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Panic Attacks and Agoraphobia: Low Dose Clomipramine Treatment

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Seventeen outpatients with panic anxiety and agoraphobia were treated with a low, flexible dose of clomipramine in an 8-week open trial. Panic attacks ceased completely in 13 patients and markedly decreased in the other four without additional therapeutic measures. Avoidance behavior disappeared in five of the seven agoraphobic patients. Overall mean dosage was 45 mg/day, with eight patients receiving clomipramine 25 mg or less. Higher doses were needed when agoraphobia was present. These results are discussed in conjunction with previous findings and lend support to serotonergic involvement in panic anxiety. Further double-blind studies are needed to confirm these results.
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RECURRENT panic attacks constitute a common and disabling psychophysiologic disorder that was found to affect 10% of all patients in an outpatient psychiatric clinic,[1] and the prevalence over 6 months in a general population survey was about 3%.[2] Panic attacks are characterized by the sudden onset of overwhelming anxiety.[3] The panic experience can be conceptualized as a traumatic life event. The unpredictable recurrence of new episodes provokes fear and often leads to the development of anticipatory anxiety and mild to severe avoidance behavior (agoraphobia). Other symptoms or behavioral complications may also develop,[4] including the aggravation of previous psychopathology.[5]

The pioneering work of Klein and Fink,[6, 7] using imipramine to block the recurrence of panic attacks, led to recognition of panic anxiety as a distinct nosological entity[4, 8] and stimulated the search for new and more effective therapies. The monoamine oxidase inhibitor phenelzine,[9] the triazolobenzodiazepine alprazolam,[10, 11] and recently the high-potency benzodiazepine clonazepam[12] have been reported to be effective in the treatment of panic attacks and agoraphobia. Several investigators in the 1970s reported on treating phobic and obsessional states with clomipramine[13–15] but did not document specific effects on panic attacks. The first study to do so[16] found that after 8 weeks of an open trial, 75% of the 20 patients were free of panic attacks; almost half of the sample required total doses of 50 mg/day or less of clomipramine. Further reports by Pecknold and associates[17] and Caetano[18] on treating panic anxiety-agoraphobia with clomipramine also showed promising results. None of these studies, however, were placebo controlled.

Despite these advances, several issues remain unsettled or controversial in the treatment of panic anxiety. Marks[19] disputes the otherwise general agreement on imipramine effectiveness, and concurrent psychotherapy in most clinical trials is a limitation for conclusive evaluation of drug-specific efficacy.[20] Although high dosages are usually required for therapeutic response to alprazolam[10] and imipramine,[20] the effective dose of clomipramine appears to be lower.[16, 18] Response of agoraphobic symptoms to drug treatment alone is also unclear.[21]

The current study was an open trial designed to assess the efficacy of clomipramine in the treatment of panic disorder and agoraphobia with panic attacks in the context of a long-term, comprehensive study of panic anxiety patients. This study was designed to: (1) Evaluate drug effects alone without other therapeutic intervention; (2) assess the lowest effective dose of clomipramine in each patient (to reduce attrition provoked by overstimulation[22] and the increase in the frequency of panic attacks[16]); (3) monitor the response of agoraphobic symptoms; and (4) to validate DSM-III criteria in Chile.

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TABLE 1. Patient characteristics (N = 17)

Diagnosis	
Panic disorder	10
Agoraphobia	7
Panic attacks duration	
Less than 1 year	10
1–2 years	4
5–10–12 years each	3
Age	
Mean	32
Range	18–43
Sex	
Female	9
Male	8
Marital status	
Married	11
Single	4
Divorced	2
Education	
8 years or less	8
9–12 years	6
13 years, or more	3

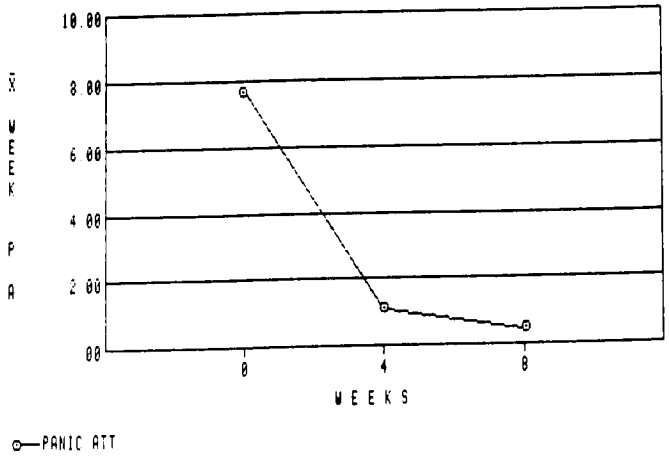

FIG. 1. Clomipramine treatment outcome. Mean weekly number of overall panic attacks (PA). One-way analysis of variance with one repeated measure ($p < 0.01$, $F = 15.44$).

