Obsessive-Compulsive Disorder

A Double-blind Trial of Clomipramine and Clorgyline

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• **Patients with obsessive-compulsive disorder who met *DSM-III* criteria and who had been ill for at least one year were studied in a double-blind, randomized, crossover comparison of the tricyclic antidepressant clomipramine hydrochloride and the monoamine oxidase inhibitor clorgyline hydrochloride. No significant improvement was evident after four weeks of treatment with placebo prior to the crossover study. Treatment with clomipramine was associated with significant improvement after both four and six weeks in measures of obsessions, anxiety, and depression. Antiobsessional responses to clomipramine did not depend on presence of depression. Improvement was correlated with plasma concentrations of clomipramine, but not with the plasma concentrations of any of its metabolites. No significant improvement was evident for the entire group with clorgyline treatment, although the conditions of individual patients did respond to the drug.**
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Until recently, obsessive-compulsive disorder (OCD) was considered refractory to most psychiatric treatments. Two developments since 1972 provided new optimism for the treatment of patients with severe OCD. Recent innovations in behavior therapy, using such techniques as response prevention and exposure in vivo have been shown to be effective and lasting treatments for as many as 80% of the OCD patients with rituals.[1-4] Unfortunately, patients with OCD without rituals or avoidant behavior and those with secondary depression did not respond as well to behavior therapy.[5,6] A second development for the treatment of both ritualizers and pure obsessionals has been the use of a variety of antidepressant medications.[7] Most often, however, reports of the effectiveness of medications were based either on uncontrolled trials or on data from single cases.

The one exception to this rule is the growing body of studies with clomipramine hydrochloride, a tricyclic antidepressant widely used in Europe and Canada, but not yet available in the United States. Thus far, there have been six double-blind studies of clomipramine treatment of OCD. Thoren and co-workers,[8] Marks and co-workers,[9] and Montgomery[10] all reported clomipramine to be more effective than placebo, although in the study by Marks et al this effect was only present for OCD patients with significant depression. In Montgomery's study, clomipramine hydrochloride was given orally in dosages of 75 mg/day; the other two studies used dosages approximately 150 mg/day. Curiously, the statistically significant clinical improvement may have developed somewhat later than is usually reported for depressed subjects (five weeks in the Thoren et al study). A fourth report, by Ananth and his colleagues in Montreal,[11] found that clomipramine but not amitriptyline hydrochloride produced statistically significant improvement in measures of obsessions, anxiety, and depression in obsessional patients who did not manifest features of endogenous depression. Ananth gave clomipramine hydrochloride in gradually increasing dosages up to 300 mg/day. A fifth study by Yaryura-Tobias and co-workers[12] found that the conditions of patients with OCD tended to relapse when the patients were withdrawn from the clomipramine regimen under double-blind conditions. Finally, preliminary results from a double-blind parallel study of clomipramine, desipramine, and placebo in children with OCD suggested equal effectiveness in each of the treatment groups.[13] A possible explanation for this nonsignificant finding with clomipramine in contrast with the studies of the drug in adults is a greater sensitivity of the children with OCD to nonspecific hospital-treatment influences.[13]

Very recently, it has been reported that monoamine oxidase inhibitors (MAOIs) might also be effective for this syndrome. Single case reports with phenelzine sulfate[14-16] and tranylcypromine sulfate[17] described marked improvement in patients with OCD. In other anxiety disorders, such as in phobic anxiety states, MAOIs have been found to

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Table 1.—Characteristics of Patients With Obsessive-Compulsive Disorder

Age, yr/Sex*	Major Symptom†	Current Illness Duration, yr*	Age at Onset of OCD, yr*	Years of Treatment*	Previous Behavior Therapy	Previous Medications or ECT‡	Previous Hospitalizations	Prior Psychiatric Diagnoses
20/M	Washing	13	7	1	Rejected	NL	1	. . .
36/F	Ruminations (washing in past)	2	7	6	Yes	TCA, BZD	2	Anorexia nervosa, in remission
19/F	Checking	3	11	2	Yes	. . .	1	. . .
42/M	Ruminations	4	29	4	Yes	TCA	1	Hyperactivity, in childhood
37/F	Ruminations, checking, washing	13	21	8	No	TCA, BZD, ECT	3	. . .
30/M	Ruminations, checking	5	25	2	Yes	NL, BZD	0	Alcohol abuse
25/M	Ruminations	2	23	4	No	. . .	0	School phobia (age 7 yr)
27/M	Ruminations	11	8	6	No	TCA	0	Encopresis (age <8 yr), social phobia
45/F	Washing	5	40	2	No	NL	0	Primary affective disorder (in remission)
57/M	Checking, washing	4	53	2	Yes	TCA, BZD	3	. . .
34/F	Checking, ruminations	13	21	1	Yes	NL	1	Agoraphobia
25/M	Ruminations	1.5	24	1	No	TCA, NL, BZD	2	. . .
19/M	Checking, ruminations	7	12	5	No	. . .	0	Simple phobias

*Mean age, 32.0 years; mean duration of current illness, 6.4 years; mean age at onset of obsessive-compulsive disorder (OCD), 21.6 years; and mean number of years of treatment, 4.1.

