Use of Clonazepam for Bipolar Affective Disorder

Gary S. Sachs, M.D.

The use of anticonvulsants as treatments for bipolar affective disorder is growing, and despite relatively scant data, anticonvulsants have become widely accepted as adjuncts to lithium therapy, particularly as alternatives to neuroleptics. Although most of the research work to date has involved carbamazepine, improvement in bipolar symptoms with clonazepam has been exhibited in controlled studies and case reports. The author summarizes studies done by the Bipolar Research Group of the Clinical Psychopharmacology Unit at Massachusetts General Hospital. The data thus far indicate that clonazepam can be added to the treatment regimen of bipolar patients and apparently reduces cycle frequency; many patients using neuroleptics and lithium can be switched to lithium and clonazepam without suffering acute relapse; and clonazepam may be associated with fewer depressive recurrences than neuroleptic treatment. *(J Clin Psychiatry 1990;51[5, suppl]:31–34)*

From 1984 to 1988, the literature reflects a growing interest in the use of anticonvulsants as treatments for bipolar affective disorder. Despite relatively scant data, anticonvulsants have become widely accepted as adjuncts to lithium therapy, particularly as alternatives to neuroleptics. Although most of the research work to date has involved carbamazepine, controlled studies by Chouinard,[1-3] as well as a number of case reports,[4-8] have described improvement in bipolar symptoms with clonazepam, another anticonvulsant.

The advantages of clonazepam include a long half-life, rapid onset of antimanic action, and no serious toxicity necessitating laboratory monitoring. If systematic study shows clonazepam to be well tolerated and effective, the drug would offer an attractive option for patients with suboptimal response to lithium alone. At the Massachusetts General Hospital, the Bipolar Research Group of the Clinical Psychopharmacology Unit (Sachs GS, Rosenbaum JF, Weilburg JB, et al.) has begun to study the efficacy of clonazepam in bipolar patients. This report summarizes our initial work, including a retrospective case series, preliminary results from a prospective study, which involved use of clonazepam and lithium as maintenance therapy, and some findings from our clinical data base.

ADJUNCTIVE CLONAZEPAM: OPEN CASE SERIES

Initially, we investigated the efficacy of clonazepam in an open retrospective case series. Psychiatrists who had prescribed clonazepam for bipolar patients participated in a semistructured interview and chart review for each patient so treated. Our systematic review of 20 clonazepam-treated bipolar patients from the Massachusetts General Hospital Clinical Pharmacology Unit[9] included 17 patients who had previously received combined lithium and neuroleptic treatment. While using clonazepam, 6 patients entirely discontinued neuroleptic medication, and 7 reduced their neuroleptic dose. The mean frequency of affective episodes per year decreased significantly, from 2.25 to 0.94 per patient per year. Improvement was also shown on the Clinical Global Impressions scale: 8 patients were rated as improved or very much improved; 1 patient was rated as worse. Based on this retrospective review, full or partial replacement of neuroleptic by clonazepam could be accomplished without clinical deterioration.

Aronson et al.,[10] however, encountered early severe relapse in 5 of 5 lithium-refractory bipolar patients openly switched from unspecified doses of neuroleptic to clonazepam over 2 to 4 weeks. All 5 subjects had a history of recurrent psychotic mania and had failed prior attempts to taper their neuroleptics. Four subjects required electroconvulsive therapy (ECT), including 1 patient who began clonazepam 1 week after completing a course of ECT and relapsed the following week. These uncontrolled results prompted termination of the study, but it is unclear whether this experience should be extrapolated to the entire subgroup of patients maintained on lithium and neuroleptics. It seems likely that factors such as the baseline neuroleptic dose, rate of tapering, severity of illness, and refractoriness of patients to prior treatments will be important in determining how or whether to switch patients from neuroleptics to alternative maintenance therapies. We tried to take these considerations into account in designing a prospective study.

