Combined Pharmacotherapy and Psychotherapy in the Acute and Continuation Treatment of Elderly Patients With Recurrent Major Depression: A Preliminary Report

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Objective: The authors examined the rate of response to the combination of nortriptyline and interpersonal psychotherapy for acute and continuation treatment of elderly patients with recurrent major depression. Method: The subjects were 73 elderly patients, 61 of whom completed treatment. Nortriptyline steady-state blood levels were maintained at 80–120 ng/ml, and interpersonal psychotherapy was administered weekly for 9.1 weeks (median) of acute therapy and was decreased from biweekly to triweekly during 16 weeks of continuation therapy. During acute treatment nonresponsive patients also received brief adjunctive pharmacotherapy with lithium or perphenazine. Results: Of the 61 subjects given adequate trials of nortriptyline and interpersonal psychotherapy, 48 (78.7%) achieved full remission (Hamilton depression rating of 10 or lower over 16 weeks of continuation therapy), 10 patients (16.4%) did not respond (Hamilton rating never below 15), and three achieved only partial remission (Hamilton rating of 11–14). Early versus late onset was not associated with a difference in response rate. During the placebo-controlled, double-blind transition to maintenance therapy, 19 (76.0%) of the 25 patients randomly assigned to placebo maintenance conditions showed continued recovery and six relapsed. None of the 24 patients assigned to nortriptyline conditions relapsed. Conclusions: Use of nortriptyline plus interpersonal psychotherapy for 9.1 weeks (median) of acute and 16 weeks of continuation therapy appears to be associated with good response and relatively low attrition but about a 25% chance of relapse during double-blind discontinuation of nortriptyline. These data require confirmation in a controlled clinical trial of acute and continuation therapy. (Am J Psychiatry 1992; 149:1687–1692)

The 1991 National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Treatment of Depression in Late Life (1) highlighted the need for clinical trials assessing the efficacy of combination pharmacotherapy and psychotherapy in the acute, continuation, and maintenance treatment of elderly patients with major depression, particularly those with recurrent illness. The published data are based on trials assessing the efficacy of a single intervention—either drug alone or psychotherapy alone but not both. Treatment success rates have been around 50%–70% in both drug (2, 3) and psychotherapy (4, 5) controlled trials enrolling older subjects with major depression, but many of these subjects were not truly elderly and most were outpatients. Also, most of these studies were relatively brief trials (generally 7 weeks or less) of acute therapy and the reports contain little information about the stability of therapeutic response during continuation therapy or about continued remission after drug discontinuation (6).
Because of the need for information regarding the efficacy of combined therapy both acutely and during continuation therapy, we report here the first 2 years of experience in the University of Pittsburgh’s Maintenance Therapies in Late-Life Depression study. The primary objective of the study is to assess the efficacy of maintenance nortriptyline and interpersonal psychotherapy (7) singly and in combination, under randomized, double-blind, placebo-controlled conditions, with respect to maintenance of recovery over a 3-year period after open-trial acute and continuation treatment of the index episode. Treatment of the index episode involves combined therapy with both nortriptyline and interpersonal psychotherapy under open-trial conditions. The investigators’ choice of combination therapy for the nonexperimental acute and continuation phases of the protocol (reported here) reflects the expectation that such an approach is likely to maximize the number of patients available for the subsequent experimental maintenance phase of the protocol. It also reduces the probability of bias on the part of patients and clinicians as to which treatment is likely to be most efficacious in the maintenance of recovery. It was required that a patient achieve remission and remain well for 16 weeks of continuation therapy (with both modalities) before random assignment to one of four maintenance therapies (medication clinic with placebo, medication clinic with nortriptyline, interpersonal psychotherapy plus placebo, and interpersonal psychotherapy plus nortriptyline). The investigators initially projected that 65% of the patients entering the protocol would meet the criteria for randomization, after remission of the index episode.

