Antidepressant Pharmacotherapy and the Treatment of Depression in Patients With Severe Traumatic Brain Injury: A Controlled, Prospective Study

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Background: Untreated or poorly treated depression in patients who suffer from traumatic brain injury can result in greater functional disability and prolonged or ineffective hospital and rehabilitation stays. Literature available on the pharmacologic treatment of depression after traumatic brain injury is scarce. This study investigated in a controlled and prospective manner the use of desipramine, a tricyclic antidepressant, in a series of patients with severe traumatic brain injury.

Method: Ten patients with severe traumatic brain injury and long-standing depression, as diagnosed by DSM-III-R criteria, were admitted to the study because of the intention to be treated with antidepressants. They were randomly assigned to blindly start on either desipramine treatment (N = 6) or placebo lead-in (N = 4). Patients starting with desipramine stayed on that drug; patients starting with placebo lead-in were blindly crossed over to desipramine after 1 month if there was no significant improvement demonstrated by DSM-III-R criteria. All rating clinicians, physicians, and patients were blind to actual treatment and any ratings data. DSM-III-R evaluations were done monthly. An affect/mood scale was done every 2 weeks.

Results: Of all patients evaluable using the DSM-III-R, 6 (86%) of 7 demonstrated resolution of depression and depressed mood during desipramine treatment. (Three received desipramine throughout the study; 3 others started taking placebo and crossed over to desipramine.) One patient refused evaluation on DSM-III-R throughout; 2 patients, both on desipramine, dropped out because of adverse effects (seizure, mania). In addition, there was statistically significant ($p = .001$) improvement over time and different rates of improvement over time in the treated and untreated groups for the affect/mood scale data.

Conclusion: Results from this small study, utilizing a blinded, placebo lead-in design appear to (1) demonstrate the clinically significant effectiveness of desipramine in treating long-standing depression in a series of patients with severe traumatic brain injury, as rated with DSM-III-R criteria; (2) show statistically significant improvement on the affect/mood scale data, favoring the treated versus untreated (placebo lead-in) group.

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As a major health problem in the United States, traumatic brain injury occurs at a rate of 2 million cases yearly, of which 500,000 require hospitalization and 80,000 develop long-term sequelae.[1] The vast majority of patients are young adults who require intensive rehabilitation because of physical and mental changes. It is largely the nonphysical processes (emotional, cognitive, and behavioral) that create impediments to rehabilitation and are most difficult to treat. Because of slow and tedious progress in coping with and adapting to these changes, patients may become depressed. Additionally, there is now convincing evidence for the role of neuroanatomical injury site on predisposition toward a neurologic or biochemically mediated depression.[2]

Most studies examining the incidence of major depression after traumatic brain injury report occurrences ranging from 19% to 55%, numbers very similar to those for depression in patients with stroke.[2–7] Taken together, the various studies imply both a pervasiveness in the occurrence of depression and what appears to be, in many patients, a prolonged course of depressive illness in this population.

Available literature on the treatment of depression after traumatic brain injury is scarce; studies are generally uncontrolled and have mixed results.[8–10] The case report of Ross and Rush,[11] in which nortriptyline was used, however, demonstrated promising results of a tricyclic antidepressant.

In this report, we present the results of a modified double-blind, placebo lead-in trial of desipramine in

Table 1. Patient Characteristics

Patient	Age (y)	Sex	Source of Injury	Time From Injury to Study Entrance (y)	Premorbid Psychiatric or Family History?	Current Psychoactive Medications	Previous Psychoactive Medications
1	23	M	Motorcycle accident	2.5	No	None	Buspirone, methylphenidate, carbidopa-levodopa, bromocriptine
2	29	M	Pedestrian	1.5	No	None	Methylphenidate, buspirone
3	22	M	Motor vehicle accident	2.5	No	None	Amantadine, amitriptyline
4	43	M	Airplane crash	0.5	No	Methylphenidate, carbamazepine	None
5	29	M	Fall	2	No	Dextroamphetamine	Methylphenidate, carbidopa-levodopa, bromocriptine
6	28	M	Assault	1	Yes[a]	Carbamazepine	Carbidopa-levodopa, methylphenidate, bromocriptine
7	25	F	Motor vehicle accident	2	No	Methylphenidate, carbamazepine	Carbidopa-levodopa
8	43	F	Motor vehicle accident	1	Yes[b]	None	Amitriptyline
9	43	F	Motor vehicle accident	1	No	Alprazolam	None
10	37	M	Motorcycle accident	1	Yes[a]	Methylphenidate	Fluoxetine

