Use of Benzodiazepines in Panic Disorder

Jonathan R. T. Davidson, M.D.

Over the past 15 years, benzodiazepines have been used successfully to treat panic disorder with agoraphobia, but not without some controversy. Efficacy and side effect data from the principal benzodiazepine outcome studies of panic disorder demonstrate that alprazolam, lorazepam, and clonazepam are all clinically effective. Clonazepam has several advantages over other benzodiazepines and can be considered a first-line agent for panic disorder. Benzodiazepines in general are therapeutically effective for a broad range of panic disorder symptoms. Their effect is rapid and maintained without dose increase over a 7- to 8-month period. Discontinuation-related difficulties can occur in a considerable number of patients, but these can be decreased in several ways.

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Panic disorder, with or without agoraphobia, is a chronic and fluctuating illness[1] with significant resulting morbidity,[2] but which responds well to pharmacologic treatment. The monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants were the first agents shown to be effective for panic disorder,[3] with subsequent studies endorsing the benefits of benzodiazepines and serotonin selective reuptake inhibitors (SSRIs).[4–7]

All effective treatments for panic disorder have both advantages and disadvantages. The therapist's task is to find the most successful treatment for an individual patient in which the benefits outweigh the risks. Individual selection of a medication, whether it be a tricyclic antidepressant, benzodiazepine, SSRI, or MAOI, should be determined according to the unique features and previous treatment history of the patient.

This review addresses the following topics with respect to the use of benzodiazepines in panic disorder: (1) evidence of clinical efficacy; (2) side effect profile and associated discontinuation-emergent phenomena; (3) advantages and disadvantages compared with other treatments; and (4) effects on quality of life and work productivity.

BENZODIAZEPINES IN PANIC DISORDER

Evidence for Clinical Efficacy

Alprazolam is the most extensively studied of all benzodiazepines in panic disorder, having been proved effective in all of its major clinical trials. These studies include the first cross-national collaborative panic study,[4] which found that a mean dosage of 5.7 mg/day of alprazolam was more effective than placebo in 481 patients with panic disorder. The dosage in this study ranged from 1 to 10 mg/day, and there was some evidence that greater responses were found at dosages exceeding 6 mg/day. The authors observed that approximately 30% of the patients needed doses in the upper range to attain optimal response. Rapid improvement was noted at Week 1 for spontaneous and situational panic attacks, phobic fears and avoidance, and anticipatory anxiety and disability. The magnitude of the response increased each week; at the endpoint (Week 8), 55% of the patients treated with alprazolam had attained a panic-free state, compared with 32% of those receiving placebo.

In two subsequent studies,[6,8] alprazolam was more effective than placebo and comparable to imipramine in 8-week trials. In the one study,[8] panic-free status was achieved by 68% of patients treated with alprazolam, 61% of those treated with imipramine, and 34% of those receiving placebo. In a larger, cross-national study,[6] 70% of patients treated with alprazolam or imipramine were panic free, compared with 50% of those receiving placebo.

Schweitzer et al.[9] found that alprazolam and imipramine produced good therapeutic results at the end of 8 weeks; these effects were maintained over an 8-month follow-up treatment period. However, the authors reported that a substantially higher percentage of patients in the alprazolam group (62%) compared with the imipramine and placebo groups (26% each) achieved a panic-free state at Week 8 and continued to receive and tolerate the medication throughout the follow-up period, indicating superior tolerance of the benzodiazepine. An analysis by Lesser et al.[10] noted that patients with secondary major depression responded as well to alprazolam as did those with panic disorder without major depression. However, the authors

From the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C.

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Reprint requests to: Jonathan R. T. Davidson, M.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710.

appropriately noted the limitations of their population, which excluded patients with melancholic and primary depression.

A 6-week study of the sustained-release form of alprazolam[11] found superior clinical efficacy compared with placebo; the mean highest dosage of alprazolam was 4.7 mg/day. An obvious advantage of the sustained release form of alprazolam is its once-daily administration.

Woods et al.[7] were unable to demonstrate any clear advantage to continued alprazolam added to imipramine treatment in patients with panic disorder over the long term.

