Use of Benzodiazepines in Social Anxiety Disorder, Generalized Anxiety Disorder, and Posttraumatic Stress Disorder

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Benzodiazepines are advantageous treatments for anxiety disorders because they work quickly. However, benzodiazepines can vary in terms of efficacy across anxiety disorders. Benzodiazepines have been found to be a superior treatment in social anxiety disorder. While benzodiazepines are effective in the treatment of generalized anxiety disorder, other treatments such as selective serotonin reuptake inhibitors may be more effective. Also, research indicates that benzodiazepines may not be effective in the treatment of posttraumatic stress disorder. Therefore, physicians need to consider the type of anxiety disorder before prescribing a benzodiazepine as a treatment.

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Benzodiazepines are advantageous treatments for anxiety disorders because they work quickly. However, benzodiazepines can vary in terms of efficacy and tolerability across anxiety disorders. Because benzodiazepines may not be uniformly effective and safe across anxiety disorders, specific diagnosis must be emphasized when considering treatment options.

SOCIAL ANXIETY DISORDER

In a meta-analysis[1] of pharmacologic treatments for social anxiety disorder, also known as social phobia, benzodiazepines were found to be the most effective treatment compared with antidepressants and anticonvulsants (Figure 1). Most of the literature on the treatment of social anxiety disorder focuses on the use of antidepressants, but early studies[2,3–6] suggest efficacy with the use of high-potency benzodiazepines such as clonazepam, bromazepam, and alprazolam. Benzodiazepines appear to be most effective in patients with no lifetime Axis I comorbidity.[7]

In a short-term pilot study,[8] 23 patients meeting the DSM-III-R criteria for social phobia were randomly assigned to either a clonazepam treatment group or a control, nontreated group for 8 weeks. Participants were required to be between the ages of 18 and 65 years and free of medication that might confound treatment and diagnosis. The average clonazepam dose was 2.75 mg/day with a maximum dose of 6 mg/day. Twenty of the original 23 participants completed the trial, and clonazepam was found to be superior to nontreatment in the management of social phobia according to the Global Improvement Scale and the Hamilton Rating Scale for Anxiety (HAM-A) ($p < .0005$, for both scales). Fear and avoidance and overall distress related to phobic avoidance as rated on the Sheehan Phobia Scale were also found to be significantly improved among clonazepam-treated patients ($p < .0005$, for all items).

In a short-term trial,[9] my colleagues and I evaluated the efficacy of clonazepam in 75 patients with social anxiety disorder. All participants had a DSM-III-R diagnosis of social phobia, an absence of major depression or panic disorder for 6 months, and a 12-month absence of alcohol or substance abuse. Participants were randomly assigned to clonazepam or placebo for 10 weeks; the mean maximum dose of clonazepam by endpoint was 2.4 mg/day. Subjects were assessed at baseline and weeks 1, 2, 4, 6, 8, and 10. Severity of symptoms was rated by the 5-point Clinical Global Impressions Scale Severity of Illness (CGI-S), and improvement was rated by the 5-point Global Improvement Scale. Seventy-five percent of patients completed the trial. Clonazepam was found to have an early and sustained effect on social anxiety disorder. Clonazepam was also found to be more effective than placebo at all time points on the CGI-S. By endpoint, 78.3% of clonazepam-treated patients had responded to treatment versus 20% of placebo-treated patients. The most common adverse effect was unsteadiness, but high rates of anorgasmia were reported, a finding that was surprising because the sexual

