The Management of Panic Disorder

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The evidence for benzodiazepines in panic disorder is compelling; along with the selective serotonin reuptake inhibitors (SSRIs), they are a standard treatment for panic and other anxiety disorders. However, extended-release formulations of these agents may prove to be as effective as the immediate-release formulations, and extended-release agents have clinical benefits that may make them more attractive treatments than the currently available, shorter-acting benzodiazepines. Because of their longer duration of action, extended-release benzodiazepines can protect against breakthrough anxiety and need to be taken only once or twice a day, which may improve compliance in some patients. Because the other standard treatments of panic disorder, the SSRIs, have a slow onset of action, adding an extended-release benzodiazepine to the treatment regimen for the initial 6 to 8 weeks could serve as an effective bridge until the desired SSRI effect is realized.

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The medications of choice for panic disorder are the high-potency benzodiazepines such as alprazolam or clonazepam, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine or sertraline, or a combination of both. However, the first agents that were shown to be effective in panic disorder were the tricyclic antidepressants (TCAs), especially imipramine, although they may not be as potent as the SSRIs and alprazolam or clonazepam. Monoamine oxidase inhibitors (MAOIs) such as phenelzine are uniquely effective and are still a treatment of choice for extremely treatment-resistant cases, or for patients who have not responded to SSRIs or newer antidepressants like the serotonin-norepinephrine reuptake inhibitors. The use of MAOIs is limited, though, because of the necessary dietary and drug restrictions.

HISTORY OF THE TREATMENT OF PANIC DISORDER

Until the introduction of benzodiazepines such as alprazolam, the standard treatments for panic were the antidepressants imipramine, a TCA, and phenelzine, an MAOI. A common theme in alprazolam studies is the struggle to find an effective dose and dose distribution that minimizes side effects; in many of the studies reported here, the maximum dose is 6 or 10 mg/day in divided doses, but the typical dose is around 5 mg/day. The outcome measures used vary; many studies use the number of full-blown panic attacks per week as a measure of an agent's efficacy, which is a poor and unreliable outcome measure. A more valuable outcome measure is the elimination of all unexpected limited-symptom attacks and associated panic anxiety symptoms. The persistence of limited-symptom attacks can reinforce and perpetuate a patient's phobias; the elimination of all unexpected limited-symptom attacks allows a patient the best chance of overcoming these phobias.

Evidence for Alprazolam in Panic Disorder

Alprazolam has been shown to be an effective treatment for panic disorder in a variety of studies. For example, a pilot study[1] compared the effect of alprazolam on symptoms of panic disorder with that of ibuprofen, an anti-inflammatory agent. Thirty-two patients with panic disorder and agoraphobia participated in a 2-week placebo washout period and were then randomly assigned to 8 weeks of treatment with either alprazolam, 2 to 6 mg/day, or ibuprofen, 0.8 to 2.4 g/day. Ibuprofen-treated patients were then switched to alprazolam, while the alprazolam-treated patients continued taking alprazolam; the dose of alprazolam could be increased up to 10 mg/day. The alprazolam-treated patients improved more quickly than did the ibuprofen-treated patients; improvement was noticed after only 1 week of alprazolam treatment.[1] In addition, alprazolam-treated patients experienced a greater degree of improvement than did the ibuprofen-treated patients. All patients improved further during the 6-week continuation period on alprazolam treatment.

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A larger double-blind, placebo-controlled study[2] compared the effectiveness of alprazolam and buspirone in 101 patients with panic disorder. The maximum doses were 10 mg/day of alprazolam and 100 mg/day of buspirone. Alprazolam was superior to both buspirone and placebo on almost every measure, whereas buspirone was not superior to placebo. More patients in the alprazolam group than the buspirone or placebo groups were rated as at least moderately improved at endpoint on both physician-rated and patient-rated scales. The alprazolam group experienced a rapid decrease in number of panic attacks, including limited-symptom attacks.

The Cross-National Collaborative Panic Study

Given the success of alprazolam in smaller studies, a large, 2-phase study was designed and conducted: The Cross-National Collaborative Panic Study.[3] Phase 1 consisted of placebo-controlled alprazolam studies in 8 centers in the United States, Canada, and Australia. Phase 2 compared alprazolam with placebo and imipramine and was carried out at 12 sites in North America, South America, and Western Europe.

In phase 1,[4] 526 patients were randomly assigned to alprazolam or placebo for 8 weeks. At the end of 3 weeks, 481 patients remained in the study, 247 in the alprazolam group and 234 in the placebo group. After that point, an additional 102 placebo-treated patients dropped out, 88 (86.3%) because of ineffectiveness of the treatment. Only 21 alprazolam-treated patients dropped out after the 3-week mark, and only 10 (47.6%) because of ineffectiveness of the treatment. Significantly more alprazolam-treated patients completed the study compared with placebo-treated patients ($p < .01$). The mean ± SD dose of alprazolam by week 8 was 5.7 ± 2.2 mg/day.