We provide in this report preliminary data on treatment success and stability of response, treatment failure, and attrition during combination acute and continuation therapy. We also report the rates of relapse during transition to maintenance treatment, where one-half of the patients are randomly assigned to placebo conditions under double-blind discontinuation conditions. We emphasize that the study is ongoing, with intake now at the halfway point, and that the data reported here are from an open trial complemented by placebo-controlled, double-blind discontinuation of nortriptyline. In light of the need for information about combination therapy identified by the 1991 NIH consensus conference (1), however, we believe that the results are sufficiently promising and instructive to warrant preliminary communication.

METHOD

Subjects

During the first 24 months of the study, 73 patients 60–80 years old (mean=67.5, SD=5.8) entered the protocol. The female/male ratio was 53/20; seven (9.6%) of the subjects were black, and 66 (90.4%) were white. The marital status distribution was as follows: widowed, N=29 (39.7%); married, N=27 (37.0%); divorced, N=9 (12.3%); never married, N=5 (6.8%); remarried, N=1 (1.4%). The mean education level was 11.8 years (SD=2.4).

Approximately 48% of the subjects responded to media announcements, and 52% were referred through traditional medical channels. Approximately 243 subjects were screened in face-to-face interviews to yield the current group of 73 (a 30% yield). The patients were required to be experiencing at least the second lifetime episode of major depression (nonbipolar, nonendogenous), to have a score on the 17-item Hamilton Rating Scale for Depression (8) of at least 17 after 14 days without psychotropic drugs, and to have had an interepisode wellness interval of at least 2 months but no longer than 2.5 years. Diagnoses were made by using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (9) in an interview conducted by trained master’s level psychiatric nurses and were confirmed in an independent interview by a senior faculty psychiatrist. Fourteen patients (19.2%) were diagnosed as having nonendogenous depression, 16 (21.9%) had probable diagnoses of endogenous depression, and 43 (58.9%) had definite diagnoses of endogenous depression. Twenty (27.4%) of the 73 patients reported that the first episode of major depression had occurred at age 60 or later (“late onset”), and 53 (72.6%) reported an earlier onset; the mean age at first episode was 47.3 years (SD=17.0). A review of past SADS-L diagnoses (definite) indicated the following rates: hypomania, 1.4% (N=1); panic disorder, 2.7% (N=2); generalized anxiety disorder, 5.5% (N=4); Briquet’s disorder, 2.7% (N=2); alcoholism, 4.1% (N=3); drug use disorder, 1.4% (N=1); and phobic disorder, 2.7% (N=2). No patients met the criteria for cyclothymic personality, labile personality, antisocial personality, obsessive-compulsive disorder, or any psychotic disorders.

Forty-two percent of the patients (N=31) had major psychosocial problems requiring social service intervention. Twenty-five percent (N=18) required inpatient hospitalization during the acute therapy of the index episode, and 11.0% (N=8) had histories of suicide attempts. The median number of prior episodes of major depression was three. Upon entry into the protocol the 73 patients had a mean Hamilton depression rating of 22.3 (SD=3.8), a Beck Depression Inventory (10) score of 24.2 (SD=9.9), and a Global Assessment Scale (11) score of 55.7 (SD=5.2). The mean duration of the index episode was 39.9 weeks (SD=35.8).

