

## DOUBLE-BLIND CLONAZEPAM VS PLACEBO IN PANIC DISORDER TREATMENT

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**ABSTRACT - Objective:** To assess the effectiveness of clonazepam, in a fixed dose (2 mg/day), compared with placebo in the treatment of panic disorder patients. **Method:** 24 panic disorder patients with agoraphobia were randomly selected. The diagnosis was obtained using the structured clinical interview for DSM-IV. All twenty-four subjects were randomly assigned to either treatment with clonazepam (2 mg/day) or placebo, during 6 weeks. Efficacy assessments included: change from baseline in the number of panic attacks; CGI scores for panic disorder; Hamilton rating scale for anxiety; and panic associated symptoms scale. **Results:** At the therapeutic endpoint, only one of 9 placebo patients (11.1%) were free of panic attacks, compared with 8 of 13 (61.5%) clonazepam patients (Fisher exact test;  $p=0,031$ ). **Conclusion:** the results provide evidence for the efficacy of clonazepam in panic disorder patients.

**KEY WORDS:** panic disorder, panic attack, clonazepam, treatment.

### Estudo duplo-cego com clonazepam e placebo no tratamento do transtorno do pânico

**RESUMO - Objetivo:** Avaliar a eficácia do clonazepam, em uma dose fixa (2 mg/dia), comparado ao placebo, no tratamento de pacientes com transtorno do pânico. **Método:** Foram selecionados randomicamente 24 pacientes com transtorno do pânico com agorafobia. O diagnóstico foi obtido através da entrevista clínica estruturada do DSM-IV. Todos os 24 pacientes foram randomicamente designados para tratamento com clonazepam (2 mg/dia) ou placebo, durante 6 semanas. Para avaliação da eficácia foram utilizadas: mudança do número de ataques de pânico em relação ao período anterior ao tratamento; escala de Hamilton de ansiedade; escala de sintomas associados ao transtorno do pânico. **Resultados:** No final da sexta semana, apenas um de 9 dos pacientes que receberam placebo (11,1%) ficaram livres de ataques de pânico, comparados a 8 de 13 (61,5%) pacientes que receberam clonazepam (prova exata de Fisher;  $p=0,031$ ). **Conclusão:** Os resultados evidenciam a eficácia do clonazepam no tratamento de pacientes com transtorno do pânico.

**PALAVRAS-CHAVE:** transtorno do pânico, ataque de pânico, clonazepam, tratamento.

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Panic disorder is a common psychiatric illness that can have a chronic course<sup>1</sup>. The symptoms include recurrent panic attacks and persistent concern about having another attack or worry about the implications and consequences of the attack<sup>1</sup>. Epidemiologic data have documented a lifetime prevalence of 1.6% - 2.2%, age at first onset in the age of 20s and higher risk in females (about twofold)<sup>2</sup>. Prompt recognition and treatment of panic attacks is important because quality of life is typically poor, chronic illness can develop and sufferers are at particular risk of developing other psychiatric conditions, such as agoraphobia, anxiety and depression<sup>3</sup>. Medications from several classes have been shown to be effective in panic disorder treatment: selective serotonin reuptake

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inhibitors (SSRI), tricyclic antidepressants and high-potency benzodiazepines and MAO-I. Benzodiazepines have been extensively studied and used in the treatment of panic disorder over the last 10 years. Many studies have reported the efficacy of alprazolam<sup>4</sup>, and there is evidence for the efficacy of others benzodiazepines, particularly clonazepam<sup>5</sup>.

Beaudry et al.<sup>6</sup> registered the first report of the efficacy of clonazepam for panic disorder patients. They reported the effectiveness of clonazepam (1-2 mg/day) in the treatment of 7 patients with agoraphobia with panic attacks and one patient with panic disorder. Subsequent work<sup>7-9</sup> continued to underscore the drug's ability to control panic attacks and anticipatory anxiety. Tesar et al.<sup>7</sup> studied 44 randomized subjects who took alprazolam (n=14), clonazepam (n=15) and placebo (n=15) for 6 weeks. The average dose of each active agent was 5.2 mg/day for alprazolam and 2.4 mg/day for clonazepam. There were no statistically significant differences between the clonazepam and alprazolam groups on any of the outcome measures: CGI (clinical global impression), PGI (patient global impression), Hamilton scale for anxiety. Both were superior over placebo. Svebak et al.<sup>8</sup> studied 12 panic disorder patients who were randomly assigned to imipramine (n=6) and clonazepam (n=6) for 6 months. It was found that both drugs were efficacious in eliminating panic attacks.

