The Role of Extended-Release Benzodiazepines in the Treatment of Anxiety: A Risk-Benefit Evaluation With a Focus on Extended-Release Alprazolam

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Immediate-release (IR) benzodiazepines have a short duration of therapeutic effect and are generally less effective for anxiety than selective serotonin reuptake inhibitors in reducing concomitant depressive symptomatology. Common criticisms of benzodiazepines also include the patient's tendency to develop a tolerance to the anxiolytic effect and a dependence on the drug itself. The newer extended-release (XR) benzodiazepine formulation was designed to increase efficacy, duration of therapeutic effect, tolerance, compliance, and ease of discontinuation. The XR benzodiazepine alprazolam has shown efficacy in panic disorder and generalized anxiety disorder comparable to the older benzodiazepine formulations. Pharmacokinetic data show that the XR formulation has a longer therapeutic effect compared with IR formulations, which reduces the potential for breakthrough anxiety symptoms. Data also indicate that the XR formulation has less abuse liability than the IR formulation. This article reviews the efficacy, safety, and discontinuation data from clinical trials of IR and XR benzodiazepines in the treatment of anxiety disorders and provides guidelines to minimize the risk of withdrawal syndrome during benzodiazepine discontinuation.

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Benzodiazepines are an important treatment option in the pharmacotherapy of anxiety disorders in general, and panic disorder in particular, but some common shortcomings of the immediate-release (IR) formulations have created a negative perception of their safety and efficacy.[1] One limitation that is commonly associated with benzodiazepines is that they are effective for symptomatic treatment only. The IR benzodiazepines have a short duration of therapeutic effect and are generally less effective than selective serotonin reuptake inhibitors in reducing concomitant depressive symptomatology.[2,3] Another common criticism of benzodiazepines is that some patients tend to develop tolerance to the anxiolytic effect and dependence on the drug. Rapid onset of action with benzodiazepines[4] has also been one of the grounds for criticism of these drugs because their fast alleviation of anxiety may encourage repeated use. For these reasons, benzodiazepines are viewed by some as potential drugs of abuse, and their use in the treatment of anxiety disorders should thus be limited.

However, benzodiazepines have advantages as well. The rapid onset of action may be a welcome effect, relatively low doses are efficacious in many patients,[5] and these drugs are associated with minimal side effects in the majority of patients.[6,7] Tolerance to the anti-anxiety effect is not the rule,[8] and when it does occur it can be managed. Dependence and withdrawal problems can be greatly minimized to facilitate successful medication discontinuation and treatment outcome.

Therefore, in light of these risks and benefits, researchers looked for a modified form of benzodiazepines that retains the benefits while eliminating the criticized characteristics. The newer extended-release alprazolam (alprazolam XR) was developed to increase efficacy, duration of therapeutic effect, tolerance, compliance, and ease of discontinuation.

PHARMACOKINETICS OF IMMEDIATE-RELEASE VERSUS EXTENDED-RELEASE ALPRAZOLAM

Extended-release (XR) benzodiazepines are specifically designed to increase the therapeutic window for the patient receiving benzodiazepine treatment. The therapeutic window is the amount of time the blood drug concentration remains below the toxicity range and above the minimum effective concentration. The IR benzodi-

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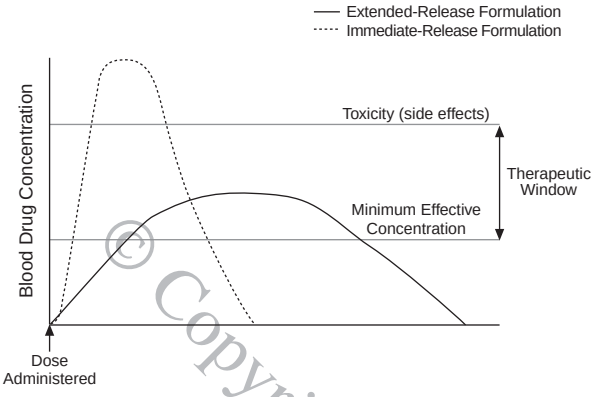
Figure 1. Comparison of Blood Plasma Concentrations With Immediate- and Extended-Release Benzodiazepines[a]



[a]Reprinted with permission from Stahl.[10]

azepines have a relatively short therapeutic window (Figure 1), but XR formulations increase that window, resulting in fewer side effects and less breakthrough anxiety before the next dose.