Almost all patients entering the protocol were under concurrent medical surveillance for chronic but stable (nonprogressive) medical disorders that did not contraindicate nortriptyline or require medications known to cause depression. Review of current medical status indicated the following frequencies of medical problems: cardiac, 41.1% (N=30); musculoskeletal, 39.7% (N=29); osteoarthritis, 30.1%; lower gastrointestinal, 32.9% (N=24); diverticulitis, 9.6%; upper gastrointestinal, 24.7% (N=18); bilateral hernia, 17.8%; genitalourinary, 39.7% (N=29); benign prostatic hypertrophy, 11.0%; vascular, 32.9% (N=24); hypertension, 20.5%; eyes, ears, nose,
and throat, 30.1% (N=22; cataracts, 12.3%; glaucoma, 5.5%); endocrine, 21.9% (N=16; thyroid, 9.6%; diabetes mellitus, 6.8%); neurologic (e.g., laminectomy, neurofibromatosis, and carpal tunnel syndrome), 13.7% (N=10); pulmonary, 15.1% (N=11; chronic obstructive pulmonary disease, 5.5%). Similarly, review of concurrent nonpsychotropic medications indicated the following rates of use: anti-inflammatory, 19.2% (N=14); endocrine, 13.7% (N=10); calcium channel blockers, 12.3% (N=9); diuretics, 15.1% (N=11); hormone replacements, 5.3% (N=4); β blockers, 6.8% (N=5); H2 blockers, 5.5% (N=4); eye medications, 4.1% (N=3); theophylline, 1.4% (N=1).

Procedure

For the patients beginning treatment on an outpatient basis, acute therapy of the index episode consisted of combination nortriptyline and interpersonal psychotherapy, with weekly visits to the outpatient research clinic. Nortriptyline was prescribed by faculty psychiatrists in doses sufficient to produce a steady-state blood level of 80–120 ng/ml. The patients were instructed to take the full daily dose of nortriptyline at bedtime, and blood samples for determination of nortriptyline levels were taken 12–16 hours later. The blood levels were monitored weekly during acute therapy and biweekly to triweekly during continuation therapy. Interpersonal psychotherapy was delivered during weekly 26-minute sessions by experienced psychotherapists trained to, and maintained at, research levels of proficiency in interpersonal psychotherapy. All therapy sessions were audiotaped, and a random sample of 20% were rated for interpersonal psychotherapy specificity. Procedures for adapting interpersonal psychotherapy to use with elderly patients have been incorporated into a manual written by several of us (E.F., C.C., S.D.L., M.D.M., and C.F.R.).

A brief course of adjunctive pharmacotherapy (4–6 weeks), i.e., lithium (0.6–1.0 mg/liter), perphenazine (4–12 mg/day), or both, was permitted if the patient had not achieved full response after 8 consecutive weeks of nortriptyline at a therapeutic steady-state level (80–120 ng/ml). After a Hamilton rating of 10 or lower was achieved, adjunctive medication was discontinued. Unless the patient maintained a Hamilton rating of 10 or lower while receiving nortriptyline (alone) plus interpersonal psychotherapy, he or she could not enter continuation therapy.

A patient entered continuation therapy after meeting two criteria: 1) a Hamilton depression rating of 10 or lower for 3 consecutive weeks and 2) a steady-state nortriptyline blood level of at least 50 ng/ml. The purpose of continuation therapy was to ensure stability of response for 16 consecutive weeks before random assignment to a maintenance therapy cell. The frequency of clinic visits decreased to every other week for the first 8 weeks of continuation therapy and then to every third week during the final 8 weeks, in anticipation of monthly visits during the 3-year experimental maintenance phase of the study.

At the end of continuation therapy, the patient was randomly assigned to one of the four maintenance treatments; there was a 50% chance of being assigned to a nortriptyline cell and a 50% chance of being assigned to a placebo condition. During the 4–6-week transition to maintenance treatment, the nortriptyline dose of the patients assigned to placebo was gradually tapered by 20%–25% weekly under double-blind conditions.

Analysis

The major outcome measure, treatment success, was defined as remission of depressive symptoms (Hamilton depression rating of 10 or lower) sustained over 16 weeks of continuation therapy, as required for random assignment to a maintenance therapy cell. Our choice of a Hamilton score of 10 or lower as indicative of remission in the elderly is consistent with the findings of Georgotas et al. (12). However, we also examined outcome by using the more stringent criterion of a mean Hamilton depression rating of 6 or less during the final two ratings (over 4 weeks) at the end of continuation therapy.

