Antidepressant Response in Late-Life Depression

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When evaluating the literature on the treatment of late-life depression, it is most critical to consider the methodology of each study, specifically: (1) Is the antidepressant treatment adequate with respect to dosing duration? (2) How is response defined, e.g., is it simply a 50% reduction in a scale score, or are there criteria for establishing which patients have truly recovered? (3) Are the outcome data given for both the intent-to-treat and completer analyses? A review of studies that meet a rigorous standard of methodology shows that (1) a therapeutic plasma nortriptyline level consistently produces a 70% to 80% remission rate in depressed patients over 60 years of age, (2) there is some scatter in the remission rates reported for fluoxetine with results ranging from 21% to 50%, and (3) studies of sertraline consistently report a remission rate of 50% or higher. Contrary to the widely held clinical belief, tricyclic treatment is not associated with a higher dropout rate compared with treatment with a serotonin selective reuptake inhibitor (SSRI). However, patients who recovered using tricyclics have lower scores on health-related quality-of-life scales than patients who recovered using SSRIs, and the long-term impact of the "tolerated" side effects of tricyclics, specifically, increased heart rate and anticholinergic effects, may be deleterious. *(J Clin Psychiatry 1998;59[suppl 10]:4–8)*

There are many treatment approaches to late-life depression, and consequently this article will not attempt to be comprehensive. Focus will be placed on the antidepressants, specifically the tricyclics and serotonin selective reuptake inhibitors (SSRIs) since most of the available data in the treatment of late-life depression comes from clinical trials using these medications. Although electroconvulsive therapy (ECT) will not be addressed, it should always be remembered that this form of therapy remains one of the most safe and effective treatments of depressive illness, especially for late-life depression.

Perhaps more important than being comprehensive is developing a strategy to critically evaluate clinical trials of antidepressant medications. Only by having such a strategy is it possible to discern what information can be helpful in constructing a risk/benefit profile for a specific treatment and what information comes from studies that are so methodologically flawed that one cannot have confidence in the results.

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The first issue in considering a clinical trial in late-life depression is the characteristics of the patient population; that is, are subjects the "young" old, for example, 60–75 years of age, or the very old, over 80 years of age? The next issue is the nature of the depressive illness, that is, whether patients meet criteria for a specific subtype such as melancholia, and how severe the illness is if rated using a standard scale such as the Hamilton Rating Scale for Depression (HAM-D). A critical consideration in late-life depression is the medical status of the patient, specifically, What is the level of medical burden?

Next, we have to consider the particulars of the treatment study itself. The most critical question is, How adequate is the antidepressant treatment? This is especially true when a trial compares 2 different antidepressant treatments. Is it a fair comparison? Are both treatments given in an optimal manner? When considering the adequacy of an antidepressant trial, we are primarily considering the dose or plasma level of the medication and the duration of treatment.

The next methodological issue is how response is defined. Most late-life depression trials, including most pharmaceutical industry–sponsored studies, define a responder as a patient who has a 50% reduction in the baseline HAM-D score. Although this criterion is widely used, there are 2 significant problems inherent in defining response as such. First, which HAM-D version are we considering? There are 17-, 21-, and 24-item versions of the HAM-D, and there are innumerable modifications that local research groups have made on the accepted versions of the HAM-D. Furthermore, there is variability in interpretation of the scoring system for the HAM-D, and so we

must be cognizant of the fact that when a depressed patient is reported to have a baseline HAM-D score of 22, this score does not have the same test/retest reliability as does, for example, a hemoglobin level. Second, patients who are severely depressed can have baseline HAM-D scores of over 30, and even though a 50% reduction in the baseline HAM-D score would classify such a patient as a responder, he or she could still be symptomatic at the end of the treatment trial. Increasingly, there has been a strong sentiment that outcome should be considered not only in terms of response rates defined as a 50% reduction in baseline HAM-D score, but also in terms of remission rate, defined as a final HAM-D score less than a predetermined number, such as 8 or 10, regardless of baseline score. The remission rate is a better indicator than the response rate of how many patients recover when given a certain treatment.

Lastly, it is important to consider outcome data in a medication trial using both the intent-to-treat and completer analyses. The intent-to-treat analysis gives a good estimate of the clinical utility of the drug, because patients who are forced to drop out because of side effects are most often going to be classified as nonresponders. For example, if 100 patients begin a trial with a given medication and 40 drop out because of side effects, and of the 60 patients who complete the trial, 40 meet remission criteria, the intent-to-treat remission rate is 40% (40/100).