In the case of alprazolam XR, the delayed release prolongs the time of maximum plasma concentration (T_{max}) to 4 to 12 hours, compared with 1 to 2 hours for a similar dosage of the IR formulation. At the same time, it decreases the maximum plasma concentration (C_{max}) by approximately 50%.[9,10] With the IR formulation, blood drug levels rapidly climb into the toxic range, which leads to greater side effects, followed by a rapid descent of blood drug levels below the minimum effective concentration. As a result, the blood drug level remains within the desired therapeutic window for only a short time. This causes what is known as the "clock-watching effect," since the therapeutic effects of the drug disappear rapidly, well before time for the next dose. In contrast, with the XR formulation, the blood drug concentrations remain within the therapeutic window for several hours, with a duration of action of 12 hours or more, compared with 4 to 6 hours with the IR formulation.[11] The XR formulation creates a much smoother plasma drug level curve, which should result in a better therapeutic outcome. The bioavailability of benzodiazepines from IR and XR formulations is the same. Likewise, the distribution, metabolism, elimination, and extent of accumulation are also similar.[9,10]

Pharmacokinetic data[9–12] show that the XR formulation has a longer therapeutic effect compared with IR formulations, without an increase in the drug's pharmacologic half life. Patients taking XR formulations achieve stable blood drug levels within the therapeutic range in 3 to 6 days,[12] and because peak blood drug levels are lower than with the IR formulations, the occurrence of side effects is reduced. Because blood drug levels remain at an effective concentration preceding the subsequent dose, the potential for breakthrough anxiety symptoms and clock watching is reduced, thereby improving compliance.

ABSORPTION KINETICS AND ABUSE LIABILITY

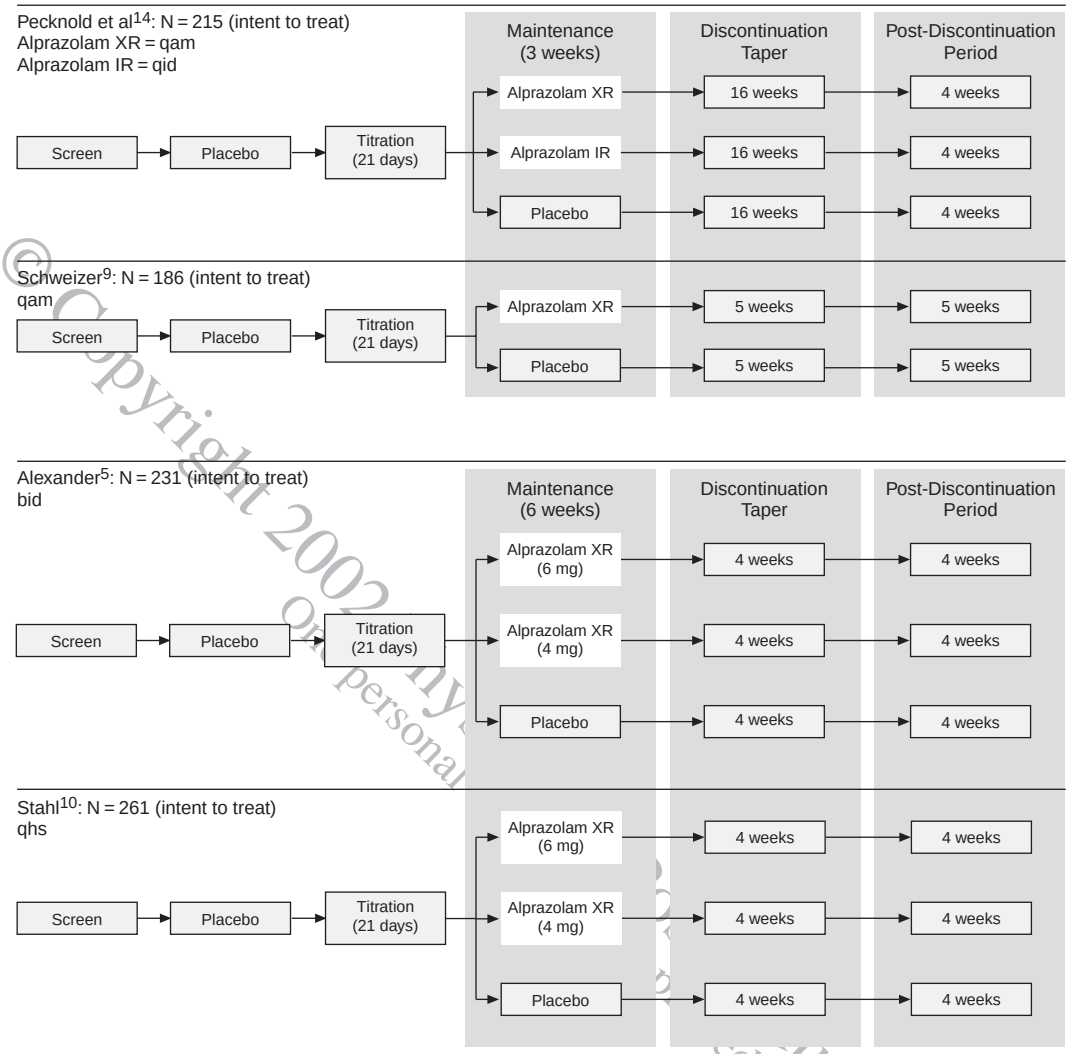
In order to assess the effect of release rate on laboratory measures of abuse liability, a double-blind crossover study[13] was conducted to evaluate the cognitive, behavioral, subjective, and reinforcing effects of immediate-release alprazolam (alprazolam IR) compared with alprazolam XR. Fourteen healthy men with histories of sedative abuse received placebo, 1 mg and 2 mg of alprazolam XR, and 2 mg and 3 mg of alprazolam IR in random order. Assessments were made 30 minutes before administration of each drug and 30 minutes, 1 hour, and 3, 5, 7, 9, 12, and 24 hours after administration. Mean C_{max} occurred 1.7 hours after administration of alprazolam IR and 9.2 hours after administration of alprazolam XR. Compared with placebo, 2 mg of alprazolam IR impaired all measures of psychomotor and cognitive performance, motor coordination, and memory, while 2 mg of the alprazolam XR affected no measures and 3 mg of alprazolam XR affected only 1 measure. Neither dose of alprazolam XR affected psychomotor and cognitive performance or subjective ratings of drug strength and liking as much as the doses of alprazolam IR did.[13] All 6 measures of positive drug effects were increased by 2 mg of alprazolam IR, while none were increased by 2 mg of alprazolam XR and only 3 were increased by 3 mg of alprazolam XR.

