

The Efficacy and Safety of Clonazepam in Patients with Anxiety Disorder Taking Newer Antidepressants: A Multicenter Naturalistic Study

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Objective: This study compared the efficacy and tolerability of clonazepam with other benzodiazepines in patients with anxiety disorders.

Methods: Inclusion criteria were as follows: age >20 years, diagnosis of anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision (DSM-IV-TR) criteria, taking only one type of antidepressant, and prescribed one of three oral benzodiazepines (alprazolam, clonazepam, or lorazepam). At baseline and week 6, clinical benefit was evaluated using the Clinical Global Impression-Severity Scale (CGI-S), Clinical Global Impression-Anxiety Scale (CGI-anxiety), and Clinical Global Impression-Sleep Scale (CGI-sleep).

Results: Among 180 patients, no differences in demographic characteristics among the three benzodiazepine groups were noted. After six weeks of treatment, all benzodiazepine groups showed significant improvements in CGI-S, CGI-anxiety, and CGI-sleep scores ($p < 0.001$). There were no differences in mean changes in CGI-S, CGI-anxiety and CGI-sleep among the three benzodiazepine groups. The incidence of side effects was significantly lower in the clonazepam group than with the other benzodiazepines. The incidences of adverse events for the clonazepam, alprazolam, and lorazepam groups were 26.7% ($n=20$), 48.4% ($n=31$), and 43.9% ($n=18$), respectively.

Conclusion: The present study suggests that clonazepam is as efficacious as other benzodiazepines for the treatment of various anxiety disorders. Furthermore, the safety profile of clonazepam was superior to the other benzodiazepines in this study.

KEY WORDS: Anti-anxiety agents; Alprazolam; Clonazepam; Lorazepam; Therapy; Anxiety disorders.

INTRODUCTION

Anxiety disorders are chronic, recurrent and serious mental illnesses that result in functional impairment and are associated with significant social costs.¹⁾ Benzodiazepines (BZDs) are useful drugs for treating anxiety dis-

orders, in part because they have a quick onset of action and are generally well tolerated.²⁾ Due to their potential addictive risk, BZDs are more commonly used for short periods of time and in conjunction with other medications, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs).³⁾ Although high potency BZDs are known to have higher risks of causing memory impairment,⁴⁾ dependency,⁵⁾ and withdrawal symptoms,⁶⁾ high potency BZDs remain an important option for patients with high levels of anticipatory anxiety and frequent anxiety attacks.³⁾ Among the many high potency BZDs available, alprazolam, clonazepam, and lorazepam are the

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most frequently recommended and widely used in the clinical setting.⁵⁾

Although similarities exist among these BZDs, differences in the pharmacologic properties exist and the efficacy of the BZDs varies across the spectrum of anxiety disorders.⁶⁾ Many experts further suggest carefully assessing the pros and cons of the diverse array of BZDs before selecting an agent for a patient.⁷⁾ Numerous previous studies have been conducted to compare the efficacy of different BZDs in the treatment of anxiety disorder.⁸⁻¹⁶⁾ However, these studies are outdated, with the most recent study having been conducted in 1991.¹⁶⁾ As stated earlier, with the introduction of novel antidepressants having anxiolytic actions, BZDs are recommended and widely used in conjunction with SSRIs or SNRIs.³⁾ Despite these facts, studies comparing the efficacy and tolerability of these three widely used BZDs in patients with anxiety disorder taking concomitant antidepressants are lacking. Moreover, as novel agents with anxiolytic effects have become available, studies in the most recent decade have typically focused on comparing the effectiveness of BZDs with other agents, including new antidepressants such as SSRIs and SNRIs, and buspirone.^{5,17)}

Randomized controlled trials are essential for determining the efficacy of any new drug before it can be placed on the market and for providing safety data for clinicians. However, these controlled trials are limited by selection bias. Also, data that may be important for application in real clinical situations might be overlooked.^{18,19)} In contrast, a naturalistic study can provide readily accessible data relevant to daily clinical application. More importantly, this type of study enables direct comparisons of specific drugs in real clinical practice.^{20,21)} Therefore, we conducted a retrospective chart review to compare the efficacy and tolerability of oral alprazolam, clonazepam, and lorazepam in "real-world" patients with anxiety disorder taking concomitant antidepressants.

