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A Short-term Open Trial of Clomipramine in the Treatment of Patients with Panic Attacks

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Clomipramine was used to treat 14 patients with panic attacks. Diagnosis was made according to DSM-III criteria for agoraphobia with panic attacks or panic disorder uncomplicated. An open evaluation of the drug over an 8-week treatment period was conducted. A total of 10 patients completed the study. Clomipramine was effective in reducing the mean number of panic attacks, the greatest response being observed in the first 2 weeks of treatment. Findings on all outcome measures showed that clomipramine was also effective in alleviating depression secondary to panic attacks, non-specific aspects of anxiety and improving phobic avoidance. There was a suggestion that responders to treatment received lower doses of clomipramine than non-responders. Further studies are required to evaluate this issue and the role of clomipramine in the treatment of panic disorders.

KEY WORDS—Panic attacks, clomipramine, open evaluation, phobic avoidance, anxiety.

INTRODUCTION

Tricyclic antidepressants have been recognized as effective treatment for phobic anxiety for over two decades. In particular the response of sudden unexpected attacks of anxiety, so-called panic attacks, to imipramine first noted by Klein and Fink (1962) altered diagnostic thinking about anxiety states. The reclassification of anxiety states under DSM-III and DSM-III-R has emphasized the importance of panic attacks in determining diagnosis. Double-blind, placebo-controlled studies have established the efficacy of imipramine in the treatment of panic attacks (Liebowitz *et al.*, 1988). The efficacy of other tricyclic antidepressants has not often been studied.

Preliminary clinical studies have suggested that the structural analogue of imipramine, clomipramine (3-chloro-imipramine), is also effective in treating phobic anxiety states. For example, Marshall and Micev (1973) reported marked response in phobic symptoms in 67 patients treated initially with intravenous drug for 3 weeks followed by oral treatment. Beaumont (1977) noted a 70–80 per cent improvement in phobic symptoms in nearly 500 patients treated with clomipramine (150 mg) for up to 12 weeks. In neither of these studies, nor in similar studies reported in the same symposium, was the issue of the effect on panic attacks addressed. Furthermore, these studies contained heterogeneous patient groups and did not include a placebo control.

Three recent large-scale studies have compared clomipramine with placebo or other antidepressants in the treatment of anxiety disorders. Clomipramine was shown to be as effective as fluvoxamine or 5-hydroxytryptophan but more effective than placebo in alleviating anxiety symptoms in a mixed group of patients with DSM-III anxiety disorders (Kahn *et al.*, 1987; Den Boer *et al.*, 1987). Neither study quantitated panic attacks in their patients. Johnston and co-workers (1988) compared clomipramine and placebo in 70 females with DSM-III agoraphobia. In this study clomipramine was clearly superior to placebo on measures of depression, anxiety, and phobic symptoms. Panic attacks were quantitated by diary and a measure, the number of days during which panic attacks occurred, was significantly decreased by clomipramine but not by placebo. Various subtypes of panic attacks, such as spontaneous attacks compared with those occurring in specific situations, were not separately investigated.

An investigation of the efficacy of clomipramine in the treatment of panic attack subtypes, as well as alleviating the symptoms of anxiety, was undertaken, in both male and female patients, using an open-label, flexible-dose design.

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PATIENTS AND METHODS

Design of study

This was an open, flexible-dose study. Approval for the study was given by the Austin Hospital Ethical Review Board. All patients gave informed consent before participating in the study. Patients were recruited from consecutive referrals to the Phobic/Panic Disorders unit. This unit has been in operation for 6 years and has evaluated both pharmacological and non-pharmacological treatments for phobic/panic disorders and participated in the Cross National Panic Disorders programme (Ballenger *et al.*, 1988). Demographic characteristics, diagnosis, duration of the present episode, and age at initial treatment are summarised in Table 1. Patients were assessed for study eligibility and kept free of psychoactive medications for 7 days before baseline evaluations. Fourteen patients were admitted to the study and treated with clomipramine for up to 8 weeks. Outcome measures were completed on admission to the study and at weeks, 1, 2, 3, 4, 6 and 8. Ten patients completed 8 weeks of treatment.