This study also calculated plasma drug levels to measure compliance to the study protocol.[4] At the end of the study, only 5.9% of alprazolam-treated patients were found to have detectable plasma diazepam or desmethyldiazepam levels, whereas 21.9% of placebo-treated patients were found to have taken diazepam. Almost all of alprazolam-treated patients (95.1%) were found to have detectable plasma alprazolam levels at the end of the study, implying that almost all of that group was compliant with their medication regimen.

Alprazolam was more effective than placebo for the treatment of panic disorder on most measures.[4] By week 4, a significant improvement ($p < .0001$) was noted on physician-rated and patient-rated global improvement scales in the alprazolam group versus the placebo group. Of patients who completed 3 weeks of alprazolam treatments, 51% were markedly improved; an additional 41% were moderately improved after 8 weeks of treatment. Alprazolam-treated patients experienced significantly more improvement than placebo-treated patients in the following areas: panic attacks (spontaneous and situational), phobic fears, avoidance behavior, anxiety, and disability. Improvement was noted after 1 week of alprazolam treatment in work, social/leisure, and family function. This quick onset of action is a major benefit of alprazolam treatment.

Phase 2, the international phase of the study, included 1168 patients.[5] After a washout period, they were randomly assigned to either alprazolam, imipramine, or placebo, treated for 8 weeks, and then tapered off the medication. After 3 weeks of treatment, 1010 patients were still participating in the study and were evaluated; 812 patients completed the study. Of the original 1168 patients, 83% of alprazolam-treated patients completed the study, 70% of imipramine-treated patients completed, and 56% of placebo-treated patients completed. Many imipramine dropouts discontinued because of side effects, whereas many placebo dropouts discontinued because of ineffectiveness of treatment. At endpoint, the mean daily doses were 5.7 mg of alprazolam and 155 mg of imipramine.

Alprazolam-treated patients experienced improvement in many areas after only 1 week of treatment—the number of panic attacks decreased in the time period, for example, whereas in the imipramine-treated group, the number of panic attacks decreased by week 6.[5] Alprazolam-treated patients improved on most measures by week 2, imipramine-treated patients, by week 4. However, by the end of the study, the 2 active treatments were associated with a similar degree of improvement, and both were significantly superior to placebo on most outcome measures.

NEW TREATMENTS FOR PANIC DISORDER

Antidepressants and benzodiazepines were the first effective treatments for panic disorder and remain valuable tools in the management of panic and other anxiety disorders. New treatments for panic disorder are also in these 2 drug classes. For example, an extended-release (XR) formulation of alprazolam is currently under development for panic disorder. Two SSRIs, paroxetine and sertraline, have been approved for the treatment of panic disorder by the U.S. Food and Drug Administration (FDA). There are publications supporting the efficacy of all SSRIs in the treatment of panic disorder.[6]

The immediate-release (IR) formulation of alprazolam that is currently available has several drawbacks, one of which is its relatively short duration of therapeutic action. Alprazolam XR has a longer duration of therapeutic action (Table 1),[7] and this minimizes interdose anxiety.

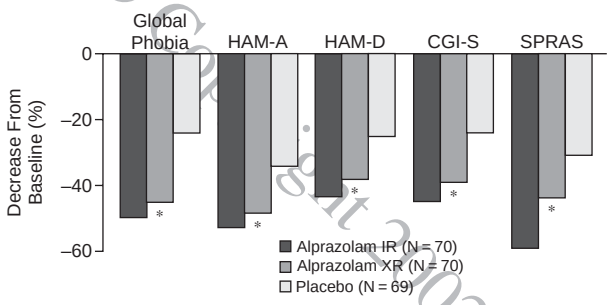
Pecknold and coworkers[8] conducted a 6-week, placebo-controlled study of alprazolam IR versus alprazolam XR that included 209 patients with panic disorder. At 3 weeks, 184 patients remained in the study. The flexible-dose study allowed a maximum dosage of 10 mg/day to be taken 4 times per day in the alprazolam IR group and 1 time per day in the alprazolam XR group. The 6-week treatment

Table l. Duration of Therapeutic Action of Benzodiazepines[a]

Drug	Duration of Therapeutic Action, h
Alprazolam	4–6
Clonazepam	6–8
Adinazolam XR	12+
Alprazolam XR	9–16

[a]Data from Sheehan.[7] Abbreviation: XR = extended release.