An alternative to using the intent-to-treat analysis is to consider patients who complete the clinical trial. This analysis reflects the remission rate in patients who tolerate an adequate dose of medication and complete the clinical trial. Using the previous example, the remission rate in the completer analysis would be 66% (40/60). The intent-to-treat and the completer analyses should be considered complementary, not competitive, approaches since they yield different but equally important results.

In regard to these methodological issues, the following discussion will contain a review of studies that used an adequate medication trial, defined remission criteria, and reported both intent-to-treat and completer analyses.

TRICYCLIC ANTIDEPRESSANTS FOR THE TREATMENT OF LATE-LIFE DEPRESSION

If one wants to consider the efficacy of the tricyclics in late-life depression, one is going to focus almost exclusively on nortriptyline. Nortriptyline is the tricyclic that induces the least orthostatic hypotension.[1] Although on a milligram per milligram basis nortriptyline has more anticholinergic effect than desipramine, the anticholinergic load is low compared with those of other tricyclic regimens. Furthermore, the relationship between plasma level of nortriptyline and clinical outcome has been established; the maximum response rate occurs when the plasma nortriptyline level is in "the therapeutic window" of 50 to 150 ng/mL.[2] Therefore, optimal tricyclic treatment of late-life depression can be defined as a therapeutic plasma level of nortriptyline given over 4 to 6 weeks.

In a study by Flint and Rifat,[3] 101 patients, having a mean age of 74 years and meeting DSM-III-R criteria for major depressive disorder, were treated with nortriptyline. The mean baseline HAM-D score was 24, and the remission criterion was a final HAM-D score ≤ 10. In this study, 60% of patients met the remission criterion in the intent-to-treat analysis, and 73% met the remission criterion in the completer analysis. The dropout rate for this study was only 17%.

Another interesting data analysis of this study occurred when the authors considered the 61 patients who met the criterion for remission at the end of the study and then determined at what week of treatment the patients first met the remission criterion. Not surprisingly, at week 1, no patient met the criterion for remission, and thus the cumulative response rate was 0. At week 2, 11% of the sample met the remission criterion; at week 3, 33% (and so the cumulative rate at the end of week 3 is 11% plus 33%, i.e., 44%). At week 4, the weekly remission rate was 25%, and for week 5, remission rate was 20%; the cumulative remission rate at the end of week 5 was 89%.

The dosing schedule for this study was as follows: nortriptyline was raised to 75 mg/day by the end of week 1, and then the dose was adjusted if necessary to reach a therapeutic plasma level. The rate of dose escalation in a trial of a tricyclic is critical, because it has been established that 90% of patients who respond to a tricyclic do so within 14 to 28 days after achieving a therapeutic plasma level.[4] If the dose escalation is slow, and a therapeutic plasma drug level is not achieved for 4 weeks, then patients might not achieve optimal response until week 6 or 8. In contrast, in studies using more rapid dose escalation, such as the Flint and Rifat study,[3] one can anticipate tricyclic response at weeks 4 and 5. The point here is that the longer that it takes to achieve a therapeutic plasma drug level of a tricyclic, the longer the time to response. Therefore, dose escalation strategies must balance the desire to achieve a therapeutic plasma level as rapidly as possible with the desire to avoid the side effects and consequent dropout that might result from too rapid dose escalation.

It is widely believed that late-life depression patients should have longer treatment trials, that is, 12 weeks. However, this study[3] reports that 89% of patients who eventually recovered did so by the end of week 5. It may be that the observation that longer treatment trials are necessary for late-life depression may reflect the slower dose escalation used for older patients rather than an intrinsic difference in the rapidity of response between young and old patients.

A study by Reynolds et al.[5] combined nortriptyline with psychotherapy for the treatment of late-life depression. In this exceptionally well designed study, 148 patients meet-

ing research diagnostic criteria for major depression and having a mean age of 68 years and a mean baseline HAM-D (17-item) score of 20 received a therapeutic plasma level of nortriptyline and once-weekly interpersonal psychotherapy. The remission criterion was very strict: a patient had to meet a final HAM-D score of ≤ 10 for 3 consecutive weeks. In this study, the intent-to-treat remission rate was 78%, the completer remission rate was 89%, and the dropout rate was only 12%.

A third study of a therapeutic plasma level of nortriptyline is from our own group,[6] and the patient sample is importantly different from those in the previous 2 studies. In this study, 42 inpatients with both cardiac illness and melancholic depression who had a mean age of 70 years and mean baseline HAM-D score of 28 were treated with nortriptyline at a therapeutic plasma level. The dosing strategy was that patients were given the full nortriptyline dose of 1.4 mg/kg by day 5, and the remission criterion was a final HAM-D score of ≤ 8. In this melancholic inpatient sample, the intent-to-treat remission rate was 67%, the completer remission rate was 82%, and the dropout rate was 19%.