Table 1. Demographic characteristics of the patient population

Age (years)	
Mean (±SD)	35·7 (±10·0)
Median	38·5
Range	19–54
Sex (%)	
Female	50%
Male	50%
Diagnosis (percentage of patients)	
Agoraphobia with panic attacks	35·7%
Panic disorder uncomplicated	64·3%
Average duration of episode (months)	44·6 (±40·2)
Age at initial psychiatric treatment (years)	33·4 (±11·2)

Diagnostic criteria

All patients were interviewed by a psychiatrist using the Structured Clinical Interview for Diagnosis by DSM-III (Spitzer and Williams, 1983). Patients admitted to the study met DSM-III criteria for panic disorder or agoraphobia with panic attacks. They had a history of recent panic attacks and had had at least three panic attacks in the previous 3 weeks. Subjects were aged between 18 and 65 years and in good physical health. They were excluded from the study if they were pregnant, lactating, psychotic, significantly depressed, suicidal or suffering from dementia. Patients with other psychiatric diagnoses, or who were taking α- or β-adrenergic blockers, or who were undergoing psychotherapy or behaviour therapy were excluded from the study.

Dosage

Tablets, containing 25 mg of clomipramine, were administered using a flexible-dosage regimen, commencing with a single tablet at night. The dose was adjusted according to the patient's response and the side-effects experienced. A maximum dose of 250 mg/day was not exceeded. Compliance with medication was assessed by pill count.

Other treatments

Patients received no other psychotropic medication throughout the study. No specific psychotherapy, other than general support, was allowed during the study. Behaviour therapy was not allowed beyond general encouragement to re-enter phobic situations, when and if the treating psychiatrist felt this was appropriate.

Measures of change

Treatment outcome was assessed from repeated measurement of several rating scales. The main purpose of this study was to assess the effect of clomipramine on the number of panic attacks experienced. The definition of panic attacks used in this study was the same as that used by Ballenger and co-workers (1988) in a study of alprazolam and placebo, and was in accordance with the DSM-III criteria for panic attacks. A diary was used to record information about the number of the panic attacks during each week. This method allows separation of the panic attacks into spontaneous (occurring without provocation) and situational (always associated with a particular situation). Anticipatory anxiety episodes (mounting anxiety when a patient anticipates entering a phobic situation) were also recorded in the patient's diary and were analysed separately.

Overall improvement or worsening during treat-

Table 2. Rating scores before and during clomipramine treatment

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8
HARS	18·8 ± 6·9	13·3 ± 5·6	12·0 ± 6·4	11·7 ± 6·3	11·7 ± 8·4	9·2 ± 7·7	7·4 ± 6·9
HDRS	10·4 ± 4·2	NR	NR	6·6 ± 3·6	NR	NR	4·5 ± 3·4
Panic attacks (spontaneous)	7·6 ± 8·4	4·5 ± 5·9	3·0 ± 4·1	2·8 ± 3·3	2·3 ± 3·0	1·1 ± 2·3	1·73 ± 1·8
Panic attacks (situational)	1·8 ± 2·4	2·2 ± 2·5	1·0 ± 1·5	1·5 ± 2·8	1·8 ± 3·3	1·2 ± 2·6	0·4 ± 0·7
Anticipatory anxiety	2·9 ± 2·8	2·3 ± 3·4	0·8 ± 1·3	1·2 ± 1·7	1·7 ± 2·3	1·5 ± 2·6	0·7 ± 1·0
Phobia	6·9 ± 2·9	6·4 ± 2·7	5·6 ± 2·6	4·9 ± 2·8	4·8 ± 3·3	4·0 ± 3·0	3·2 ± 3·0
Disability, work	6·3 ± 2·8	4·6 ± 3·6	4·3 ± 3·4	4·1 ± 2·9	3·9 ± 3·2	4·1 ± 2·9	2·3 ± 2·7
Disability, social	5·3 ± 3·8	5·1 ± 3·1	5·2 ± 3·2	4·1 ± 3·6	4·7 ± 3·3	4·5 ± 3·3	2·9 ± 2·8
Disability, family	4·2 ± 3·2	3·8 ± 3·4	3·7 ± 3·3	3·6 ± 3·5	4·2 ± 3·4	3·2 ± 2·8	2·2 ± 2·2
Disability, global	3·8 ± 0·9	3·6 ± 1·2	3·7 ± 1·1	3·3 ± 1·4	3·3 ± 1·3	2·9 ± 1·5	2·7 ± 1·4
Physician CGI	5·0 ± 0·0	5·8 ± 1·5	6·8 ± 1·6	7·7 ± 1·1	7·3 ± 1·6	7·9 ± 1·4	8·4 ± 0·5
Patient CGI	5·0 ± 0·0	5·8 ± 2·1	6·6 ± 1·6	7·1 ± 2·5	6·3 ± 3·1	7·3 ± 2·2	8·1 ± 1·5
n	12	12	12	12	12	11	10