Figure 1. Alprazolam XR vs. Alprazolam IR vs. Placebo in Panic Disorder[a]



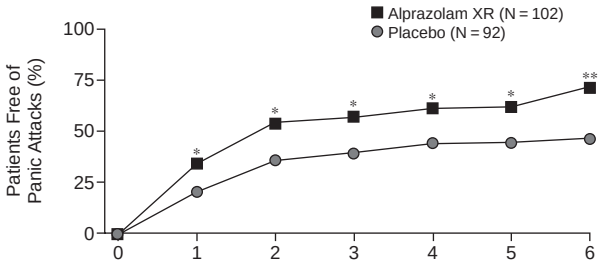
[a]Data from Pecknold et al.[8] Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, IR = immediate release, SPRAS = Sheehan Patient Rated Anxiety Scale, XR = extended release.
*For all measures, alprazolam XR = alprazolam IR > placebo, $p < .05$.

period was preceded by a 1-week washout period to ensure that patients were drug free before starting alprazolam treatment. At the end of week 6, the mean ± SD alprazolam IR dose was 3.95 ± 1.86 mg/day, and the mean alprazolam XR dose was 4.35 ± 2.30 mg/day.

On most outcome measures, both formulations of alprazolam were significantly more effective than placebo in the treatment of panic disorder (Figure 1).[8] Both active treatment groups experienced significantly fewer panic attacks than the placebo group after 1 week of treatment; the difference was only maintained in the alprazolam IR group, however. After 6 weeks of treatment, 80% of the alprazolam IR group and 83% of the alprazolam XR group were rated as at least much improved on the Clinical Global Impressions-Improvement scale (CGI-I), compared with 60% of the placebo group. On other measures, results for the alprazolam XR group were not quite as robust as those for the IR group, although this difference was not significant. The authors hypothesized that interdose anxiety may be to blame for the difference, and that twice-a-day dosing of alprazolam XR may be more appropriate.

Schweizer and colleagues[9] conducted a 6-week, flexible-dose study comparing 1 to 10 mg/day of alprazolam XR, given in the morning, with placebo. Of the 194 patients included in the intent-to-treat analysis, 102 were randomly assigned to alprazolam XR, and 92 were randomly assigned to placebo. The mean ± SD daily dose of alprazolam XR at

Figure 2. Alprazolam XR vs. Placebo in Panic Disorder[a]



[a]Data from Schweizer et al.[9] Abbreviation: XR = extended release.
*$p < .05$.
**$p < .01$.

week 6 was 4.7 mg. At the end of the study, alprazolam XR was significantly superior ($p < .05$) to placebo on all clinical endpoints, including mean change in frequency of panic attacks from baseline, number of patients with at least a 50% decrease in number of panic attacks, percentage of patients free of panic attacks (Figure 2), and mean change from baseline on the CGI-I and CGI-Severity of Illness scale (CGI-S). Many patients in the study had received previous drug therapy for panic disorder (81 in the alprazolam XR group and 80 in the placebo group). Of these, 68 (84%) of 81 alprazolam-treated patients rated alprazolam XR as more or much more effective than their previous treatments compared with only 31 (39%) of 80 placebo-treated patients ($p < .001$).

Holland and others[10] reported a 12-week, single-blind, multicenter study comparing alprazolam XR (2–6 mg/day; N = 129) and clomipramine (50–150 mg/day; N = 128). Although many of the endpoint measures showed similar efficacy, alprazolam XR had a quicker onset of action. Alprazolam XR patients were more likely to complete the first 4 weeks of treatment and were more likely to stay in the study for the full 12 weeks. In addition, there were more dropouts for adverse side effects and lack of efficacy in the clomipramine group compared with the alprazolam XR group.

Selective Serotonin Reuptake Inhibitors

Although paroxetine and sertraline are the only SSRIs approved by the FDA for the treatment of panic disorder, all SSRIs have been shown to be helpful for panic disorder in a variety of studies.[6,11–15] With the benzodiazepines, they have become standard treatments for panic disorder over the older antidepressants.