†Denotes chief complaint. *Washing* indicates washing rituals due to fears of contamination of self or others; *ruminations*, reminations of doubt or intrusive abhorrent thoughts or urges; and *checking*, checking rituals usually coupled with ruminative doubt.

‡ECT indicates electroconvulsive therapy; NL, neuroleptics; TCA, tricyclic antidepressants; and BZD, benzodiazepines.

be an effective treatment[18,19] In one study by Sheehan and co-workers, a three-month double-blind parallel trial of phenelzine, imipramine, and placebo was used to treat patients with endogenous anxiety.[20] These investigators found that both active drugs had anxiolytic properties and that both yielded significant changes from baseline in the obsessive-compulsive items of the Symptom Checklist-90.[20] Although the subjects in this study did not have OCD, the response of similar anxiety symptoms to both imipramine and phenelzine suggested to us the usefulness of trying an MAOI in patients with OCD.

We performed a double-blind placebo-controlled study of clomipramine and clorgyline hydrochloride for patients with OCD. Clorgyline is an MAOI that is selective for MAO-A, the enzyme subtype that preferentially metabolizes serotonin and norepinephrine in the brain.[21] Previous reports demonstrated that clorgyline is an effective antidepressant in patients with primary affective illness.[22-25] We chose to compare the two drugs in a crossover design, as OCD is an uncommon disorder.

SUBJECTS AND METHODS

Twenty-four subjects from nine states were referred to the OCD research program at the Clinical Center of the National Institutes of Health, Bethesda, Md. Each subject underwent a full inpatient psychiatric and medical evaluation, including two diagnostic interviews, physical examination, clinical laboratory studies (eg, serum chemistry studies, complete blood cell count, and thyroid function tests), and psychological tests. Additional historical data were obtained from family interviews and records of past hospitalizations when available.

Inclusion criteria were the elements of the *DSM-III* diagnosis of OCD.[26] These include current obsessions ("recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic") or compulsions ("repetitive and seemingly purposeful behaviors that are performed according to certain rules or in a stereotyped fashion . . . with a sense of subjective compulsion coupled with a desire to resist the compulsion . . . ") causing significant "interference with social or role functioning" in the absence of a primary psychiatric disorder (eg, depression or schizophrenia). In addition to these *DSM-III* criteria, we screened only patients who had been ill for at least one year and patients at least 18 years of age. Exclusion criteria, besides primary depression or schizophrenia, were presence of major medical illness or history of leukotomy or other neurosurgery.

In cases with both obsessions and depression present, the distinction between primary and secondary depression can be difficult. We defined the depressive symptom to be secondary to obsessional disorder if (1) the severe obsessional symptoms preceded the affective symptoms by at least two months, and (2) the patient described his or her depression as resulting from a loss of functioning due to obsessional symptoms. In one case, a patient was included who had had an episode of primary affective illness without obsessional symptoms 12 years earlier. Obsessive-compulsive symptoms (incapacitating washing rituals) began for the first time five years prior to admission. She became "depressed" several months later, but on admission stated "this has never been like my severe depression; then I was totally blue, now I'm mostly scared." Although no other patient had a history of primary affective illness, several (including some without depressive features) showed neuroendocrine and sleep EEG abnormalities similar to those seen in subjects with endogenous depression. Three patients had parents with primary affective illness; two others had fathers who had been treated for alcoholism.

Three of the 24 subjects evaluated for the study were excluded on diagnostic grounds. Two of these had affective symptoms that appeared before the obsessional complaints. In a third subject, auditory hallucinations and paranoid delusions developed suggestive of a schizophrenic disorder after two days of hospitalization. Of the remaining 21 subjects, eight did not reach the active drug trial. During a brief inpatient assessment period, off all drugs, two subjects were found to have medical abnormalities that led to nonresearch treatment regimens. Two others whose conditions improved sufficiently during the evaluation period no longer met inclusion criteria. The conditions of both subjects subsequently relapsed, but the patients declined to participate in the research