These 3 studies taken together represent what can be expected with a therapeutic plasma level of nortriptyline when the drug is used to treat late-life depression. All of the studies report a robust response rate even when using strict remission criteria, and none of the studies report a dropout rate higher than 20%. However, as will be discussed later, dropout rate does not tell the whole story about the adverse side effects of medication, and there is reason to have concern about the impact of the "tolerated" side effects of nortriptyline over the extended time period that patients are exposed to this medication.

SEROTONIN SELECTIVE REUPTAKE INHIBITORS IN THE TREATMENT OF LATE-LIFE DEPRESSION

Our discussion of the efficacy of SSRIs in the treatment of late-life depression will focus on fluoxetine, paroxetine, and sertraline. Two large studies of fluoxetine treatment in late-life depression have been done. Mesters et al.[7] gave open fluoxetine treatment to 308 patients meeting DSM-III-R criteria for major depressive disorder. The mean age of the sample was 66 years, mean baseline HAM-D score was 25, and the dosing schedule was fluoxetine 20 mg/day for 8 weeks. The remission criterion in this study was a final HAM-D score ≤ 10. Only 35% of patients met remission criteria in the intent-to-treat analysis, 50% of patients met remission criteria in the completer analysis, and 29% of patients dropped out.

In a second, large, well-designed clinical trial,[8] fluoxetine was compared with placebo in 671 patients meeting diagnosis for DSM-III-R criteria for major depressive disorder. The mean age was 68, and mean baseline HAM-D (21-item) score was 24. The dosing schedule of this study was fluoxetine 20 mg/day for 6 weeks, and the remission criterion was a HAM-D score ≤ 7 after 4 weeks of treatment. In this study, the remission rates for the intent-to-treat analysis were 21% for fluoxetine and 13% for placebo, and the remission rates in the completer analysis were 27% for fluoxetine and 16% for placebo. Although fluoxetine was significantly more effective than placebo in both intent-to-treat and completer analyses, the remission rate for medication was disappointingly low.

The data available on the effect of paroxetine in treatment of late-life depression are limited. The 2 studies available do not report remission rates and have relatively small numbers of patients. The first study is a double-blind comparison of paroxetine with clomipramine in 79 patients with DSM-III-R major depressive disorder who had a mean age of 69 years and a mean baseline HAM-D (21-item) score of 27.[9] The dosing schedule was paroxetine 20 mg/day for 1 week and then 30 mg/day for the remaining 5 weeks of the protocol. Only response rates (defined as a 50% reduction in baseline HAM-D score) were reported. The intent-to-treat response rate for paroxetine was 50%, the completer response rate was 65%, and the dropout rate was 23%. The second study compared paroxetine with amitriptyline in 90 patients meeting DSM-III-R criteria for major depressive disorder who had a mean age of 72 years and a mean baseline HAM-D score of 21.[10] As in the previous study, response rates (50% reduction from baseline HAM-D score) were reported; the intent-to-treat response rate for paroxetine was 60%, the completer response rate was 76%, and the dropout rate was 21%.

These studies of paroxetine are most informative as to the dropout rate one can anticipate when using this medication in the treatment of late-life depression, but the data on efficacy are of limited usefulness given the methodological problems.

In contrast to paroxetine, 2 large studies of sertraline in late-life depression have been conducted. The first was a double-blind, randomized comparison of sertraline and nortriptyline in 210 patients meeting DSM-III-R criteria for major depressive disorder who had a mean age of 68 years and a mean baseline HAM-D score of 25; the remission criterion was a final HAM-D score ≤ 10.[11] Both the sertraline and nortriptyline doses were controlled by the treating clinician and ranged from 50 through 150 mg/day for sertraline and from 25 through 100 mg/day for nortriptyline. The duration of treatment was 12 weeks.

It would be anticipated that in this study the remission rate for nortriptyline would be less than that reported in trials using a therapeutic plasma nortriptyline level. Therefore, this study is informative with respect to response rates for sertraline, but is not a fair comparison of sertraline with nortriptyline because the nortriptyline treatment is not optimal. In this study, the intent-to-treat remission rate was 51% for sertraline compared with 42% for nortriptyline, and the completer remission rate was 62% for

sertraline compared with 51% for nortriptyline. The dropout rate was 29% for sertraline and 33% for nortriptyline.

