Nortriptyline and Interpersonal Psychotherapy as Maintenance Therapies for Recurrent Major Depression
A Randomized Controlled Trial in Patients Older Than 59 Years

Charles F. Reynolds III, MD
Ellen Frank, PhD
James M. Perel, PhD
Stanley D. Imber, PhD
Cleon Cornes, MD
Mark D. Miller, MD
Sati Mazumdar, PhD
Patricia R. Houck, MSH
Mary Amanda Dew, PhD
Jacqueline A. Stack, MSN
Bruce G. Pollock, MD
David J. Kupfer, MD

Context Elderly patients with major depression are at high risk for recurrence, increased mortality, and chronic disability.

Objective To determine the efficacy of maintenance nortriptyline hydrochloride and interpersonal psychotherapy (IPT) in preventing recurrence of major depressive episodes in patients older than 59 years.

Design A 2 x 2 randomized, double-blind, placebo-controlled clinical trial, stratified by therapist.

Setting University-based psychiatric research clinic.

Patients Of a total of 187 patients with recurrent nonpsychotic unipolar major depression (average age, 67 years; one third aged ≥70 years) recruited through clinical referral and media announcements, 107 were fully recovered after open acute and treatment continuation with nortriptyline and IPT. These patients were randomly assigned to 1 of 4 maintenance therapy conditions.

Interventions Monthly medication clinic with nortriptyline hydrochloride (80-120 ng/mL steady-state levels) (n = 24); medication clinic with placebo (n = 29); monthly maintenance IPT with placebo (n = 21); and monthly maintenance IPT with nortriptyline (n = 22).

Main Outcome Measure Recurrence of major depressive episode.

Results The time to recurrence of a major depressive episode for all 3 active treatments was significantly better than for placebo. Recurrence rates over 3 years were as follows: nortriptyline and IPT, 20% (95% confidence interval [CI], 4%-36%); nortriptyline and medication clinic visits, 43% (95% CI, 25%-61%); IPT and placebo, 64% (95% CI, 45%-83%); and placebo and medication clinic visits, 90% (95% CI, 79%-100%). Combined treatment with nortriptyline and IPT was superior to IPT and placebo and showed a trend to superior efficacy over nortriptyline monotherapy (Wald χ² = 3.56; P = .06). Subjects aged 70 years and older had a higher and more rapid rate of recurrence than those aged 60 to 69 years.

Conclusion In geriatric patients with recurrent major depression, maintenance treatment with nortriptyline or IPT is superior to placebo in preventing or delaying recurrence. Combined treatment using both appears to be the optimal clinical strategy in preserving recovery.

JAMA. 1999;281:39-45
www.jama.com

©1999 American Medical Association. All rights reserved.
Depression in old age can be effectively treated during acute and continuation therapy over 6 to 12 months. However, to meet the public health challenges posed by old-age depression for the next 20 years, one of the major priorities for intervention research is to find maintenance treatments with long-term efficacy in preventing recurrence. The goal of this research has been to assess the efficacy of antidepressant medication (nortriptyline hydrochloride) and of interpersonal psychotherapy (IPT) in helping elderly depressed patients to maintain recovery and to prevent or delay recurrence. The long-term prognosis for geriatric depression has generally been considered mixed, with only one quarter to one third of patients robustly well at 1 to 3 years of follow-up in naturalistic studies. Patients older than 70 years appear to have a particularly brittle response that is prone to relapse and present special challenges for long-term clinical management. Furthermore, other studies have indicated that old age at first onset of illness increases the risk of recurrence and that the shorter the symptom-free interval, the greater the risk for recurrence. Hence, once effectively treated, how can elderly patients with major depression (especially recurrent depression) be kept well? That has been the primary question addressed by the current study.

Until now, there have been no studies of maintenance psychotherapy in the depressed elderly, or of combined treatment with medication and psychotherapy. However, we think it important that psychotherapeutic approaches be developed and assessed in conjunction with pharmacotherapy in maintenance research, especially for depressed older patients who cannot or will not take antidepressant medication, as well as for patients for whom psychosocial factors such as bereavement, role transition, and interpersonal conflict are clinically significant.