Table 2.—Change in Outcome Variables, Clomipramine and Clorgyline

Rating Scales*	Clorgyline (n=11)†		Clomipramine (n=12)†	
	Baseline	6 wk	Baseline	6 wk
Observer Ratings				
CPRS-OC subscale	10.0±3.6	8.9±4.2	10.6±2.0	7.0±1.8‡
CPRS-OC modified subscale	6.6±1.9	6.6±2.6	7.4±1.2	5.3±1.1‡§
Obsessive-compulsive rating	12.3±2.5	11.8±3.0	13.0±2.6	10.2±1.8‡‖
Global				
Impairment	6.9±1.9	6.2±2.0	7.2±1.9	5.0±1.9‖
Obsessive-compulsive	7.4±1.7	7.1±1.8	8.2±1.5	5.7±1.6§‖
Anxiety	6.0±2.1	5.6±2.5	5.9±1.8	4.4±1.6‡
Depression	5.1±2.8	4.5±2.8	5.3±2.0	3.7±2.0‖
Hamilton Depression Scale	16.6±6.6	17.7±11.2	18.0±6.0	10.7±6.7‖
Self-ratings				
Leyton Obsessional				
Inventory Symptom	32.2±5.7	34.1±8.1	27.6±9.1	26.2±8.7
Trait	13.3±5.4	13.5±3.5	11.1±4.8	11.3±4.4
Resistance	41.9±21.8	34.3±16.1	35.0±18.3	33.0±18.8
Interference	44.7±16.9	37.5±18.0	38.6±20.6	29.5±16.9
Compulsive checklist	49.7±36.3	44.6±35.2	48.0±38.8	33.2±24.4‡
POMS				
Tension anxiety	52.4±7.4	48.5±12.3	50.6±10.1	46.2±8.7‡
Depression	53.5±11.1	51.5±12.8	52.6±12.4	46.2±10.5‖
Anger	53.5±9.0	48.7±12.2	52.6±12.1	45.7±10.4‖
Vigor	45.7±7.9	47.0±9.0	42.7±6.1	48.1±8.1
Fatigue	54.4±9.8	54.1±11.8	53.4±9.8	48.3±11.0
Beck Depression Inventory	19.8±10.7	20.2±17.0	19.0±12.8	13.7±9.1‡

*CPRS-OC indicates Comprehensive Psychiatric Rating Scale—Obsessive-Compulsive; and POMS, Profile of Mood States.
†Mean±SD.
‡$P<.05$.
§$P<.01$, two-tailed t test for paired data (six weeks v baseline).
‖$P<.01$, two-tailed t test for paired data (clomipramine change score v clorgyline change score).

study. Four other patients, all of whose conditions deteriorated during this initial inpatient washout period, also declined to participate.

For the remaining 13 patients who entered the drug studies (eight men, five women), the mean age was 32.0 years (range, 19 to 57 years) and the mean duration of illness was 6.4 years (range, 1.5 to 13 years). Table 1 summarizes the demographic data for this group. In five of the 13, OCD developed by age 12 years, and in the remainder after age 21 years. Six of the subjects had received behavior therapy (exposure without response prevention in four cases) without success. All but four had undergone previous medication trials. Six had had previous treatment with tricyclic antidepressants: three received imipramine, two nortriptyline hydrochloride, and one imipramine and amitriptyline. Of these six, one had previously received phenelzine and one had received electroconvulsive therapy. None of these treatments had been successful.

Procedure

After the inpatient evaluation, seven patients were treated as outpatients; these patients continued in psychotherapy with the referring physician. Six others, all from distant locales, remained in the hospital where they worked at volunteer jobs (as tolerated) and received both individual and group supportive therapy (despite lack of evidence for specific efficacy).

The research followed a six-month, placebo-controlled, double-blind crossover design, as follows: first, placebo was given for four weeks; then drug A for six weeks; then placebo for four weeks; then drug B for six weeks; finally, placebo for four weeks. In group 1, drug A was clomipramine and drug B clorgyline; in group 2, this was reversed. A fixed number of capsules was given four times each day throughout the study. All capsules were identical in appearance.