[a]Cocaine and/or alcohol abuse.
[b]Treatment with diazepam and amitriptyline for 4 years prior to injury.

patients with severe traumatic brain injury. Our study goal was to replicate the efficacy we had seemingly experienced clinically with desipramine, a strongly noradrenergic tricyclic antidepressant, and to measure this in a blinded, controlled manner utilizing DSM-III-R (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*) criteria and the affect/mood scale as developed by Robinson and Szetela,[12] neither of which had been confirmed for use in this population at the start of this study. (More recently, Jorge and colleagues[13] demonstrated the effectiveness of DSM-III-R in both establishing the diagnosis of depression and following depression over time in patients with traumatic brain injury.)

METHOD

Study Population

Over the course of a 1½-year period, 10 patients with severe traumatic brain injury were referred to the study by their attending physicians, because of an intention to treat with antidepressants due to suspected depression, with the understanding that the patients would be at the facility long enough to participate in the study. All patients had a minimal period of posttraumatic amnesia of 1 week and were in the range of cognitive function levels 4 to 6 on the Rancho Los Amigos Head-Injury Scale.[14] The intention-to-treat indication was established so as to mimic actual clinical practice as closely as possible. All patients had been in a state of depression for at least 2 months and often longer, prior to the study entrance. Informed consent was obtained prior to study entrance. Individual patient data and medication history are presented in Table 1.

Study Design

All 10 patients admitted to the study were examined for electrocardiogram abnormalities and seizure histories as might be clinically recommended before treatment with tricyclic antidepressants (TCAs). Concurrent psychoactive medications were allowed, but no dosage adjustments could be made except for anticonvulsant drugs. Baseline screening involved psychiatric evaluation for depression utilizing DSM-III-R criteria by the study neuropsychiatrist (A.B.J.), and affect/mood scale[12] evaluations by treating clinicians and a study team member. Relevant laboratory data including thyroid function tests and serum drug concentrations were obtained.

Patients were randomly assigned to start with desipramine or placebo lead-in. Because of ethical considerations and anticipated lagtime prior to TCA response, the placebo period was set at 1 month, unless there was a consensus of improvement in the first month. After 1 month of placebo, if there was no significant clinical improvement as noted on DSM-III-R (see below), desipramine was blindly introduced.

Desipramine was increased to 150 mg/day after 1 month; then to the 150- to 300-mg/day range at 2 months and beyond. However, each change of dose throughout the study was dependent on results of serum concentrations, side effect monitoring, and blinded clinical evaluations.

The DSM-III-R is a nine-symptom checklist, and we tallied the number of symptoms at each evaluation to examine for changes. Improvement on DSM-III-R was defined as a ≥ 50% reduction in number of symptoms. Neither the treating staff nor the study evaluator were aware of each other's findings throughout the study. All were blinded to actual treatment during the study. Patients

Table 2. DSM-III-R and Affect/Mood Scale Scores

Initial Study Treatment	DSM-III-R[a] Baseline	DSM-III-R[a] 1-Month	DSM-III-R[a] Final	Affect/Mood Scale[b] Baseline	Affect/Mood Scale[b] 1-Month	Affect/Mood Scale[b] Final	Length of Treatment (mo)
Placebo							
Patient 3	DM + 3	DM + 3	DM + 3	2.6	2.5	2.5	3
Patient 5	DM + 6	DM + 3	0	1.7	1.6	1.5	3
Patient 7	DM + 5	DM + 3	1	1.6	1.6	1.3	3
Patient 8	3	DM + 3	0	2.2	2.2	1.2	2.5
Desipramine							
Patient 1[c]	DM + 5	DM + 2	…	Not available	…	…	1.5
Patient 2	DM + 8	DM + 3	0	Not available	Not available	Not available	2
Patient 4	DM + 8	DM + 6	0	2.1	1.5	1.3	2
Patient 6	Not available	Not available	0	2.0	1.6	1.6	2.0
Patient 9[c]	DM + 5	…	…	2.0	…	…	…
Patient 10	DM + 3	DM + 2	0	2.2	1.8	1.5	3