RESULTS

Attrition

Of the 73 patients enrolled, 12 (16.4%) were removed from the study during screening or acute therapy. The reasons for attrition were treatment refusal or noncompliance (N=8), intercurrent medical conditions contraindicating further use of nortriptyline (N=3), and spontaneous remission during the 2-week psychotropic-drug-free observation period before the start of acute therapy (N=1). Two additional patients were lost during continuation: one died of a myocardial infarction, and one left the study against medical advice. Thus, a total of 59 patients (80.8% of those entering the study) completed the acute and continuation trial of combination nortriptyline and interpersonal psychotherapy (at least 26 weeks of acute therapy in the case of nonresponders).

Treatment Response

Sixty-one patients (83.6% of those entering) completed acute treatment and were therefore considered to have had adequate trials. Of the 61 completers, 48 (78.7%) responded fully; an additional three patients had partial responses (Hamilton scores of 11–14). Ten of the 61 patients who completed acute treatment were nonresponders (Hamilton depression ratings of 15 or higher) after at least 26 weeks of acute treatment (mean=35.8, SD=19.4), representing a treatment failure rate of 16.4%. Thus, 65.7% of those who entered and 78.7% of those who had adequate exposures to treatment could be considered treatment responders according to a criterion of a Hamilton score of 10 or less. Ac-
TABLE 1. Treatment Characteristics and Depression Scores for Elderly Depressed Patients Who Did or Did Not Respond to Combined Nortriptyline and Interpersonal Psychotherapy

<table>
<thead>
<tr>
<th>Group and Time</th>
<th>Time From Intake (weeks) Mean SD</th>
<th>Nortriptyline Dose (mg/day) Mean SD</th>
<th>Nortriptyline Blood Level (ng/ml) Mean SD</th>
<th>Hamilton Depression Score Mean SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full and partial responders (N=51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment start</td>
<td>2.3 1.6</td>
<td>80.7 30.7</td>
<td>88.6 27.0</td>
<td>18.9 4.4</td>
</tr>
<tr>
<td>First response</td>
<td>13.3 8.0</td>
<td>83.1 35.0</td>
<td>88.7 28.5</td>
<td>6.7 2.8</td>
</tr>
<tr>
<td>Remission</td>
<td>33.6 12.4</td>
<td>63.0 32.3</td>
<td>95.7 29.0</td>
<td>22.5 4.1</td>
</tr>
<tr>
<td>Declaration of failure</td>
<td>35.8 19.4</td>
<td>9.7 29.0</td>
<td>19.7 5.3</td>
<td></td>
</tr>
</tbody>
</table>

*17-item Hamilton Rating Scale for Depression.

cording to the more stringent criterion of a Hamilton score of 6 or less, 56.2% of those who entered and 67.2% of those who received adequate trials would be considered responders (N=41).

Age at first episode (<60 or ≥60 years) was not specifically associated with rate of treatment success. Of the 20 late-onset patients, 14 (70.0%) responded fully, and of the 33 early-onset patients, 34 (64.2%) responded fully.

Among the 51 patients with full or partial responses were five patients (9.8%) who relapsed during continuation therapy (Hamilton depression rating of 17 or above) but were successfully restabilized for the 16-week period of symptomatic remission required for random assignment to a maintenance therapy cell. The 10 nonresponders included four patients who showed brief symptomatic remission but subsequently relapsed and could not be restabilized.

Of the 25 patients assigned to placebo maintenance conditions, six (24.0%) relapsed during double-blind discontinuation of nortriptyline. Three had been assigned to placebo plus maintenance interpersonal psychotherapy, and three had been assigned to placebo plus medication clinic. None of the patients assigned to continuation of full-dose nortriptyline (N=24) suffered a relapse during the double-blind 4-6-week transition to maintenance therapy (Fisher's exact test, p=0.02).

The nortriptyline doses and blood levels and the Hamilton depression scores before and during treatment are shown in table 1. The Hamilton scores showed a mean drop of 71.0% (SD=12.2%) in the full and partial responders versus 9.2% (SD=29.7%) in the nonresponders.

