The Development of Clonazepam as a Psychotropic: The Massachusetts General Hospital Experience

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The pathophysiology of anxiety disorders is not clearly understood; therefore, clinical observation, case reports, and case reviews continue to enhance physicians' understanding of disease and treatment mechanisms. At Massachusetts General Hospital (MGH), physicians and researchers are guided by the recognition that available approved treatments are a small subset of what is sensible to try in anxiety disorders and have thus chosen to remain open minded and prepared to challenge assumptions about therapeutic agents and to explore new uses, including early work with high-potency benzodiazepines. Clinical trials established alprazolam as efficacious for panic disorder, and the agent was widely prescribed for patients at MGH after its approval. Soon, however, clinical observation suggested a short duration of benefit for a given dose in some patients. In some cases, patients who missed a dose reported rebound worsening. In response to the apparent problematic pharmacokinetics of alprazolam, members of the MGH psychiatry department pursued investigation that ultimately established the antipanic efficacy of clonazepam as well as examined its effectiveness in the treatment of other disorders, such as bipolar disorder and social phobia. The process of exploring new uses of older agents remains a worthy effort while we await newer agents with innovative mechanisms of action.

(J Clin Psychiatry 2004;65[suppl 5]:3–6)

Until the pathophysiology of anxiety disorders is more deeply understood, physicians and researchers will continue to rely on clinical observations to advance treatment options. Observations, case reports, and clinical reviews generate hypotheses that enable researchers to use more formal methods to enhance physicians' understanding of disease and treatment mechanisms. As with the treatment of other psychiatric disorders, approved treatments are a small subset of what is reasonable to try in treating anxiety disorders. When Massachusetts General Hospital (MGH) began its research program of anxiety disorders nearly 20 years ago, one of the first treatments to be examined was alprazolam for panic disorder. Eventually, this early investigational effort became a model for the psychiatry department's approach to clinical investigation.

The use of high-potency benzodiazepines in panic disorder at MGH began more than 20 years ago with a clinical observation made by David V. Sheehan, M.D., when he and colleagues were investigating the new agent alprazolam, which was initially thought to be an antidepressant. Sheehan theorized that if alprazolam was effective as both an antianxiety and antidepressant agent, then it might treat a condition that he had been studying since his residency—panic disorder. As alprazolam emerged as efficacious for patients with panic disorder, it soon was being widely prescribed for patients at MGH. For many, alprazolam proved to be a miracle treatment either as a monotherapy or in combination with tricyclic antidepressants (TCAs). Additionally, unlike TCAs and monoamine oxidase inhibitors (MAOIs), which at the time were the standard treatments for panic disorder, alprazolam worked immediately, was well tolerated, and lacked the short- and long-term side effect burden that sometimes accompanied the use of TCAs and MAOIs.

However, soon my colleagues and I began to notice a problem with the pharmacokinetics of alprazolam. Although alprazolam was effective, it appeared to be effective only for a short time, and patients who missed a dose frequently reported worsening or reemergent symptoms. This interdose rebound effect became known as clock-watching, and it caused us to question whether alprazolam was unique in antipanic efficacy not because of its putative antidepressant effects, but because of its high potency. The concern that alprazolam's benefit in panic disorder might be associated with high potency inspired my colleagues and me to test the effectiveness of clonazepam, another high-potency benzodiazepine, which was labeled as an anticonvulsant. High doses of clonazepam were approved for pediatric epilepsy, which suggested the likelihood of safety, while the long half-life of clonazepam suggested that it would improve quality of life for patients with

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This article is derived from the roundtable meeting "Revisiting the Use of High-Potency Benzodiazepines," which was held July 11, 2003, in Boston, Mass., and supported by an unrestricted educational grant from Solvay Pharmaceuticals.