CLONAZEPAM VS. NEUROLEPTIC AS ADJUNCTS TO LITHIUM MAINTENANCE

Patients

Over the past 13 months, we have followed patients monthly who have a diagnosis of bipolar affective disorder or schizoaffective disorder. These patients had been treated with lithium and a neuroleptic as their maintenance

From the Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston.

The author acknowledges the assistance of Mary Noeth and Samantha Meltzer in establishing the clinical database project.

Reprint requests to: Gary S. Sachs, M.D., Clinical Psychopharmacology Unit, Massachusetts General Hospital, 15 Parkman Street, Boston, MA

ther to openly switch to clonazepam and neuroleptic or to continue their present treatment. Prior to being approached for the study, patients were randomized to a treatment group. Patients were entered into the follow-up only if they and their treating clinician consented to patient participation in the assigned group.

Additionally, patients met eligibility criteria that included having had onset of illness prior to age 45; a minimum of three well-documented affective episodes, including at least one episode of mania during the last 5 years; age between 21 and 65 years; history of at least one episode while on adequate lithium therapy; history of neuroleptic use during the preceding year and current daily neuroleptic dosage equivalent to haloperidol 10 mg or less; no substance abuse during the past 6 months; and not being acutely suicidal. Patients were scheduled for baseline evaluation only if they had been out of the hospital and had no changes made in their medication for at least 8 weeks.

Trained interviewers administered the 31-item Hamilton Rating Scale for Depression (HAM-31), the Brief Psychiatric Rating Scale (BPRS), and a modified Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C). Interviewers were instructed to rate all symptoms on the SADS-C without regard to the presence of pathologic mood state or other presumed etiology (such as drug-induced akathisia). Patients were also asked to keep a diary in which they answered questions pertaining to common symptoms of affective disorder and use of caffeine, alcohol, and prescribed medication (diary available upon request).

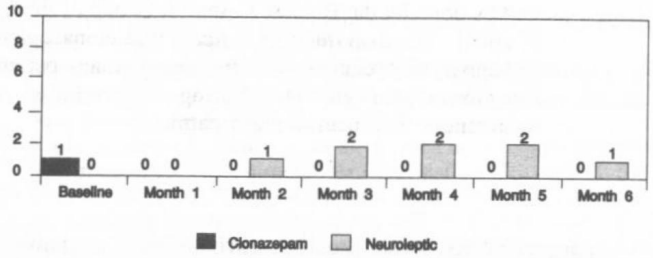
At monthly follow-up interviews, rating instruments were repeated with questions soliciting symptomatology that had occurred the preceding week. Diaries, when available, were used both to enrich the data for the most recent week and to augment questions directed at determining a clinical status for each week during the study. Each status was defined to be clinically pertinent and to allow criteria for the determination of onset and offset of affective episodes. Assignment of the weekly clinical status was carried out at the time of the monthly interview on the basis of all available information and was reviewed by one of the primary investigators. For each week, patients were designated as acutely ill (meeting full DSM-III-R criteria for the diagnosis of an acute episode of mania or major depression); continued symptomatic (patient does not meet criteria for acutely ill, but has three or more symptoms rated moderate or greater and has not met criteria for recovered since last met criteria for acutely ill); recovering (patient does not meet criteria for acutely ill and has no more than two symptoms rated moderate or greater and has not met criteria for recovered since last met criteria for acutely ill); recovered (has met criteria for recovering for 8 consecutive weeks since last acutely ill or continued symptomatic and has no more than two symptoms rated moderate or greater); or roughening (has met criteria for recovered but during current week has three or more symptoms rated moderate or greater). Statistical comparisons of group means were made by using Stu-

Table 1. Mean of Baseline Characteristics

Group	Age (y)	Dosage (mg)		Duration of Illness (y)
		Lithium	Neuroleptic[a]	
Neuroleptic maintenance (N=6)	44.2	1300	2.5	13.2
Clonazepam maintenance (N=5)	43.5	1450	4.2	13.0

[a]Equivalent to haloperidol.