Lorazepam[12] and clonazepam (reference 13 and unpublished data on file, Hoffmann-La Roche, Nutley, N.J.) also have been shown to be clinically effective for panic disorder. Tesar et al.[13] found that clonazepam was as effective as alprazolam and that both medications were superior to placebo. To date, this is the only trial comparing two benzodiazepines and placebo in patients with panic disorder.

In their 6 week-study, Tesar et al.[13] administered clonazepam up to a mean maximum dosage of 2.5 mg/day, compared with 5.3 mg/day for alprazolam. Good clinical efficacy was seen on observed ratings of global severity of illness, disability, and phobic distress and on patient-rated global improvement. Fifty percent of patients in the clonazepam group, 46% of those in the alprazolam group, and only 14% of those in the placebo group were panic free for 2 consecutive weeks. Although these percentages are somewhat lower than those in the alprazolam studies, the difference between active drug and placebo remains the same.

Possible advantages of clonazepam over alprazolam are its longer duration of action and more gradual time to onset of peak activity. In addition, clonazepam may cause fewer withdrawal-related symptoms.

Adverse Effects

Side effects of alprazolam and clonazepam in clinical trials generally were similar, conforming to the expected profile of benzodiazepine actions. In a report by Noyes et al.,[14] the greatest differences in the percentage of patients experiencing side effects in the alprazolam group, compared with those in the placebo group, were seen for sedation (34%), ataxia (16%), slurred speech (9%), fatigue (5%), decreased libido (7%), constipation (7%), amnesia (3%), and increased appetite (2%). However, the authors caution that these side effects may not all have been medication related, since insomnia, palpitations, tremor, nausea, light-headedness, dizziness, and difficulty urinating occurred more often in the placebo group than the alprazolam group.

The overall acceptance rate in the Noyes et al. study,[14] as indicated by completion of the entire study, was 84% with alprazolam and 50% with placebo. A similar patient acceptance rate was seen in the second cross-national collaborative study,[6] in which 83% of patients treated with alprazolam, 70% of those treated with imipramine, and 56% of those receiving placebo completed the entire 8-week treatment period. In the Noyes et al. study,[14] which evaluated more than 520 patients, 12 of 263 patients in the alprazolam group discontinued the drug because of sedation (N = 5), intoxication (N = 3), mania (N = 2), depression (N = 1), and hepatitis (N = 1). Six of the 262 patients in the placebo group discontinued treatment because of anxiety (N = 2), sedation (N = 1), stimulation (N = 1), and unknown reasons (N =2).

Discontinuation-Emergent Symptoms

Pecknold et al.[15] reported a 27% incidence of rebound panic attacks after alprazolam was discontinued; they also described a withdrawal syndrome in 35% of patients treated with alprazolam, compared with none of the patients receiving placebo. These phenomena were observed during a 4-week discontinuation period after an 8-week treatment period.

Rickels et al.[16] evaluated patients when alprazolam was discontinued after 8 months of treatment. Thirty-three percent of patients were unable to completely stop the drug after a 4-week taper, but most managed fairly well during the 3-week post-taper assessment during which they received no alprazolam. In this study, patients had been taking a mean dosage of 5.5 mg/day of alprazolam. The authors noted the following characteristic withdrawal symptoms: anxiety, insomnia, light-headedness, hyperacusis and increased sense of smell, tremor, poor concentration, depersonalization, sweating, headache, decreased appetite, nausea, and restlessness. The severity of baseline panic attacks and male sex predicted withdrawal symptom difficulties. Although most withdrawal symptoms subsided, patients experienced an increased level of panic attacks even 3 weeks after the drug was tapered.

In a study published in 1990,[17] Davidson noted that the following factors are likely to increase the risk of withdrawal difficulties: age, personality type, use of a short half-life benzodiazepine, use of other drugs that lower the seizure threshold, previous history of withdrawal difficulties, longer duration of treatment, rapid withdrawal from medication, lack of available support systems, and increased consumption of alcohol.