This study builds on the work of Frank et al, who demonstrated the efficacy of the tricyclic antidepressant (TCA) imipramine hydrochloride and of IPT in preventing or delaying recurrences of major depression in midlife patients. We hypothesized that recurrence rates would be significantly higher in the placebo condition than in any of the active treatment conditions, that time to recurrence would be shorter in the placebo condition than in any of the active treatment conditions, and that combined treatment with nortriptyline and IPT would be superior to either treatment alone in preventing recurrences.

**METHODS**

**Study Site and Study Population**

The study was conducted at a university-based geropsychiatric research clinic. Over a 7-year period, we recruited 187 elderly patients with recurrent, nonpsychotic, nondysthymic, unipolar major depression, of whom 180 actually began treatment (Table 1). Patients were required to be 60 years or older and to meet expert clinical judgment and research diagnostic criteria, as established by structured interview with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version, for recurrent nonpsychotic unipolar major depression. Patients were also required to be at least in their second lifetime episode, with an interepisode wellness interval of no longer than 3 years, a Hamilton Depression Rating Scale (17-item) score of 17 or greater, and a Folstein Mini-Mental State Examination score of 27 or greater. All subjects provided written informed consent.

We screened 687 subjects to yield the study group of 187. Of the 500 subjects excluded, 119 had single episodes of major depression; 63 had interepisode wellness intervals longer than 3 years, 43 presented medical contraindications to the use of nortriptyline; and 23 had dysthymia as well as major depression. Additional reasons for exclusion included: 12 who failed to meet study age criteria, 24 with delusional depression, and 135 with other psychiatric diagnoses. Excluded patients were offered treatment at the Benedum Geriatric Center at the University of Pittsburgh Medical Center, Pittsburgh, Pa. Reliable data concerning treat-

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics at Study Entry*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>Age at entry, y</td>
</tr>
<tr>
<td>Men, %</td>
</tr>
<tr>
<td>White, %</td>
</tr>
<tr>
<td>Married, %</td>
</tr>
<tr>
<td>Education, &lt;12 y, %</td>
</tr>
<tr>
<td>Clinical characteristics</td>
</tr>
<tr>
<td>Age at lifetime onset, y [median]</td>
</tr>
<tr>
<td>Episode, No. [median]</td>
</tr>
<tr>
<td>Duration of current episode, wk [median]</td>
</tr>
<tr>
<td>Interepisode wellness, mo</td>
</tr>
<tr>
<td>Situational depression, %</td>
</tr>
<tr>
<td>Endogenous, definite, %</td>
</tr>
<tr>
<td>Requiring hospitalization during index episode, %</td>
</tr>
<tr>
<td>Research diagnostic criteria anxiety disorder, lifetime, %</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression score</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
</tr>
<tr>
<td>Global Assessment Scale score</td>
</tr>
<tr>
<td>Mini-Mental State Examination score</td>
</tr>
<tr>
<td>Interpersonal Support Evaluation List score</td>
</tr>
<tr>
<td>Appraisal</td>
</tr>
<tr>
<td>Belonging</td>
</tr>
<tr>
<td>Tangible</td>
</tr>
<tr>
<td>Self-esteem</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale score</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index score</td>
</tr>
<tr>
<td>History of suicide attempts, %</td>
</tr>
</tbody>
</table>
ment history were not generally available. Of the patients who began active treatment, 48.7% were clinically referred, 42.6% were recruited through the media and community presentations, and 8.7% learned of the study by word of mouth.23

**Study Design**
Patients received open treatment initially using a combination of nortriptyline hydrochloride (with plasma steady-state levels of 80-120 ng/mL) and weekly IPT to achieve a remission of depressive symptoms, as defined by a score of 10 or less on the 17-item Hamilton Depression Rating Scale. During acute treatment 92 (51.1%) of 180 patients received adjunctive pharmacotherapy with lithium or perphenazine, as reported elsewhere.11 Twenty-eight (18.4%) of 159 patients who completed acute and continuation treatment failed to remit at all or to show stable remission and were judged to be resistant to treatment.11 Following successful acute treatment, patients entered a 16-week period of continuation therapy to ensure stability of remission and full recovery. Continuation treatment consisted of combined nortriptyline and IPT, using the same dosage of nortriptyline as used during the acute phase, but with the frequency of IPT reduced to every other week. Patients whose remissions were stable for 16 weeks were then randomly assigned to 1 of 4 maintenance therapy conditions: (1) medication clinic with nortriptyline hydrochloride (80-120 ng/mL); (2) medication clinic with placebo; (3) monthly maintenance IPT and nortriptyline; or (4) monthly maintenance IPT with placebo. Nortriptyline and placebo tablets were identical in size (9 mm in diameter), weight (250 mg), and appearance. For patients randomly assigned to a maintenance placebo condition, nortriptyline was slowly discontinued over 6 weeks under double-blind conditions. Patients remained in maintenance therapy for 3 years or until recurrence of a major depressive episode, whichever occurred first.