ment was rated by both physicians and patients each week on a global scale. This scale ranged from 1 (equivalent to 'very bad, could not be worse') to 10 (equivalent to 'normal') with a mid-point of 5 ('no change'). Any increases in the value of the scale above 5 were clinical improvements.

The severity of phobias was rated on an overall scale from 0, 'no phobias' to 10, 'extremely distressing or restricting'. This scale is similar to that used by Marks and Matthews (1979) and assesses the impact of phobias on the patient's life. Phobic avoidance behaviour was rated on a five-point scale from 0 (never) to 4 (always avoid) for a main phobia that patients particularly wanted treated. Degree of disability in three areas: occupation, social and family–home life, was assessed with a 10-point visual analogue scale.

Anxiety was rated using the Hamilton Anxiety Rating Scale and depression with the Hamilton Depression Rating Scale. Side-effects were also rated weekly using a 42-item scale rated from 0, 'none' to 3, 'severe'.

The 90-item symptom checklist (SCL-90; Derogatis *et al.*, 1973) was completed at baseline weeks 1, 3, 6 and 8 of treatment.

Statistics

The ability of clomipramine to effect changes in psychopathology, as measured by the standardized rating scales employed, was assessed using a repeated measures analysis of variance. The MANOVA subprogram of SPSS-X was used to perform the analysis.

RESULTS

Overall outcome

Clinical ratings at baseline, weeks 1, 2, 3, 4, 6 and 8 for all patients remaining in the study at that time point are shown in Table 2. Repeated measures analysis of variance showed statistically significant improvements from baseline for the Hamilton anxiety ($p < 0{\cdot}0005$), Hamilton depression ($p < 0{\cdot}005$), SCL-90 ($p < 0{\cdot}05$), disability-total ($p < 0{\cdot}05$), patient global ($p < 0{\cdot}05$) and physician global ($p < 0{\cdot}0005$) rating scales. Other rating scales, while indicating clinical improvements, did not show statistically significant changes from baseline (Table 2).

The principal objective of this study was to evaluate the effects of clomipramine on panic attacks. Spontaneous and situational panic attacks and anticipatory anxiety episodes were examined separately and all decreased from baseline (Table 2). Spontaneous and situational panic attacks were summed and the reduction from baseline was calculated for each patient. Responders were defined as those patients who achieved a 75 per cent reduction in the number of panic attacks from baseline. Using this criterion five of 10 completers (50 per cent) were responders at the end of week 8, eight (80 per cent) at week 6, six (60 per cent) at week 4, and five (50 per cent) at week 3. Four other