ADVANTAGES AND DISADVANTAGES OF ANTIPANIC DRUGS

All effective treatments, whether pharmacologic or psychotherapeutic, have potential drawbacks. Thus, the clinician must choose a particular treatment by weighing its risks and benefits. The primary advantages of benzodiazepines in panic disorder are their rapid onset, broad-spectrum anxiolytic action (which extends beyond the simple suppression of panic attacks), favorable side-effect profile,

general safety, and high patient acceptability. The principal disadvantages of benzodiazepines in panic disorder include impaired psychomotor performance and alertness, withdrawal symptoms on discontinuation, and potential for abuse. Benzodiazepines also may be less effective than antidepressants in patients with concomitant major depressive disorder, although this claim is in some dispute.[10]

While the SSRIs generally are regarded as pharmacologic advances, several potentially troublesome observations have been made with respect to their use in panic disorder. For example, Fux et al.[18] observed a 9% incidence of delayed-onset depressive symptoms, despite good antianxiety response, in patients treated with fluvoxamine who had no prior history of depression. The difficulties disappeared when fluvoxamine was discontinued, only to return when another SSRI was introduced. The authors noted that the use of imipramine or clonazepam staved off the depression. Black et al.[19] reported the appearance of fluvoxamine withdrawal symptoms in 86% of patients when the drug was abruptly discontinued. These symptoms, which included dizziness, incoordination, headache, nausea, and irritability, peaked at about Day 5.

Tricyclic antidepressants are poorly tolerated by many patients. When used over the long term, these drugs may increase blood pressure and heart rate.[20,21]

CONCLUSION

Consistent evidence in the literature supports the therapeutic effects of alprazolam and clonazepam in patients with panic disorder with agoraphobia and in those with panic disorder alone. Such a high level of positive outcomes is unusual in the psychotropic drug field.

Benzodiazepines tend to exert their therapeutic effects early in treatment and may be more acceptable to patients than other antipanic drugs. There is some evidence for a dose-effect relationship with alprazolam and other triazolo benzodiazepines in panic disorder.

The principal problem related to benzodiazepine use is withdrawal symptoms when the drug is stopped. Several variables influence the frequency and intensity, as well as the risks, of withdrawal symptoms. As a general rule, if a benzodiazepine is used for more than about 1 month of treatment, the drug should be discontinued at a slow rate and the patient should receive support for any distressing withdrawal symptoms.

Despite the controversies associated with physical dependence, benzodiazepines remain a useful treatment for panic disorder. Benzodiazepine therapy can still be considered a primary treatment for panic disorder with or without agoraphobia.

Drug names: alprazolam (Xanax), clonazepam (Klonopin), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others).

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Discussion

Use of Benzodiazepines

Dr. Barlow: Are there any differences between clonazepam and alprazolam in terms of efficacy and side effects?

Dr. Rosenbaum: In a small study, we found that the efficacy of these two drugs is similar. Where there were small differences, they favored clonazepam. For instance, the dropout rate was slightly lower in the clonazepam group, the percentage of patients who were panic free was higher, and the emergence of depression was observed only in the alprazolam group (N = 2).

In a study done in the mid-1980s, more than 80 patients with panic disorder who were being treated with alprazolam and who were experiencing interdose rebound were given the option of switching to clonazepam. More than 80% of the patients switched to clonazepam. Most of these patients reported improved symptom control with clonazepam and did not experience what was called clock-watching.

Dr. Shear: What are the recommendations for use of benzodiazepines in women of child-bearing age? Given the epidemiology of panic disorder, many patients may be taking benzodiazepines when they want to become pregnant.

Dr. Davidson: With clonazepam, there appear to be no absolute contraindications to its use in women who plan to become pregnant. Studies have shown that other benzodiazepines also are unlikely to cause problems during pregnancy.

Dr. Rosenbaum: Our approach for a patient with panic disorder who is taking any medication, but benzodiazepines in particular, and who plans to become pregnant or has an unplanned pregnancy is to refer that woman to a panic control therapy program and attempt to discontinue the drug. In most cases, however, we just go to a lower level of dosing.

Dr. Charney: Is there any reason to worry more about a pregnant woman taking a benzodiazepine than one who is taking an antidepressant?