In addition, a multiple choice procedure designed to assess the relative reinforcing effects of each condition was administered 24 hours after each drug. The amount of money patients were willing to pay to take the drug was significantly greater than placebo for both doses of alprazolam IR but for neither dose of alprazolam XR. These results suggest that abuse liability is related to both dose and release rate (IR vs. XR), and alprazolam XR appears to have less abuse liability than alprazolam IR.

PANIC DISORDER STUDIES

There have been 4 multicenter clinical studies[5,9,10,14] of approximately 1000 patients with panic disorder treated with alprazolam XR (Figure 2). Pecknold et al.[14] compared alprazolam XR with alprazolam IR and placebo, Schweizer[9] compared a single dose of alprazolam XR with placebo, and Alexander[5] and Stahl[10] compared 2 different doses of alprazolam XR with placebo. The studies had similar designs, with a placebo run-in period, a 3-week titration period, and either a 3- or 6-week maintenance period. The studies also included a complex discontinuation design to examine and compare withdrawal-related symptoms between alprazolam XR and alprazolam IR, between the 2 different XR doses, and/or between alprazolam XR

Figure 2. Study Design of 4 Trials of Alprazolam XR in Panic Disorder[a]



[a]Reprinted with permission from Stahl.[10] Abbreviations: IR = immediate-release, XR = extended-release.

and placebo. The design and results of these studies will now be described in detail.