### Treatment Variables

The median duration of acute treatment for the 61 patients who completed treatment was 9.1 weeks (range=2.7-37.3). For the group of full and partial responders the mean duration of acute treatment was 11.2 weeks (SD=7.8), and the median was 10.0 weeks (8.6 weeks for the full responders and 26.6 weeks for the partial responders). (These calculations do not take into account the additional time needed to restabilize the five patients who relapsed during continuation therapy.) An examination of cumulative response time indicated that 44 (72.1%) of the treatment completers (86.3% of the 51 total responders) entered the continuation phase by 17 weeks. The nortriptyline doses and steady-state blood levels are shown in table 1.

During acute therapy, 17 (33.3%) of the total responders received brief courses (4-6 weeks) of adjunctive lithium carbonate (0.6-1.0 meq/liter) or perphenazine (4-12 mg/day). Inpatients were more likely to receive augmentation therapy: 13 of 18 (72.2%). Remission had to be sustained, however, after discontinuation of adjunctive medication for a minimum of 3 weeks before the patient was entered into the continuation treatment phase of the protocol. Adjunctive lithium or perphenazine was not allowed during continuation therapy.

### DISCUSSION

The rate of full response in this study (65.7% of enrolled patients and 78.7% of completers) obtained with a combination of pharmacotherapy and psychotherapy is encouraging, since the study group consisted of elderly patients with highly recurrent major depression and moderate to severe impairment. Furthermore, the observation that 67.2% of the treatment completers had Hamilton scores of 6 or less by the end of continuation therapy suggests that the majority of the successfully treated patients had few residual depressive symptoms, a problem frequently noted in clinical trials for late-life depression. Such a finding also suggests that lower expectations for the quality of response in the elderly may not be justified. The overall attrition rate (16.4%) compares favorably to rates of 24%-42% typically reported in geriatric clinical trials (2, 3, and unpublished 1991 report by L.W. Thompson and D. Gallagher-Thompson), and the low failure rate (16.4%) also compares favorably to rates reported in the literature (30%-40%).

Furthermore, we used a conservative definition of treatment success, one requiring stability of response (remission) for 16 consecutive weeks of continuation.
therapy. Without such a requirement, the true clinical significance of “treatment success” is diminished. The mean reduction in Hamilton depression ratings, 71.0%, is also clinically meaningful. This concept is further supported by increases in GAS scores from 55.7 (SD=5.2) at study entry to 76.6 (SD=5.8) at the start of continuation therapy and to 82.3 (SD=5.5) at the end of continuation therapy.

The use of a double-blind, placebo-controlled design for the transition to maintenance therapy permits a further assessment of the stability of recovery. With a 4–6 week transition to maintenance and a 20%–25% reduction of nortriptyline dose weekly and concurrent introduction of placebo, 19 (76.0%) of 25 patients randomly assigned to placebo showed no evidence of relapse. The 24.0% relapse rate among the placebo patients (versus 0% relapse among the nortriptyline patients) suggests several possibilities: 1) the brittle nature of the response of some geriatric patients; 2) the possible need for a longer period of continuation therapy; 3) the need for a longer period for drug discontinuation, with a slower rate of drug withdrawal; and/or 4) a discontinuation effect of interpersonal psychotherapy in some patients.

These results, while promising, are based on the open-trial, uncontrolled phase of the larger study. By design, control groups (monotherapy with placebo, nortriptyline, or interpersonal psychotherapy) are not used during this phase, the purpose of which is to maximize the number of remitted patients available for the experimental maintenance phase (which uses random assignment, placebo control, and double-blind procedure). Hence, the current results must be viewed as preliminary, and generalization to clinical practice can be made only with caution. Furthermore, both phases of the protocol (open acute/continuation, controlled maintenance therapy) are being carried out in a treatment-intensive research clinic where patients are monitored very closely. The magnitude of nonspecific effects is difficult to estimate in the absence of a placebo control during the acute/continuation phase. Finally, it should be borne in mind that the study group consists of “young old” patients (60–80-year-olds) who are living in the community and have little functional impairment in activities of daily living, not medically frail “old old” who are institutionalized (13).