Dr. Jefferson: There is a 2% to 3% incidence of major malformation in pregnant women who do not take any medication. Yet if a problem occurs in a woman taking medication, whether a benzodiazepine or an antidepressant, the medication will be blamed, even though you cannot show a statistical difference in the incidence of malformation.

Dr. Ballenger: In our practice, we try to minimize drug use. We seek a balance between the difficulty of staying on the drug and the difficulty of withdrawal symptoms or reemergence of the panic disorder. Our obstetricians tell us that the risk of teratogenesis is very low with these medications and probably does not compare with the risk of withdrawal symptoms or reemergence of the disorder.

Dr. Rosenbaum: There is the question of organ dysgenesis but also the more difficult one of behavioral teratogenicity, which is harder to evaluate. Looking back over 20 years of practice, I can recall several patients who now have healthy children only because they were taking medication. They would never have considered becoming pregnant if their disorder had not been controlled or the treatment withdrawn as a precondition.

In this situation, the physician must make a decision based on incomplete data. However, a knee-jerk, panic response to the announcement that a patient on drug treatment is pregnant is inappropriate. Our perinatal consultation group headed by Lee Cohen has had patients come to them after their physician told them they must have an abortion because they were taking drugs. After consultation, they completed their pregnancy and had successful outcomes; some of the patients remained on treatment throughout the pregnancy.

Dosing Considerations

Dr. Rapaport: I am concerned that drug doses shown to be effective in studies of patients with panic disorder seem to be much higher than those used clinically.

Dr. Shear: I think that is most often true of studies that do not combine pharmacologic treatment with nonpharmacologic interventions. In clinical practice, patients typically receive psychosocial therapy in addition to drug treatment. In these cases, positive results can be achieved with lower drug doses.

Dr. Ballenger: An initial study on dosing considerations showed that half doses of alprazolam were better than no treatment. At least two subsequent studies, one we did and one by another group, found that 2 mg of alprazolam, compared with 6 mg of alprazolam, worked in a significant number of patients. However, in one study, many of the patients in the lower dose group were receiving concomitant benzodiazepines, even though this was not part of the protocol.

Doses of alprazolam used in clinical practice generally range from 1.5 to 10 mg.

Dr. Rosenbaum: We need to emphasize the importance of both continuing and intensifying treatment in patients with panic disorder. Primary care physicians may treat patients with low doses of alprazolam, and the patients report feeling a little better. Yet they may still be having frequent panic attacks, agoraphobia, and general constriction of daily activities requiring continued efforts to improve treatment.

Dr. Ballenger: Patients almost always settle for less than ideal improvement. If the physician does not keep pushing for maximum improvement, patients end up being inadequately treated.

Dr. Davidson: Primary care physicians must ask patients about quality-of-life issues. For example, are they still avoiding going to the supermarket?

Dr. Rosenbaum: Is suboptimal dosing more of a concern with benzodiazepines than with antidepressants?

Dr. Pollack: Prospective data from our longitudinal study indicate that patients treated with antidepressants tended to receive relatively higher doses than those treated with benzodiazepines. Benzodiazepines were more likely to be given at very low doses. Interestingly, it appears that the patients themselves are insisting on being treated with lower doses of benzodiazepines, because of moral concerns.

Dr. Davidson: Is that a drug-specific phenomenon?

Dr. Pollack: Some patients want to take just enough to feel better, and some are scared of becoming addicted.

Dr. Ballenger: Other data show that patients usually are underdosed, whether they are treated with an antidepressant or a benzodiazepine. Yet it is hard to underdose some of the serotonin selective reuptake inhibitors.

Dr. Rosenbaum: If patients are driving the benzodiazepine dosing, the issue is how much the physician is trying to educate patients to facilitate treatment. Physicians may believe they are acting in the best interests of the patient if they can use a low dose of a benzodiazepine and then discontinue it as soon as possible. Yet for many patients, panic disorder is a chronic condition, so why focus on discontinuing medication early? If patients were being treated with an antidepressant, the sophisticated clinician might consider it appropriate to keep them on the drug for several years if their condition was chronic or recurrent.