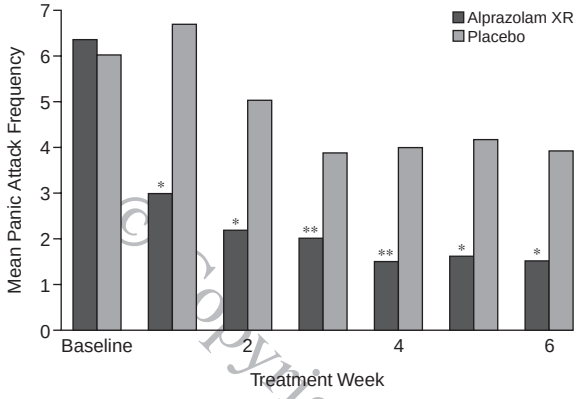
Study Design

Pecknold et al.[14] compared alprazolam XR with alprazolam IR and placebo in a double-blind, placebo-controlled trial using a flexible dosing schedule and a flexible discontinuation schedule. Alprazolam XR was administered once daily in the morning and alprazolam IR was taken 4 times per day. Treatment was started at 1 mg/day with a titration goal of 6 mg/day by day 26. Of the intent-to-treat group of 215 patients, 184 completed 3 weeks of medication. There was a completer rate of 94% for 6 weeks in the IR group, 97% in the XR group, and 87% in the placebo group.

Schweizer[9] compared alprazolam XR with placebo in 186 patients in a flexible dosing schedule, followed by a fixed 5-week discontinuation period. In this study, alprazolam XR was administered once daily in the morning, initiated at 1 mg/day and increased every 3 to 4 days as tolerated, to a maximum dose of 10 mg/day (or 10 tablets of placebo).

Both studies had a 3-week titration period in which the dose was rapidly increased until the maintenance dose was achieved. The dropout rates for both the placebo and alprazolam XR groups were higher than the rate for the alprazolam CT group in both studies. However, after the maintenance dose was achieved, the dropout rate for the placebo-treated group was significantly higher than for the active drug groups in both studies. Pecknold et al.[14] used a 4-week post-discontinuation interview and symptom assessment, and Schweizer[9] used a 2-week post-discontinuation interview for side effects.

Figure 3. Mean Frequency of Total Panic Attacks at Endpoint (LOCF) Analysis in Patients Treated With Alprazolam XR Compared With Placebo[a]



[a]Data from Schweizer.[9] Abbreviations: LOCF = last observation carried forward, XR = extended release.
*p < .05; **p < .01.

Alexander[5] compared alprazolam XR, 2 mg b.i.d. and 3 mg b.i.d., with placebo for 6 weeks. All patients who received the active drug started at 0.5 mg b.i.d., titrating to 2 mg b.i.d. (in 7 days) or 3 mg b.i.d. (in 11 days) over a 2-week period. Stahl[10] used once-daily dosing with bedtime administration, and patients receiving active medication were titrated to either 4 mg/day or 6 mg/day within 2 weeks. Fixed doses in both studies were then maintained for 6 weeks, followed by a 4-week discontinuation period. The final discontinuation week included further randomization of alprazolam XR-treated patients so that half of the patients had their doses tapered from 1 mg to 0 mg, while the other half had their doses tapered to an intermediate 0.5-mg dose before achieving the 0-mg dose. Both Alexander[5] and Stahl[10] administered a 2-week post-discontinuation interview, and side effects were elicited by open-ended questioning.

Efficacy and Safety Results

On global measures, Hamilton Rating Scale for Anxiety (HAM-A) score, phobia, and work disability measures, both active treatments in Pecknold et al.[14] were equally effective and significantly more efficacious than placebo. In Schweizer,[9] the mean weekly frequency of major panic attacks over the 6-week treatment period was reduced in the alprazolam XR treatment group. Improvement began with an abrupt decrease in panic attacks during the first week of treatment and remained consistent through the entire treatment period (Figure 3), with similar effects in anticipatory anxiety. Patients rated the efficacy of alprazolam XR as much more effective than or at least equally as effective as previous treatments in 84% of cases, compared with 41% in the placebo group. The most frequently reported treatment-emergent side effects in both Pecknold et al. and Schweizer were sedation, decreased coordination, and nervousness.

In Alexander,[5] statistically significant improvements, indicated by a decrease in number of panic attacks and by clinical global improvements, were observed with both doses of alprazolam XR within the first week of treatment. Results in the alprazolam XR groups demonstrated efficacy, but the differences from placebo were lost at week 8 due to high placebo response rates. In a reevaluation excluding 4 centers with placebo response rates exceeding 75%, alprazolam XR was found to be significantly superior to placebo. The most common treatment-emergent side effects reported in Alexander were sedation, decreased coordination, and depression.