In a review of 25 double-blind antidepressant drug studies published between 1964 and 1986 that focused on patients over 55 years of age, Gerson et al. (2) concluded that “drugs are clearly superior to placebo; they show comparable therapeutic efficacy—about 50% improvement in Hamilton Psychiatric Rating Scale for Depression scores versus 20% to 25% on placebo.” In perhaps the most rigorous study to date, Georgotas et al. (12) reported a rate of response (Hamilton rating of 10 or lower) of 60% for both nortriptyline and phenelzine versus 13% response rate for placebo among depressed patients 55 years of age and older who were treated for 7 weeks. Georgotas et al. (14) also reported additional benefit from extending the antidepressant medication trial past 7 weeks to 9 weeks. Addition of this 2-week period was associated with an increase in the response rate to 69%. A caveat would appear to be appropriate in interpreting these data on extending duration of therapy: if a trial goes on long enough, some patients may improve spontaneously.

The most extensive research experience with the psychotherapy of late-life depression was reported by Thompson et al. (4). These investigators reported a study of 91 elderly outpatients with a major depressive disorder (more than 50% with recurrent major depression) who were treated with 16 to 20 sessions of behavioral, cognitive, or brief psychodynamic psychotherapy. The authors used a 6-week delayed-treatment control condition and reported a 24% dropout rate overall. The major finding of the study was that “by the end of six weeks patients in the [active] treatment conditions showed improvement, whereas controls did not. Overall, 52% of the treatment sample attained remission by termination; another 18% showed significant improvement.”

These studies using drug alone or psychotherapy alone for elderly outpatients with major, unipolar, non-delusional depression resulted in treatment success rates of 60%–70% at 6–9 weeks, versus 0%–13% for wait-list/control or placebo conditions. Our current experience of using combination nortriptyline and interpersonal psychotherapy has yielded a somewhat higher success rate (78.7% for the completers) and a dropout rate of only 16.4%, over an acute treatment period lasting a median of 9.1 weeks in all completers (range=2.7–37.3 weeks), in a somewhat older and medically more complicated population. Although this comparison might be viewed as evidence of the superiority of combined pharmacotherapy and psychotherapy, it is probably confounded by different durations of acute therapy (7–9 weeks for Georgotas et al. [12, 14], 6 weeks for Thompson et al. [4], and 2.7–37.3 weeks in the current study), the use of adjunctive medication in the current study, and possible differences in referral biases, portals of entry, subject inclusion/exclusion criteria, and definitions of outcome. More recently, Thompson and Gallagher-Thompson have reported an improvement rate of over 90% in elderly depressed outpatients (mean age=66.7 years) treated with combination desipramine and cognitive-behavior therapy over 6–10 months (unpublished 1991 report). In that study, “improvement” meant a reduction of symptoms great enough that the patient no longer qualified for a Research Diagnostic Criteria diagnosis of major depressive disorder. This success rate appears similar to ours (78.7%), except that their definition of “improvement” may have allowed greater residual symptoms.

Prospective, controlled clinical trials will be necessary to demonstrate the superiority of combination therapy over monotherapy in the acute/continuation treatment of major depression in elderly patients. Such a trial is indicated by comparison of the current preliminary results with published data from controlled trials assessing monotherapeutic interventions. In addition to their
possible clinical utility, such trials would possess clinical face validity by mimicking actual clinical practice and might illumine the possible synergy frequently hypothesized for combination therapy. The low dropout rate observed (16.4%) may partly account for the encouraging preliminary outcome here.

REFERENCES

1. NIH Consensus Development Panel on Depression in Late Life: Diagnosis and treatment of depression in late life. JAMA 1992; 268:1018–1024