Rapid Benefit of Intravenous Pulse Loading of Clomipramine in Obsessive-Compulsive Disorder

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Objective: *The authors conducted a randomized, double-blind, placebo-controlled trial of intravenous versus oral pulse loading of clomipramine in patients with obsessive-compulsive disorder to test two hypotheses: 1) intravenous pulse loading will cause greater immediate improvement than oral pulse loading and 2) patients who respond to pulse loading will continue to improve during 8 weeks of oral clomipramine treatment.* *Method:* *Fifteen patients with DSM-III-R obsessive-compulsive disorder of at least 1 year's duration and baseline Yale-Brown Obsessive Compulsive Scale scores of 17 or higher were enrolled in the study. Yale-Brown scale ratings were made 4.5 days after double-blind oral or intravenous pulse loading of clomipramine, and patients were then given 150 mg/day of oral clomipramine with increases of 25 mg every 4 days to 250 mg/day as tolerated or, in two cases, other selective serotonin reuptake inhibitors (SSRIs).* *Results:* *The first hypothesis was confirmed: 4.5 days after the second pulse-loaded dose, six of seven patients given intravenous clomipramine but only one of eight given oral medication responded to the drug. After 8 weeks of oral clomipramine, the results partially supported the second hypothesis: four of six patients who had responded to intravenous clomipramine continued their improvement, but those who had responded to pulse loading did not improve statistically significantly more than those who had not.* *Conclusions:* *Intravenous pulse loading of clomipramine may be a valuable new treatment for obsessive-compulsive disorder, particularly for patients who have failed oral treatment trials.*

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Obsessive-compulsive disorder responds slowly to orally administered selective serotonin reuptake inhibitors (SSRIs). For example, after 4 weeks of clomipramine treatment, mean scores on the Yale-Brown Obsessive Compulsive Scale (1) decreased by only about 20% (2, 3). "Clinically meaningful improvement" (a decrease of 35% or more) usually takes about 6 weeks to develop (4). Each available SSRI (clomipramine, sertraline, fluoxetine, fluvoxamine, and paroxetine) benefits about 45% to 60% of patients with obsessive-compulsive disorder (5, 6). However, we cannot predict which patient will respond to which drug or will be unresponsive to all five drugs, and 8 to 10 weeks are needed for each treatment trial (4, 7).

One SSRI, clomipramine, is available in intravenous form. In Europe, intravenous clomipramine is commonly used to treat obsessive-compulsive disorder and major depression in both outpatients and inpatients (8–13).

Available data suggest that, in obsessive-compulsive disorder, intravenously administered clomipramine reduces symptoms much more quickly than oral clomipramine and is better tolerated. Warneke (14–16) reported moderate to marked improvement in nine patients toward the end of 14 daily infusions or shortly thereafter and stated that about half of 30 patients with obsessive-compulsive disorder experienced "moderate to marked improvement." Fallon et al. (17) reported a 39% average decrease in symptom scores in three of five patients with obsessive-compulsive disorder after 14 consecutive weekday infusions. Patients unable to tolerate adequate doses of oral clomipramine easily tolerated intravenous clomipramine. In an earlier study (18), we reported that five patients with obsessive-compulsive disorder treated with gradually increased doses of intravenous clomipramine improved to a marked degree within 4 weeks, i.e., almost twice as fast as in trials of oral clomipramine. Sallee et al. (19) reported a decrease of about 30% in obsessive-compulsive disorder symptom scores in three adolescents within 36 hours of re-

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ceiving two infusions of clomipramine (75 mg and 200 mg) in 2 days. In addition, patients unresponsive to adequate trials of oral clomipramine have subsequently benefited from intravenous clomipramine (14, 17).

In view of these findings, we conducted a double-blind, placebo-controlled trial of intravenous versus oral pulse loading of clomipramine to test the following hypotheses:

1. Intravenous pulse loading of clomipramine (150 mg on day 1 and 200 mg on day 2) will produce a marked decrease in obsessive-compulsive disorder symptoms within 4.5 days of the second dose, and this decrease will exceed that produced by double-blind, oral pulse loading of identical doses of clomipramine. We defined a "marked decrease" as a 25% or greater decrease in Yale-Brown scale score (7). Patients experiencing this decrease are called "responders."

