

# Clonazepam Augmentation Of Paroxetine In The Treatment Of Panic Disorder: A One Year Naturalistic Follow-Up Study

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## Abstract

**Background:** Recent studies have examined the proper role of benzodiazepine pharmacotherapy in the treatment of Panic Disorder (PD). The purpose of this naturalistic outcome study is to evaluate the possible clinical benefits and safety of paroxetine/ clonazepam combination therapy in the acute treatment phase (weeks 1-16) of PD. We also compare the treatment outcome of paroxetine plus short-term clonazepam versus paroxetine monotherapy at one year follow-up.

**Method:** Seventy-seven patients with PD with or without agoraphobia participated in our study. All 77 patients received paroxetine (up to 40 mg per day) and 30/77 patients received paroxetine plus clonazepam (up to 1.5 mg/day) for the first 12 weeks of treatment. Patients were assigned to receive clonazepam in a non-randomized fashion. A gradual clonazepam taper was started after week 8, and the clonazepam was discontinued at week 12. The patients in both groups were then continued on paroxetine monotherapy for a total of 12 months. The Panic Self-Questionnaire" (PSQ) was administered to all patients on a monthly basis for one year.

**Results:** The majority of the patients responded well to the pharmacological treatment. Patients showed a statistically significant improvement at four weeks, eight weeks, sixteen weeks and twelve months follow-up. At four weeks and eight weeks follow-up, the paroxetine-clonazepam group reported lower levels of panic symptoms compared to the paroxetine monotherapy group (df:1,  $p < 0.01$ ). At the sixteen week, and twelve month follow-up visits, there were no statistically significant differences between the two groups ( $p = NS$ ) in terms of treatment response. Also, there was no significant difference between the PD and the PD with Agoraphobia (PDA) groups at baseline and at all follow-up points. Age, sex and, duration of illness had no significant effect on treatment outcome.

**Conclusion:** The combination of paroxetine and clonazepam was more beneficial than paroxetine alone during the acute phase of treatment. During the subsequent maintenance phase, however, there was no significant difference between the two groups. We suggest that clonazepam may be useful as an anti-panic agent during the acute treatment phase of PD, but long-term use is not recommended.

## INTRODUCTION

Panic disorder (PD) is a common psychiatric illness that can have a chronic course (1). Epidemiological data has documented a lifetime prevalence of 1.6%-4.2%, and the illness usually begins during young adulthood with a female to male preponderance (2).

Prompt identification and treatment of PD is important because patients with PD have poor quality of life, and there is an increased risk of developing comorbid psychiatric conditions, such as agoraphobia and depression (3).

Medications that have proven effective in PD include the selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, benzodiazepines and MAO inhibitors (4,5,6).

According to the current American Psychiatric Association practice guidelines, SSRI's should be considered as first-line agents in the treatment of panic disorder since these agents have the most favorable balance of efficacy and adverse effects (7). Despite these clear guidelines, benzodiazepines are widely used in the long-term treatment of PD (8). Long-term benzodiazepine treatment, however, carries risks of

physiological dependence, disruption of sleep architecture, and mood disturbance, as well as an increased risk of falls in the elderly (9,10,11).

Recent studies have focused on the role of benzodiazepine use in the acute phase of treatment for PD. Dannon et al (12), in a short-term naturalistic study, reported evidence of the early anti-panic efficacy of paroxetine/clonazepam co-administration in the early phase of treatment for PD. Goddard et al (13) conducted a randomized, double-blind, placebo-controlled trial and documented the efficacy of combination therapy with the SSRI sertraline plus clonazepam for the rapid stabilization of PD symptoms in the acute phase of treatment. In another controlled trial, Pollack et al (14) demonstrated that in the initial stage of PD pharmacotherapy, combined treatment with paroxetine and clonazepam resulted in a more rapid response than with paroxetine alone, but after three weeks, no differential benefit was seen in patients receiving combination therapy. There is evidence, therefore, that the proper use of benzodiazepines for PD may be as a short-term adjunctive agent at the initiation of SSRI treatment only. Adding a benzodiazepine to the treatment regimen for the initial 4 to 12 weeks could serve as a effective bridge to control anxiety symptoms until the desired SSRI effect is attained.