METHODS

Subjects

This study was a retrospective, multi-center trial assessing the efficacy and safety of 3 types of BZDs (alprazolam, clonazepam, and lorazepam) in patients with anxiety disorders. Data was obtained from a retrospective psychiatric chart review of patients between January 1, 2005 and February 28, 2012 in 14 different hospitals located in Korea. The subjects included were >20 years, meeting the diagnosis of anxiety disorder according to the Diag-

nostic and Statistical Manual of Mental Disorders 4th edition, text revision (DMS-IV-TR) criteria, taking only one type of antidepressant for more than 6 weeks, and were prescribed one of three oral BZDs (alprazolam, clonazepam, or lorazepam) for 6 weeks. Patients taking more than two types of antidepressants, using other anxiolytics (i.e., other BZDs or buspirone), or not having one of the anxiety disorders as their primary diagnosis were excluded from the study.

Methods

Before conducting the study, an introductory workshop was held in Seoul, Korea. In the workshop, the study design and methodology were thoroughly explained to the investigators and a case-report form, which included details on demographics and various clinical parameters, was also introduced. In addition, workshops were held regularly in order to improve inter-rater reliability. All investigators were board-certified psychiatrists of Korea. Case-report forms were completed by investigator(s) in each affiliated hospital and then sent to the authors (K.U.L., and S.M.W.), who compiled the data in a computerized database.

At baseline and week 6, clinical benefit was evaluated using the Clinical Global Impression-Severity Scale (CGI-S), Clinical Global Impression-Anxiety Scale (CGI-anxiety), and Clinical Global Impression-Sleep Scale (CGI-sleep). The primary outcome measure was mean change in CGI-S from baseline to week 6, whereas mean changes in CGI-anxiety and CGI-sleep from baseline to week 6 were key secondary measures. Moreover, we also compared the doses of the 3 BZDs prescribed by converting alprazolam and clonazepam doses to lorazepam equivalent doses based on the equivalence criteria provided in a renowned psychiatry textbook (alprazolam 0.25 mg=clonazepam 0.5 mg=lorazepam 1.0 mg).²²⁾ All adverse events were recorded using National Cancer Institute Common Toxicity Criteria version 3.0. The study was carried out according to the Declaration of Helsinki and good clinical practices. The institutional review board at each study site approved the study protocol (approval number: XC12RIMI0012).

Statistical Analysis

All statistical analyses were performed using SAS/PC version 9.2 (SAS Institute Inc., Cary, NC, USA). Differences between the three groups were analyzed using one-way analyses of variance (ANOVA) for the continuous variables and Pearson's chi-square test for categorical variables. The significance level was set at $p < 0.05$

(two-tailed). In terms of one-way ANOVA, Bonferroni correction was used for *post-hoc* analysis to counteract the problem of multiple comparisons.

RESULTS

Participant Characteristic

A total of 180 patients participated in the present study. Patients' baseline demographic and clinical characteristics for each of the BZD groups are shown in Table 1.

The mean age was lower in the clonazepam group (44.2±16.3) than in the alprazolam (49.4±15.0) and lorazepam groups (50.3±16.7), although the difference was not statistically significant (*p*=0.07). The three groups did not show significant differences in any demographic characteristic, including sex ratio, occupation, marital status, religion, socioeconomic status, and education. Also, the baseline CGI-S, CGI-anxiety, and CGI-sleep scores did not significantly differ among the three groups. However, the lorazepam group contained a statistically lower number of panic disorder patients than the clonazepam and alprazolam groups.

Table 2 represents the proportion of antidepressants

used in the three treatment groups. In all three groups, the most commonly prescribed antidepressant was escitalopram, followed by paroxetine.