2. Responders to pulse-loaded clomipramine will maintain this benefit and will have improved more (as measured by the Yale-Brown scale) after 8 weeks of open-label oral clomipramine than nonresponders. That is, the responders' head start in symptom reduction will keep their improvement ahead of that of nonresponders for at least 2 months. Improvement will be measured from the predrug baseline score.

METHOD

Patients

Eligible patients met DSM-III-R criteria for obsessive-compulsive disorder based on Structured Clinical Interview for DSM-III-R (20) results, had been ill for at least 1 year, and had a minimum Yale-Brown scale score of 17. Patients with DSM-III-R major depression were eligible if the depression began after the obsessive-compulsive disorder and obsessive-compulsive disorder was the primary diagnosis, strongly dominating the clinical picture. After the study had been explained to them, all study subjects gave written informed consent. For subjects aged 18 or younger, we obtained written informed consent from both parent and child.

Study exclusion criteria were age less than 15 or more than 50 years; pregnant, nursing, or of childbearing potential and not using an effective contraceptive method; a history of schizophrenia, bipolar disorder, posttraumatic stress disorder, borderline personality disorder, or anorexia; IQ less than 70; drug or alcohol abuse or dependence within the past 6 months; a history of clinically significant, severe adverse reactions to clomipramine; a history or evidence of clinically significant physical or laboratory abnormality, medical disease, risk factors for seizure disorder, or medical contraindications to treatment with tricyclic antidepressant drugs; exposure to ECT, a monoamine oxidase inhibitor within 4 weeks, a depot neuroleptic or fluoxetine within 6 weeks, or any other regular, daily psychotropic or corticosteroid (except topical) within 2 weeks of starting clomipramine.

Clomipramine Dose and Administration

Clomipramine for intravenous administration is manufactured by CIBA-GEIGY and distributed in Europe and Asia. The drug vials contain 25 mg of clomipramine, 54 mg of glycerine as an excipient, and 2 ml of distilled water. We obtained and administered intravenous clomipramine under Investigational New Drug permit number 36,784. Hospital pharmacists prepared materials for double-blind administration.

Patients were randomly assigned to either intravenous or oral pulse-loaded clomipramine. They were admitted to an inpatient research unit the night before clomipramine administration. The following morning at 9:00 a.m. they received an intravenous test dose of 12.5 mg of clomipramine in normal saline for neuroendocrine studies to be reported elsewhere. Double-blind, placebo-controlled pulse loading of clomipramine began at 6:30 p.m. that evening, preceded by oral administration of 250 mg of trimethobenzamide hydrochloride to reduce nausea. On day 1, over 90 minutes, patients received double-blind either 150 mg of intravenous clomipramine in 500 mg of normal saline or normal saline alone (placebo) (19). As the infusion began, patients took double-blind oral doses of 150 mg of clomipramine or of placebo. Cardiac monitoring was in place throughout the infusion period and for 30 minutes afterward. Nursing staff monitored vital signs and side effect complaints every 15 minutes during the infusions and every 30 minutes for 2 hours afterward; during this time patients remained at bed rest. The infusion procedure was repeated 24 hours later with 200 mg of clomipramine (or normal saline) and 200 mg of oral clomipramine (or placebo). The patient was discharged from the inpatient unit the following morning.

Patients previously unable to tolerate oral clomipramine were allowed to enroll in the study because the experience of others suggested that such patients tolerate and usually benefit from intravenous clomipramine (14, 17).

Following the method of Pollock et al. (21), we gave oral clomipramine to the patients 4.5 days after the second pulse-loaded dose. The starting dose was 150 mg, increased by 25 mg every fourth day to 250 mg/day as tolerated (17).

Laboratory Methods

We obtained a blood sample immediately after the second pulse-loaded infusion to assay peak plasma levels of clomipramine and desmethylclomipramine. These levels were not substantially affected by the first morning's 12.5-mg challenge dose. Clomipramine has a half-life of about 40 hours (21), but clomipramine levels are only about 20 ng/ml and desmethylclomipramine levels are not detectable 3 hours after a 10-mg intravenous dose of clomipramine (22).

Clomipramine and desmethylclomipramine levels were determined by using a normal-phase high performance liquid chromatography method with a lower limit of quantitation of 1 ng/ml. Extraction recoveries typically range from 90% to 101%. Within- and between-day coefficients of variation range from 1.6% to 12.1% (23).