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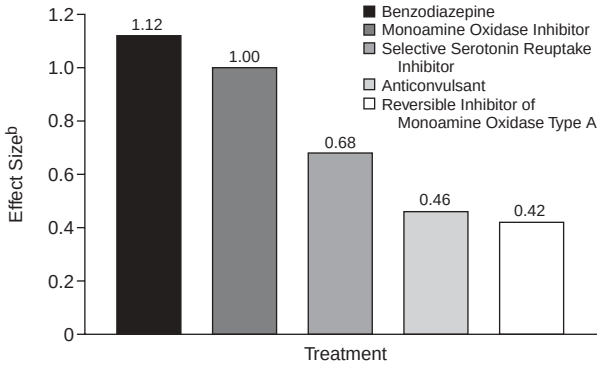
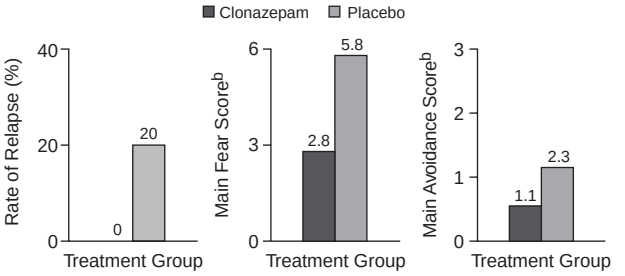
Figure 1. Pharmacotherapy in Social Anxiety Disorder: Meta-Analysis of Efficacy Studies[a]



[a]Reprinted with permission from Hidalgo et al.[1]
[b]Effect size weighted to balance sample size.

Figure 2. Relapse Prevention and Efficacy With Clonazepam Continuation in Social Anxiety Disorder[a]



[a]Adapted from Connor et al.[11]
[b]Fear and avoidance measured with Marks-Sheehan Main Phobia Severity Scale.

side effects of benzodiazepines had not been stressed in previous literature. Forgetfulness and impaired concentration were also side effects appearing more often with clonazepam than placebo.

Later, our group conducted a 2-year follow-up study[10] among patients who had participated in our short-term trial.[9] During the intervening 2 years, treatment was naturalistic. Of the original 75 participants, 56 subjects participated in follow-up telephone interviews and self-assessment ratings. According to the Sheehan Disability Scale, there was a significant advantage in function among participants who had taken clonazepam 2 years earlier than those who received placebo ($p < .0001$). Less severe baseline symptoms also predicted a better outcome.

Another study[2] observed the effects of clonazepam in a long-term trial. Twenty-six outpatients with DSM-III-R–diagnosed social phobia were evaluated with clonazepam treatment. Clonazepam doses ranged from 0.5 to 5.0 mg/day, with a mean maximum dose of 2.1 ± 1.0 mg/day. Clinical efficacy was rated based on a 3-point CGI scale. Treatment duration extended from 1 to 29 months, with a mean duration of 11.3 months. At endpoint, 22 (84.6%) patients showed good improvement with clonazepam treatment. In the follow-up phase, doses of clonazepam were adjusted in response to side effects or to a clinical decision based on patients' symptoms. During follow-up, the mean dose, including doses for patients who had discontinued treatment, was 0.94 ± 0.66 mg/day. Marked or moderate success with clonazepam treatment was found again in 22 (84.6%) of the 26 patients. Adverse effects to clonazepam were reported in 15 participants, with the most common side effect being sedation/drowsiness/tiredness. An important secondary finding was that a reduction of clonazepam dosage did not reduce the efficacy among patients. Doses of 2 to 3 mg/day of clonazepam were found to be as effective as 4 mg/day of clonazepam and were associated with a reduction in side effect occurrence.