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Table 1. Clonazepam Research Conducted by Massachusetts General Hospital Psychiatry Department

Author	Year	Duration	Results
Spier et al[4]	1986	Varied	39/50 patients, many previously poorly responsive to treatment, responded with no serious side effects to 1.9 mg/day
Beckett et al[5]	1986	8 weeks	A patient, who partially responded to alprazolam, had a panic attack provoked by CO_2 inhalation, then was retested under the same conditions after clonazepam treatment and did not have an attack
Tesar and Rosenbaum[6]	1986	Varied	7/10 treatment-resistant patients were panic-free after clonazepam treatment
Pollack et al[7]	1986	1 year	Clonazepam was a safe and effective 1-year treatment for patients with panic disorder and agoraphobia
Herman et al[8]	1987	58 weeks	41/48 patients with alprazolam interdose anxiety were switched to clonazepam, which subsequently decreased interdose anxiety for most of the patients
Tesar et al[9]	1987	6 weeks	Interim analysis of data from a double-blind, placebo-controlled trial in panic disorder showed no statistically significant differences between alprazolam and clonazepam on outcome measures, although both drugs were superior to placebo
Sachs et al[10]	1990	Varied	Clonazepam successfully replaced neuroleptics in 6/17 bipolar patients previously treated with lithium and neuroleptics, and some severely ill patients were rated as much or very much improved after clonazepam treatment
Reiter et al[11]	1990	Varied	9/11 patients with social phobia responded to clonazepam
Tesar et al[12]	1991	6 weeks	Full analysis of data from a double-blind,[6] placebo-controlled study showed no significant differences between alprazolam and clonazepam and no tendency for one drug to be favored over the other
Pollack et al[13]	1993	1.5 years	Logitudinal study reevaluated findings of a 6-week trial[12] of alprazolam and clonazepam and showed that 78% of patients remained on mean doses for alprazolam and clonazepam while maintaining benefits
Otto et al[14]	1993	10 weeks	Discontinuation of alprazolam or clonazepam was more successful for patients in a cognitive-behavioral therapy program than not, and at 3 months 77% of the patients in the program had not returned to benzodiazepine treatment
Rosenbaum et al[15]	1997	16 weeks	At the end of the dose-maintenance phase, clinical improvement was observed in all treatment groups, but improvement was clearly differentiated in 4 higher-dose clonazepam groups; 1 to 2 mg/day offered best balance of efficacy and tolerability over 0.5 mg/day or placebo
Otto et al[16]	2000	12 weeks	Social phobia patients randomly assigned to clonazepam or cognitive-behavioral group therapy were equally likely to respond to treatment, although clonazepam improved some measures more at 12 weeks

panic disorder by eliminating the interdose rebound effect. Following up the work of others[1–3] in the field, through numerous clinical studies[4–16] and observation, we have since found that clonazepam was effective and subsequently continued to use clonazepam to treat patients with panic and other affective disorders.

Since the mid-1980s, several studies[4–16] have been published by members of the MGH psychiatry department that establish the antipanic efficacy of clonazepam as well as its use in the treatment of other disorders, such as bipolar disorder and social phobia (Table 1). Additionally, my colleagues and I published research[14,15] on the effect of discontinuing clonazepam and other high-potency benzodiazepines in patients with panic disorder and the efficacy of pharmacotherapy with clonazepam and cognitive-behavioral group therapy (CBGT) in patients with panic disorder and social phobia.[14,16]

The first published study[4] of clonazepam from MGH included 22 patients who had been diagnosed with panic disorder and 28 patients who had been diagnosed with agoraphobia with panic attacks. Forty-one of the 50 patients had previously responded poorly to standard pharmacologic therapies; however, when these patients received a mean ± SD dose of 1.9 ± 1.0 mg/day of clonazepam, 39 (78%) responded well without serious adverse events. Although the study was retrospective and uncontrolled, it suggested that clonazepam, like alprazolam, might be effective in blocking panic attacks.

A true antipanic drug should block spontaneous as well as carbon dioxide (CO_2) inhalation–provoked panic attacks. Therefore, to test the efficacy of clonazepam in preventing panic attacks, my colleagues and I conducted a study[5] in which a 30-year-old woman with panic disorder and phobic avoidance, who had partially responded to alprazolam, underwent a CO_2 inhalation test and sustained a full-featured panic attack. Eight weeks after the first test, we tested the patient again and found that after clonazepam treatment of 1 mg 3 times a day, no panic attack occurred following CO_2 inhalation. This marked the first time a provoked panic was successfully blocked by clonazepam, and my colleagues and I believed the study to be proof-of-principle that clonazepam, in fact, was a true antipanic drug.