Efficacy and Safety Evaluation

We rated patients' symptoms with the 10-item Yale-Brown scale and the 17-item Hamilton Depression Rating Scale (24). Ratings took place immediately before the infusion of 150 mg of clomipramine (or saline) and 4.5 days after the infusion of 200 mg of clomipramine (or saline). The investigators were blind to whether patients had received intravenous or oral clomipramine.

Beginning 4.5 days after the second infusion, patients were seen weekly for 4 weeks and again at the end of week 8, when the trial ended. At each visit, we recorded the patient's blood pressure and pulse, inquired about adverse events, and rated obsessive-compulsive disorder symptoms.

Statistical Methods

We used Student's t test, two-tailed, to look for significant demographic and clinical differences between the two treatment groups at baseline and to test for differences in Yale-Brown scale scores at baseline, day 4.5, and after 8 weeks of oral clomipramine treatment. We used Fisher's exact test to test whether the group receiving intravenous medication was more likely than the group receiving oral medication to experience a 25% or greater decrease in Yale-Brown scale score at day 4.5. We used the Spearman rank correlation to look for a linear relationship between peak plasma clomipramine levels and change in Yale-Brown scale scores at day 4.5.

RESULTS

We enrolled 15 patients: seven were randomly assigned to intravenously pulse-loaded clomipramine and eight

TABLE 1. Characteristics of Patients With Obsessive-Compulsive Disorder Receiving Pulse-Loaded Intravenous or Oral Clomipramine

Characteristic	Intravenous Clomipramine		Oral Clomipramine	
	Mean	*SD*	*Mean*	*SD*
Age (years)	33.4	4.3	29.1	4.3
Duration of illness (years)	12.6	9.1	14.1	14.6
Baseline Yale-Brown Obsessive Compulsive Scale score	27.7	7.4	25.9	5.5
Baseline 17-item Hamilton Depression Rating Scale score	11.1	9.0	12.1	11.7
	N		*N*	
Male	6		7	
Female	1		1	
Onset before age 18	4		8	
Failed an oral clomipramine trial[a]	4		4	
Failed two or more selective serotonin reuptake inhibitor trials	5		5	
Failed three or more selective serotonin reuptake inhibitor trials	5		3	
Comorbid major depression	3		2	

[a]≥200 mg/day of clomipramine for ≥8 weeks.

to orally pulse-loaded clomipramine. There were no statistically significant differences between the two groups in mean age, duration of illness, number who had failed previous adequate trials of oral clomipramine, mean baseline Yale-Brown scale score (and range), or mean baseline Hamilton depression scale score (table 1). In the group receiving intravenous medication, three patients had comorbid major depression, one had comorbid dysthymia, and one had comorbid panic disorder.

The immediate outcome was consistent with our first hypothesis: 4.5 days after the second pulse-loaded dose of clomipramine, six of the seven patients given intravenous clomipramine experienced a marked response (i.e., a 25% or greater decrease in Yale-Brown scale score). The mean decrease in Yale-Brown scale score for the six patients was 40.8% (range=26.3%–55.5%) (table 2). Only one of the eight patients receiving oral clomipramine experienced a marked response (p=0.009, one-tailed Fisher's exact test). Further, the mean Yale-Brown scale score at day 4.5 of the group given intravenous pulse loading (mean=16.7, SD=3.3) was statistically significantly lower than that of the group given oral pulse loading (mean=25.0, SD=7.9) (independent samples t=2.59, df= 13, pooled variance, p=0.02).

Unfortunately, peak plasma clomipramine and desmethylclomipramine levels were available for only six of the seven patients receiving double-blind intravenous pulse loading and only one of the eight patients receiving double-blind oral pulse loading. The peak plasma levels of the patients given intravenous pulse loading were four to 14 times higher than the level of the patient given oral pulse loading. The peak plasma clomipramine level and the percent decrease in Yale-Brown scale scores (table 2) were not statistically significantly correlated (r_s=0.39, N=7) (for p=0.05, r_s must reach 0.71). Moreover, the single nonresponder to intravenous pulse loading had the second highest peak plasma clomipramine level (table 2).