High placebo response rates in Stahl[10] prevented meaningful efficacy conclusions, but fewer side effects were reported in both Alexander and Stahl than in the other 2 studies, even though the dose was fixed by protocol and could not be adjusted to meet individual patient needs.

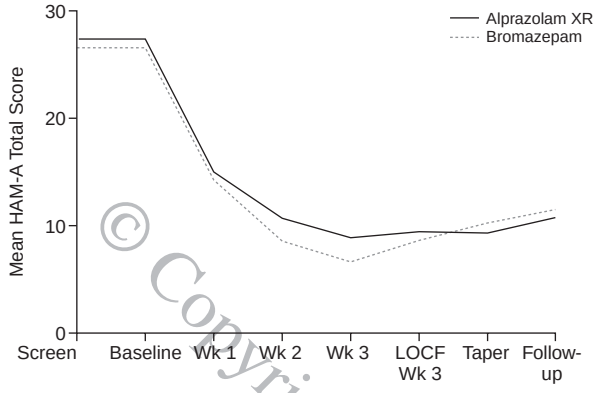
Generalized Anxiety Disorder

A double-blind, randomized, parallel-group study[15] compared 2 mg/day of alprazolam XR administered once daily at bedtime with 9 mg/day of bromazepam divided into 3 daily doses in patients with generalized anxiety disorder (GAD). Prior to randomization, the patients were free of any psychotropic medication for a minimum of 3 to 7 days and diagnosed as having GAD using modified DSM-III-R criteria. After 21 days of double-blind treatment, patients entered a 1-week titration period during which they received half of the previous dose (1.0 mg of alprazolam XR or 4.5 mg of bromazepam) daily. Efficacy and safety were assessed at screening, at baseline prior to randomization, and weekly thereafter for the next 5 weeks. The primary assessment tool was the HAM-A, and patients were considered responders if they had a reduction of at least 50% from baseline in the total HAM-A score. Other assessment tools used included the Clinical Global Impressions-Severity of Illness and -Improvement scales. Both alprazolam XR and bromazepam resulted in comparable efficacy (> 70% response) during 4 weeks of treatment (Figure 4), and both drugs were well tolerated. Discontinuation-related effects were mostly none to mild and did not differ between the groups. The anxiolytic effect of 1 daily dose of alprazolam XR was similar to that of 3 daily doses of bromazepam. Advantages of alprazolam XR included rapid onset of action, satisfactory tolerance, and ease of administration.

DISCONTINUATION

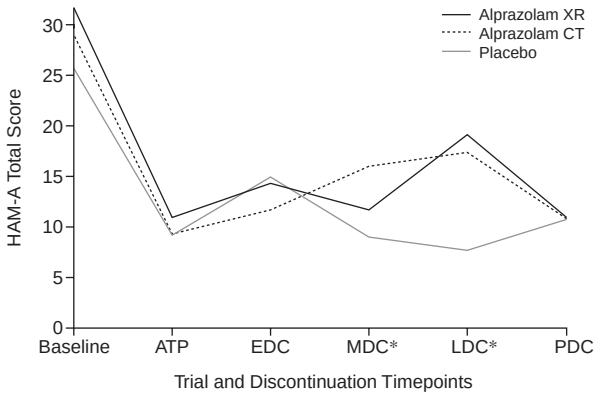
Since most psychiatric illnesses are chronic, they require long-term pharmacologic treatment. Relapse of the underlying disorder resulting from discontinuation of any psychotropic medication is, unfortunately, the rule rather

Figure 4. Mean HAM-A Total Scores by Study Week in Patients Treated With Alprazolam XR or Bromazepam for GAD[a]



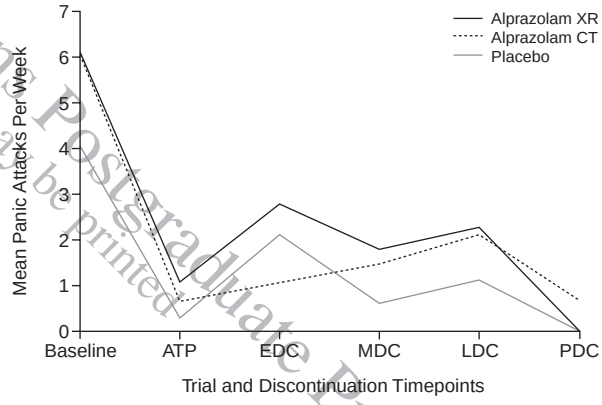
[a]Adapted with permission from Figueira.[15] Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, LOCF = last observation carried forward, XR = extended release.