[a]DSM-III-R data represent the number of actual symptoms reported/elicited from patient. "DM" refers to "depressed mood" and is a separate symptom of DSM-III-R, but in addition to other symptoms, (see text).
[b]Affect/mood scale data represent the mean total scores of all reporting disciplines (nursing, speech/language, occupational therapy, physical therapy) utilizing a 4-point scale (see text).
[c]Study dropout.

starting on desipramine treatment continued with the drug for the study duration. Thus placebo patients, in essence, served as their own controls.

The affect/mood scale was developed by Robinson and Szetela as a nurses' rating scale for their study of depression in patients with stroke.[12] It is a 25-item scale divided into three separate sections including verbal communication, observations of patient behaviors, and observations of patient mood, with ratings ranging from 1 (not at all) to 4 (to an extreme degree). The scale was demonstrated to be reliable and valid in patients with stroke. For the purpose of reliability in this study, the same treating therapist from each discipline (speech and language, physical therapy, occupational therapy, nursing) evaluated the patient throughout the study. Combined mean scores were obtained for each evaluation and, in a manner similar to that used for the DSM-III-R, we compared the total mean score at baseline, monthly, and end of study.

Any adverse effects were reported by therapists in the routinely scheduled (every other week) interdisciplinary rounds format or by the attending physician, resident physician, patient's nurse, or study neuropsychiatrist.

RESULTS

DSM-III-R data and affect/mood scale scores for all 10 patients are reported in Table 2. Because of the recent study by Jorge and colleagues[13] in which they found that "there were almost no patients with depressive symptoms without a depressed mood," we decided by post hoc analysis to list the symptom of depressed mood separately, but in addition to other symptoms of the DSM-III-R, in Table 2. Six patients were started with desipramine and four with placebo. There were no outstanding differences between patients starting with placebo or those starting on desipramine treatment in terms of mean age (30 vs. 33 years), time from injury to study entrance (1.9 vs. 1.3 years), or previous psychiatric history (25% vs. 33% of patients). All 4 patients starting with placebo were blindly crossed over to desipramine after 1 month because of lack of substantial improvement on DSM-III-R.

DSM-III-R Evaluations

Three of 6 patients starting with desipramine (Patients 2, 4, 10) and 3 of 4 patients starting with placebo (Patients 5, 7, 8) demonstrated nearly complete resolution of depression on desipramine. Although Patients 1 and 2 had a 50% or greater reduction in depressive symptoms within the first month of active treatment with desipramine, overall response was in accordance with the usual 4- to 8-week time course of tricyclic antidepressants. Only Patient 3 demonstrated no improvement on DSM-III-R throughout the study. Patient 1 had a 50% reduction in symptoms at 1 month (with desipramine), but was withdrawn from the study because of seizure occurrence. Patient 9 (desipramine) was withdrawn owing to development of mania, and Patient 6 refused all interviews on DSM-III-R. We attempted a repeated measures analysis of variance (ANOVA) of DSM-III-R change scores for patients from baseline to 1 month, 1 month to the end, and total change scores. These data showed that patients starting on desipramine treatment had greater symptom reduction at each point of comparison, but none of the differences were statistically significant due to the small sample size.

Affect/Mood Scales

Complete information was available for affect/mood scale data on 3 patients in the desipramine group (Patients 4, 6, 10) and 4 patients starting with placebo (Patients 3, 5, 7, 8). Patient 9 was a study dropout while Patients 1 and 2 had multiple therapists, which rendered the data unreliable.