After 8 weeks of oral clomipramine treatment, our second hypothesis was only partially supported (table 2). Four of the six patients who were responders to intravenous clomipramine at day 4.5 maintained or increased their improvement (mean decrease in Yale-Brown scale score from predrug baseline=59%, range=39%–74%). One responder to intravenous clomipramine permanently lost the response after 1 week of oral treatment, and one partially lost the response and dropped out at week 4 of oral clomipramine treatment because of discouragement. Two patients who were nonresponders to a previous adequate trial of oral clomipramine were responders at both day 4.5 and after 8 weeks of oral treatment. The other two patients given intravenous medication who had been unresponsive to oral clomipramine were nonresponders after 8 weeks of oral clomipramine treatment. Interestingly, these two patients had the highest peak plasma clomipramine levels.

In the group given oral pulse loading, the only responder at 4.5 days (patient 8) refused oral clomipramine because he had previously tolerated it poorly and without much benefit (table 2). He improved further on 150 mg/day of sertraline. Patient 12, having failed an adequate trial of clomipramine, also refused oral clomipramine maintenance and was treated with 80 mg/day of paroxetine but did not respond. After 8 weeks of oral clomipramine treatment, the seven patients who were nonresponders on day 4.5 of oral pulse loading had varying outcomes: three achieved a 25% or greater decrease in Yale-Brown scale score (range=28%–84%); two remained nonresponders; and two dropped out. Patient 14, having failed a previous adequate trial of clomipramine, refused oral clomipramine maintenance after experiencing "absolutely no change" at day 4.5. He later failed to benefit from open-label intravenous pulse loading of clomipramine, with a peak plasma clomipramine level of 182 ng/ml. Patient 15 dropped out because her obsessive-compulsive disorder worsened; she subsequently responded to open-label intravenous pulse loading of clomipramine.

Contrary to our second hypothesis, last-observation-carried-forward analysis revealed no statistically significant difference between mean Yale-Brown scale scores after 8 weeks of oral clomipramine treatment of the seven patients who were responders (mean=15.6, SD=9.9) and the eight nonresponders (mean=20.5, SD=11.1) on day 4.5 of pulse loading (independent samples t=0.90, df=13, pooled variance, p=0.38). Note that in the groups given intravenous and oral pulse loading, the proportion of responders after 8 weeks of oral clomipramine treatment was similar: four (57%) of seven patients given intravenous pulse loading and four (50%) of eight patients given oral pulse loading.

Comorbid depression often, but not always, improved

TABLE 2. Yale-Brown Obsessive Compulsive Scale Scores and Serum Clomipramine and Desmethylclomipramine Levels in Patients With Obsessive-Compulsive Disorder Receiving Pulse-Loaded Intravenous or Oral Clomipramine

Patient	Peak Serum Level (ng/ml)		Yale-Brown Scale Score						Percent of Decrease in Score at Day 4.5
					Week of Oral Clomipramine Treatment				
	Clomipramine	Desmethyl-clomipramine	Baseline	Day 4.5	1	2	4	8	
Patients given intravenous clomipramine									
1[a]	232	10	36	16	20	5	10	10	55.5
2[a]	667	15	36	20	30	29	32	35	44.4
3	—	—	31	18	6	—	10	15	41.9
4	288	10	18	11	—	15	15	—[b]	38.9
5[a]	241	10	29	18	19	20	20	20	37.9
6	211	8	19	14	13	11	10	5	26.3
7[a]	507	9	25	20	27	27	22	28	20.0
Patients given oral clomipramine									
8[c]	—	—	25	17	20	20	—	9	32.0
9	—	—	17	14	14	16	17	17	17.6
10[a]	48	18	29	27	24	21	17	21	6.9
11	—	—	25	24	—	6	—	4	4.0
12[a,d]	—	—	19	19	—	—	18	15	0.0
13	—	—	35	35	32	28	23	11	0.0
14	—	—	30	30	30	—[b]	—[b]	—[b]	0.0
15	—	—	27	34	33	38	—[b]	—[b]	(25.9)[e]

[a]Failed a previous adequate trial of oral clomipramine.
[b]Dropped out.
[c]Tolerated poorly without benefit 150 mg/day oral clomipramine in previous trial; maintenance treatment was oral sertraline, 150 mg/day.
[d]Also failed previous adequate trials of fluoxetine and sertraline; maintenance treatment was oral paroxetine, 80 mg/day.
[e]Score increased rather than decreased.