Figure 5. Relapse of Generalized (Anticipatory) Anxiety During Discontinuation of Alprazolam XR, Alprazolam CT, or Placebo[a]



[a]Reprinted with permission from Pecknold et al.[14] Abbreviations: ATP = active treatment phase, CT = compressed tablet, EDC = early-discontinuation, HAM-A = Hamilton Rating Scale for Anxiety, LDC = late-discontinuation, MDC = middle-discontinuation, PDC = post-discontinuation, XR = extended release.
*p < .05.

Figure 6. Relapse of Panic Attacks During Discontinuation of Alprazolam XR, Alprazolam CT, or Placebo[a]



[a]Reprinted with permission from Pecknold et al.[14] Abbreviations: ATP = active treatment phase, CT = compressed tablets, EDC = early-discontinuation, LDC = late-discontinuation, MDC = middle-discontinuation, PDC = post-discontinuation, XR = extended release.

than the exception. For example, discontinuation of lithium in bipolar patients carries a high risk of relapse within the first year.[16] Similarly, schizophrenic patients who respond well to chronic antipsychotic treatment have a very high chance of relapse after discontinuation, regardless of the type of antipsychotic.[17] Likewise, discontinuation of antidepressants in remitted depressed patients results in relapse in many patients who have experienced recurrent episodes in the past. Anxiety disorders are no exception to this rule, and discontinuation of benzodiazepines carries a risk of both relapse of the underlying anxiety disorder and the emergence of temporary withdrawal symptoms. In patients with anxiety disorders, there is significant clinical overlap between relapse symptoms and withdrawal symptoms, which often makes them difficult to differentiate.

Relapse, Withdrawal, and Dropout

Discontinuation data comparing the XR benzodiazepine with IR benzodiazepines and placebo for relapse rates in panic disorder confirm that the XR and IR formulations produce similar results (Figures 5 and 6). At the end of the 3-week maintenance period in the Pecknold et al.[14] study, patients began a discontinuation phase. Patients were evaluated for relapse and withdrawal symptoms at early-, mid-, late-, and post-discontinuation phases. The discontinuation period lasted 16 weeks, and the post-discontinuation evaluation took place 4 weeks after the late-discontinuation period. The late-discontinuation phase was the period in which a relatively robust return of symptoms was seen. However, at post-discontinuation the symptoms had subsided, and both anxiety and total number of panic attacks were similar for the placebo and active drug groups. These results illustrate that during a limited late-discontinuation period, specific medical symptoms may arise that might resemble a relapse of the illness. However, these symptoms are transient, of minor to moderate magnitude in the majority of patients, and subside after discontinuation is complete.

It has been shown that panic disorder patients have greater difficulty withdrawing from medication than GAD patients. The author of this review compared benzodiazepine withdrawal symptoms between patients with GAD and patients with panic disorder. After a 2-month open trial of alprazolam IR, 36 patients with panic disorder and 35 patients with GAD entered a controlled discontinuation

Table 1. Clinical Ratings of Patients Treated With Alprazolam IR Seen at Follow-Up at Different Timepoints[a]

Analysis	Baseline* Mean (SD)	End of Study** Mean (SD)	Follow-Up Mean (SD)
CGI	4.6 (0.8)	3.5 (1.5)	3.4 (1.1)
HAM-D	14.3 (5.4)	11.3 (8.1)	7.8 (4.4)
WSA	3.5 (0.8)	2.8 (1.3)	2.5 (0.9)
Phobia scale	7.0 (1.8)	5.9 (5.6)	4.0 (2.5)
Number of panic attacks	4.6 (3.4)	3.5 (7.9)	0.9 (2.6)

[a]Data from Klein et al.[18] and Klein.[20] Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, NS = not significant, WSA = Work and Social Adjustment scale.
*Baseline vs. follow-up significant for all rating scales: $t \geq 3.82$, $df = 25–51$; $p < .002$.
**End of study vs. follow-up significant for HAM-D: $t = 3.0$, $df = 50$; $p < .005$.