Efficacy

After 6 weeks of treatment, all BZD groups showed statistically significant improvement compared to their

Table 2. Comparison of antidepressant use among treatment groups

Drug	Group		
	Clonazepam (n=75)	Alprazolam (n=64)	Lorazepam (n=41)
Citalopram	2 (2.7)	0 (0)	0 (0)
Escitalopram	24 (32.0)	25 (39.1)	14 (34.1)
Fluoxetine	7 (9.3)	4 (6.3)	5 (12.2)
Fluvoxamine	0 (0)	1 (1.6)	0 (0)
Paroxetine	22 (29.3)	19 (29.7)	8 (19.5)
Sertraline	6 (8.0)	2 (3.1)	3 (7.3)
Duloxetine	1 (1.3)	0 (0)	3 (7.3)
Milnacipran	1 (1.3)	0 (0)	0 (0)
Venlafaxine	6 (8.0)	4 (6.3)	3 (7.3)
Mirtazapine	3 (4.0)	5 (7.8)	3 (7.3)
Others	3 (4.0)	4 (6.3)	2 (4.9)

Values are presented as number (%).

Table 1. Comparison of demographic and clinical characteristics among three treatment groups

Variable	Group			<i>p</i> value
	Clonazepam (n=75)	Alprazolam (n=64)	Lorazepam (n=41)	
Age (yr)	44.2±16.3	49.4±15.0	50.3±16.7	NS
Sex, Female	43 (57.3)	42 (65.6)	20 (48.8)	NS
Occupation, Not working	25 (33.3)	19 (29.7)	14 (34.1)	NS
Marital status, Single	22 (29.3)	10 (15.6)	11 (26.8)	NS
Religion, Yes	62 (82.7)	54 (84.4)	38 (68.3)	NS
Socioeconomic status				
High	9 (12.0)	12 (18.8)	5 (12.2)	NS
Med	54 (72.0)	38 (59.4)	21 (51.2)	
Low	8 (10.7)	10 (15.6)	9 (22.0)	
Education				
<9 years	13 (17.3)	9 (13.1)	7 (17.0)	NS
Principal diagnosis				<0.05
Panic disorder	34 (45.3)	23 (35.9)	6 (14.6)	
Social anxiety	15 (20.0)	7 (10.9)	7 (17.1)	
PTSD	6 (8.0)	6 (9.4)	2 (4.9)	
OCD	6 (8.0)	9 (14.1)	6 (14.6)	
GAD	8 (10.7)	13 (20.3)	10 (24.4)	
Specific phobia	0 (0)	1 (1.6)	3 (7.3)	
Anxiety disorder, NOS	6 (8.0)	5 (7.9)	7 (17.0)	
Outpatient	72 (96.0)	61 (95.3)	40 (97.6)	NS
CGI-S	4.92±0.93	4.92±0.97	4.76±0.99	NS
CGI-anxiety	4.89±0.94	4.78±0.95	4.78±1.15	NS
CGI-sleep	3.73±1.42	3.56±1.48	3.78±1.39	NS

Values are presented as mean±standard deviation or number (%).

NS, not significant; PTSD, posttraumatic stress disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; NOS, not otherwise specified; CGI-S, Clinical Global Impression-Severity Scale.

One-way ANOVA for continuous variables and Pearson's chi-square test for categorical variables.

baselines in all three efficacy measures, including CGI-S, CGI-anxiety, and CGI-sleep. However, there were no significant differences in any of the three efficacy measures among the three BZD groups. Table 3 illustrates the efficacy comparison among the three BZD groups in the treatment of anxiety disorders.

Doses of the 3 BZDs prescribed were also compared using lorazepam equivalent dosage. Baseline, maximum, week 6, and mean doses were significantly higher in the alprazolam group than in the clonazepam and lorazepam groups. No significant differences were found between the clonazepam and lorazepam groups (Table 4).

Safety

Table 5 summarizes rates of adverse events among the 3 BZD groups. The total incidence of adverse events was significantly lower for the clonazepam (26.7%) group than for the alprazolam (48.4%) and lorazepam groups (43.9%) ($p < 0.05$). The rate of somnolence was significantly high-

Table 3. Comparison of efficacy among three benzodiazepines in the treatment of anxiety disorders