Figure 1. Patients Meeting Criteria for Acute Mania or Depression



Results

Referral, computer search, and review of clinic charts with individual psychiatrists identified 190 bipolar or schizoaffective patients. From these potential subjects, screening procedures determined 53 were eligible. All eligible patients were randomized, and the treating psychiatrists were again contacted. In 11 instances, psychiatrists or patients refused to enter the study because of group assignment: 7 were assigned to clonazepam and 4 were assigned to neuroleptic. An additional 20 patients refused to participate regardless of their group assignment. In all, 22 patients have been enrolled. This analysis presents the data on the first 12 patients enrolled into the clonazepam maintenance (CM) (N=6) or neuroleptic maintenance (NM) (N=6) groups for at least 12 weeks.

Baseline characteristics. No significant demographic differences were found between the groups (Table 1). At baseline the CM group used more neuroleptic (CM=4.2 mg; NM=2.5 mg, NS) and more lithium (CM=1450 mg; NM=1300 mg, NS). Along with higher levels of medication, the CM group had a higher mean BPRS score and more symptoms rated moderate or greater on the SADS-C. The only significant difference found at baseline was higher mean BPRS score in the CM group (CM=39.6; NM=26; $p < .02$); however, the CM group averaged about twice as many symptoms rated moderate or greater on the SADS-C (CM=8.8; NM=4.2, NS). Thus the CM group began the study significantly more symptomatic. Comparisons between the groups are therefore based on the occurrence of acute episodes in individual patients and as mean changes from baseline.

Occurrence of acute affective episodes. On the basis of the patient interview, monthly SADS-C, and daily diary assignment of weekly clinical status, two new episodes that met criteria for acute illness were detected (Figure 1). These were both episodes of major depression in the NM group. In the CM group, one patient entered the study meeting formal criteria for mania but was rated continued symptomatic at all follow-up visits. No patient has been

Figure 2. Brief Psychiatric Rating Scale Scores (Monthly Group Means)

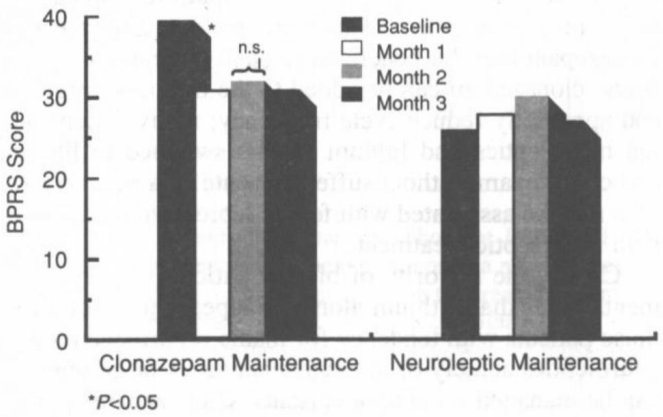
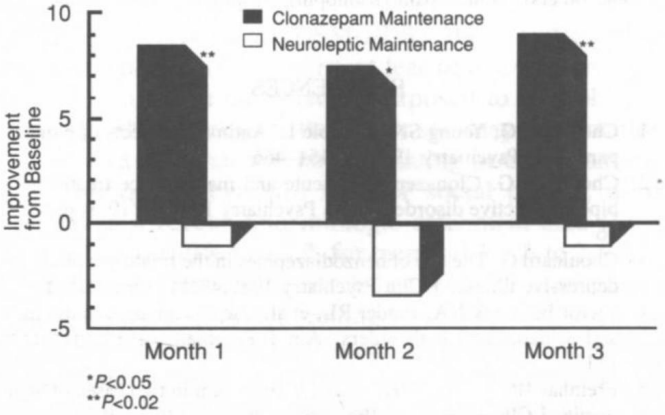