In a double-blind, placebo-controlled study, Ballenger and colleagues[13] studied the effect of paroxetine versus placebo in 278 patients with panic disorder. Patients were randomly assigned to placebo or 10 mg/day, 20 mg/day, or 40 mg/day of paroxetine. All paroxetine doses were well tolerated, but the 40-mg/day dose was significantly more

Table 2. Benefits of Pharmacotherapy for Panic Disorder[a]

Condition	Efficacy per Drug Class		
	High-Potency Benzodiazepines	TCAs	SSRIs
Decrease in panic attacks	Marked	Marked	Marked
Rapidity of response	Marked	Mild	Mild
Decrease in anticipatory anxiety	Marked	Mild	Mild
Decrease in phobic avoidance	Moderate	Mild	Moderate
Antipanic efficacy	Marked	Marked	Marked
Antidepressant efficacy	None	Marked	Marked

[a]Data modified after Rickels and Schweizer.[17] Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Risks of Pharmacotherapy for Panic Disorder[a]

Condition	Frequency/Severity per Drug Class		
	High-Potency Benzodiazepines	TCAs	SSRIs
Sedation/psychomotor impairment	Moderate	Moderate	Not present/mild
Anticholinergic effects	Not present	Marked	Not present/very mild
Orthostatic hypotension	Not present	Moderate	Not present
Hyperstimulation	Not present	Moderate	Mild/moderate
Physical dependence	Moderate	Not present	Not present
Discontinuation symptoms	Marked	Mild	Mild
Risk of abuse/dependence	Mild	Not present	Not present
Weight gain	Not present	Moderate	Not present/mild
Sexual dysfunction	Mild	Mild/moderate	Moderate/marked

[a]Data modified after Rickels and Schweizer.[17] Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

effective than placebo in many areas, including frequency and intensity of full panic attacks, frequency of limited-symptom panic attacks, phobias, anxiety, and depression. The superior effect of paroxetine, 40 mg/day, was noticeable by week 4 on most measures.

Pollack and coworkers[15] conducted a flexible-dose, placebo-controlled study of 176 patients with panic disorder. After 10 weeks of treatment, sertraline-treated patients experienced significantly fewer panic attacks than did placebo-treated patients; this difference was apparent by the end of week 2. Sertraline was a more effective treatment than placebo on a number of secondary outcome measures as well, such as the CGI-I, CGI-S, the Panic Disorder Severity Scale, and functioning and quality of life assessments.

Benzodiazepines Versus SSRIs

In a meta-analysis of 36 published trials in panic disorder, antidepressants were found to be more effective than high-potency benzodiazepines only in reducing depressive symptomatology.[16] Both classes were effective in reducing panic attacks, achieving a panic-free state, or improving anxiety, agoraphobic avoidance, and overall impairment. Tables 2 and 3, from another meta-analysis[17] of the pharmacotherapy of panic disorder, provide an overview of the benefits and risks of antidepressants and benzodiazepines. Both classes of drugs are effective, yet each has its drawbacks. However, the strengths and weaknesses of these 2 classes fit to make an effective combination treatment: initial treatment with a benzodiazepine such as alprazolam plus an SSRI, followed by maintenance treatment with an SSRI only. This regimen takes advantage of the fast-acting nature of the benzodiazepines and the safety of long-term treatment with the SSRIs, which have no abuse or dependence liability. Goddard et al.[18] conducted a double-blind, placebo-controlled study comparing sertraline plus clonazepam (N = 22) versus sertraline plus placebo (N = 25). Patients took sertraline for 12 weeks; during the first 4 weeks of sertraline treatment, they were randomly assigned to receive clonazepam or placebo, after which the clonazepam was tapered over 3 weeks. Both groups were then followed over an additional 5 weeks of sertraline treatment. The combination provided an early onset of benefit in week 1. There was no evidence of an increased dropout owing to benzodiazepine taper after week 4. The authors concluded that rapid stabilization of panic attacks is a safe and helpful strategy in panic disorder.[18]

CONCLUSION

Alprazolam is one of the standard treatments for anxiety and panic disorder, because it is effective and has a quick onset of action. However, the standard IR formulation of the agent must be administered at least 3 or 4 times a day to prevent interdose breakthrough anxiety, a regimen that may have a negative impact on patient compliance. This regimen increases the chance that patients may forget to take a dose, and it may make other patients feel "dependent" on their medication. Alprazolam XR, with its longer

duration of action, can be taken once or twice a day. Taking two thirds of the daily dose in the morning at breakfast and the remaining one third in the evening after supper lessens the times per day the patient takes the drug but keeps the dosing tied to easy-to-remember daily events, such as meals. The evening dose does not need to be as high as the morning dose since patients require less medication while they are asleep. For these reasons, alprazolam XR may prove to be a more useful treatment for panic disorder than shorter-acting benzodiazepines and may increase patient compliance. Because the other standard treatments of panic disorder, the SSRIs, have a slow onset of action, adding an extended-release benzodiazepine to the treatment regimen for 6 to 8 weeks can serve as an effective bridge until the desired SSRI effect is realized.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), diazepam (Diastat, Valium, and others), imipramine (Tofranil and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, alprazolam XR, buspirone, clomipramine, diazepam, imipramine, phenelzine, and adinazolam are not approved by the U.S. Food and Drug Administration for the treatment of panic disorder.

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