During the same year, Tesar and I[6] conducted another study of patients (N = 10) with panic disorder, with or without agoraphobia, who had been resistant to standard pharmacologic treatments. Patients received an average of 3.8 mg/day of clonazepam, ranging from 1.5 to 8.0 mg/day, for varied lengths of time. Results indicated that spontaneous panic attacks and anticipatory anxiety were eliminated in 7 of the 10 patients when sufficient doses of clonazepam were achieved, and 3 others had only mild-to-moderate symptom persistence. These findings further underscored the efficacy of clonazepam in the treatment of panic disorder.

With any treatment for chronic and recurring disorders, physicians need to know it is not only effective with acute use but that it will continue to work over time without

the occurrence of tachyphylaxis. Clinical experience at MGH had indicated that benzodiazepines demonstrated long-term effectiveness without tachyphylaxis. These observations were confirmed in a 1-year study[7] of 50 patients with a primary Axis I diagnosis (by DSM-III criteria) of panic disorder or agoraphobia with panic attacks who were treated with varying doses of clonazepam. Of the 50 patients, 20 remained on clonazepam therapy in the clinic after 1 year, and 1 achieved complete remission of symptoms and was taken off the medication after 44 weeks. Eighteen of the 20 patients who remained on clonazepam for 1 year maintained positive responses with clonazepam treatment, and only 2 had poor responses. Overall, researchers reported that in the relatively treatment-refractory sample, clonazepam appeared to be a safe, effective, and easily administered medication that did not lose efficacy over time.

Because clonazepam seemed efficacious and less problematic than alprazolam, my colleagues and I[8] attempted to determine whether a switch from alprazolam to clonazepam could be successfully accomplished in 48 consecutive patients meeting DSM-III criteria for panic disorder who had been treated with alprazolam but were disturbed by interdose anxiety. Of the 48 patients, 41 who had been taking a mean of 2.95 mg/day of alprazolam for a mean duration of 58 weeks were switched. Thirty-nine of the 41 patients continued a mean dose of 1.5 mg/day of clonazepam for a mean duration of 40 weeks, and 34 (82%) rated clonazepam treatment to be "better" than treatment with alprazolam due to decreased frequency of administration and the lack of interdose anxiety. Five of the 39 patients felt clonazepam was "the same" as alprazolam, but chose to continue treatment with it, and 2 reported that clonazepam was "worse" and elected to switch back to alprazolam. On the basis of the results of this study, my colleagues and I surmised that although patients with panic disorder can be adequately treated with either alprazolam or clonazepam, clonazepam may reduce or eradicate troubling pharmacokinetic adverse events (such as early morning anxiety and emergence of anxiety between doses) in some patients as well as reduce the need for frequent dosing.

After examining the effects on patients of switching from alprazolam to clonazepam, my colleagues and I[9] decided to conduct a prospective 6-week, double-blind, placebo-controlled study to determine not only whether clonazepam was at least as effective as alprazolam in reducing the frequency of panic attacks, but whether both were superior to placebo. By the end of the 6-week trial, 44 of 60 subjects showed no statistically significant differences between clonazepam and alprazolam on the clinically meaningful outcome measures of total number of panic attacks, percentage of time subjects experienced anticipatory anxiety, extent of phobic avoidance, and extent of phobic fear. However, both agents were significantly superior to placebo on each of these measures ($p = .015$, $p = .006$, $p = .001$, and $p = .004$, respectively), and interim analysis of the data supported the inclusion of clonazepam in the treatment of panic disorder.

Other researchers[3, 17–19] had suggested that clonazepam would be useful in bipolar disorder. My colleagues and I hypothesized that clonazepam might be a useful substitute for neuroleptics, which at the time were commonly prescribed for bipolar disorder but were associated with an increased risk of tardive dyskinesia.[20,21] Therefore, we decided to conduct a retrospective review[10] of clinical experience with adjunctive clonazepam as a maintenance treatment for patients with bipolar affective disorder. Clonazepam had been prescribed either as a part of the maintenance regimen or on an as-needed basis for acute exacerbations of illness. Results indicated that for 6 of 17 patients who had previously received combined lithium and neuroleptic treatment, clonazepam successfully replaced the neuroleptics. Overall, 8 of the 17 patients (including 3 who were initially rated most severely ill) were rated as much improved or very much improved after the switch.

Colleagues and I[11] then decided to examine the efficacy of clonazepam in 11 patients with both generalized and performance social phobia. Nine of the 11 patients responded to daily doses of clonazepam that ranged from 0.75 to 3 mg, and we subsequently concluded that because only 2 of the 9 subjects had comorbid panic disorder, the benefit for social phobic symptoms probably occurred independent of clonazepam's putative efficacy for panic disorder.