Figure 3. Change From Baseline: Brief Psychiatric Rating Scale Scores



Course of symptoms by change in group mean scores. At all follow-up visits, the CM group mean BPRS (which was significantly greater than the NM group mean at baseline) was decreased significantly compared to the CM baseline and was no longer significantly different from the NM group mean (Figure 2). After the baseline evaluation, the BPRS showed little change in either group. Over the first three monthly follow-up visits, the change from the baseline BPRS was nearly constant in both groups (Figure 3). The change from baseline in group mean BPRS scores at each month was significantly greater for clonazepam, but this reflects, in part, a floor effect due to the NM low baseline scores.

Based on the SADS-C, there were no significant differences in symptom counts (Figure 4). The CM group started with more symptoms, but by the third month the mean for the CM group was 1.4 symptoms less than the NM mean (NS).

Conclusions

We found switching patients from lithium and neuroleptic to lithium and clonazepam resulted in no significant clinical or statistical indication of worsening affective morbidity. The only statistically significant findings—higher baseline BPRS scores in the clonazepam group and

Figure 4. Schedule for Affective Disorders and Schizophrenia, Change Version: Symptoms Rated Moderate or Greater

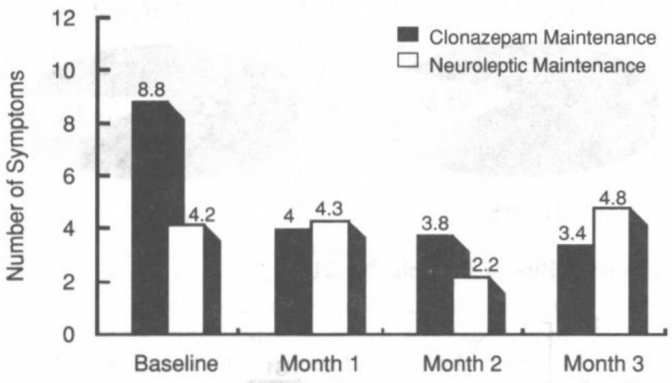


Table 2. Treatments for Bipolar (N=215) and Schizoaffective Patients (N=42)

	Patients (N=257)	
Treatment	N	%
Lithium	172	66.9
Neuroleptic	94	36.7
Clonazepam	51	19.8
Anticonvulsant other than clonazepam	43	16.7
Benzodiazepine other than clonazepam	29	11.3
Antidepressant	82	31.9

treated patients—are consistent with other trends, suggesting that the CM group was more symptomatic at baseline. Therefore, the statistical advantage of clonazepam over neuroleptic may represent actual clinical benefit due to clonazepam, benefit due to discontinuation of neuroleptic, regression to the mean, or the floor effect in the NM group due to the low level of pathology at baseline.

Clinical Data Base

Among the sources of therapeutic pessimism concerning the treatment of bipolar illness is the surprising inability of retrospective studies examining open clinical data to detect the prophylactic benefit of lithium. We are conducting a review of data collected from our clinic to compare with reports (Markar and Mander,[11] Grof,[12] and Dickson and Kendall[13]) that failed to find the anticipated statistically significant advantage for patients treated with lithium. Thus far, we have begun to collect data (Table 2) on the pattern of treatment of 257 patients (bipolar, N=215; schizoaffective, N=42). Although about two thirds of this population receive lithium, in relatively few is the response sufficient for lithium maintenance to serve as monotherapy: 21.5% of the bipolars, 14.4% of the entire population (Figure 5).

These data support the expectation drawn from Prien and colleagues' study[14] that about 15% of patients will have good response to lithium. Our data could be interpreted to mean that about 80% of bipolar patients and 100% of schizoaffective patients require additional or alternative treatments.