Figure 1. Individual Affect/Mood Scale Scores

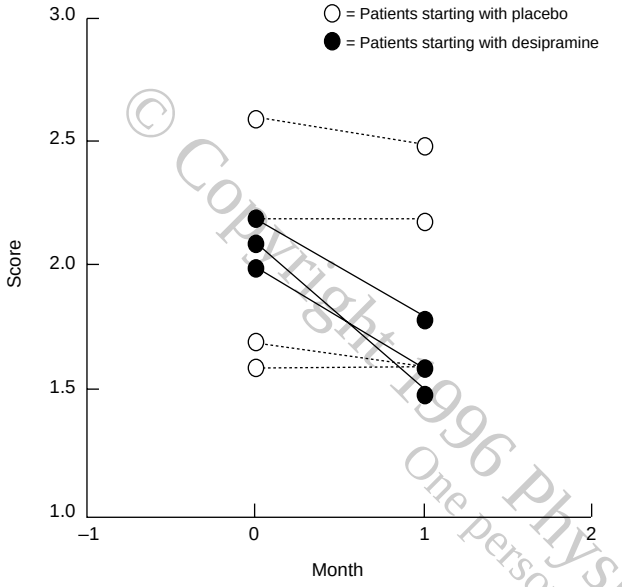
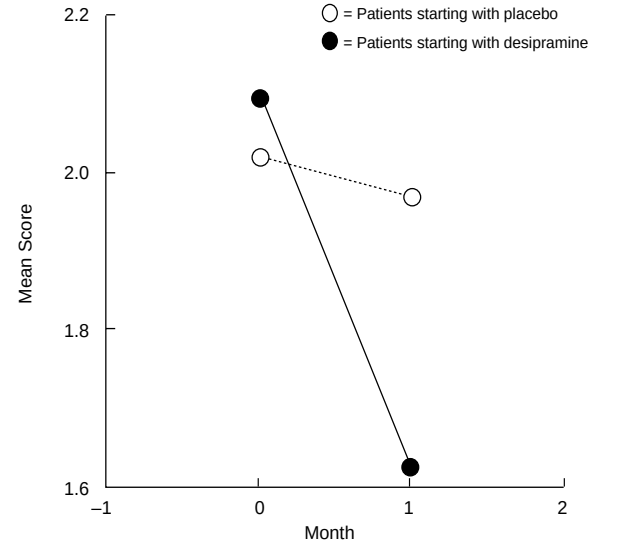


Figure 2. Mean Affect/Mood Scale Scores



We examined the affect/mood scale data in a similar manner as the DSM-III-R results, by utilizing a repeated measures ANOVA. There was significant ($p = .001$) improvement over time overall and different rates of improvement over time in patients starting on desipramine treatment rather than placebo. These data are presented more clearly in Figures 1 and 2 in which both the individual patient changes from baseline to 1 month and the mean group changes from baseline to 1 month are graphically displayed.

Response to desipramine. Five of the 6 patients with resolution of depression on DSM-III-R attained "therapeutic" desipramine concentrations in the range of 100 to 300 μg/mL at doses ranging from 150 to 300 mg/day. Only Patient 4 had resolution of depression on DSM-III-R at what might be considered a subtherapeutic concentration of 80 μg/mL, despite a final desipramine dose of 300 mg/day, (due to a suspected drug interaction with carbamazepine[15]). One patient (Patient 3) did not respond to desipramine throughout the study, despite a final serum concentration of 240 μg/mL.

Side Effects

Generally, few side effects were reported, albeit some significant ones. In addition to the serious seizure suffered by Patient 1, Patient 5 suffered minor seizure activity during desipramine treatment, but continued in the study without further problems or anticonvulsant treatment. Patient 9 was withdrawn because of the occurrence of severe mania within 2 weeks of desipramine initiation; Patient 6 developed action tremors at 200 mg/day of desipramine, which were resolved when the dose was lowered to 150 mg/day.

DISCUSSION

This study is among the first to systematically demonstrate the effectiveness of a standard antidepressant treatment, desipramine, for patients with severe traumatic brain injury in a controlled and prospective manner. The study findings would appear to lend support to the conclusions of Jorge and colleagues[13] in which DSM-III-R criteria were demonstrated to be a sensitive and reliable diagnostic measure of depression in patients with traumatic brain injury. Post hoc analysis of the DSM-III-R data also tends to support another contention of Jorge et al. in that nearly all patients referred to the study for treatment of depression had depressed mood. In the current study, 6 (86%) of 7 patients with long-standing depression who were able to finish the study and be evaluated on DSM-III-R had resolution of nearly all depressive symptoms, including depressed mood. This is comparable with, although somewhat greater than, the 70% to 75% of functionally depressed patients who might normally respond to antidepressant treatment and, as such, may be an artifact of the small study sample.