phase.[18] Adjunctive carbamazepine[19] or placebo was added in a randomized, double-blind fashion, followed after 1 week by a single-blind dose reduction of alprazolam by approximately 25% on every third day. The dose was reduced by 50% within the first week of discontinuation, and the entire discontinuation was complete for most patients, depending on the initial dose, between 2 and 3 weeks. Although 52% of the patients were able to discontinue the drug and remain drug-free for 1 week, only 37% completed the study by maintaining benzodiazepine-free status for 4 weeks. The survival and dropout rates of patients during the withdrawal period revealed that among patients receiving placebo adjunctive therapy, those with panic disorder had a significantly greater dropout rate than patients with GAD. Klein et al.[18] suggested that panic disorder patients become intolerant to discontinuation because withdrawal symptoms actually precipitate panic attacks and, therefore, cause a more rapid relapse to the clinical syndrome, especially if the withdrawal is aggressive.

Long-Term Follow-Up

A long-term, naturalistic follow-up[20] of the original cohort from the Klein et al. study[18] took place to evaluate patients for their current medications and symptomatology. Of the 71 original patients, 52 were evaluated 12 to 18 months after the study was completed. At that time, 25% of patients were taking no medication and reported no problems, 25% were taking antidepressants, and 50% were taking benzodiazepines, the majority of which were alprazolam. However, of those who were still taking alprazolam IR, the mean daily dose at follow-up was 1.0 mg/day, compared with 3.4 mg/day during the study. Moreover, none of the patients taking alprazolam were taking a higher dose during follow-up than during the study. No significant differences between panic disorder and GAD patients were evident at the time of follow-up. Also at the time of follow-up, 78% of patients reported none or minimal anxiety symptoms, and 89% had none or only minimal functional deficit, as compared with 100% reporting moderate to severe anxiety symptoms and 57% reporting significant functional deficit before entering the study. However, although GAD patients survived acute discontinuation more successfully than panic disorder patients, during follow-up, GAD patients tended to use higher doses of benzodiazepines than panic disorder patients (50% of original dose vs. 25% of original dose, respectively).

Clinical ratings at different timepoints for all follow-up patients showed that those patients who were remarkably symptomatic at the beginning of the study had similar clinical ratings at the end of the original study, 4 weeks after completion of alprazolam discontinuation (Table 1). However, patients' follow-up ratings were much lower, which clearly proves that patients maintained a robust clinical response over an extended period. These findings further support the 4-week post-discontinuation data obtained from patients with panic disorder in the Pecknold et al.[14] study. Both studies suggest that although patients who discontinue from benzodiazepine treatment may develop minor withdrawal symptoms, a full relapse is unlikely and symptoms eventually subside.

GUIDELINES TO MINIMIZE THE RISK OF WITHDRAWAL SYNDROME

Whether beginning or discontinuing benzodiazepine treatment, it is important to take steps to minimize the risk of withdrawal symptoms. Whenever possible, prescribe benzodiazepines for time-limited use. If long-term use is indicated, the optimal strategy is to use the lowest effective dose of a long half-life or XR preparation, administered as needed by the patient. Consider adjunctive therapy, such as cognitive-behavioral therapy, that might reduce the patient's need for medication. During the discontinuation period, educating, preparing, and maintaining communication with patients is critical and can make the difference between a positive and negative outcome. An empathic and reliable physician-patient relationship may also reduce the patient's need for medication and make the patient more compliant when a drug taper and discontinuation are indicated.

CONCLUSION

In summary, benzodiazepines, primarily long-acting and XR formulations, remain an important treatment option in the pharmacotherapy of anxiety disorders in general and panic disorder in particular. Benzodiazepines have a rapid onset of action and are associated with minimal side effects in the majority of patients. Data support the use of XR benzodiazepines for a longer therapeutic effect, fewer side effects, reduced occurrence of breakthrough anxiety, ease of administration and discontinu-

ation, and lower abuse potential. Tolerance to the anti-anxiety effect is not the rule, and many patients maintain long-term efficacy at a relatively low dose. Tolerance to the drug, as well as dependence on the drug, can be minimized by adequate dosing in combination with additional treatment approaches. Successful medication discontinuation can be facilitated by optimal timing of discontinuation, a gradual tapering of medication, adequate support and patient education, combined with cognitive-behavioral therapy, which can facilitate smoother discontinuation.

Drug names: alprazolam (Xanax and others), carbamazepine (Tegretol and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine is not approved by the U.S. Food and Drug Administration for the treatment of alprazolam discontinuation.

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