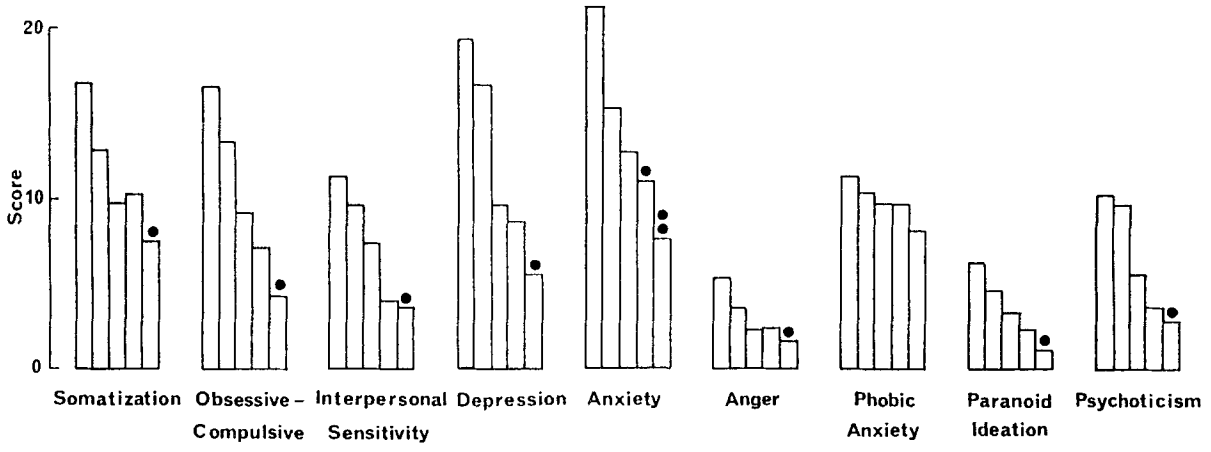

Figure 1. Mean scores for SCL-90 factors at baseline weeks 1, 3, 6 and 8 of clomipramine treatment. Significant decreases from baseline were observed for somatization, obsessions–compulsions, depression and anxiety using repeated measures analysis of variance. • $P < 0.05$, •• $P < 0.01$

patients achieved a fall of 50–75 per cent in the number of panic attacks by week 8, while the other patients did not improve at all. Of the responders so defined, three of the five were panic-free, while the other two responders experienced occasional panic attacks.

As shown in Table 2, the overall phobia score diminished to 50 per cent of initial value by week 8, although this change was not statistically significant due to the associated large variability. The phobia subscale of the SCL-90 also recorded a small decrease from baseline but was not statistically significant. At baseline 60 per cent of patients avoided their main phobia very often or always. At end point this had fallen to 28 per cent of patients, while in patients who completed 8 weeks of treatment 20 per cent reported they avoided very often or always. No avoidance was reported by 40 per cent of patients after 8 weeks.

The SCL-90 symptom profiles of the patients at baseline and throughout the study are shown in Figure 1. There were some statistically significant changes and the mean values of the ratings for each of the factors, except phobic anxiety, decreased during clomipramine treatment. Repeated measures analysis of variance showed that the symptom constructs somatization ($p < 0.05$), obsessions and compulsions ($p < 0.05$), depression ($p < 0.05$) and anxiety ($p < 0.01$) all decreased significantly from baseline. Changes in the other symptom constructs were not statistically significant. The results for depression and anxiety on this self-rating scale concur with the observations made using the clinician-rated scales.

Dosage

The mean dose of clomipramine increased from 65 ± 17.5 mg/day at the end of week 1 to 100 ± 32.5 mg/day at week 3. Thereafter the increments in average dose were smaller, such that the means were 115 ± 45, 117.5 ± 50 and 122.5 ± 50 mg/day at weeks 4, 6 and 8 respectively. At week 8 the average dose for the responders to medication was 95.8 ± 36.8 mg/day compared to 162.5 ± 43.3 mg/day for partial or non-responders.

Drop-outs

Four patients did not complete 8 weeks treatment with the study drug. One patient completed 6 weeks of treatment and was withdrawn due to lack of efficacy. One patient, also withdrawn for lack of efficacy, completed 4 weeks of treatment. A further patient was withdrawn after 1 week of treatment with 50 mg of clomipramine daily because of a hyperstimulatory effect of the drug. The fourth patient failed to keep her appointment after the baseline ratings were performed. Data from this patient were not included in the side-effects analysis.

Side-effects

During treatment the mean total score for side-effects decreased to about half of its initial value. Since side-effects scales, at least at baseline, often quantitate the symptoms of the disorder, the raw scores were not analysed in detail. Instead side-effects were assessed from new events, i.e. those which were not present at baseline and from events which were present at baseline but increased in severity during the course of treatment. All events falling into these two categories were recorded as side-effects irrespective of when they occurred during treatment. Side-effects from all patients entered into the study were analysed in this way. Table 3 lists the side-effects and their frequency of occurrence. Typical of a tricyclic antidepressant, anticholinergic effects, particularly dry mouth, were prominent. Other frequently reported side-effects encompassed those usually reported with tricyclic antidepressants. In addition, change in libido, retarded ejaculation and myoclonic jerks were troublesome side-effects in male patients. Nasal congestion was also reported as a new event, but it was not clear that this occurred only as a result of clomipramine treatment. Most side-effects were of mild to moderate severity and diminished in both frequency and severity with continued administration (there were nearly four times as many side-effects recorded after 1 week of treatment as after 8 weeks). Only one patient was withdrawn from treatment as a result of intolerable side-effects, as described above.