A simple measure of severity of illness and treatment outcome is the number of medications used. Looking at the frequency distribution for these data (Figure 6), we find the modal number of medications is two (excluding

Figure 5. Current Treatment: Lithium Monotherapy

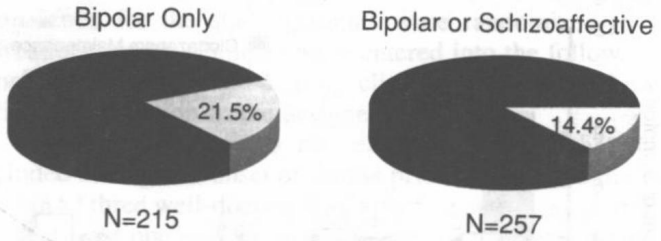


Figure 6. Bipolar Patients (N=215)

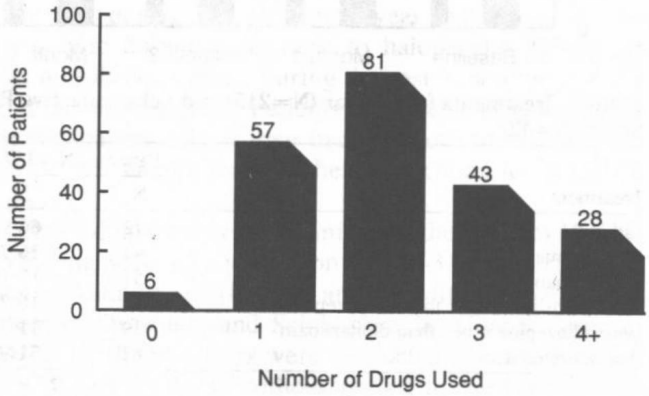
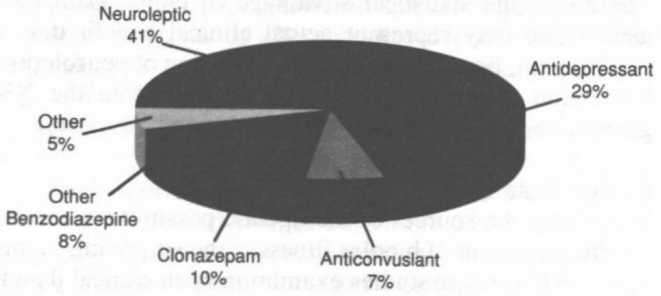


Figure 7. Current Treatment: Lithium and One Other Drug (N=61)



low-dose propranolol). Among the patients treated with two medications, it is of interest to consider those patients treated with lithium and one other drug (Figure 7). Among these patients (N=61), we find about 41% on a neuroleptic, 29% on an antidepressant, and nearly another 25% on drug treatment with anticonvulsant properties (i.e., carbamazepine, valproate, clonazepam, and other benzodiazepines). The combination of clonazepam and lithium was used by 10%. We plan to continue to collect data on this particular group to compare the course and treatment needs of patients receiving these combined treatments.

SUMMARY

We are studying the use of clonazepam for bipolar patients in several ways. Thus far, the data indicate that clonazepam may be beneficial to such patients in several ways: clonazepam can be added to the treatment regimen and apparently reduce cycle frequency; many patients using neuroleptics and lithium can be switched to lithium and clonazepam without suffering acute relapse; clonazepam may be associated with fewer depressive recurrences than neuroleptic treatment.

Clearly the majority of bipolar patients require treatments other than lithium alone. It appears that not all of those patients with tendency for manic recurrence require neuroleptics acutely or for maintenance. A large segment can be managed on anticonvulsants. Clonazepam appears to be an effective agent in general clinical practice.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), clonazepam (Klonopin), propranolol (Inderal and others).

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DISCUSSIONS

TOLERANCE AND SIDE EFFECTS

Dr. Rosenbaum: One of the intriguing issues on the subject of tolerance is that there appears to be a differential tolerance to side effects, which is well documented in the trials with alprazolam and clonazepam. The sedation and ataxia evident in Weeks 1 to 3 are largely gone by Week 6, whereas antipanic effects tend to be sustained.