Clonazepam has some atypical features in comparison with other benzodiazepines, including the demonstration of elevated serotonin levels in the brain suggesting that this drug may also act by increasing the concentration of the neurotransmitter at synaptic receptor sites<sup>10</sup>. The pharmacodynamic and pharmacokinetic characteristics of clonazepam<sup>11</sup> may be advantageous in the treatment of panic disorder, like the emergence of interdose rebound anxiety, which is observed at times with the shorter-acting antipanic benzodiazepines, alprazolam and lorazepam. The half-life of clonazepam is longer (20 to 80 hours), allowing once or twice-a-day dosing. In addition, the long half-life of clonazepam may reduce the severity of the withdrawal syndrome during discontinuance compared with that associated with alprazolam. Clonazepam was also found to be useful in patients treated with alprazolam by reducing the interdose rebound anxiety<sup>12</sup>, possibly because its longer elimination half-life.

A trial<sup>13</sup> suggested that clonazepam may be a safe and effective alternative for patients who are treatment resistant, for those intolerant of antidepressant adverse effects (phenelzine, imipramine, desipramine, trazodone and amitriptyline), and for those having breakthrough panic ("interdose rebound") on alprazolam treatment. In this open trial, after clonazepam treatment (1.5-8 mg/day, average duration of 8 to 68 weeks) 7 of 10 patients who had been resistant to standard pharmacological treatments of panic attacks and agoraphobia achieved cessation of their attacks while 3 had mild to moderate symptom persistence.

The objective of this study was to assess the effectiveness of clonazepam, a fixed dose (2 mg/day) for 6 weeks, compared with placebo in the treatment of panic disorder patients.

## METHOD

We randomly selected twenty-four panic disorder subjects with agoraphobia at the Laboratory of Panic & Respiration in the Federal University of Rio de Janeiro, who agreed to participate in this protocol. The diagnosis was obtained using the structured clinical interview (SCI)<sup>14</sup> for DSM-IV<sup>1</sup>. The study design of the investigation were explained to the patients and they signed a voluntary written informed consent for their participation in this study. The protocol complying with the principles laid down in the Declaration of Helsinki was approved by our local Ethical Committee.

To participate the subjects were required to be between the ages of 18 and 55, report at least three panic attacks in the last two consecutive weeks before the first challenge test day. They should be free of psychotropic drugs for at least one week and test negative for benzodiazepines and other medications. All patients underwent a physical examination and laboratory tests to ensure they were healthy enough to participate in the study. Exclusion criteria were the existence of any current mental disorder (other than panic disorder), history of psychosis or bipolar disorder, epilepsy, pregnancy, substance abuse within the prior 6 months and major medical disorders (uncontrolled thyroid, renal, hepatic, cardiac, pulmonary, or endocrinological diseases as determined by the physical examination, vital signs, or laboratory evaluations).

At each visit, weakly, patients were given a diary to record any panic attacks between visits. Efficacy assessments included: 1) change from baseline in the number of panic attacks; 2) CGI (clinical global impression) scores for panic disorder (change from baseline with respect to panic disorder, phobic avoidance, and anticipatory anxiety); 3) Hamilton rating scale for anxiety (HAM-A) and panic associated symptoms scale (PASS)<sup>15</sup>. The PASS measures the severity of the core symptoms of panic disorder: panic attacks (situational, spontaneous and limited symptom); anticipatory anxiety (average percentage of waking hours and intensity on a 0-10 scale); and phobias (on a 0-10 scale that is a global score of how distressing or restricting phobias have been).

*Data Analysis* - A two-way ANOVA was used to evaluate the differences among measurements. When pairwise multiple comparisons were required, Tukey test was applied. Fisher exact test and t test were also used. The significant level was set at 5%.