Variable	Group		
	Clonazepam (n=75)	Alprazolam (n=64)	Lorazepam (n=41)
CGI-S			
Baseline	4.92±0.93	4.92±0.97	4.76±0.99
Week 6	2.76±0.80	2.77±0.79	2.90±0.89
Change*	2.16±1.12 [†]	2.16±1.03 [†]	1.85±0.94 [†]
CGI-anxiety			
Baseline	4.89±0.94	4.78±0.95	4.78±1.15
Week 6	2.63±0.75	2.69±0.73	2.88±1.01
Change*	2.27±1.15 [†]	2.09±0.94 [†]	1.90±0.99 [†]
CGI-sleep			
Baseline	3.73±1.42	3.56±1.48	3.78±1.39
Week 6	2.07±0.78	2.08±0.98	2.34±0.97
Change*	1.67±1.19 [†]	1.48±1.08 [†]	1.44±1.12 [†]

Values are presented as mean±standard deviation.

*Change=Week 6–baseline.

[†] $p < 0.001$ for paired *t*-test.

Analysis of variance; all *p* values are not significant.

CGI-S, Clinical Global Impression-Severity Scale.

Table 4. Comparison of dose prescribed among three benzodiazepines by using lorazepam equivalent dosage

Variable	Group			<i>p</i> value	Post-hoc
	Clonazepam (n=75)	Alprazolam (n=64)	Lorazepam (n=41)		
Original dose (mg)					
Baseline	0.64±0.29	0.60±0.32	1.12±0.89		
Maximum	0.76±0.36	0.75±0.42	1.36±0.89		
Week 6	0.71±0.37	0.71±0.40	1.27±0.87		
Mean	0.79±0.32	0.71±0.39	1.30±0.86		
Lorazepam equivalent dose* (mg)					
Baseline	1.28±0.57	2.41±1.27	1.17±0.89	<0.001	B>A, C
Maximum	1.51±0.73	3.00±1.67	1.36±0.89	<0.001	B>A, C
Week 6	1.43±0.74	2.82±1.60	1.27±0.87	<0.001	B>A, C
Mean	1.40±0.64	2.78±1.60	1.30±1.60	<0.001	B>A, C

Values are presented as mean±standard deviation.

*Clonazepam 0.5 mg=alprazolam 0.25 mg=lorazepam 1 mg.²²⁾

A, clonazepam group; B, alprazolam group; C, lorazepam group.

Table 5. Incidence of adverse events among three treatment groups

Adverse event	Group			<i>p</i> value
	Clonazepam	Alprazolam	Lorazepam	
Total	20 (26.7)	31 (48.4)	18 (43.9)	<0.05
Somnolence	7 (9.3)	23 (35.9)	6 (14.6)	<0.001
Ataxia	0	0	0	
Gastrointestinal symptoms	1 (1.3)	3 (4.8)	4 (9.8)	NS
Sexual dysfunction	0 (0)	1 (1.6)	2 (4.9)	NS
Dizziness	6 (6.7)	6 (9.4)	2 (4.9)	NS
Agitation	1 (1.3)	0 (0)	2 (4.9)	NS
Headache	1 (1.3)	3 (4.8)	3 (7.3)	NS
Memory problem	2 (2.7)	7 (10.9)	1 (2.4)	NS

Values are presented as number (%).

NS, not significant.

er for the alprazolam group (35.9%) than the clonazepam (9.3%) and lorazepam groups (14.6%) ($p < 0.001$). All reported side effects were mild in severity and no serious adverse event was noted.

DISCUSSION

The purpose of the present study was to compare the efficacy and safety of alprazolam, clonazepam, and lorazepam in patients with anxiety disorder who are taking a concomitant antidepressant. In line with previous studies, all three BZDs showed statistically significant improvement in anxiety symptoms compared to baseline, however, no differences were noted between the agents.⁸⁻¹⁶ Since BZDs are sometimes viewed as a “necessary evil”,³ it is recommended to use the lowest dose possible.²³ In this respect, the fact that the dose prescribed at baseline, at week 6, and the mean and the maximum dose were all significantly lower with clonazepam than with the other two BZDs is noteworthy. However, although we used equivalence conversion criteria that was based on the most renowned psychiatry textbook (alprazolam 0.25 mg=clonazepam 0.5 mg=lorazepam 1.0 mg),²² controversy exists regarding such calculations.^{24,25} Therefore, our result should be interpreted cautiously.