Subjects and Methods

Subjects

Eighteen consecutive patients at a general hospital outpatient psychiatric clinic in Santiago, Chile, were accepted for the trial. Diagnoses were based on DSM-III criteria and were obtained by consensus among the investigators. Major depressive disorders were not excluded if the depressive episode occurred after the onset of the panic attacks, which happened in one case. Two patients also met criteria for dysthymic disorder. Characteristics of the 17 patients who completed the trial are shown in Table 1. Seven of the 10 panic patients had avoidance symptoms not severe enough to meet the criteria for agoraphobia. Most of the patients came from a low socioeconomic level. Seven patients had previously been treated unsuccessfully with benzodiazepines.

Assessment

A psychiatric and medical evaluation was done to exclude major medical or psychiatric illness. Results were measured using a self-rated panic attacks scale that registered frequency and symptoms and classified the crisis as major or minor; a major attack was indicated not by number of symptoms but rather by reports of feeling a "sense of impending loss of control" during the attack. Marks and Gelder's disability scale[23] (ranging from grade 1, no symptoms and no dysfunction, to grade 5, severe symptoms with working and social function radically changed), and the Hamilton Anxiety (HAM-A) and Depression (HAM-D) scales (22 items) were also administered before treatment and at weeks 4 and 8. A global improvement scale ranging from 1–5 to indicate worse, same, mildly improved, markedly improved, and no symptoms was completed by both patients and therapists at weeks 4 and 8 of treatment. Side effects were measured six times using an open-ended 20-item scale, with five possible levels of severity for each complaint (0 meaning absent, to 4 meaning sufficient intensity to force reduction or termination of medication).

Treatment procedures

A washout period of 2 weeks preceded initiation of treatment. Three patients continued the occasional use of diazepam 5–10 mg and another, bromazepam 3 mg. Clomipramine was started at 12.5 mg (at night) and raised weekly (or even reduced) following tolerance and response to treatment. Maximum permitted dose was 75 mg by week 8.

Patients were seen once a week during the first month and every 2 weeks in the second month. They were encouraged to expect improvement, but there was no additional therapeutic intervention.

Results

One patient dropped out of the study for economic reasons. Only four out of 17 patients who completed the treatment were still experiencing panic attacks by week 8; the remaining 13 patients (76%) were free of panic attacks at the end of the trial. Figure 1 shows that clomipramine treatment produced a significant overall decrease from a mean of almost 8 panic attacks per week to less than one ($p < 0.01$). The frequency of weekly crises in the four patients with residual panic attacks markedly decreased as well (to one-fourth of the pretreatment mean), and no patient was experiencing major attacks by the end of the trial. Three of these four patients had a diagnosis of agoraphobia with panic attacks (Table 2).

TABLE 2. Number of weekly panic attacks for patients with residual crisis

Patient	Diagnosis	Week 0		Week 4		Week 8	
		Major	Minor	Major	Minor	Major	Minor
1	PD[a]	3	4	—	1	—	2
2	AgPA	0.3	17	—	3	—	2
3	AgPA	1	3	—	1	—	1
4	AgPA	3	7	—	5	—	3

[a] PD, panic disorder; AgPA, agoraphobia with panic attacks.

Panic versus agoraphobic patients

Analysis of variance showed no significant differences in mean number of panic attacks for the panic disorder versus agoraphobic patients, as shown in Figure 2.

Disability

Before treatment, most patients exhibited marked to severe disability, but by week 8 only two patients remained markedly disabled (Table 3). Thus, for 15 patients (88%), disability was absent or mild, meaning that symptoms, if they existed, did not interfere with normal activities. The two disabled patients were both agoraphobic. Mean disability scores decreased significantly after treatment ($p < 0.001$).

Global clinical improvement

All 17 patients rated themselves as markedly improved or asymptomatic on the clinical improvement scale. Therapist ratings accorded with patient ratings by week 8 (Table 4). A paired *t*-test showed that improvement was significant when week 4 was compared with week 8 ($p < 0.001$).