## RESULTS

The patients were 14 women and 10 men with a mean age ( $\pm$ SD) of 37 ( $\pm$ 6,9) years. In the clonazepam group were 9 women and 5 men (mean age $\pm$ SD = 37,5 $\pm$ 6,6 years) and in the placebo group were 5 women and 5 men (mean age $\pm$ SD = 36,8 $\pm$ 7,2 years). The difference of age between the two groups was not statistically different (t test,  $p=0,780$ ). One woman of the clonazepam group was excluded because she had a major depression episode. Other woman of the placebo group was dropped out in the 2<sup>nd</sup> week because she was worse.

At the endpoint, only one of 9 placebo patients (11,1%) were free of panic attacks, compared with 8 of 13 (61,5%) clonazepam patients (Fisher exact test,  $p=0,031$ ) (Table 1).

In the placebo and clonazepam groups the CGI in first day ("baseline") were 4,7 $\pm$ 0,8 and 4,4 $\pm$ 0,7, respectively. After 6 weeks of treatment with placebo and clonazepam, this scores were 3,5 $\pm$ 1,2 and 1,5 $\pm$ 0,8 (two-way ANOVA with Tukey test,  $F=13,885$ ,  $df=1$ ,  $p<0,05$ ). At the end of 6 weeks PGI (patient global impression) in the clonazepam group were 2 $\pm$ 0,87. In the placebo group this score were 3,1 $\pm$ 1,66 (t test,  $p=0,108$ ). It was also found an important reduction in anticipatory anxiety and phobias in the clonazepam group, when compared to placebo group. The percentage of waking hours in the clonazepam group at baseline and at endpoint were 55 $\pm$ 32,9 x 14,7 $\pm$ 7,6. In the placebo group these scores were 51 $\pm$ 27,6 x 40,5 $\pm$ 25,5 (t test,  $p=0,037$ , statistically significant). In the placebo group 3 of 9 (33,3%) patients had reduction of 50% or more in the scores of Hamilton scale. In the clonazepam group 10 of 13 (76,9%) patients had reduction of 50% or more in this score (Fisher exact test,  $p=0,079$ ) showing an important reduction of anxiety in clonazepam group compared to placebo, although not statistically significant.

Table 1. Efficacy outcomes of the placebo and clonazepam groups.

	Placebo group (n=9)		Clonazepam group (n=13)	
	baseline	endpoint	baseline	endpoint
Status panic free	-	11,1%	-	61,5% <sup>a</sup>
CGI	4.7 $\pm$ 0.8	3.5 $\pm$ 1.2	4.4 $\pm$ 0.7	1.5 $\pm$ 0.8 <sup>b</sup>
PGI	-	3.1 $\pm$ 1.66	-	2 $\pm$ 0.87 <sup>c</sup>
Anticipatory anxiety (average percentage)	51 $\pm$ 27.6	40.5 $\pm$ 25.5	55 $\pm$ 32.9	14.7 $\pm$ 7.6 <sup>d</sup>
Intensity of anticipatory anxiety	7.7 $\pm$ 1.9	6 $\pm$ 2.3	8 $\pm$ 1.8	3 $\pm$ 2.6 <sup>e</sup>
Score of phobias	7 $\pm$ 3.5	5.8 $\pm$ 2.7	8.4 $\pm$ 1.5	3.5 $\pm$ 2.6 <sup>f</sup>
50% reduction in Hamilton score	-	33,3%	-	76,9% <sup>g</sup>

CGI, Clinical global impression; PGI, patient general improvement.

<sup>a</sup> Fisher exact test,  $p=0,031$ ; <sup>b</sup> Tukey test,  $df=1$ ,  $p<0,05$ ; <sup>c</sup> T test,  $p=0,108$ ; <sup>d</sup> T test,  $p=0,037$ ; <sup>e</sup> T test,  $p=0,034$ ;

<sup>f</sup> T test,  $p<0,001$ ; <sup>g</sup> Fisher exact test,  $p=0,079$ .

Table 2. Adverse effects reported by the patients of the clonazepam and placebo groups.