In the present study, we examine the possible clinical benefits and tolerability of short-term potentiation of paroxetine with clonazepam in the early treatment phase of PD. We also compare the treatment outcome of paroxetine plus short-term clonazepam augmentation versus paroxetine monotherapy as measured at the one-year follow-up visit.

## **METHODS**

### **SAMPLE**

This study was conducted at the Sheba Medical Center in Israel and was on-going for 12 months. Subjects were referred to the outpatient psychiatry clinic either through the emergency room or by a family physician. The patients completed a semi-structured interview performed by a senior psychiatrist (PND, II). All referred patients who met DSM-IV diagnostic criteria for PD and panic disorder with agoraphobia (PDA) and who matched our inclusion and exclusion criteria (n=77) were enrolled in the study. Among the 77 patients who were eligible to enroll in the study, all 77 patients agreed to participate in the study. We presume that we had no dropouts at the enrollment phase because the patients were actively seeking treatment for their symptoms,

and our treatment protocol was based on standard pharmacotherapy for the treatment of panic disorder. Inclusion criteria were: (1) age over 18 years, (2) no comorbid psychiatric diagnosis on axis I, and (3) no major physical disorder. Exclusion criteria included substance abuse and patients receiving any intensive psychological intervention during the twelve months treatment phase. All patients gave their informed consent upon entering the study, and the study was approved by the hospital Ethics Board and the local Helsinki Committee for clinical trials.

### **PROCEDURE**

All study subjects received paroxetine. This drug was chosen in part for practical reasons, as it was one of the first SSRIs covered by the government's health insurance. Paroxetine dosage was gradually increased up to 40mg/day over the first month of treatment. Thirty patients were assigned to receive also open-label clonazepam, up to 1.5 mg/day. The administration of adjunctive clonazepam was assigned in a non-randomized fashion. The clonazepam was prescribed, by the treating psychiatrist (PND, II) according to clinical judgement and the patient's preference.

Adjunctive clonazepam was administered for 8 weeks and then was gradually tapered over a 3-week period (reduced every 3 days in decrements of 0.25 mg/day prior to discontinuation). The clonazepam was discontinued at week 12. Assessment of clonazepam withdrawal and rebound symptoms was performed by clinical interviews during the tapering and discontinuation phase. After clonazepam discontinuation, the patients in both groups were continued on paroxetine monotherapy for a period of 12 months. Patients were assessed at the outpatient clinic every month during the 12-month follow-up phase.

### **INSTRUMENT**

Clinical improvement was measured by the Panic Self-Questionnaire, (PSQ) (15). The PSQ is a self-report tool that measures the number of panic attacks per week and is a well studied instrument which has been shown to quantify panic symptoms in a reliable manner. In this study, relapse was defined as the presence of one or more panic attacks per week.

### **STATISTICS**

Statistical analysis was performed with t-tests, analysis of variance (ANOVA), ANOVA with repeated measures, and  $\chi^2$  tests. Level of significance was set at 0.05, unless otherwise stated. SPSS (version 5.1) was used for the

statistical analyses.

**RESULTS**

According to the results of the Panic Self-Questionnaire (PSQ) administered at baseline, there were no significant differences in the illness severity of the two groups prior to treatment. Other demographic and baseline measurements are shown in Table 1. Out of the seventy-seven patients who entered the study, 65 patients completed the full twelve month protocol, 34 with PD and 31 with PDA. Paroxetine alone was received by 47/77 patients, and 30/77 patients also received paroxetine plus short-term clonazepam. None of the patients reported drug or alcohol abuse. The study population was generally in good physical health and included patients with mild cardiovascular disease (n=3), stable hypertension (n=4), and non-insulin dependent diabetes mellitus (NIDDM) (n=5). Two patients had comorbid hypertension and NIDDM.

