Antidepressant Therapy After Stroke
A Double-blind Trial

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Twenty-seven inpatients participating in a stroke rehabilitation program were randomized to receive either placebo or trazodone hydrochloride (Desyrel) beginning a mean (± SEM) of 44 ± 4 days after stroke. The target dosage was 200 mg/d. Patients with either a clinical diagnosis of depression or abnormal Zung depression scores showed a consistent trend toward greater improvement in Barthel activities of daily living (ADL) scores with trazodone than with placebo. An abnormal dexamethasone suppression test result was associated with significant improvement in the Barthel ADL scores of patients receiving trazodone (38 ± 6 vs 20 ± 6 for placebo). Patients with stroke and evidence of depression are therefore likely to benefit from treatment with trazodone.

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The prevalence of depression after major hemispheric stroke is from 30% to 50%. There are only anecdotal reports concerning the benefit of antidepressant drug therapy on stroke rehabilitation outcomes. There have been decreased levels of norepinephrine and serotonin in the locus ceruleus and in noninfarcted regions of the ipsilateral hemisphere. If one believes the monoamine theory of depression, then pharmacologic intervention with antidepressants would seem to be a logical way of augmenting norepinephrine and serotonin neurotransmitter systems. Newer antidepressants with relatively less effect on cardiac conduction and less anticholinergic activity, such as trazodone hydrochloride (Desyrel), would seem to be ideal drugs for the geriatric stroke population with its high prevalence of cardiac disease and poststroke urinary incontinence.

Because of the difficulty of diagnosing depression in patients with varied neuropsychological deficits, we decided to study patients both with and without evidence of depression, as indicated by any one of three criteria: (1) clinical diagnosis of depression, (2) abnormal Zung depression score, and (3) abnormal dexamethasone suppression test (DST) results.

The present study was designed to test the effect of trazodone antidepressant drug therapy on stroke rehabilitation outcome. We chose to assess behavior as measured by the Barthel ADL Scale rather than severity of depression as our independent variable. We have observed that depressed patients with stroke are withdrawn, apathetic, disinterested in their self-care, and poorly motivated to progress in their rehabilitation program. Scoring self-care, transfer, and ambulation behaviors in aphasic, apraxic, anosognosic patients with stroke is, in our opinion, a more objective way to measure patient motivation than are serial Hamilton or Zung depression scores.

PATIENTS AND METHODS
Sequentially admitted inpatients in a stroke rehabilitation program were solicited for participation in the study. Patients were assessed during the second week of their rehabilitation hospital stay. Patients both with and without evidence of depression were enrolled in the study. Patients taking antiarrhythmic medications or those with a history of myocardial infarction within the preceding month were excluded from the study. Written informed consent was obtained from the patient or next of kin in each case. Patients were assigned to either treatment or placebo groups according to a table of random numbers.

Trazodone hydrochloride (50 mg) or placebo in an identical capsule was administered orally by the nursing staff, with dosage increments of one capsule every three days to a target dosage of 200 mg each evening for the remainder of the rehabilitation hospitalization. Patients were assessed daily for side effects. If the
attending physician, unaware of treatment group assignment, noted signs or symptoms possibly due to trazodone, the dosage was either lowered or held constant for an additional three days before the next scheduled dose increment. If the attending physician, patient, or family noted unacceptable side effects, even with the lowest dosage (one capsule each evening), the study was discontinued.

The diagnosis of stroke was based on the clinical history and the findings of neurologic examination and computed tomography. The diagnosis of depression was based on Diagnostic and Statistical Manual of Mental Disorders, ed 3 criteria. Patients were said to be depressed if they fulfilled criteria for either “major depression” or “dysthymic disorder.”

Patients were scored on the Zung Depression Scale. Initially the Zung self-reporting depression score sheets were given to the patients, but it was found that they were usually unable to persist at the task and complete them. Patients were therefore interviewed and asked to respond to each item on the self-rated depression scale. The scores for aphasic patients were based on observation of their daily behavior. Scores range from 25% to 100%, with scores of 50% or greater indicating significant depressive symptomatology. Interrater reliability for scoring the Zung Depression Scale was assessed by calculating an \( F \) statistic for scores generated by three raters examining the same 12 patients. There were no significant differences among the three raters (\( F_{2,22} = 2.22, P = .13 \)).

Patients were also scored on the Barthel ADL Scale every two weeks during their rehabilitation program. This scale ranges from 0 to 100, with 100 representing self-care independence. The test-retest reliability coefficient for repeated Barthel scores on nine patients by the same raters after a three-day interval was .96 (\( P < .001 \)).

The DST response was assessed by giving 1 mg of dexamethasone orally at 11 PM. The following day at 8 AM and at 4 PM, blood was obtained for cortisol determinations. The DST result was said to be abnormal if either the 8 AM or the 4 PM blood cortisol level was greater than 5 µg/dL (140 nmol/L). Standardization of the DST results in our laboratory for normal elderly controls and for patients with stroke has been previously published.