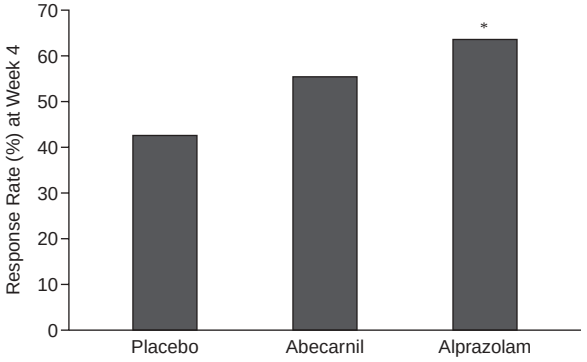
Connor and colleagues[11] conducted a 2-part trial to assess the rates of response and relapse and to assess the safety and efficacy of clonazepam over 11 months. The first phase was an open-label trial with 56 participants, all treated with clonazepam. Participants were between the ages of 18 and 55 years, with a DSM-III-R diagnosis of social phobia. After 6 months, all subjects with a rating of good clinical response on the CGI scale ($N = 36$) were then randomly assigned to either a continuation treatment or a discontinuation treatment group. The continuation group continued on the prescribed doses of clonazepam for a period of 5 months and, at week 44, underwent a rapid 3-week taper period. The discontinuation group began a double-blind, placebo-controlled, slow fixed-dose taper. Outcomes were measured using the Marks-Sheehan Main Phobia Severity Scale (MSPSS), the Benzodiazepine Withdrawal Checklist, the CGI-S and the CGI-Improvement (CGI-I) scale, and the Brief Social Phobia Scale. At endpoint, none of the patients in the continuation group had experienced a relapse of symptoms, while 4 patients (20%) in the discontinuation group had experienced relapse. These data were found to be significant ($p < .05$) after being analyzed with the Kaplan-Meier survival analysis. Participants in the continuation group were also found to have less fear and avoidance as assessed by the MSPSS than participants in the discontinuation group (Figure 2).

Based on the research, the benzodiazepine clonazepam is highly effective in short-term treatment and also appears to carry some relapse-preventing effects if given for a year. Alprazolam had a 38% response rate[6] and bromazepam had an 82% response rate[5] both in studies that had placebo response rates of 20% in social anxiety disorder. Using a lower dose may benefit patients with less severe cases of social anxiety disorder.

GENERALIZED ANXIETY DISORDER

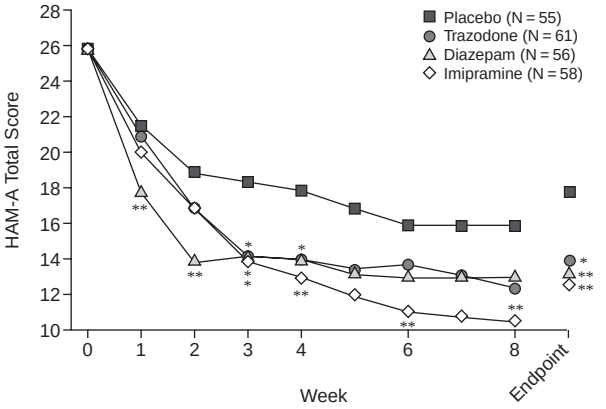
Benzodiazepines have been shown to be beneficial in treating generalized anxiety disorder (GAD) because they

Figure 3. Benzodiazepine Response in Generalized Anxiety Disorder[a]



[a]Adapted from Lydiard et al.[12] Response = CGI rating of 1 or 2. Abecarnil is a partial benzodiazepine agonist.
*p < .05 alprazolam vs. placebo.

Figure 4. Imipramine, Diazepam, and Trazodone in Generalized Anxiety Disorder[a]



[a]Reprinted with permission from Rickels et al.[13]
*p < .05 compared with placebo.
**p < .01 compared with placebo.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

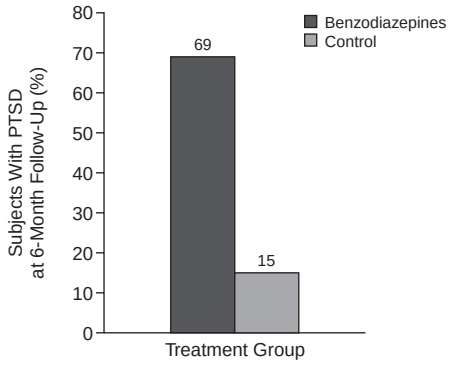
work quickly and are well tolerated. Most people with GAD who are given benzodiazepines will improve. However, despite studies that have found benzodiazepine treatment to be effective, most of the comparative studies[13,14] suggest that antidepressant treatment may be more effective for GAD than benzodiazepine treatment, especially in the presence of comorbid mood or anxiety disorders. Since GAD is considered a chronic condition, a long-term effective treatment is necessary. With treatments that work rapidly, such as benzodiazepines, the effect of the drug quickly reaches its maximum efficacy, but with antidepressant treatment, a slow but steady pattern of improvement is seen with an overall slightly better effect by endpoint.[13,14]

In a multicenter, short-term trial,[12] 180 outpatients with a current DSM-III-R diagnosis of GAD were randomly assigned to receive the partial benzodiazepine agonist abecarnil, the benzodiazepine alprazolam, or placebo. The effects of alprazolam treatment were rapid, with a significant decrease in HAM-A scores seen as early as week 1. However, both alprazolam and abecarnil treatments were more effective than placebo by week 4, with no differences seen between the 2 treatment groups (Figure 3).