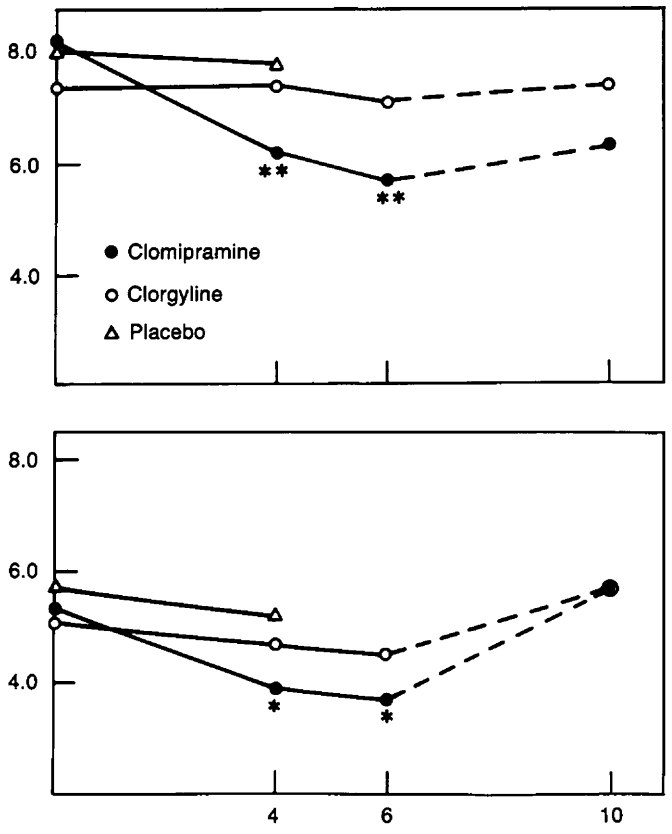
After a two-week washout period, each patient was begun on placebo for four weeks. At the end of this placebo period, each subject was randomly assigned to receive either clorgyline or clomipramine by alternating between the two active drugs. Each drug was given for six weeks. Clorgyline was given in doses of 30 mg/day from the first day of the trial. Clomipramine hydrochloride was given initially in doses of 100 mg/day, escalating to 300 mg/day as tolerated. Later, the protocol was changed to begin clomipramine hydrochloride at 50 mg/day, with increases of 50 mg every two days to a maximum of 300 mg/day, as tolerated. The intercrossover second placebo period was set at four weeks.

Patients with marked improvement after the first drug trial were invited to leave the study just prior to the second drug trial. At the end of the study, patients were given the option of "open" treatment with either clomipramine or tranylcypromine (instead of clorgyline, whose supply was limited).

This study was approved by the Clinical Research Review Committee of the National Institute of Mental Health (NIMH) at the Clinical Center of the National Institutes of Health. Each subject gave informed consent for the investigation.

Assessment

The design of sensitive and valid assessment scales for obsessional symptoms has been one of the most challenging aspects of research in this area.[7] There is no widely accepted rating scale for measuring change in patients with OCD. We chose a variety of observer ratings and self-ratings based on earlier studies in patients with OCD. The observer ratings were as follows: (1) The Comprehensive Psychiatric Rating Scale—Obsessive-Compulsive (CPRS-OC) subscale developed by Thoren and co-workers.[8] This subscale, consisting of eight items rated 0 to 3, has a 97% interrater reliability and is sensitive to change.[10] (2) A modified form of the CPRS-OC subscale that included only those five items that re-



Changes on National Institute of Mental Health scales in obsessions (top) and depression (bottom) in patients receiving clomipramine (n=12), clorgyline (n=11), and placebo (n=13). Dashed lines denote changes during postdrug placebo periods. Significant changes from baseline ratings (asterisk, $P<.05$; double asterisk, $P<.01$; two-tailed t test for paired data) are evident only with clomipramine.

flected obsessional symptoms (compulsive thoughts, rituals, concentration difficulty, lassitude [slowness], and indecision). (3) The Obsessive-Compulsive Rating Scale developed by Rapoport et al.[13] This is a four-item scale (preoccupation with rituals, number of rituals, degree of interference, time spent resisting urges) rated from 1 (none) to 5 (extremely severe), with a correlation coefficient for interrater reliability of .68. (4) The NIMH Global Scales, including functional impairment, obsessive-compulsive symptoms, anxiety, and depression rated from 1 (no difficulty) to 15 (most severe). The obsessive-compulsive subscale was developed along the lines of the other previously reported subscales.[27] (5) The Hamilton Depression Scale[28] in a lengthened form.[27] This form includes Hamilton's research items for symptoms of depersonalization, paranoia, and obsession-compulsion.[28] In addition, there are three supplemental items (hopelessness, helplessness, worthlessness). The maximum score on this 24-item scale is 76. In depressed subjects, scores obtained by two or our raters of this lengthened scale have correlated above .90.

The self-rated measures were as follows: (1) The Leyton Obsessional Inventory, originally developed as an interviewer-administered test by Cooper to separate obsessional neurotics from "houseproud" housewives.[29] We used a self-administered version of this scale similar to one validated by Snowdon.[30] (2) The Profile of Mood States scored for the tension-anxiety, depression, anger, vigor, and fatigue subscales.[31] (3) The Compulsion Checklist, which consists of 60 items of everyday activities rated from 0 to 3 for degree of inhibition, developed by Philpott.[33] (4) The Beck Depression Inventory.[32] (5) The NIMH side-effects questionnaire.