Adverse effect	Clonazepam (n = 13)		Placebo (n = 9)	
	n	%	n	%
Somnolence	7	53.8	-	-
Ataxia	4	30.8	-	-
Memory problems	2	15.4	1	11.1
Dizziness	3	23.0	2	22.2
Irritability	1	7.6	-	-
Depression	1	7.6	-	-
Libido decrease	1	7.6	-	-
None	2	15.4	6	66.6

The most common adverse effects associated with the use of clonazepam were neuropsychiatric events: somnolence, reported by 7 (53,8%) and ataxia, reported by 4 (30,76%) patients. Other side effects that occurred with patients of the clonazepam group were memory problems (n=2, 15,38%), dizziness (n=3, 23%), irritability (n=1), depression (n=1) and libido decrease (n=1). Six (66,6%) of the placebo group and 2 (15,38%) of the clonazepam group reported no adverse events during the 6 weeks of the study (Table 2).

## DISCUSSION

The results of the current study suggest that the administration of clonazepam reduces panic attacks and anxiety in panic disorder patients. Clonazepam was superior over placebo in the study's efficacy outcomes (panic attacks, anticipatory anxiety and phobias). Although in a small sample the results of clonazepam reducing anxiety and panic attacks are striking and statistically significant, when compared over placebo.

Our results are consistent with some studies reported previously. Tesar et al<sup>16</sup>, in their 6 week-study with administered clonazepam up to a mean maximum dosage of 2.5 mg/day, compared with 5.3 mg/day of alprazolam and placebo. Good clinical efficacy was seen on observed ratings of global severity of illness, phobic distress and on patient-rated global improvement, on clonazepam and alprazolam groups. Fifty percent of patients in the clonazepam group, 46% of those in the alprazolam group and only 14% of those in the placebo group were panic free at the end of the study.

Beauchair et al<sup>17</sup> in their 4 week study with 29 panic disorder patients compared the efficacy of a mean daily dose of clonazepam 2.3 mg over placebo, double-blindly. It was found that clonazepam was superior (with statistical significance) in reducing the number of panic attack and Hamilton scores. The treatments were also compared with respect to the frequency of responders at endpoint as defined by 50% or greater reduction from baseline in CGI Severity of Panic Disorder score. There were 11 (84.6%) of 13 responders in the clonazepam-treated group compared with 1 (6.5%) of 16 in the placebo-treated group (statistically significant).

Rosenbaum et al<sup>18</sup>, in a multicenter trial of clonazepam versus placebo, with a sample of 413 panic disorder patients found out that clonazepam was superior to placebo in changing the number of panic attacks from baseline, as well as changes in the mean duration of anticipatory anxiety, frequency of avoidance behaviour and phobic fear.

Moroz and Rosenbaum<sup>19</sup> also in a multicenter trial with 455 panic disorder patients, who were randomly assigned to treatment with clonazepam (n=230) or placebo (n=225), found that the

number of patients who were free of panic attacks was greater in the clonazepam group (62%) than in the placebo group ( $p < 0.001$ ). Also, the percent of subjects achieving a 50 percent reduction in panic attacks was greater in the clonazepam group (79%) than in the placebo group (57%) ( $p < 0.001$ ).

In our study clonazepam in a fixed dose of 2 mg/day was safe and well tolerated. The main adverse events reported by patients were neuropsychiatric events, specially somnolence and ataxia. In this respect, our results are similar to that of Rosenbaum et al<sup>18</sup> and Moroz and Rosenbaum<sup>19</sup>.

The analysis of the data presented supports our major study hypotheses that clonazepam is superior to placebo in the treatment of panic disorder, having a marked therapeutic effect in these patients with panic attacks. The frequency of panic attacks, phobic avoidance, anticipatory anxiety, and free floating anxiety often seen in panic disorder patients all showed significant improvement.

## Conclusion

This trial provide evidence for the efficacy of clonazepam in panic disorder. Our results are supported by the evidence in the literature of the therapeutic effects of clonazepam in patients with panic disorder. Despite the controversies associated with dependence and adverse events<sup>20</sup> clonazepam is an useful treatment option for panic disorder.

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