In a double-blind, placebo-controlled trial,[13] the efficacy of antidepressants and benzodiazepines were compared in patients with GAD. A total of 230 patients were randomly assigned to receive the benzodiazepine diazepam, the antidepressant imipramine or trazodone, or placebo for a period of 8 weeks. Participants were required to be between 18 and 70 years of age; have a DSM-III-R diagnosis of GAD; have a score of 18 or higher on the HAM-A and a minimum score of 8 on the Covi Anxiety Scale; and be free of any Axis I disorders other than GAD. Treatment response was assessed using the 14-item HAM-A scale, the 21-item Hamilton Rating Scale for Depression (HAM-D), the Covi Anxiety and Raskin Depression scales, the CGI-S scale, and the 80-item Hopkins Symptoms Checklist. Assessments were made at baseline, weeks 1 through 4, and weeks 6 and 8. Diazepam was the most rapidly effective treatment, producing significant improvement by week 2. Imipramine, however, produced slightly more improvement by week 4 and showed statistically significant improvement compared with placebo at weeks 6 and 8 on the HAM-A. Imipramine also differed significantly from diazepam by week 8 in the psychic HAM-A factor ($p < .05$). The CGI-S score and the Covi Anxiety Scale score showed similar treatment effects in favor of all 3 drugs; however, the Covi Anxiety Scale appeared to slightly favor antidepressants (Figure 4).

Another study[14] found a statistically significant difference in favor of antidepressants over a benzodiazepine. The study consisted of 81 DSM-IV–diagnosed patients with GAD between the ages of 18 and 65 years with a score of at least an 18 on the HAM-A, at least a 38 on the State Trait Anxiety Inventory (STAI), and 14 or less on the HAM-D. Participants were randomly assigned to paroxetine (20 mg/day), imipramine (50 to 100 mg/day), or 2'chlordesmethyldiazepam (3 to 6 mg/day) for a period of 8 weeks. Assessments were made at baseline and 2, 4, and 8 weeks; efficacy was measured using the HAM-A total score and psychiatric and somatic clusters, the HAM-D, the Covi Anxiety Scale, the CGI-S, and the CGI-I. A total of 63 patients displayed significant improvement. The antidepressants imipramine and paroxetine showed the greatest efficacy after week 4 on the HAM-D, and by week 8 imipramine and paroxetine showed significantly greater improvement than the benzodiazepine 2'chlordesmethyldiazepam on the HAM-A ($p < .05$). Imipramine and paroxetine were also found to be more effective in reducing psychic symptoms, whereas

Figure 5. Benzodiazepine Monotherapy in Posttraumatic Stress Disorder (PTSD)[a]



[a]Data from Gelpin et al.[16] Alprazolam (N = 3) or clonazepam (N = 10) vs. no treatment (N = 10).

2'chlordesmethyldiazepam was more effective in reducing somatic symptoms.

Data indicate that benzodiazepines are uniformly effective and generally well tolerated in the treatment of GAD. In fact, one study[15] found that patients with panic disorder treated with alprazolam were more likely to suffer from withdrawal symptoms when treatment was withdrawn than were patients with GAD treated with the same dosage of alprazolam. Benzodiazepines can be used to quickly treat the symptoms of GAD; however, antidepressants may be more effective for the long-term treatment of GAD.

POSTTRAUMATIC STRESS DISORDER

Little research exists on the use of benzodiazepines to treat posttraumatic stress disorder (PTSD), and what is available[16,17] suggests that benzodiazepines may not be the most useful treatment for PTSD. Also, data from one study[18] indicated that the discontinuation of long-term treatment with benzodiazepines may cause severe withdrawal symptoms in patients with PTSD.