along with improvement in obsessive-compulsive disorder. At day 4.5, the obsessive-compulsive symptoms of all three patients given intravenous clomipramine who had comorbid depression improved, but only two experienced diminished depression (Hamilton depression scale decreases of 29% and 66%). In the group receiving oral medication, both the obsessive-compulsive disorder and the depression of one patient improved (Hamilton depression scale score decreased by 32%); the other experienced no improvement in either condition (Hamilton depression scale score increased by 30%). After 8 weeks of oral clomipramine treatment, the pattern of results continued unchanged in the group given intravenous pulse loading (the two depressions remitted); in the group given oral pulse loading, the day 4.5 double responder had continued improvement in obsessive-compulsive disorder and remission of depression, but the day-4.5 obsessive-compulsive disorder nonresponder had remission of depression at the end of week 4 of clomipramine treatment but still had no response in obsessive-compulsive disorder. The patient with comorbid dysthymia, who received intravenous clomipramine, experienced no improvement in obsessive-compulsive disorder or dysthymia.

Two patients experienced troubling adverse events. One patient, who had a past history of panic disorder, experienced a panic attack and mild dystonia after the double-blind infusion of 150 mg of clomipramine and declined the second infusion. She nonetheless was a responder at day 4.5. The second patient became hypotensive and bradycardic about 10 minutes after the second double-blind infusion (200 mg of clomipramine) ended, while the nurse was drawing blood for a plasma level. This may have been an anxiety-induced vasovagal attack, since the patient later said that he had been quite worried when the nurse had difficulty obtaining his blood sample. His symptoms responded rapidly to 0.5 mg of intravenous atropine and volume expansion with 500 ml of normal saline.

During pulse loading, three of seven patients given intravenous clomipramine had no side effects. The other four, including the two with the adverse events just described, had mild side effects, including nausea (N=3), dizziness (N=2), dry mouth (N=2), sweating (N=2), restlessness (N=1), flushing (N=1), drowsiness (N=1), restless sleep (N=1), and polyuria (N=1). Three of the eight patients given oral clomipramine had no side effects. The other five had mild side effects, including nausea (N=3), sweating (N=1), drowsiness (N=1), fatigue (N=1), abdominal distress (N=1), and nervousness (N=2).

DISCUSSION

Although limited by a small number of patients, our double-blind, placebo-controlled study results clearly suggest that pulse loading of intravenous clomipramine produces a large and rapid decrease in obsessive-compulsive disorder symptoms and that oral pulse loading does not. The four- to 14-times higher peak plasma clomipramine levels in the group receiving intravenous medication than in the one patient given oral medication begin to suggest that the greater efficacy of intravenous

clomipramine may be related to rapid attainment of high plasma levels. The mean plasma clomipramine level 8 to 10 hours after intravenous pulse loading (mean= 171 ng/ml, SD=50) (21) is indistinguishable from that seen after 12 weeks of oral clomipramine at a maximum stable dose of 239.4 mg/day (SD=57.0) (mean= 169.9 ng/ml, SD=102.1) (25).

Our results stand in contrast to those observed in major depression. Oral pulse loading of imipramine produces a dramatic response within 72 hours (26), but intravenous pulse loading of clomipramine does not produce a faster or larger response than oral pulse loading (21). Given that the groups receiving oral and intravenous medications in that study achieved mean plasma clomipramine levels in excess of 100 ng/ml, perhaps most patients in both groups exceeded a threshold level required for an antidepressant effect. That threshold may be higher in obsessive-compulsive disorder, in view of the often-voiced clinical opinion that higher SSRI doses are needed to treat obsessive-compulsive disorder than to treat major depression (4).

In obsessive-compulsive disorder, the rapidity of symptom relief induced by intravenous pulse loading far exceeds that induced by oral pulse loading or standard oral dosing regimens (2, 3). This result cannot be explained by the "drama" associated with intravenous lines, cardiac monitors, and inpatient admission because our double-blind study design assured that the group given oral pulse loading experienced the same drama.

Pulse loading of intravenous clomipramine also improves obsessive-compulsive disorder symptoms faster than gradually escalated intravenous dosing of clomipramine. In an open-label study, six of seven patients receiving pulse-loaded doses but none of 20 patients receiving gradually escalated intravenous doses had marked decreases in obsessive-compulsive disorder symptoms at day 4.5 (unpublished data of L.M.K. et al.).

Two of the four patients who had been nonresponders to adequate previous trials of oral clomipramine responded during and after intravenous clomipramine pulse loading. Our experience with these patients echoes the observations of Warneke (14) and Fallon et al. (17), who used open-label, gradually escalated doses of intravenous clomipramine.