The randomization schedule was generated by the project statistician at the beginning of the trial and given to the research pharmacist. The individual randomization was stratified by therapist and blocked in units of 4 subjects. The method to generate the allocation schedule was a Fortran program using the DIGITAL VAX/VMS operating system randomization subroutine based on the permutation procedure described by Fleiss.24 Only the pharmacist and the open monitoring committee (J.M.P. and C.C.) had knowledge of randomized assignment to nortriptyline or placebo. The treatment team, outcome assessors, and data analyst were blind to treatment assignment.

As shown in **Figure 1**, 124 (68%) of 180 treated patients recovered and were randomly assigned to a maintenance therapy condition. Of these, 13 relapsed during the transition to maintenance (that is, during double-blind discontinuation of nortriptyline and substitution of placebo) and 107 fully recovered patients began maintenance treatment.

We chose nortriptyline for 2 reasons. First, our review of the literature on the treatment of geriatric depression concluded that the available database supported the efficacy of nortriptyline as the

---

**Figure 1. Participant Flow**

- **Screened Patients (N = 687)**
  - Excluded (n = 500)
  - Entered Into the Study (n = 187)
    - 5 Spontaneous Remitters
    - 2 Treatment Refusers
  - Entered Acute Treatment (n = 180)
    - 159 (88.3%) Completed (134 Remitters, 6 Partial Remitters, and 19 Nonresponders)
    - 21 Dropped Out (8 Treatment Refusers, 6 Medical Complications, 2 Noncompliant, 2 Adverse Effects, and 1 Each Delusional, Bipolar, Death)
  - Entered Continuation Treatment (n = 140)
    - 133 (95%) Completed (119 Fully Recovered, 5 Partially Recovered, and 9 Relapsed and Nonresponsive)
    - 7 Dropped Out (Refused Further Treatment or Noncompliant)
  - Randomized to Maintenance Treatment (n = 124)
    - 123 Continued in Study
      - 1 Refused
  - Entered 6-wk Transition to Maintenance (n = 123)
    - 110 Completed Transition (107 Fully Recovered, 3 Partial)
    - 13 Relapsed During Transition
  - Began Maintenance Treatment (N = 107)
    - 59 Recurred
    - 6 Dropped Out for Medical Reasons
    - 5 Refused Further Treatment

- **Nortriptyline and Interpersonal Psychotherapy (n = 22)**
  - 1 Refused Treatment
  - 2 Medical Dropouts

- **Nortriptyline and Medication Clinic (n = 24)**
  - 4 Medical Dropouts

- **Placebo and Interpersonal Psychotherapy (n = 21)**
  - 4 Refused Treatment

- **Placebo and Medication Clinic (n = 29)**
best antidepressant available.\textsuperscript{25} Second, our pilot work supported nortriptyline’s favorable adverse effect profile in the elderly. Similarly, we chose IPT because, as originally developed by Klerman et al.\textsuperscript{12} it included specific foci on grief, interpersonal disputes, and role transitions, problems that were prevalent in our patient population and relevant to the onset of depression.

Each patient was seen monthly during maintenance treatment by the same 2 clinicians who had treated him/her during acute and continuation treatment, a nonphysician clinician and a coinvestigator psychiatrist, both blind to pharmacotherapy assignment. Patients in the medication clinic condition were seen for 30-minute visits; they received no specific psychotherapy but were queried about their symptoms and any possible adverse effects. Blood samples for nortriptyline were drawn at each clinic visit. Plasma nortriptyline levels were determined by high-performance liquid chromatography.\textsuperscript{26} All visits, both medication clinic and psychotherapy, included orthostatic blood pressure and pulse determinations, weight, and clinical ratings (Hamilton Depression Rating Scale, Beck Depression Inventory, Global Assessment Scale, and Asberg Side-Effect Rating Scale).\textsuperscript{21,27-29} These data were reviewed by a nonblind monitoring committee (J.M.P. and C.C.), which adjusted the dosage of nortriptyline hydrochloride to ensure a steady-state level of 80 to 120 ng/mL.