The affect/mood scale data surprisingly demonstrated statistically significant ($p = .001$) improvement at 1 month for patients starting desipramine rather than placebo. While the validity of the scale remains in question for patients with traumatic brain injury, the results presented here—even in this small sample size—may warrant further examination of the scale in this population.

Some methodological issues are apparent and require discussion. First, the placebo period was 1 month in dura-

tion, with crossover to desipramine if there was no significant improvement. This perhaps makes the study less strong than if there had been one treatment group and one placebo group throughout, as was done by Lipsey and colleagues[16] in their initial study of antidepressants and poststroke depression. While we acknowledge this shortcoming, it was our feeling that the suggestive evidence from accumulating literature on treatment of poststroke depression made a prolonged placebo period ethically untenable.

One problem of our approach is the question of possible placebo response within the placebo group, which could then carry over into the treatment section. First, abrupt response to placebo in antidepressant trials (of non-brain-injured patients) most often occurs within 2 weeks of treatment and rarely persists.[17,18] Thus, the minor improvement on DSM-III-R at 1 month in 2 patients started on desipramine treatment is not consistent with a placebo response.

Moreover, the finding that the affect/mood scale data demonstrated statistically significant ($p = .001$) differences in the first month favorable to patients starting with desipramine rather than those starting with placebo is at odds with the possibility of a placebo response. The issue of spontaneous response of depression after traumatic brain injury appears to be an unlikely occurrence. All patients referred to the study had persistent depression that had not been alleviated by other psychotherapeutic drugs.

The number of desipramine-related side effects was small but potentially serious. Two patients suffered seizures during desipramine treatment, 1 of which was serious enough to cause drug discontinuation, even though the patient improved while on desipramine treatment (Patient 1). This patient had no prior seizure history. One other patient had a minor seizure of short duration that was self-limiting and did not recur, despite continued treatment with desipramine. Similarly, there was no prior seizure history. We have previously reported on the association of tricyclic antidepressants and seizures in patients with traumatic brain injury.[19] It is important to note that although this is a potentially serious problem, the occurrence of a seizure is often not clinically significant and may present after administration of other types of antidepressants as well, as was the case for Patient 1 who later seized on fluoxetine treatment.[20] Additionally, the subgroup of traumatic brain injury patients most susceptible to TCA-reduced seizure threshold appears to be the functionally lower level (Rancho Los Amigos level 2 or 3) patients with the most severe neurologic impairments.[19]

Response to desipramine can occur within the first month of treatment, especially for symptoms such as irritability or anergia. However, resolution of depressed mood in this study appeared to require between 1 to 2 months of treatment, with desipramine doses, sufficient enough to provide serum concentrations of 100 to 300 μg/mL, depending on individual response.[21]

In summary, we believe this study provides support for the effectiveness of desipramine as an antidepressant treatment of patients with severe traumatic brain injury. It is a preferable choice among tricyclics because of its nonsedating and sometimes stimulating properties and relative lack of serious anticholinergic side effects. However, like most antidepressants, it may lower seizure threshold and must be monitored for this. Thus at this time, support for desipramine as a first choice in post–traumatic brain injury depression must be carefully weighed against newer agents, such as serotonin selective reuptake inhibitors, for which the reported generally advantageous side effect profiles must be balanced by knowledge of unproven antidepressant efficacy in this population as well as by a lack of long-term data, even as reports of epileptogenic effects accumulate.[22] Moreover, experimentally and experientially, there may be differences in response and recovery of patients that favor noradrenergic agents (TCAs) rather than serotonergic agents, which make the tentative conclusions of this paper important in that, because of an absence of literature in this area, it demonstrates desipramine to be a significant treatment for the pervasive and persistent problem of depression in patients with traumatic brain injury.[23,24] Further studies on these important issues will continue to be necessary.

Drug names: alprazolam (Xanax), amantadine (Symmetrel), amitriptyline (Elavil and others), bromocriptine (Parlodel), buspirone (BuSpar), carbamazepine (Tegretol and others), carbidopa-levodopa (Sinemet), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), methylphenidate (Ritalin), nortriptyline (Pamelor and others).

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