Dr. Patterson: In our population, there also seems to be a euphorigenic effect with alprazolam that, like ataxia, resolves with time.

Dr. Munjack: On the other hand, the cognitive impairment that occurs with benzodiazepines sometimes does not go away. Sedation does, but some people remain fuzzy for many months.

Dr. Pollack: That may be one of the reasons why doses tend to decrease over time, as patients seek the lowest effective dose, perhaps in response to cloudiness or impairment.

Dr. Rosenbaum: If benzodiazepines are discontinued, there's an apparent functional shift of enhanced receptor sensitivity to benzodiazepine antagonists. Benzodiazepine antagonists may increase alertness and ability to learn. Therefore, there may be a transient augmentation in cognitive function, with benzodiazepine discontinuation acting like an antagonist and enhancing learning.

BENZODIAZEPINES IN PANIC DISORDER

Dr. Bodkin: The literature suggests that benzodiazepines are equally effective in panic disorder at equipotent dosages, including, presumably, diazepam, chlordiazepoxide, and lorazepam. Is that true?

Dr. Rosenbaum: Our field is hampered by limitations of acute clinical trial methodology. We have a hard enough time demonstrating drug-placebo differences with agents we believe to be effective. When you add a treatment that has some effect, given the N's that we typically muster for our clinical trials, we're destined to introduce a type II error that makes active treatments look statistically indistinguishable.

PANIC ATTACKS

Dr. Munjack: Your report, Dr. Svebak, seems a little out of step with the literature, in that most studies of imipramine and even benzodiazepines do not show 100% recovery from panic attacks. Can you explain your results?

Dr. Svebak: Several factors are involved. One is the very careful medical screening, which itself provides relief in that patients know they're not suffering from any dangerous disease. That may account for the 50% reduction in panic attacks from screening to the baseline week. habits that might interfere with panic complaints. I counsel them to undertake physical exercise regimens—moderate enough not to provoke lactic acid secretion—and increase their aerobic capacity. I also show them in the lab how to assume more normal breathing patterns.

In general, I think the patients feel better taken care of. In Bergen, anxiety patients have actually organized themselves into a group called Only Anxiety to counteract what they perceive as a lack of understanding from the public.

Dr. Rosenbaum: What drugs are typically used to treat panic disorder in Norway?

Dr. Svebak: We use the more traditional benzodiazepines, oxazepam and diazepam. Clomipramine has also been frequently prescribed. The dose levels of clomipramine were probably well above what should be recommended, because patients tended to report a number of obvious side effects.

Dr. Rosenbaum: Is panic disorder viewed as a dramatically treatable disorder?

Dr. Svebak: There's been a change in the way we regard the treatment of panic disorder. It's being more widely accepted as a disorder and is getting increased attention in terms of drug use. One good reason for doing these studies is to inform psychiatrists and general practitioners about choosing more appropriate drug treatment.

Dr. Tesar: I'd like to suggest another reason for the excellent response your patients have. Is it possible that European patients, in general, have a higher degree of tolerance for discomfort than American patients? Studies on back pain demonstrate a low incidence of surgeries and corrective procedures for European patients compared with our own patients.

Dr. Svebak: I can't answer a question like that, but I wouldn't think there would be a difference. Certainly, back pain has a very complicated etiology and shouldn't really be compared with panic disorder.

The only interesting and peculiar finding is that all these panic disorder patients complain of pain in the neck and shoulders, and they have cold hands and feet.

PANIC DISORDERS IN CHILDREN

Dr. Rosenbaum: Are there critical periods of "plasticity" in an illness during which successful interventions can be associated with maintenance of recovery when treatment is discontinued?

Dr. Graae: Certainly, there are reports that relatively young children, if successfully treated, may maintain that recovery in the absence of medication seemingly indefinitely.

Whether that will hold true in follow-up studies remains to be seen. The notion that there may be crucial developmental periods at which that kind of intervention might stick is worth exploring.

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