Self-ratings were obtained on a weekly or end-period basis, depending on the scale. Patients were encouraged to fill out their rating scales at a routine time. Observer ratings were always completed by a blind rater. Every patient had the same rater throughout the study, although several different raters were used for the entire group.

Monthly plasma samples were obtained throughout the study to monitor liver function, electrolyte levels, and blood cell counts. As part of this routine, clomipramine plasma levels were measured in the last two weeks of the drug trial: 12 hours after the previous dose of drug, blood was drawn into heparinized tubes with nonplasticizer stoppers, and plasma levels of the parent compound and the demethylated and hydroxylated metabolites were assayed by reverse-phase, high-performance liquid chromatography with electrochemical detection, with limit of detection approximately 5 ng/mL for all of the compounds.

Analysis

The study was designed to answer the following questions: Will patients' conditions improve from baseline ratings with either drug? Will one drug be more effective? Will obsessional changes be related to changes in depression? To answer the first question, scores at six weeks were compared with baseline values for each patient using Student's t test for paired data. This "within-group" comparison was performed for each drug. We then compared the drugs with each other by a similar t test for the pairs of difference scores (baseline to six weeks). These difference scores in obsessional symptoms were then correlated by linear regression with the analogous scores for depression ratings and with plasma levels of clomipramine and its metabolites.

Carry-over effects, minimized, it was hoped, by the long second placebo period, were assessed by Student's t test that compared ratings at the fourth (pre–drug A) week with the 14th (pre–drug B) week. Sequence effects were assessed by unpaired comparisons of each drug in each sequence (ie, drug A v drug B).

RESULTS

Twelve subjects completed the placebo-clomipramine-placebo sequence, 11 the corresponding clorgyline sequence, and ten the entire crossover sequence with all three treatments. Three patients dropped out after the first drug trial. The conditions of two had improved while receiving clomipramine, the third had received clorgyline without benefit. The condition of this third patient deteriorated further during the postclorgyline placebo phase. He refused to participate further in the research study, but was subsequently treated elsewhere with a tricyclic antidepressant, with only modest success.

Table 2 shows baseline and sixth-week endpoint ratings for all the subjects from either sequence. Within-group comparisons of 19 variables (from eight scales) disclosed no improvement compared with baseline ratings while receiving clorgyline. Clomipramine was effective in ameliorating scores on 13 of the 19 measures. In addition, the Leyton interference score was reduced, but the degree of reduction did not quite reach significance ($P=.056$). To estimate the time course of these effects, we reanalyzed the same measures after four weeks of treatment with both drugs. Every variable with a significant effect present after six weeks also showed a significant effect after four weeks; however, the magnitude of these effects was less marked after four weeks.

Direct comparison of the drugs by a paired t test of difference scores (baseline minus six weeks) for the ten subjects who completed both trials showed that improvement seen with clomipramine surpassed that seen with clorgyline on the CPRS-OC modified subscale, the Global OC Scale, and the OC rating scale. Of these ten subjects, only one displayed more improvement with clorgyline than with clomipramine in the obsessional symptoms measured by these scales. As a second between-groups comparison, data from all 13 subjects from the first drug trial (seven receiving clorgyline, six clomipramine) were analyzed separately so as to include the three dropouts. Again using difference scores (baseline minus six weeks) for each drug group, Student's t test corroborated the paired comparison of ten subjects, as differences with clomipramine were significantly greater than differences with clorgyline ($P<.05$) for the Global OC scale and the OC rating scale.

Effects related to the research design were similarly analyzed. No carryover effect from the first drug trial was evident, as the baseline for drug B approximated the baseline for drug A on all measures for each drug. Pooling the two baseline values for scales

Table 3.—Change in Depression and Obsessions With Clomipramine for Subjects With Most and Least Secondary Depressive Symptoms

	Baseline*		% Change From Baseline at 6 wk*		
	Hamilton Depression Score (24 Items)	Modified CPRS-OC	Hamilton Depression Score	Modified CPRS-OC	Global OC
Most depressed (n=3)	26.3±4.6	7.7±1.1	34.3±17.9	15.9±16.7	23.5±10.3
Least depressed (n=3)	11.7±1.1	6.7±1.1	57.7±29.3	25.0±8.3	34.3±13.6

*Mean±SD. CPRS-OC indicates Comprehensive Psychiatric Rating Scale—Obsessive-Compulsive.

Table 4.—Drug Dosage and Plasma Levels of Clomipramine and Its Metabolites*

	Mean±SD	Range
Dosage, mg	236±67	100-300
Plasma levels, ng/mL		
Clomipramine	136±64	60-272
8-OH clomipramine	53±23	17-88
Total tertiary amines*	190±82	77-335
Desmethylclomipramine	290±161	109-530
8-OH desmethylclomipramine	150±83	53-286
Total secondary amines†	440±241	173-816

*Clomipramine plus 8-OH clomipramine.
†Desmethylclomipramine plus 8-OH desmethylclomipramine.