Table 3. Side-effects of clomipramine treatment

New events
Dry mouth (24), sedation (12), tremor (11), change in libido (10), nasal congestion (10), excessive sweating (9), excitement/nervousness (8), retarded ejaculation (8), irritability (8), constipation (8), insomnia (7), blurred vision (7), nausea/vomiting (7), tachycardia (6), impaired mentation (6), fatigue (6), decreased appetite (6), myoclonic jerks (5), sleep disturbance (5).

Increasing events
Tremor (9), dry mouth (6), fatigue (6), excessive sweating (5), tachycardia (4).

DISCUSSION

The major finding of this study was that clomipramine alone reduced the frequency of panic attacks in the majority of patients who completed the 8-week trial. This was not a placebo-controlled study and the results need to be interpreted with caution. Furthermore it was conducted in a small patient population over a short treatment duration. Nevertheless this study supports findings from other clinical trials that clomipramine is effective in treating panic attacks. Earlier studies reported good effects in phobic anxiety but did not document the effect on panic attacks (Marshall and Micev, 1973; Marshall, 1977). Beaumont (1977) reported an open evaluation in 765 general-practice patients with agoraphobia or social phobia treated with clomipramine for 12 weeks. A total of 480 completed the study with over 50 per cent of patients being rated symptom-free. Although the study did not quantitate panic attacks, it did rate 'physiological accompaniments' of anxiety which at 12 weeks of treatment showed a 76 per cent improvement from baseline. These physical accompaniments were not necessarily panic attacks but may have been, suggesting an efficacy of clomipramine in their treatment. Subsequent open evaluations showed that clomipramine was effective in reducing panic attacks in at least 75 per cent of patients with panic disorders (Gloger *et al.*, 1981; Pecknold *et al.*, 1982; Grunhaus *et al.*, 1984). Most recently Gloger *et al.*, (1989) reported a marked decrease in the number of panic attacks in 17 patients treated with clomipramine. Avoidance behaviour was also reduced in the patients with agoraphobia with panic attacks without any specific behaviour therapy programme. Cassano *et al.*, (1988) compared clomipramine and imipramine in the treatment of panic attacks over 10 weeks and found both drugs effective. There was a small non-significant advantage for clomipramine over imipramine in alleviating panic.

Clomipramine was compared with placebo, 5-hydroxy tryptophan or fluvoxamine in two studies which included patients with agoraphobia with panic attacks or other anxiety disorders. The effects on panic attacks were not detailed in these studies, but it was noted that if panic attacks were present initially they were substantially reduced in patients who made a good response to treatment. Clomipramine was superior to 5-hydroxytryptophan, which was superior to placebo in alleviating anxiety symptoms (Kahn *et al.*, 1987). Clomipramine was equi-

potent with fluvoxamine in alleviating anxiety over a 6-week treatment period (Den Boer *et al.*, 1987).

Johnston *et al.* (1988) treated 70 women with agoraphobia for 8 weeks with either clomipramine or placebo. Clomipramine was superior to placebo in increasing the number of days per seven panic episodes reported. Measures of phobias also decreased significantly without any specific behavioural intervention. Taken together these studies suggest that 60–80 per cent of patients might expect to have significant reduction of their panic attacks with 4–8 weeks of clomipramine treatment. Whether or not this effect is sustained in long-term treatment, or further therapeutic gains can be made, has yet to be addressed by appropriate studies. Furthermore, the issue of the maintenance of therapeutic benefits following drug withdrawal needs to be assessed in controlled evaluations.

