup>6,37,40</sup> did not clearly describe their blinding processes. Only 4 studies clearly described performing an ITT analysis for all outcomes.<sup>36,38,40,42</sup> Begg test suggested that small study effects were present, raising the possibility of publication bias. The use of broad measures of PD severity (eg, HAM-A, counts of PAF) in included studies is a further limitation. Such measures lack the advantages of specific ratings scales for PD (eg, Panic and Agoraphobia Scale<sup>43</sup> and PD Severity Scale<sup>44</sup>) that measure across multiple domains of PD symptoms and have greater sensitivity in detecting placebo-drug differences in PD. The use of broad measures may not provide reliable evidence of an overall treatment effect, specifically in domains not associated with panic attacks (eg, quality of life).<sup>45</sup> A further limitation of this data set is the absence of systematic measures of the known adverse event profile of these agents, restricting risk-benefit assessment.

Despite these limitations, this meta-analysis suggests that alprazolam is no more effective than other benzodiazepines in the treatment of PD. This needs to be considered along with

alprazolam’s propensity for tolerance, dependence, and toxicity. It is unlikely that its use is restricted to PD and is likely to extend into other mood and anxiety disorders where evidence of preferential efficacy and safety in contrast to other therapies is also absent. Current practice guidelines for PD recommend the use of evidence-based psychological therapies<sup>46</sup> (eg, cognitive behavioral therapy) or SSRIs as first-line monotherapy<sup>1-3</sup> for PD. The advantage of combining therapies remains unclear.<sup>47,48</sup> A few studies have compared the utility of high-potency benzodiazepines, primarily clonazepam, as adjunctive therapy to SSRIs.<sup>49,50</sup> These studies suggest possible short-term advantages to coadministration, but this effect is not sustained beyond a few weeks of treatment. No study has used alprazolam as an adjunct treatment to date.

When compared with placebo, alprazolam’s efficacy in PD<sup>51</sup> has been demonstrated. Other studies have also demonstrated the efficacy of diazepam,<sup>6,43,52</sup> lorazepam,<sup>17,41,53</sup> and clonazepam<sup>54,55</sup> in the treatment of PD. In the short term, alprazolam has not shown clinically different tolerability as compared with other agents; however, studies were not powered for noninferiority or for adverse events.

For the longer term, however, alprazolam has consistently demonstrated significant rebound anxiety, withdrawal symptoms,<sup>23-27</sup> and a propensity for abuse.<sup>32</sup> Alprazolam is also a commonly used drug in overdose situations,<sup>56,57</sup> where it exhibits greater toxicity than other benzodiazepines.<sup>33</sup> It is likely that these effects relate to alprazolam’s short half-life, high potency, and multiple daily dosing requirements.<sup>30,31</sup> For these reasons, clonazepam, a high-potency benzodiazepine with longer half-life,<sup>58</sup> has received attention as an alternative to alprazolam, particularly in patients experiencing interdose anxiety.<sup>59</sup> A few studies have demonstrated successful discontinuation of clonazepam,<sup>54,60</sup> with decreased withdrawal symptoms attributed to its prolonged elimination half-life.<sup>58</sup>

As previously mentioned, alprazolam prescription rates are increasing<sup>28-30</sup> despite no longer being a recommended first-line treatment strategy for PD.<sup>1-3</sup> Alprazolam remains the most prescribed psychotropic drug in the United States.<sup>61</sup> This increase in prescription volume, even if a proportion is attributable to use in other disorders (eg, generalized anxiety disorder), is not supported by clinical guidelines or new clinical trial data.

In a qualitative study of youths<sup>62</sup> attending drug treatment, addiction to alprazolam was perceived to occur very early in treatment, and medical professionals were identified as the drug's greatest facilitators. Inappropriate prescription and management of a medication is more likely to occur when the prescriber is less familiar or has less experience with the appropriate use of the medication. Education campaigns<sup>63</sup> and medication restrictions<sup>63</sup> have been partially effective in reducing inappropriate alprazolam prescribing. However, given the risk versus benefit equation for alprazolam use and the wider availability of more commonly used alternatives, a critical reevaluation of its place in the future treatment of PD is warranted.

#### AUTHOR DISCLOSURE INFORMATION

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