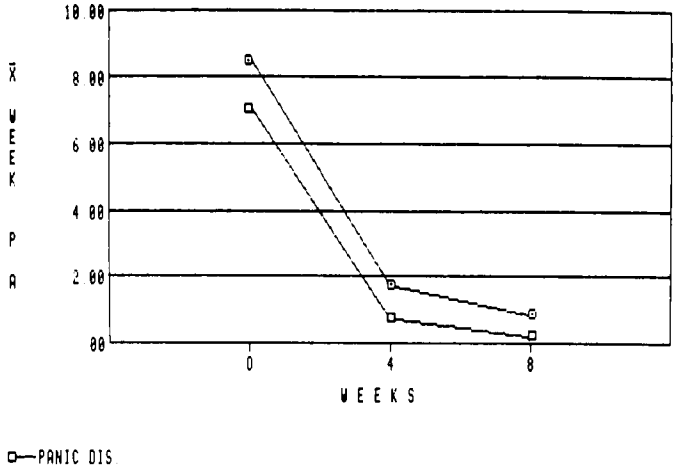

FIG. 2. Clomipramine treatment outcome. Mean weekly number of panic attacks in panic disorder and agoraphobic patients. One-way analysis of variance with one repeated measure, panic disorder versus agoraphobics (p = not significant).

TABLE 3. Disability scale scores

Disability	Week 0	Week 4	Week 8
Grades[a]			
4–5	11	2	2
3	4	8	0
1–2	2	7	15
Total N patients	17	17	17
Mean score	3.65	2.53	1.65*

[a] Grades: 1, absent; 2, mild; 3, moderate; 4, marked; 5, severe.
*$p < 0.001$, $F = 59.56$, one way analysis of variance with one repeated measure.

TABLE 4. Patients and therapists ratings for Global Clinical Improvement Scale

	Grade				
	1. Worse	2. Same	3. Mild improvement	4. Marked improvement	5. No symptoms
Patients[a]					
Week 4	—	—	8	8	1
Week 8	—	—	—	8	9
Therapists[b]					
Week 4	—	1	6	10	0
Week 8	—	—	—	8	9

[a] Week 4 versus 8, paired *t*-test (two-tailed) $p < 0.001$; $t = -6.98$.
[b] Week 4 versus 8, paired *t*-test (two-tailed) $p < 0.001$; $t = 5.83$.

Hamilton anxiety and depression

Figure 3 shows a significant decrease in both HAM-A and HAM-D scores ($p < 0.001$); one panic patient missed the first anxiety rating and one agoraphobic patient missed both anxiety and depression week 4 ratings, and these patients were excluded from statistical analysis (HAM-A, N = 15 and HAM-D, N = 16). Mean scores dropped from the 20–25 range to less than 5 points on both scales.

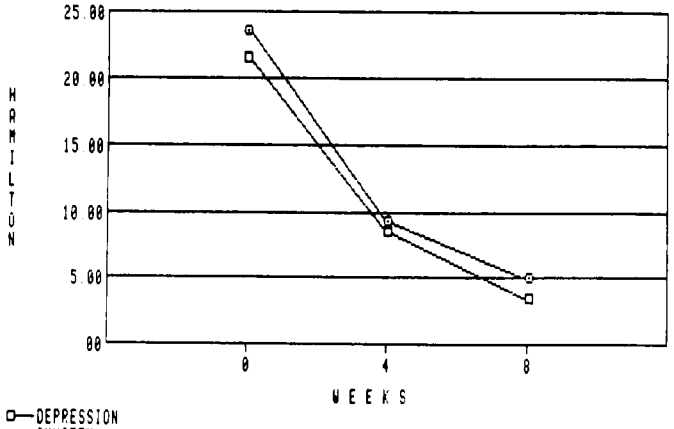

FIG. 3. Hamilton anxiety and depression ratings. Mean values before and after clomipramine treatment. Anxiety scores, one way ANOVA with one repeated measure ($p < 0.001$, $F = 79.63$). Depression scores, one way analysis of variance with one repeated measure ($p < 0.001$, $F = 48.33$).

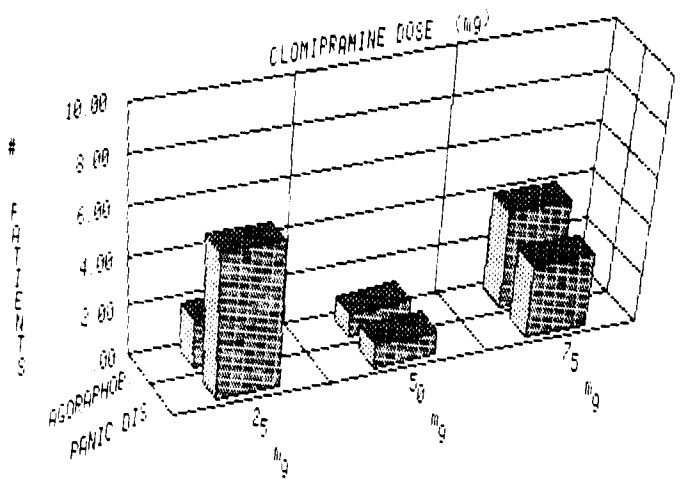

FIG. 4. Effective clomipramine dosage. Patient distribution according to diagnosis.