**Figure 1**

Table I: Demographic and baseline measurements \*

	Group A	Group B	p
	Count (%)	Count (%)	
	(N=25)	(N=40)	
Mean Age (years)	28.7± 8.9	32.6±5.9	NS
Gender (MF)	13 (52%)/12(48%)	20(50%)/20(50%)	NS
Diagnosis (PD/PDA)	14 (56%)/11(44%)	20 (50%)/20(50%)	NS
Comorbid physical problems	4 (16%)	6 (15%)	NS
Weight at baseline (kilograms)	66.9 ± 7.9	66.2 ± 8.4	NS
PSQ (panic attacks/week)	5.9± 1.4	6.2 ± 1.4	NS

\* Group A: adjunctive clonazepam treatment, Group B: paroxetine monotherapy  
 PD = panic disorder, PDA = panic disorder with agoraphobia  
 PSQ = Panic Self- Questionnaire

Paroxetine was given in a mean dose of 28.2±5.4 mg/d in the paroxetine group and, 27.8±5.6 mg/d in the paroxetine and clonazepam group (NS). In both groups, the final paroxetine dose was achieved by the fourth week of treatment. Clonazepam was given in a mean dose of 0.75±0.33 mg/day for eight weeks. The subsequent taper and discontinuation was well tolerated, without withdrawal symptoms or re-emergent panic symptoms related to clonazepam discontinuation. All patients who received clonazepam were successfully tapered off the clonazepam and remained benzodiazepine-free through the 12-months follow-up. Only 12 patients, 7 females and 5 males, dropped out due to side effects. These included 7 patients who received paroxetine alone and 5 patients who received adjunctive clonazepam. Three patients suffered from severe gastrointestinal side effects, whereas 5 female patients and the 4 male patients suffered from palpitations, restlessness and insomnia.

Dropouts occurred mainly during the first three weeks of treatment.

Eighty-five percent of the patients (65/77) responded favorably to the study treatment. The clonazepam-paroxetine group, however, had significantly lower rates of panic symptoms as measured at the four and eight week visits. The improvement according to ANOVA with repeated measures (F:(1, 65), df:1, p<0.01; Pearson  $\chi^2$ : 0.054; value = 4.846 and F (1,65),df:1, p<0.05; Pearson  $\chi^2$ : 0.046; value = 3.745, respectively) was statistically significant at four and eight weeks. At the 16-week and 52-week follow-up points, the improvement of the study groups was similar and there was no statistically significant difference between the two groups (p=NS).

Table II summarizes the PSQ scores in the adjunctive clonazepam patients and the paroxetine monotherapy group. At both four weeks and eight weeks, those receiving adjunctive clonazepam treatment had a lower number of panic attacks than those receiving paroxetine alone. These differences were not maintained after eight weeks.

**Figure 2**

Table II: PSQ scores in treatment groups \*

	Group A	Group B	p
Baseline	5.9 ± 1.4	6.2 ± 1.4	NS
4 weeks	3.5 ± 2.1	5.1 ± 0.9	<0.01
8 weeks	2.8 ± 1.7	3.1 ± 1.2	<0.05
16 weeks	1.2 ± 0.3	1.1 ± 0.05	NS
52 weeks	0.9 ± 0.4	0.7 ± 0.2	NS

There was no significant difference between the PD and PDA groups at baseline, four weeks, eight weeks, sixteen weeks, and twelve months follow-up. Response to treatment was not significantly affected by age, sex and duration of illness. Elderly patients (>60) responded positively to treatment as did the younger patients.

Table III summarizes the relapse rates and side effects as measured at the 12 month visit. Weight gain and sexual side effects were measured at the 12-month follow-up visit. Relapsing patients gained more weight than patients who achieved full recovery (5.9±3.3 kg), (t=2.2; 95% CI = ±4.8; p<0.05). Weight gain was significantly greater among the clonazepam group (t=3.1; 95 % CI (confidence interval) = ± 3.8; p<0.01). No significant differences were observed between patients with regard to gender or age.

Sexual side effects including loss of libido, erectile

dysfunction, and anorgasmia were assessed clinically at the 12 month visit. Sexual problems were more common in patients treated with clonazepam (60%) than among the paroxetine monotherapy group (45%) (df=1,  $\chi^2=5.8$ ,  $p=0.05$ ).