(Hamilton Depression and CPRS-OC modified) where a trend toward a difference at baseline was evident, did not change the results from the within-group analysis (ie, clomipramine continued to show significant improvement on both scales, no significant change was evident on clorgyline). Sequence effects, assessed by a group t test for change scores on drug A v drug B suggested only one significant effect ($P<.05$). This was in the Leyton symptom score (scores more likely to increase with drug B). This single finding out of 19 variables was within the statistical probability of a chance occurrence.

Although the study was not designed to compare the responses to the drugs with responses to placebo, comparison of ratings prior to placebo and after four weeks of placebo administration did provide some measure of a "nonspecific" treatment response. There was no evidence of improvement on any of the 19 variables assessed for drug effects (two of these are shown in the Figure). Furthermore, analysis of inpatients separately from outpatients showed no evidence of any effect from hospitalization, per se. Comparing clomipramine effects for the three most depressed and three least depressed patients suggested that high pretreatment depression ratings were not essential for treatment response (Table 3).

Plasma levels of clomipramine (Table 4) positively correlated with reductions in obsessional symptoms ($r=.63$) on the CPRS-OC modified subscale (Table 5). No such relationship was present for clomipramine plasma level and changes in depression or for any of the other metabolites and clinical changes. The levels of each of the metabolites, but not of clomipramine itself, were highly correlated with dosage.

Side effects were prevalent on placebo, were somewhat worse with clorgyline, and worse still with clomipramine. Each patient described weakness and fatigue while receiving placebo. A brief, acute neurotoxic reaction to the first dose of clomipramine occurred in three of the six patients who had received treatment with clorgyline first. This reaction included hyperreflexia, tremor, rigidity, and clonus in the lower extremities. A full description has appeared elsewhere.[34] In these cases, the study was terminated for at least three days, then each patient was put back on a regimen of placebo prior to beginning with a lower dosage of clomipramine. Further complications with clomipramine included delayed ejaculation in five patients, tremor in two, and sedation in four. Several patients complained of putative anticholinergic symptoms (constipation was of particular concern to patients with cleaning rituals). One patient became hypomanic, with an attendant loss of obsessional symptoms. Her dosage of clomipramine was lowered, the hypomania quickly resolved, and washing rituals returned. Clorgyline was generally well tolerated. In two patients, orthostatic hypotension developed requiring a decrease in dosage. In both cases, this complication developed just as clinical improvement was beginning. The decrease in dosage was associated with a relapse of symptoms. Several patients described insomnia, increased activity, and even racing thoughts while receiving clorgyline, but these symptoms were generally interpreted as "feeling good."

In general, discontinuation of clomipramine led to relapse of obsessional symptoms, often with severe depression (even in patients previously euthymic). The relapse occurred within three days to three weeks. In two patients, this effect was not evident, and in a third, relapse occurred initially but reoccurred in only a very attenuated form three months later after a second drug trial. Four patients have been followed up while receiving clomipramine for six months or more, with continued improvement. In two of these patients, lowering the dosage after one year of treatment led to a rapid return of symptoms. Three other patients were treated with tranylcypromine rather than clomipramine after the study because of side effects with clomipramine. The conditions of all three improved initially with treatment, but in two cases the drug was discontinued within six months because of either side effects or attenuation of therapeutic effects.

COMMENT

Our results suggest that clomipramine was more effective than clorgyline or placebo in relieving obsessional symptoms. Of the ten subjects who received both drugs, the conditions of seven improved to some extent while receiving clorgyline, but in all but one case the improvement was greater with clomipramine. Clorgyline was not an effective antidepressant in this group (only four patients had reductions in Hamilton Depression Scale scores), in contrast with previously reported results with depressed subjects who had considerably higher baseline depression ratings. There were two other major findings from our study. First, in contrast to earlier studies with clomipramine, there was a surprisingly high correlation between plasma levels of clomipramine and change in obsessional symptoms. The reason for this discrepancy with earlier reports is not entirely clear. Second, depression is not a necessary prerequisite for clomipramine response.