The drop-out rate in this study was 29 per cent (four of 14 patients with baseline ratings did not complete 8 weeks of treatment). This rate is comparable to other studies using antidepressants for panic disorders. For example Cassano *et al.* (1988) had 38 per cent of patients withdraw from clomipramine treatment while Johnston *et al.* (1988) reported a drop-out rate of 35 per cent. In this study four patients withdrew for various reasons. One patient was withdrawn because of side-effects of the drug, two patients for lack of effect, while the fourth patient did not attend for appointments. The patient withdrawn due to drug side-effects experienced a hyperstimulatory response to medication after two doses of 50 mg. Such hypersensitivity reactions after a few doses of tricyclics in panic patients have been noted before (Levin and Liebowitz, 1987). Overstimulation has also been noted in panic patients treated with the specific serotonin reuptake inhibitor, fluoxetine (Gorman *et al.*, 1987). Hyperstimulatory responses may occur as a result of serotonin 'agonist-like' effects of antidepressants at the start of therapy.

The dimunition in phobic avoidance behaviour observed is noteworthy. This result suggests that patients may have instituted their own programme of behaviour therapy since they were encouraged to enter phobic situations. Significant changes in avoidance behaviour accompanying treatment with clomipramine-only treatments have been noted by others (Gloger *et al.*, 1989). In this study too there was no formal behavioural programme, but a patient-initiated programme cannot be discounted.

The dose of clomipramine needed for effective control of panic attacks has varied widely in the studies to date. Gloger *et al.* (1989) used an average of 45 mg/day with several patients receiving 25 mg/day or less. Cassano *et al.* (1988) used a mean of 128 mg/day with a range of 25–300 mg/day. Johnston *et al.* (1988) reported an average dose of 82·8 mg/day, while Kahn *et al.* (1987) used up to 150 mg/day as a maximum. Earlier studies (Beaumont, 1977) suggested a range of 25–250 mg/day in phobic disorders, the majority of patients receiving 50 mg/day. The average dose in our study of 122·5 mg/day at week 8 with a range of 50–225 mg/day is similar to that of Cassano *et al.* (1988). The lower mean dose (95·8 mg/day; range 50–125 mg/day) in responders to medication than in partial or non-responders (165·2 mg/day; range 150–225 mg/day) suggests that lower doses may be more effective. This observation also needs to be interpreted cautiously. The flexible dosage regimen employed, and the titration of dose to response, could conceivably lead to higher doses of medication in non-responders. A double-blind trial of high-dose versus low-dose clomipramine would be needed to confirm differential responses. At present titration of the dose from an initial 25 mg/day to symptomatic control would be appropriate.

Non-responders to medication were not distinguished from responders by the severity of their illness except on the self-reported disability scales for work and social functioning. (Non-responders rated themselves more severely dysfunctional compared to the responders.) Whether or not in a larger sample such differences would be of predictive value requires further study. Failure to respond to clomipramine may be related to non-compliance or rapid drug metabolism. Notwithstanding non-compliance, inadequate dosage or insufficient treatment length do not appear to offer an explanation for treatment failures in the present study.

The mechanism by which antidepressants exert their antipanic effects remains unclear. Neurotransmitter involvement in the aetiology of panic disorders has been suggested by several authors, with serotonergic (Kahn and van Praag, 1988) noradrenergic (Charney and Heninger, 1986) and GABA (Hoehn-Saric, 1982) systems being involved in current hypotheses. The efficacy of the relatively specific serotonin reuptake inhibitor clomipramine and the more specific drugs fluoxetine and fluvoxamine in the treatment of panic, argues for the serotonin hypothesis. Coupled with the results from recent neuroendocrine challenge tests (Kahn *et al.*, 1988) and platelet serotonin reuptake studies (Norman *et al.*, 1989) hyperactive serotonin recep-

tors in panic present a testable hypothesis of both aetiology and treatment effects. The clinical efficacy of more specific serotonin antagonists in treating panic, as well as refined neuroendocrine challenge tests, will doubtless provide new insights into which serotonin receptor subtypes are important in panic disorders.

Clomipramine has been shown to be effective in reducing the number of panic attacks experienced by most subjects in this study. Even in patients who were withdrawn due to ineffective medication, there was a reduction in the number of panic attacks. This report confirms the findings from several short-term evaluations in which clomipramine was found to be efficacious in treating panic attacks. Clomipramine was generally well tolerated and had no effects of clinical significance on laboratory function tests. The results suggest that further controlled studies are warranted.

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