**Figure 3**

Table III: Relapse rates and side effects as measured at the 12 month visit \*

	Group A * (N=25) Count (%)	Group B * (N=40) Count (%)	df	$\chi^2$	p
Relapse	4 (16%)	6 (15%)	1	3.6	NS
Weight gain (kilograms)	6.9±3.3 (28%)	5.4±3.7 (14%)	1	7.5	<0.01
Sexual dysfunction	15 (60%)	18 (45%)	1	5.8	0.05

\* Group A: adjunctive clonazepam treatment, Group B: paroxetine monotherapy

**DISCUSSION**

Despite the widespread use of combined SSRIs and benzodiazepine treatment for PD, only a small number of studies have examined the safety and efficacy of this therapeutic strategy. Our preliminary study supports existing evidence that clonazepam is a safe and effective anti-panic agent, especially in the early stage of treatment of PD (16,17). The results of our study show that initiating combined benzodiazepine-SSRI treatment followed by benzodiazepine taper after a few weeks may provide early benefit while avoiding the potential adverse consequences of long-term combination therapy. At both the four-week and eight-week follow-up visits, the paroxetine-clonazepam group reported significantly lower rates of panic symptoms (as measured by the PSQ) than the paroxetine monotherapy group.

The gradual taper and discontinuation of clonazepam during weeks 8-12 of our trial was well tolerated, and there was no evidence of withdrawal or rebound symptoms. This supports findings by Goddard et al (18) in which clonazepam/sertraline combination therapy was administered during weeks 1-4 of treatment, and then the benzodiazepine was successfully tapered and discontinued during weeks 5-8 of the trial. This positive experience with clonazepam contrasts with earlier reports in which alprazolam/imipramine combination therapy for PD was efficacious in the early phase of treatment, but the alprazolam was difficult to taper (19).

It is important to note that the patients in the combination group were able to maintain their good treatment response even after discontinuation of clonazepam. After 4 months and 12 months follow-up, there was no significant difference between the two groups in terms of rates of panic symptoms.

These results are consistent with Pollack's randomized, double-blind study in which he demonstrated that the use of adjunctive clonazepam after week 12 of treatment confers no additional advantage over paroxetine monotherapy (14). Restricting the use of benzodiazepines to the acute phase of treatment (i.e., weeks 1-12) allows the patient to avoid the adverse effects of long-term benzodiazepine use.

Interestingly, in our study, the adjunctive clonazepam patients had a higher rate of weight gain and sexual side effects as measured at the 12-month visit. Since clonazepam was discontinued during the 3rd month of the study, it is not clear why the clonazepam group had a higher incidence of side effects nine months later. Since the clonazepam group was selected in a non-randomized fashion, it is possible that the patients who received short-term clonazepam may represent a group with increased severity of PD which may in turn correlate with an increased sensitivity to the SSRI side effects.

The primary weakness of this preliminary study is the lack of randomization as well as the lack of a double-blind, placebo-controlled methodology. The fact that clonazepam was administered in a non-randomized, open label fashion limits the validity of our findings, for we cannot rule out the possibility that the improved outcome in the clonazepam group was due to either rater or selection bias. Also, due to limitations in our study methodology (such as the single site study design, the relatively small sample size, and the exclusion of patients with other comorbid axis I diagnoses) we cannot generalize our findings to everyday clinical practice. It is important to note, however, that one major finding of our study was the easy tolerability of clonazepam taper and discontinuation during weeks 8-12, and this conclusion is not negatively affected by our naturalistic study design.

The data from our preliminary study, together with a limited number of studies to date, suggests that clonazepam can be an effective anti-panic agent during the initial phase of the treatment. Initiating combined treatment followed by benzodiazepine taper after 6-8 weeks may provide early benefit while avoiding the potential adverse consequences of long-term combination therapy. The co-administration of paroxetine and clonazepam appears to be a safe and beneficial strategy for stabilizing moderate to severe panic disorder. Double-blind, randomized, placebo-controlled studies using a larger patient sample are needed in order to confirm our results.

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