The general side effect profiles of the three BZDs observed in our study were in accordance with previous research.¹⁷ All of the side effects were mild in severity and there were no serious adverse events. The total incidence of adverse events was significantly lower for the clonazepam group than for the alprazolam and lorazepam groups. The high lipid solubility and faster elimination half-life of the high potency BZDs are known to be associated with the severity of side effects.^{25,26} Interdose withdrawal symptoms are reported to be higher in patients taking high potency short-acting BZDs such as alprazolam. Therefore, clonazepam’s lower lipid solubility and slower elimination half-life could explain its lower incidence of adverse events. Moreover, clonazepam’s absence of drug interactions with antidepressants could also be an important factor because all of our subjects were using a concomitant antidepressant.^{27,28} Somnolence was more frequently observed in the alprazolam group than in the clonazepam and lorazepam groups. The higher dose prescribed for the alprazolam group than for the other two groups could have been a contributing factor to the increase in somnolence because higher BZD doses are associated with increased risk of this side effect.²⁹

Several limitations of the present study need to be

acknowledged. First, the naturalistic design of the study could be a shortcoming because non-random assignment to treatment groups and un-blinded ratings can influence results. Second, the study included only two assessment time points and examined effects after a relatively short period (6 weeks). Clonazepam’s long half-life and high potency profile is a major clinical concern because withdrawal symptoms can both appear and last for months after the drug is stopped, a phenomenon that would only be evident in a longer-term study. In addition, although the difference was not statistically significant, the mean age was lower in the clonazepam group than in the alprazolam and lorazepam groups, which could have caused bias in our study. The sample size among the three groups was also not equal. The fact that the lorazepam group had a statistically lower number of patients with panic disorder than the other groups could be a limitation because the effects of BZDs could vary depending on the type of anxiety disorder being treated.^{3,6} Although demographic data was not significantly different among the three groups, there was a trend ($p=0.07$) of difference in age. Thus, with a bigger sample size, the age difference could have become statistically significant. Information regarding patient’s life events and somatic disorders were also not included in the demographic data. Psychological and physical dependence, which is not rare in patients taking BZDs, should also have been discussed. The study included all of the anxiety-spectrum disorders and more than 10 different kinds of antidepressants and doses, which have varied anti-anxiety effects. Furthermore, it was not possible to exclude the effects of the specific combination of medication (SSRI) on the efficacy of alprazolam, clonazepam, and lorazepam. Changes in CGI-S, CGI-anxiety, and CGI-sleep had been selected as our primary efficacy measure. Although these indices are simple and easy to use, HAMA and HAMD give more information on evaluating the efficacy of drug treatment. Muscular relaxation is one of the important side effects of clonazepam, but it has been neglected in the present study. Finally, all of our subjects were Korean, so studies focusing on other ethnicities are needed in order to generalize our results to the general population.

Despite these limitations, our study has several important clinical implications. To the best of our knowledge, no previous study has directly compared the efficacy and tolerability of these BZDs in patients taking newer antidepressants such as SSRIs, SNRIs, and others. The uniformly Korean population, although we have listed it as one of the limitations of our study, is also a strength be-

cause considerable evidence indicates that the metabolism of BZDs differs depending on the patient's ethnicity as it relates to cytochrome P450 polymorphisms.^{30,31)} The treatment groups had comparable demographic characteristics, baseline anxiety severity, and types of concomitant antidepressants. These factors minimize the risk of confounding biases. Clonazepam was initially licensed as an anti-epileptic agent, but previous studies demonstrated that it was also useful in a wide variety of psychiatric conditions including social anxiety disorder and panic disorder (PD).^{32,33)} Our study replicated previous research by showing that alprazolam, clonazepam, and lorazepam are equally effective in patients with anxiety disorder. Our study also extended and updated previous research by comparing these three BZDs in patients who were also taking newer antidepressants. Since other studies have indicated that clonazepam may have different functions in patients with social anxiety disorder or panic disorder,^{34,35)} further studies are needed to shed light on these issues. In conclusion, our results indicate that clonazepam could be an appropriate choice of medication for the treatment of anxiety disorder in patients using a concomitant antidepressant because it requires a lower dose and provides a more favorable side effect profile than lorazepam or alprazolam.

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