Documenting treatment response in obsessional patients poses some complex problems to the clinical researcher. Our clinical impression that has been shared by others (M. Asberg, MD, oral communication, Dec 15, 1981) is that obsessional patients tend to report more symptoms as they improve. A major aspect of the illness is the secretiveness with which patients carry out avoidant or checking rituals. The rater might not even know about some symptoms until the patient begins to master them. Although self-ratings might circumvent this difficulty, these patients have particular problems in assessing their own status. In some cases, the ratings become a ritual in themselves—requiring checking and rechecking. For patients with obsessional

Table 5.—Correlation of Plasma Levels of Drug and Metabolites With Clinic

	Dosage	Clomipramine	8-OH Clomipramine	Clomipramine Plus 8-OH Clomipramine	Desmethylclomipramine
Dosage	...	.26	.69‡	.41	.74‡
Plasma levels					
Clomipramine	...	...	.65‡	.98§	.07
8-OH clomipramine	...	...	...	.80§	.55
Clomipramine plus 8-OH clomipramine	...	...	...	...	.21
Desmethylclomipramine	...	...	...	...	...
8-OH desmethylclomipramine	...	...	...	...	...
Desmethylclomipramine plus 8-OH desmethylclomipramine	...	...	...	...	...
Modified CPRS-OC† change	...	...	...	...	...
Hamilton Depression change	...	...	...	...	...

*Plasma levels were measured by high-pressure liquid chromatography, reverse phase with electrochemical detection.
†CPRS-OC indicates Comprehensive Psychiatric Rating Scale—Obsessive-Compulsive. Hamilton Depression change indicates change scores (baseline rating *v* drug period) computed from week of plasma level measurement.
‡$P<.05$.
§$P<.01$.

doubt, deciding between a rating of "much" and "severe" on an item such as indecisiveness poses obvious difficulties. Furthermore, slowness, which is a common manifestation of this illness, prevents patients from completing their ratings. Often, patients with more severe symptoms have great difficulty filling out the forms. Finally, some patients, consistent with the rigidity that may be seen in compulsive character disorder, resisted changing self-ratings until long after clinical improvement was noted by observers. This may explain why the Leyton Obsessional Inventory, used by us as a self-rating, did not show significant change with clomipramine, in contrast with other clomipramine studies that used this scale as an observer rating.[35]

The difference in responsiveness to the two drugs could not be due to order effects or inpatient *v* outpatient status, as the study was counterbalanced and each patient served as his or her own control. As several patients showed modest improvement while receiving clorgyline, we considered that the dose or duration might have been inadequate. Previous studies using 30 mg/day of clorgyline in depressed patients found a significant clinical response and a 90% reduction in urinary levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) at four weeks.[36] In four patients, we analyzed urine for changes in MHPG and found an equivalent (ie, 86%) reduction in the levels of this urinary metabolite. This suggested that the 30-mg dosage of the drug was adequate for inhibition of the MAO-A enzyme in OCD patients. As platelet MAO is type B, it is minimally affected by clorgyline (between 11% and 34%) and hence could not be used as an indicator of drug effect.[36,37] Although it is conceivable that a longer trial of clorgyline would have proved more effective, there was no change between four- and six-week rating points to suggest a trend in this direction. Finally, it may be that clorgyline, although pharmacologically more specific, is clinically less effective in OCD patients than are mixed inhibitors such as phenelzine or tranylcypromine. Previous reports[14-17] with these two drugs in patients with OCD suggested response within two weeks at dosages used for antidepressant effects.

We could estimate the comparability of clorgyline with tranylcypromine, but only in the three patients who received tranylcypromine subsequently. The condition of each had responded somewhat to clorgyline during the double-blind trial. During an open trial with tranylcypromine, one complained of more side effects than he had while receiving clorgyline. He was re-treated with clorgyline, with continued improvement and without adverse effects. The two other patients showed improvement with tranylcypromine commensurate with their response to clorgyline. One other patient with OCD, who refused to participate in the research study after the initial washout phase, has been followed up while receiving tranylcypromine (15 mg/day) for two years with marked reduction of symptoms.

Conceivably, inhibition of the B form of the MAO enzyme could be more important than MAO-A inhibition for antiobsessional effects. Increases in dopamine or phenylethylamine, both substrates of MAO-B, might provide a beneficial effect that would be absent with clorgyline. Such a mechanism has been hypothesized for deprenyl, a selective MAO-B inhibitor, which has been used to treat patients with hysteroid dysphoria.[38] Curiously, the obsessional patients whose conditions improved most while receiving clorgyline in our study described marked activation that kept them so involved in work or social activities that there was little time to attend to the intrusive thoughts or urges. This activation may have been due to some inhibition of MAO-B while receiving clorgyline, although previous studies with depressed subjects suggested that this is only a modest effect.[36,37] Whatever the mechanism, activation may be a key aspect of the antiobsessional response to MAOIs. In a separate study, we found similar therapeutic results with the activation induced by dextroamphetamine sulfate in obsessional patients.[39]

What predicts clomipramine response? Treatment effects were present in ruminators as well as ritualizers; in patients with childhood onset as well as in those with adult onset. Patients whose conditions had not improved with other tricyclics in the past did respond to clomipramine.