The diagnosis of depression, Zung depression scores, DST results, and Barthel ADL scores were all recorded without knowledge of the patient's treatment group.

Because of the small sample size, nonparametric techniques were chosen for data analysis. Two-by-two contingency table comparisons between trazodone and placebo groups were assessed by means of Fisher's Exact Test. Interval scale data comparisons between the two groups were assessed by means of the Wilcoxon rank sum test.

**RESULTS**

Table 1 shows that there were no significant initial differences for the two treatment groups with respect to age, sex, interval since stroke, side of lesion, or initial Zung depression scores. The initial Barthel ADL scores were noted to be significantly lower for trazodone-treated patients than for placebo-treated controls in the subgroup with abnormal DST results. The possible effect of this bias on treatment response is discussed below. Data are presented separately for each of the clinical markers for depression used in this study.

Table 2 presents the mean improvement in Barthel ADL scores for patients receiving trazodone vs placebo. Results are shown separately for patients with a clinical diagnosis of depression, patients with abnormal Zung depression scores, patients with abnormal DST results, and patients without evidence of depression. There is a trend for those with either a clinical diagnosis of depression or abnormal Zung depression scores to improve more with trazodone than with placebo. The difference, however, does not reach statistical significance. Patients with abnormal DST results did improve significantly more with trazodone than with placebo. The change in Barthel ADL scores did not differ significantly between patients with left hemisphere lesions and those with right hemisphere lesions.

The mean duration of treatment (±SEM) was 22 ± 6 days for the trazodone group vs 25 ± 4 days for the placebo group. Two patients in the trazodone group and three in the placebo group were able to reach and maintain the target dose of four capsules per day (200 mg/d of trazodone hydrochloride or placebo). The study was discontinued because of perceived side effects in six patients in the placebo group (in four because of sedation, in one because of nausea, and in one because of lightheadedness) and in six patients in the trazodone group (in four because of sedation, in one because of eye discomfort, and in one aphasic patient who refused it for
unknown reasons). The prevalence of side effects did not differ significantly for patients with any of the three clinical markers for depression listed in Table 2.

The small number of patients treated does not allow for the statistical analysis of dose-response data.

**COMMENT**

The clinical diagnosis of depression in the stroke population is difficult. Anosognosia, pseudobulbar emotional lability, aphasia, dysprosody with impairment of verbal and nonverbal emotional expression, and the effect of a major illness on vegetative functions all cloud the diagnostic picture. Previous studies have shown that the DST response is correlated with the clinical assessment of depression in the stroke population. It is objective, easily determined, and reproducible.

Our data show a consistent trend toward greater improvement in Barthel ADL scores for patients with evidence of depression who received trazodone. The DST result, however, was the only marker for depression that reached statistical significance as an indicator of response to trazodone. All seven patients with abnormal DST results treated with trazodone were also thought to be clinically depressed. Four of nine patients with abnormal DST results receiving placebo were thought to be clinically depressed. The DST response may define a subpopulation of stroke patients most likely to benefit from antidepressant therapy with trazodone. There appears to be little risk of side effects, as those were seen equally frequently in both treatment and placebo groups.

Reference to Table 1 shows that among the subgroup with abnormal DST results, trazodone-treated patients had significantly lower initial Barthel ADL scores than those receiving placebo. To determine the effect of this bias might have on treatment outcome, we calculated the Pearson correlation coefficient for initial Barthel ADL score vs final Barthel ADL score in the 13 patients receiving placebo. The correlation coefficient is 0.82 ($P < .001$), indicating that—in patients without active treatment—the lower the initial Barthel ADL score, the poorer the outcome. Thus, if there is any bias affecting the trazodone-treated group it would reduce rather than augment the improvement noted.

An earlier study from our center showed that an abnormal DST result without subsequent antidepressant drug therapy was not a predictor of rehabilitation outcome. The present study confirms our earlier observation. Patients with abnormal DST results who received placebo showed improvements in their Barthel ADL scores that did not differ significantly from those shown by patients with normal DST results who received placebo ($20 \pm 6$ vs $26 \pm 8$, respectively). With active treatment intervention, however, those with abnormal DST results showed significantly greater improvement in Barthel ADL scores than did those receiving placebo (Table 2).

We are aware of only one other controlled trial of antidepressants in the stroke population. In this study by Lipsey et al, no improvement in ADL scores was seen for the treatment group (nortriptyline) vs the placebo group. Both groups, however, were studied more than four months after stroke. Functional recovery has usually begun to plateau by this time. Our data indicate that antidepressant drug therapy for depression in the subacute poststroke phase (two weeks to three months after stroke) may enhance rehabilitation outcome. The presumed mechanism is increased patient motivation and more active participation in the rehabilitation program.

**References**