Most responders to intravenous pulse loading improved further when switched to oral clomipramine. One permanently lost the early response, and one partially lost the response and discontinued clomipramine treatment. Whether the lost or diminished therapeutic effect was related to the lower serum clomipramine levels produced by oral dosing deserves study. Although the mean Yale-Brown scale scores after 8 weeks of oral clomipramine treatment of the patients who were or were not responders at day 4.5 of pulse loading were not statistically significantly different, the difference (5 points on the Yale-Brown scale, representing about one-half of a standard deviation) appears clinically meaningful; the absence of statistical significance may reflect low statistical power because of the small number of patients in our study.

The improvement in obsessive-compulsive disorder in our patients with and without comorbid depression is consistent with the finding that oral clomipramine is effective in nondepressed patients with obsessive-compulsive disorder (2).

Five of the seven patients given intravenous clomipramine had only minor side effects. The panic attack experienced by one patient is not a contraindication to intravenous clomipramine in patients with histories of panic; the likelihood of this reaction is unknown. The instance of hypotension and bradycardia together with reports of cardiovascular side effects of intravenous clomipramine (8, 13) suggest that careful cardiovascular monitoring is indicated during intravenous clomipramine infusions. In our opinion, pulse loading of intravenous clomipramine is contraindicated for patients with heart disease, a history of severe adverse reactions to oral clomipramine, risk factors for seizure disorder, or medical contraindications to treatment with tricyclic antidepressants.

We can only speculate on the neurophysiological mechanisms underlying the rapid response to intravenous clomipramine pulse loading because the pathophysiology of obsessive-compulsive disorder remains poorly understood. We know that intravenous pulse loading, by avoiding first-pass liver metabolism, achieves higher serum clomipramine levels, and presumably higher brain concentrations, than does oral pulse loading (21).

Clomipramine is a potent inhibitor of serotonin reuptake and penetrates the blood-brain barrier easily. Concentrations in the brain are 10 times those in plasma after a single parenteral dose (27). Could higher brain concentrations explain why some nonresponders to oral clomipramine respond to intravenous clomipramine? Given the evidence suggesting that the pathophysiology of obsessive-compulsive disorder involves deficient serotonin neurotransmission (28), we may speculate that the higher brain concentrations of clomipramine achieved by intravenous pulse loading either lead to rapid desensitization of serotonergic receptors or initiate changes in postsynaptic serotonergic neurons (G-protein signal transduction, cyclase and phosphatidylinositol second messenger activity, or gene expression) that usually can be maintained by oral clomipramine.

Tricyclic antidepressants related to clomipramine can affect gene expression in the brain. For example, desipramine increases hypothalamic glucocorticoid receptor mRNA (29), and imipramine decreases tyrosine hydroxylase mRNA in the locus ceruleus (30). In rats, however, the levels of mRNAs encoding serotonergic receptors, their synthetic enzymes, and the 5-HT transporter are not affected by up to 1 month of treatment with tricyclic or SSRI antidepressants (31). Still, the high brain tissue levels of clomipramine rapidly achieved by intravenous pulse loading may more strongly affect the expression of genes involved in obsessive-compulsive disorder's pathophysiology than do the brain levels associated with standard oral dosing.

Larger-scale, double-blind trials are needed to confirm our observations regarding the effects of intrave-

nous clomipramine pulse loading. To examine further the possible relationship between therapeutic response and plasma clomipramine levels, peak and subsequent plasma levels of clomipramine, 8-OH clomipramine (32), desmethylclomipramine, and 8-OH desmethylclomipramine should be obtained for all patients. If our therapeutic results are confirmed, then intravenous clomipramine pulse loading would be a valuable new treatment for obsessive-compulsive disorder. First, this method appears to save months of waiting to see whether clomipramine will be effective, since those who ultimately benefit almost always experience substantial therapeutic response within 5 days of the second infusion. Second, patients unresponsive to oral clomipramine and other SSRIs seem to have about a 50% chance of responding to intravenous clomipramine pulse loading. Third, if patients rapidly improve after two intravenous infusions, their motivation to cooperate with further treatment would be greatly enhanced.

Since some patients have difficulty tolerating oral clomipramine (3), future research might profitably investigate whether a response to intravenous clomipramine pulse loading can be maintained by oral doses of SSRIs with different side effect profiles.

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