Patients assigned to monthly maintenance IPT were seen during 50-minute sessions by experienced clinicians (2 with master’s degrees in social work, 1 with a master’s degree in education counseling, and 1 with a doctorate in clinical psychology). Psychotherapists were trained to research levels of proficiency and received ongoing supervision by 4 of the investigators (E.F., S.D.I., C.C., and M.D.M.). These same clinicians also provided medication-clinic management to patients randomly assigned to medication clinic. All medication clinic and monthly maintenance IPT sessions were audiotaped for rating of elements specific to IPT and to medication clinic to ensure treatment integrity and compliance with manual-based treatment delivery procedures.\textsuperscript{30} We monitored compliance with pharmacotherapy via education of patient and family members, pharmacy pill counts, weekly reminders and checks, and by examination of nortriptyline level-to-dose ratios over time.\textsuperscript{31}

Recurrence of a major depressive episode, as defined by research diagnostic criteria, was determined by structured psychiatric interview performed by a research nurse and independent clinical confirmation by a senior psychiatrist. There were no protocol deviations from the study as planned.

**Statistical Methods**

We used Kaplan-Meier survival analysis with log-rank statistics to test for differences in the survival function of the maintenance treatment groups, followed by post-hoc pairwise comparisons. For pairwise comparisons we used a Cox proportional hazards model with 3 dummy variables representing the 4 treatment groups that allowed comparison of the hazard functions. A Cox model also allowed us to test and control for the effects of possible covariates such as age at study entry, number of prior episodes of major depression, duration of acute therapy, social support (Interpersonal Support Evaluation List\textsuperscript{23}), and chronic medical burden (Cumulative Illness Rating Scale for Geriatrics\textsuperscript{32}). The proportionality assumption of the Cox model was tested using the placebo group as the reference. The fit of the model was also judged using Martingale residuals.

**RESULTS**

A total of 107 patients who had fully recovered began maintenance treatment. Analysis of recurrence was performed on data from these subjects (**Figure 2** and **Table 2**). Because 5 subjects were still ac-

![Figure 2. Recurrence Rates of Major Depressive Episodes](http://jama.jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/4590/ on 04/29/2017)
tive at the time of the final outcome analysis (3 in nortriptyline and IPT and 2 in nortriptyline and medication clinic), Table 2 presents the outcome data with the active subjects censored. These 5 patients had all completed at least 2 years of maintenance treatment without recurrence.

The survival analysis showed a highly significant effect for active treatment over placebo in preventing recurrence of major depressive episodes ($\text{log rank} = 34.31, P < .001$). The best outcome was observed in patients assigned to the combined treatment condition, with 80% remaining depression-free. A Cox proportional hazards model using 3 dummy variables representing the 4 treatment groups was then fit with age group as a covariate. The proportionality assumption was tested and met. On pairwise analysis, each of the active treatment conditions was significantly better than placebo: nortriptyline and IPT ($P < .001$); medication clinic with nortriptyline ($P < .001$); and IPT with placebo ($P = .003$). Combined treatment was superior to IPT and placebo ($P = .003$) and showed a trend to superior efficacy over medication clinic with nortriptyline ($Wald \chi^2 = 3.56, P = .06$). Nortriptyline and medication clinic vs IPT and placebo did not differ ($P = .16$).

Most recurrences took place in the first year of treatment (TABLE 3). Of 17 recurrences in patients taking maintenance nortriptyline, 9 were associated with noncompliance as inferred from variability in level-to-dose ratios.$^{30}$ Six of 17 recurrences in a nortriptyline condition were not associated with pharmacological indices of noncompliance. In the remaining 2 cases, data were incomplete. The proportion of patients in combined treatment was the same in noncompliant (3/9) and compliant (2/6) patients.