The researchers in a study[16] of acute stress disorder observed the effect of early administration of benzodiazepines to trauma survivors with high levels of initial distress. A total of 23 patients who had recently undergone a traumatic event and met the DSM-III-R PTSD Criterion A were recruited into the study. Subjects who had taken psychotropics prior to the trauma and patients who had suffered a coma, head injury, or loss of consciousness during the trauma were excluded from the study. Thirteen participants were treated with benzodiazepines and matched to an untreated control group. Participants were interviewed at 1 and 6 months by a research psychiatrist. Outcome measures included Horowitz Impact of Event Scales (IES), STAI, Mississippi Rating Scale for Combat-Related PTSD-Civilian Trauma Version (MISS), and heart rate scores. Although benzodiazepine treatment did reduce physiologic arousal, the overall conclusions were that, contrary to expectation, subjects treated with benzodiazepines were not found to differ significantly from the control group on the IES, STAI, or MISS scores at 1 or 6 months. In fact, after 6 months, 9 (69%) of the benzodiazepine-treated subjects and 2 (15%) of the control subjects met the PTSD diagnostic criteria, so administration of benzodiazepines soon after trauma did not alleviate the development of PTSD. People who received no treatment had a lower incidence of PTSD after 6 months (Figure 5).

In a similar study conducted by Mellman and colleagues,[17] the short-term treatment of acute PTSD was investigated. All 22 participants had been admitted to a level I trauma center following life-threatening incidents and were manifesting early PTSD symptoms. Subjects were randomly assigned to receive either placebo or temazepam. PTSD was assessed at the initial evaluation, 1 week after medication discontinuation, and at final assessment, 6 weeks after initial assessment, using the Clinician-Administered PTSD Scale. In the total study population, PTSD severity was significantly reduced ($p < .04$), but 6 (55%) of the 11 temazepam-treated subjects had PTSD at final assessment, while 3 (27%) of the 11 control subjects had PTSD. The authors concluded that short-term benzodiazepine treatment soon after trauma may alleviate distress but does not prevent PTSD.

One study[18] found that discontinuing long-term benzodiazepine treatment in PTSD patients can result in severe withdrawal symptoms. A group of 8 patients with a DSM-III-R diagnosis of PTSD were withdrawn from long-term alprazolam treatment. Patients had been treated with 2 to 9 mg/day of alprazolam for between 1 and 5 years. As treatment was withdrawn, all of the patients suffered from severe reactions including anxiety, sleep disturbances, and hyper-alertness. Six of the 8 patients also suffered from homicidal ideation. Caution was advised when discontinuing alprazolam treatment among patients with PTSD.

Benzodiazepines may play a role in PTSD as an adjunctive treatment with selective serotonin reuptake inhibitors. However, to rely on benzodiazepines as monotherapy or to think of them as prevention of PTSD following a trauma is not advised. As a rule, benzodiazepines should be used with caution in PTSD treatment.

SUMMARY

Benzodiazepines can be effective in treating anxiety disorders; however, they may not be effective in all types of anxiety. Benzodiazepines are efficacious in the treatment of social anxiety disorder and GAD. However, physicians should use caution when treating PTSD with benzodiazepines. Because the efficacy of benzodiazepines

varies across anxiety disorders, it is important for physicians to first consider the diagnosis before prescribing a benzodiazepine treatment.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), diazepam (Valium, Diastat, and others), imipramine (Tofranil, Surmontil and others), paroxetine (Paxil and others), temazepam (Restoril and others), trazodone (Desyrel and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, alprazolam, bromazepam, clonazepam, diazepam, and imipramine are not approved by the U.S. Food and Drug Administration for the treatment of generalized anxiety disorder (GAD), social anxiety disorder, and posttraumatic stress disorder (PTSD); temazepam is not approved for the treatment of PTSD; trazodone is not approved for the treatment of PTSD or GAD; and abecarnil and 2'chlordesmethyldiazepam are not approved for the treatment of GAD.

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