Our data do not support the notion that depression is necessary for clomipramine response. Not only did nondepressed patients respond equally well in terms of obsessional symptoms, but there is not a significant correlation between antiobsessional and antidepressant effects. Elsewhere,[40] we showed in a single case analysis that, during successive treatments with clomipramine, there were equivalent reductions in obsessional symptoms during each

Change*				
8-OH Desmethyl-clomipramine	Desmethyl-clomipramine Plus 8-OH Desmethyl-clomipramine	Modified CPRS-OC† Change	Hamilton Depression Change†
.81§	.77§	−.25	−.13
.20	.11	.63‡	−.49
.76§	.62‡	.09	−.29
.38	.27	.52	−.47
.94§	.99§	−.29	−.40
. . .	.97§	−.26	−.39
. . .	. . .	−.29	−.40
. . .	. . .	. . .	.41
. . .	. . .	. . .	. . .

treatment period despite markedly different baseline depression ratings. These results contradict those of Marks et al,[9] who found drug effects only in the most depressed obsessional patients. The difference between results in the two studies cannot be attributed to the level of depression, as the patients showed roughly equivalent Hamilton Depression Scale scores when corrections were made for the different forms of the scale used. One potential difference resides in the treatment design. Marks et al administered clomipramine for four weeks during the outpatient phase, then admitted the study patients into the hospital for either exposure or relaxation treatment. As some obsessional patients with depression have been previously shown to be unresponsive to behavioral treatments,[5] the difference they noted in drug response between the more- and less-depressed subgroups may partly reflect the difference in response to the nonpharmacologic treatment. If, for instance, the nondepressed subjects responded better to the behavioral treatment, then drug effects would be obscured. Two other studies relevant to this issue suggested, in accordance with our findings, that depression is not essential for an antiobsessional response to clomipramine. Thoren and co-workers[8] in an open trial of clomipramine found nonsignificant differences in depression ratings between responders and nonresponders to the drug. Another study by Ananth et al[11] reported no relationship between antidepressant and antiobsessional changes. In this report, the authors claimed that only nondepressed patients were included; however, the significant changes in depression scale scores on clomipramine raises a question of just how nondepressed their OCD patients were. Subgroups of more-depressed and less-depressed patients were not identified in this study.

Our data, then, suggest that a broad spectrum of OCD patients may benefit from clomipramine. However, within a six-week treatment trial, the benefit is not always dramatic. Obsessional measures in our patients averaged about a 30% improvement (34% improvement on the CPRS-OC subscale), with each patient showing at least mild improvement at either four or six weeks. These results approximate the finding by Thoren et al[8] of 42% improvement on the CPRS-OC subscale. Although no patient had a total resolution of obsessional complaints within the six-week trial, four continued to progress to almost total remission of symptoms, with marked improvement in functioning during several months of subsequent treatment. In general, improvement consisted of a decreased intensity of the symptoms. Most patients described the change as "I still have the thoughts but they don't bother me as much, I've got so many other things on my mind now." Work and social activities usually relinquished prior to treatment were resumed after several weeks of therapy with clomipramine, and served as critical distractors from obsessional thoughts. Stopping the drug led to relapse even after prolonged treatment. Although clomipramine's therapeutic effects seem more subtle than the efficacy of many drugs in other anxiety and affective disorders, one must remember that OCD is a chronic illness refractory to such nonspecific interventions as placebo and hospitalization, and often is unresponsive to traditional psychotherapy.

A further question relates to the mechanism of clomipramine's effect. Others[41] suggested that this antiobsessional effect may be related to the potency of clomipramine at blocking neuronal uptake of serotonin. Support for this hypothesis comes from a report[41] that *l*-tryptophan has antiobsessional effects and that low CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid predict poor response to clomipramine.[42] Our finding that the plasma level of clomipramine correlated with decreases in obsessional ratings may support a relationship between antiobsessional effects and a specific action of clomipramine. However, such a correlation has not been found in earlier studies with either obsessional[42,43] or depressive[44,45] subjects. Our finding of a positive relationship represents data from a small number of subjects with a low range of improvement scores, and thus needs replication. Furthermore, desmethylclomipramine, which is present at a two-fold greater concentration in plasma, has powerful inhibitory effects on the reuptake of both norepinephrine and serotonin. Although one is tempted to speculate that the clomipramine plasma level correlations with obsessional changes reflect serotonergic uptake blockade, and that the weak correlations of desmethylclomipramine with mood changes reflect noradrenergic uptake blockade, these effects are only two among many pharmacologic actions of the drug and its metabolites. Further studies with more putatively selective serotonin-uptake blockers, eg, zimelidine hydrochloride or alaproclate,[46] and with biochemical measures of amine turnover will be necessary to support or refute a "serotonin hypothesis" of OCD.

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