We examined 3-year outcomes in patients aged 60 to 69 years ($n = 69$) and in those 70 years or older ($n = 38$) in a survival analysis using the Kaplan-Meier method. As shown in Figure 3 and Table 4, older age was associated with a higher and more rapid rate of recurrence during the first year of maintenance with nortriptyline and medication clinic, IPT and placebo, and placebo and medication clinic conditions. Only combined treatment with nortriptyline and IPT effectively prevented recurrence during the first year of maintenance therapy in subjects 70 years or older. In subjects aged 60 to 69 years, each of the monotherapies and combined therapy were equally effective in preventing recurrence during the first year.

Several clinical variables have been associated with higher liability to recurrence in naturalistic studies of late-life depression. These include older age at index

<table>
<thead>
<tr>
<th>Year of Maintenance</th>
<th>Nortriptyline and IPT ($n = 5$)</th>
<th>Nortriptyline and MC ($n = 12$)</th>
<th>Placebo and IPT ($n = 16$)</th>
<th>Placebo and MC ($n = 26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (100)</td>
<td>8 (67)</td>
<td>9 (56)</td>
<td>22 (84)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>4 (33)</td>
<td>5 (31)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (13)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

*PIT indicates interpersonal psychotherapy; MC, medication clinic.
episode, number of previous episodes, extent of chronic medical burden and associated disability, time to remission, and social support. Higher age at study entry was associated with a greater liability to recurrence ($P = .05$), but none of the other measures were significant covariates in a Cox proportional hazards model. There was also no relationship between referral source and outcome, with similar recurrence rates observed in patients who were clinically referred and self-referred.

Attrition for reasons other than recurrence of depression was low during maintenance treatment. Six (10%) of 58 subjects in a maintenance nortriptyline condition were dropped because of intercurrent medical problems contraindicating the further use of nortriptyline, compared with 0 (0%) of 61 in placebo. Four (6.6%) of 61 subjects in a maintenance placebo condition left the study against medical advice, compared with 1 (1.7%) of 58 taking nortriptyline. One patient committed suicide 1 year after leaving the study against medical advice.

**COMMENT**

To our knowledge, this is the first placebo-controlled study of maintenance pharmacotherapy and psychotherapy in old-age depression. The data confirm our hypothesis that maintenance nortriptyline and IPT, together and singly, would be superior to medication clinic visits and no pharmacotherapy in preventing or delaying recurrence of major depressive episodes. In addition, we observed a clinically significant effect for combined treatment over monotherapy in the prevention of recurrence. This effect was clearest during the first year of maintenance treatment, when most recurrences took place, especially in patients 70 years or older. The current data extend the observations of Frank et al$^{19}$ into old age, replicating their findings in midlife patients with recurrent depression for the superior maintenance efficacy of a TCA (imipramine) and IPT. However, one important difference in outcomes is that the current study suggests a clinically significant advantage of combined medication and psychotherapy over medication alone in the elderly, an advantage not apparent in the midlife study. The late-life data also support the concept of increased liability to recurrence as a function of older age at study entry, as evidenced especially by the brittle response of subjects aged 70 years or older during the first year of maintenance treatment. We did not detect a significant effect of chronic medical burden or time to remission on the liability to recurrence.

Two published studies have supported the efficacy of continuation or maintenance pharmacotherapy for preventing recurrences of major depression in the elderly. Georgotas et al$^{19}$ reported relapse rates of 17% for nortriptyline and 20% for phenelzine sulfate in elderly depressed patients during 4 to 8 months of continuation therapy. The Old Age Depression Interest Group in the United Kingdom$^{15}$ reported that elderly patients with major depression are 2.5 times less likely to suffer recurrence of major depression while taking dothiepin hydrochloride maintenance (75 mg/d for 2 years) than taking placebo. In a subsequent placebo-controlled comparison of nortriptyline and phenelzine in 1-year maintenance therapy, Georgotas et al$^{16}$ reported that “patients administered phenelzine (n = 15) did significantly better with 13.3% recurrences than patients administered either nortriptyline (n = 13; 53.8% recurrences) or placebo (n = 23, 65.2% recurrences).” It is important to note that the nortriptyline window used in the study by Georgotas et al$^{16}$ was 50 to 170 ng/mL, which is outside the recognized therapeutic range.