Eventually, the full analysis[12] of the placebo-controlled comparison of varied doses of alprazolam, clonazepam, or placebo[9] was completed. The dropout rate was high in the placebo group; 83% of patients assigned to alprazolam and 92% assigned to clonazepam completed the study, compared with only 36% of placebo recipients. Results indicated that both clonazepam and alprazolam were superior to placebo for the treatment of panic disorder, measured by the number of panic attacks, overall panic distress, social and work disability, and global assessments of severity of illness and improvement. No significant differences were detected between the two active agents, and there was no consistent tendency for one agent to be favored over the other. Sedation and ataxia were reported to be mild and transient and did not interfere with treatment outcomes.

Pollack et al.[13] continued the examination of the effectiveness of alprazolam and clonazepam in panic disorder to determine long-term effectiveness by reevaluating the findings of our 6-week, randomized trial[12] in a 1.5-year follow-up study. Longitudinal results showed that 78% of the patients had remained on the medication and the mean dosages for alprazolam and clonazepam had not increased. Poor outcome at follow-up was associated with total duration of the disorder, agoraphobic subtype, and the presence of comorbid social phobia. These studies suggested that many patients achieve and subsequently maintain benefit with long-term treatment of alprazolam or clonazepam.

One criticism of high-potency benzodiazepines is that although they are effective as acute and long-term treatments for panic disorder, patients who decide to discontinue treatment may experience some discomfort. Patients with panic disorder are extraordinarily sensitive to bodily sensations, a concept called "anxiety sensitivity," and this sensitivity can make discontinuing treatment difficult. Otto et al.[14] tested the theory that cognitive-behavioral therapy (CBT) for patients with panic disorder may target that vulnerability factor and aid in the discontinuation of benzodiazepine treatment. Patients who had been treated for panic disorder with either alprazolam or clonazepam were assigned to either a slow-taper discontinuation condition alone or the slow taper in conjunction with 10 weeks of group CBT. Discontinuation was more successful for patients in the CBT therapy program than for patients in the slow-taper alone program. No difference in the likelihood of discontinuation existed between patients receiving alprazolam and clonazepam, and at 3 months 77% of the patients in the CBT program had not returned to benzodiazepine treatment.

My colleagues and I[15] conducted a large, multicenter, parallel-group, placebo-controlled study to analyze the efficacy, safety, and discontinuation of clonazepam by dose in 413 patients with panic disorder. Patients were randomly assigned to receive placebo or 1 of 5 fixed-daily dosages of clonazepam—0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, or 4.0 mg. Although efficacy measurements at the end of the dose-maintenance phase indicated clinical improvements in every treatment group, there was a clear differentiation of benefit for patients receiving one of the 4 higher doses of clonazepam from those receiving the 0.5-mg dose or placebo.

Finally, a randomized study[16] was conducted to examine the efficacy of clonazepam versus cognitive-behavioral group therapy for treating social phobia and to determine potential predictors of treatment response. Patients with social phobia (N = 45) were randomly assigned to treatment, and clinician-rated and patient-rated symptom severity was assessed at baseline and after 4, 8, and 12 weeks. Results revealed that patients in both treatment conditions improved significantly, with greater improvement seen with clonazepam on some measures at week 12. Symptom severity was negatively associated with treatment success for both treatment groups, but additional factors failed to predict outcome. Patients who had been assigned to receive clonazepam or CBGT were equally likely to respond to acute treatment.

An orally disintegrating form of clonazepam has been added to the pharmacopoeia for patients with anxiety disorders, which may improve convenience for patients who dislike or have difficulty taking tablets and capsules.

The panorama of work at MGH concerning the management of anxiety disorders has spanned about 20 years. In attempting to discover better treatments, physicians and researchers at MGH have made clinical observations, have taken them seriously, and have been unrelenting in following up with research on these therapeutic technologies. The goal of that work is to make a contribution to the psychiatric pharmacopoeia. New uses of available agents can provide valuable clinical insight, improve outcomes, and advance treatment.

Drug names: alprazolam (Xanax), clonazepam (Klonopin), famotidine (Pepcid), zolmitriptan (Zomig).

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

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