Dr. Rapaport: Some clinicians who mainly treat depressed patients have two attitudes toward benzodiazepines. One is that low-to-moderate doses of a benzodiazepine are really a nonpharmacologic treatment. When they report treatment in clinical studies, they often ignore the fact that patients have received many accessory doses of benzodiazepines. The other is the attitude that the higher doses of benzodiazepines recommended for panic disorder will poison the patient and should not be used. Although much of this attitude derives from concerns about abuse, these physicians also have a moral stance that patients enjoy taking the benzodiazepine.

Dr. Ballenger: That attitude is not supported by clinical data. Studies have shown no escalation of dose or indications of abuse among patients with panic disorder who do not have a previous history of substance abuse.

Dr. Davidson: Physicians also have concerns about withdrawal symptoms with benzodiazepines. However, studies suggest that these symptoms are fairly benign when the dose is tapered off slowly.

Dr. Ballenger: In a sense, these drugs are stigmatized. Data do not support the abuse of benzodiazepines by patients with panic disorder. These patients tend to decrease their doses, and you have to fight with them to ensure that they take an adequate dose. Their tendency is to go the other way, in part because of the stigmatization issue. When the treating physician stops an effective treatment, some patients experience withdrawal symptoms because their body has become "used to" or dependent on the drug. That is not evidence of abuse.

Data suggest that if the clinician works with the patients to ensure they reduce the dose when they are ready and over 2 to 4 months, the percentage of patients who have significant withdrawal symptoms approaches zero. In our cross-national study, 35% of patients experienced significant withdrawal symptoms at five of seven sites. At the other two sites, none of the patients experienced problems. At one of these sites, patients were immediately entered into a behavior therapy trial and were encouraged, helped, and supported by the clinicians while the benzodiazepine was withdrawn. At the other site, clinicians told patients, "It's just withdrawal, it's not going to hurt you. Call me if it gets worse tomorrow." The attitude of the physicians—whether it was stigmatizing or reassuring—was the difference in the equation. Also, these results were achieved with the benzodiazepine being withdrawn over 1 month, which I think is too fast in patients with panic disorder.

Dr. Davidson: I think 3 to 6 months is a more realistic time frame for withdrawing benzodiazepines, especially in patients who have been taking these drugs for a number of years. If discontinuation is done slowly with proper preparation and proper support, withdrawal is not a major problem.

Dr. Marshall: There is almost no medical reason to discontinue benzodiazepines quickly.

Treatment-Emergent and Comorbid Depression

Dr. Barlow: Is there a differential effect on comorbid depressive symptoms between clonazepam and alprazolam?

Dr. Rosenbaum: There have been reports of emergent depression with both drugs. In our study, there were two cases of emergent depression in the alprazolam group and none in the clonazepam group. However, one clinical review indicated that as many as 10% of patients treated with clonazepam alone develop depressive symptoms, which resolve with decreasing dose, changing treatment, or adding an antidepressant.

Dr. Davidson: In an Israeli study, investigators reported that 9% of patients with panic disorder treated with fluvoxamine developed clinically significant depression. These patients had no history of depression. Treatment with imipramine or clonazepam alleviated the depression, but symptoms returned when patients were again treated with fluvoxamine.

Dr. Jefferson: Some reports also link imipramine to depression. Patients who improve with this drug may experience a postpanic depression.

Dr. Ballenger: Let me emphasize that depression in patients with panic disorder typically resolves once patients are receiving effective medication. In cases of mild depression, patients tend to improve whether they receive an antidepressant or a benzodiazepine. For more severe or recurrent depression, patients might respond better to an antidepressant. However, this issue is not well studied.

Dr. Shear: In a study we did with the Massachusetts General group, we were unable to show an overall difference between the benzodiazepine alprazolam and the antidepressant imipramine in treating patients with panic disorder and comorbid depression. When we looked at core symptoms of depression, we noted that some specific symptoms responded better to imipramine than alprazolam. Most of the patients had mild depression, but some were severely depressed. However, we were not able to separate this group statistically.