Although the applicability of the current findings to patients seen by primary care or other nondonpsychiatric physicians is unclear, patients such as those in our study are now more likely to be seen in general practice settings, since the managed care revolution. Similarly, a substantial proportion of older patients (at least 119 of the 687 screened for this study) experience a first episode of depression in later life. Although treatment for these patients was not addressed in this study, recent data from Flint and Rifat$^{37}$ suggest that such patients also have a high liability for recurrence even after 2 years of successful maintenance pharmacotherapy. What are the implications, then, of the current study for general medical practice?

We suggest that the continuation of combined medication and psychotherapy may represent the best long-term treatment strategy for preserving recovery in elderly patients with recurrent major depression. The clinical characteristics of elderly patients may provide clues as to why combined treatment is an effective strategy for maintaining wellness in the face of high liability to recurrence of depression. Elderly depressed patients, whether in primary care or psychiatric practice, are often characterized by high levels of medical comorbidity, impaired subjective sleep quality, and frequently occurring issues of bereavement, role transition, and interpersonal conflict. High levels of chronic medical burden, impaired sleep quality, and depletion of psychosocial resources highlight the challenge of getting such patients well and keeping them free of depression. In other words, the clinical context of major depression in later life is complex both medically and

### Table 4. Recurrences as Function of Age*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Nortriptyline and IPT (n=16)</th>
<th>Nortriptyline and MC (n=17)</th>
<th>Placebo and IPT (n=17)</th>
<th>Placebo and MC (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>2 (13%) [0-29]</td>
<td>6 (35%) [12-58]</td>
<td>11 (65%) [42-88]</td>
<td>17 (89%) [75-100]</td>
</tr>
<tr>
<td>≥70</td>
<td>3 (33%) [2-64]</td>
<td>6 (55%) [26-64]</td>
<td>5 (63%) [30-96]</td>
<td>9 (60%) [71-100]</td>
</tr>
</tbody>
</table>

*Five active subjects were treated as censored observation. IPT indicates interpersonal psychotherapy; MC, medication clinic.
psychosocially, contributing to the increase in observed brittleness of long-term response, especially after age 70 years. A combined treatment approach may be best suited for dealing with both the biological and psychosocial substrates of old-age depression. It may also encourage better compliance with pharmacotherapy. Hence, we recommend that all older patients with recurrent depression be referred for psychotherapy, even if the pharmacotherapy is managed by the primary care physician.

More data are needed from studies of patients 70 years or older, as emphasized by a recent update of the NIH Consensus Development Conference on late-life depression. Moreover, although norryptiline is still useful, clinical practice, particularly in primary care settings, has evolved during the past decade from TCAs to selective serotonin reuptake inhibitors. Many physicians are disinclined to prescribe TCAs to elderly patients. Thus, controlled assessment of the maintenance efficacy of the serotonin reuptake inhibitors in the elderly is needed, since no such data exist. More heterogeneous study populations, including patients with a broader range of cognitive impairment and medical illness, would serve to enhance the generalizability of findings regarding long-term treatment strategies in old-age depression. Aside from generalizability issues, however, decisions about treatment choices must depend not only on effectiveness but also on relative costs. Treatment choices must depend not only on effectiveness but also on relative costs. Hence, we recommend that all older patients with recurrent depression be referred for psychotherapy, even if the pharmacotherapy is managed by the primary care physician.

Funding/Support: This work was supported by National Institute of Mental Health grants P30 MH52247 (Dr. Reynolds CF), P30 MH50915 (Dr. Kupfer), R17 MH43832 (Dr. Reynolds), and K05 MH00295 (Dr. Reynolds).

Acknowledgments: We thank the clinicians (Lin Ehrenpreis, MD, XSW, Julie Malloy, MSW, Cynthia F. Paradis, CRNP, Maryann A. Scherlitzauer, MSN, Rebecca Silberman, PhD, Elizabeth Weber, CRNP, Lee Wolfsen, MD, and Jean Zaltman, MSW) and staff (Diana Donnelly and Donna Ulrich) of the Late-Life Depression Clinic of the Department of Psychiatry for their dedication and expert care of the patients participating in this research.

REFERENCES