A second double-blind, random-assignment trial compared sertraline with fluoxetine. This sample of 225 patients was somewhat unusual because the mean duration of the current episode of major depressive disorder was 9 years; that is, it was a sample of patients with chronic major depressive disorder.[12] The mean age was 68 years, mean baseline HAM-D score was 25, and the dose of drug was from 50 through 100 mg/day for sertraline and from 20 through 40 mg/day for fluoxetine. The treatment trial was 12 weeks. In this study, the intent-to-treat remission rates were 45% for sertraline and 46% for fluoxetine, the completer remission rates were 59% for sertraline and 60% for fluoxetine, and the dropout rates were 32% for sertraline and 33% for fluoxetine.

This study also reported an important and intriguing analysis of the response pattern of a subsample of 75 patients (42 treated with sertraline, 33 treated with fluoxetine) with a mean age of 75 years. For both fluoxetine and sertraline, 95% of patients who achieved a greater than 50% reduction from baseline HAM-D score did so by the end of week 8. As with the results of the Flint and Rifat study,[3] these data challenge the clinical wisdom that antidepressant trials in late-life depression must extend to 12 weeks.

A review of the antidepressant studies previously discussed reveals the following observations regarding remission rates. All 3 nortriptyline studies report relatively high remission rates, and good remission rates are consistently reported for sertraline. However, there appears to be somewhat of a scatter in the remission rates reported for fluoxetine, and adequate data are not available on which to base conclusions about paroxetine.

DROPOUT RATES AND ADVERSE EVENTS

Although we have been focusing on the benefits of antidepressants in the treatment of late-life depression, there is another equally important dimension that must be considered, namely, the risks. In the studies reviewed, the dropout rate for nortriptyline is consistently comparable to the rate reported for any of the SSRIs. Although patients may drop out for different reasons when being treated with a tricyclic versus an SSRI, these studies do not support the belief that the tricyclics are more problematic; however, there is an important caveat to this conclusion. Most research studies primarily include patients who are medically healthy. This is a crucial dimension where research studies differ from clinical practice. The clinician must treat many depressed patients with concurrent medical conditions. The side effect and dropout rates associated with tricyclic treatment in this patient population are undoubtedly higher than those reported in studies of healthy depressed patients.

However, even in patients who tolerate medication and complete the clinical trial, we must raise a concern about the impact of the tolerated side effects. Patients with depression receive medication not for the 8 or 12 weeks that constitute the duration of a standard clinical trial, but rather for a minimum of 6 months; since many of these patients have recurrent illness, they may be on medication for the rest of their lives. Therefore, it is necessary to ask what the impact is of changes induced by medication that may not be apparent in 8 or 12 weeks, but that may be manifest and have important clinical significance when the medication is given for 6 months or 6 years.

In fact, there are 2 specific concerns about the impact of long-term nortriptyline treatment. It has been documented that nortriptyline increases heart rate by an average of 10%.[13] What is the effect of increasing heart rate 10% over many years? This is an especially relevant question in patients who have an underlying cardiac condition such as ischemic heart disease in which increased heart rate can have deleterious effects. Another problem is the long-term impact of the anticholinergic effect of tricyclics. The chronic dry mouth induced by drug use can lead to serious dental problems. Furthermore, as late-life depression patients get older, their cognitive functions may be more vulnerable to anticholinergic effects. It would be easy to overlook the anticholinergic contribution to cognitive decline in an elderly patient who has been successfully treated and maintained on treatment with tricyclics for many years.

An extension of this discussion is the assessment of the quality of life of a patient taking antidepressants. This consideration is especially germane to studies of late-life depression. In the nortriptyline/sertraline comparison study,[11] a standardized instrument was used to assess quality of life and produced some intriguing data; in many dimensions including physical health, psychological health, leisure time satisfaction, and overall total score, the effect of sertraline versus that of nortriptyline was statistically significant.

CHOOSING AN ANTIDEPRESSANT TO TREAT LATE-LIFE DEPRESSION

When faced with making treatment decisions for a patient with late-life depression, one must consider a number of variables. First, what are the nature (diagnostic subtype) and severity of the depressive illness? What are the type and severity of the patient's comorbid medical conditions? What medications does the patient need to take? The answers to these questions must be matched to the information available on the efficacy and side effect profiles of the different antidepressants available.

This is the necessary process to select the "best" medication treatment for a given patient. We must eschew the simplistic and reductionistic concept of "first-line treatment," which represents the promotion of a single medication as the drug of choice for whoever walks in the door.

As clinicians, we are responsible for making an informed match between the specific patient and the most appropriate treatment. The more comprehensive our knowledge about the patient and about the efficacy profile and short- and long-term side effects of medications, the more effectively we will treat late-life depression.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft).

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