When agoraphobic and panic patient scores were compared, significantly higher rates were found in the agoraphobic subgroups throughout the trial in both the anxiety and depression scales. Mean anxiety scores (weeks 0, 4, 8) were 27, 13, and 6.5 points for agoraphobic patients and 20.8, 6.5, and 3.7 ($p < 0.02$) for panic patients. Mean depression scores were 21.1, 11.3, and 6.1 for agoraphobic and 16.9, 7.1, and 2.8 ($p < 0.02$) for panic patients.

Dosage

Effective dosage according to diagnosis is shown in Figure 4. Eight patients (six panic and two agoraphobic) received clomipramine 25 mg or less (mean, 18.76 mg; range, 6.25–25), two patients (one panic and one agoraphobic) received 50 mg, and seven patients (three panic and four agoraphobic) were treated with 75 mg. Fisher's exact test showed a nonsignificant trend towards an association between dose and diagnosis, with panic disorder patients needing lower doses than agoraphobics (mean dose 40 mg vs. 56.25 mg). Overall mean dose was 45 mg. Five patients (30%) complained of initial worsening of their condition (that is, increased number of panic attacks).

Response to treatment, defined by a noticeable decrease in number and intensity of panic attacks, was perceived in 7–20 days. Five patients reported characteristic tricyclic side effects, but did not require reduction or discontinuation of the drug. The most common complaints were dry mouth, high pulse rate, sweating, and diminished sexual drive.

Discussion

The main finding of this 8-week open trial is that clomipramine, at low doses and without additional therapeutic measures, appears highly effective in the treatment of panic disorder and agoraphobic patients, although confirmation is required in placebo-controlled studies. Panic attacks ceased completely in 76% of the sample; those patients with residual symptoms at week 8 might have benefitted from further dose increases, but the design of this trial, which called for slow augmentation of dosage, did not allow for testing this hypothesis. All patients rated themselves as markedly improved or asymptomatic by the end of the study. In five of the seven agoraphobic patients, avoidance behavior ceased in the absence of other therapies, suggesting that most agoraphobics may not need behavior therapy after their panic attacks are controlled; these findings are in some disagreement with previous reports on imipramine treatment.[21] The fact that only one of the 18 patients withdrew from the study suggests that careful titration of dosage may be helpful in maintaining compliance.

The current results are in accordance with our previous findings[16] but because concomitant supportive psychotherapy was used in the earlier trial, these data provide stronger support for a drug-specific effect.

An interesting and unexpected finding is that the dosages needed suggest a bimodal distribution of patients (Fig. 4), panic patients tending to require lower doses than agoraphobics. This observation should be confirmed using a larger sample. It may be explained by significantly higher rates of depressive and anxiety symptoms in agoraphobics as compared with panic patients, as measured by Hamilton scores, but it may also be an artifact of the small sample size. When clinical diagnosis is compared, two of the seven agoraphobics had an affective disorder (one major depression and one dysthymic disorder), whereas only one of the 10 panic patients had an affective disorder. Mavissakalian and colleagues[24] suggested that imipramine exerts its antipanic effect at lower doses than those required for antidepressant effect, but that effective antiphobic doses might be in the antidepressant dose range. They also suggested in view of their plasma levels active metabolite data, that imipramine's specific effect on panic might be mediated by its serotonergic rather than noradrenergic action.

The overall mean dose of 45 mg of clomipramine in the present report is much lower than doses reported with imipramine[5]; this result might be explained by differences in the equivalence mg per mg of both drugs, or by the relatively specific serotonergic action of clomipramine as compared with imipramine. Nevertheless, the confirmation that small doses of clomipramine would really do significantly better than placebo is only possible in a double-blind study.

Neurotransmitter involvement in panic anxiety is still controversial; Hoehn-Saric[26] concludes that present evidence suggests that GABA-ergic, noradrenergic, and

serotonergic systems are involved in the psychobiology of anxiety. Some authors have stressed noradrenergic abnormal regulation in panic anxiety,[27] whereas others have noted enhanced platelet serotonin uptake and have concluded that serotonergic pathways may be important.[28-29] 5-Hydroxytryptamine receptor supersensitivity was proposed recently by Gentil Filho[30] as the possible mechanism of action of antipanic drugs. Both low effective dosage and the initial exacerbation of symptoms found in this study might support the serotonergic hypothesis, as well as the clinical impression that clomipramine could be highly specific in panic anxiety. Carr and Sheehan[31] and Liebowitz and associates[32] recently argued that more attention should be given to the possible involvement of serotonergic systems in the physiopathology of panic anxiety.[31, 32]

Finally, the fact that panic anxiety-agoraphobic patients were diagnosed with DSM-III criteria and improved with treatment in a Latin American population of low socioeconomic status adds cross-cultural validation to changes in the nosology of anxiety disorders.[3]

Acknowledgments

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