

# Antidepressant Treatment of Melancholia in Older Adults

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**Objective:** *This is the first prospective trial in an outpatient sample comparing the effect of nortriptyline with sertraline in the treatment of depression with and without melancholia. We hypothesized that patients with melancholia would respond better to nortriptyline than sertraline, whereas among patients without melancholia, nortriptyline and sertraline would have equal efficacy. Methods:* We conducted a randomized 12-week trial comparing sertraline with nortriptyline in the treatment of patients with nonpsychotic, unipolar major depression stratified by the presence of melancholia. One hundred ten unipolar depressed patients with and without melancholia comprised our intent-to-treat sample. Seventy-two were nonmelancholic depressed and randomly assigned to treatment with sertraline ( $N = 40$ ) or nortriptyline ( $N = 32$ ). Thirty-eight were melancholic depressed and randomly assigned to treatment with sertraline ( $N = 18$ ) or nortriptyline ( $N = 20$ ). **Results:** *The test of the interaction of medication group and melancholia status on response was not statistically significant. Among patients with melancholia, response rates were 47% to sertraline and 75% to nortriptyline, whereas among patients without melancholia, response rates were 51% to sertraline and 42% to nortriptyline. The odds of response for patients with melancholia treated with nortriptyline compared with sertraline was 3.46. The odds of response for patients without melancholia treated with sertraline compared with nortriptyline was 0.69. Similar findings were obtained in the remission and continuous outcome analyses. Conclusion:* *This study did not find a significant difference between sertraline and nortriptyline in the treatment of depressed older adults with melancholia.* (Am J Geriatr Psychiatry 2014; 22:46–52)

**Key Words:** Randomized clinical trials, antidepressants, melancholia, nortriptyline, sertraline

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## INTRODUCTION

Some major depressive subtypes predict differential treatment response to antidepressant medication.

Specifically, patients with delusional depression respond poorly to monotherapy with a tricyclic antidepressant (TCA)<sup>1–4</sup> but respond to combination antidepressant–antipsychotic treatment or

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electroconvulsive therapy.<sup>3,5,6</sup> In patients with the atypical subtype, a series of randomized controlled trials compared a monoamine oxidase inhibitor (phenelzine) with a TCA (imipramine) and placebo<sup>7,8</sup> and consistently reported superior efficacy for the monoamine oxidase inhibitor compared with both placebo and the TCA. Vascular depression may be a subtype of late-life depression<sup>9–11</sup> that, especially in the presence of executive dysfunction, may have a lower rate of response to antidepressant medication.<sup>12–15</sup>

A number of studies have shown that patients with melancholic depression show a favorable response to TCAs.<sup>16,17</sup> Evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are less effective than TCAs in the treatment of older adults with melancholic depression.<sup>18,19</sup> Two prospective studies by the Danish University Antidepressant Group compared an SSRI with clomipramine in the treatment of adult inpatients with melancholic depression. The first study<sup>20</sup> found that 60% of the clomipramine group responded (Hamilton Rating Scale for Depression [HRSD] score < 7) compared with 30% of the citalopram group. In the second study,<sup>21</sup> 58% of the clomipramine group responded after 6 weeks compared with 25% of the paroxetine group. Roose et al.<sup>22</sup> compared the efficacy of fluoxetine in elderly inpatients with unipolar major depressive disorder and cardiac disease with that of nortriptyline in an historic comparison group and found an intent-to-treat response rate of 67% among nortriptyline-treated patients with melancholia compared with 23% of fluoxetine-treated patients with melancholia. Navarro et al.<sup>23</sup> found similar results in a mixed sample of elderly inpatients and outpatients. However, not all studies show that TCAs are superior to SSRIs in the treatment of older adult patients with melancholic depression. For example, Mulsant et al.<sup>24</sup> compared 12 weeks of treatment with nortriptyline and paroxetine in 116 elderly inpatients and outpatients with depression and found no differences in the efficacy of the two drugs among patients with melancholia.

Although the findings from inpatients and mixed samples are suggestive, the hypothesis that TCAs are superior to SSRIs in the treatment of older adult outpatients with melancholia has yet to be tested in a prospective study. Results of a 6-week clinical trial comparing nortriptyline with fluoxetine in the treatment of adult outpatients with melancholia provide some support for this hypothesis, but this study was a reanalysis of existing data.<sup>18</sup> In this study, we

report results from the first prospective, randomized, controlled trial comparing the efficacy of an SSRI (sertraline) to a TCA (nortriptyline) in older adult outpatients. We expected medication condition to interact with diagnostic subtype (melancholic versus non-melancholic) in determining antidepressant response. In particular, we hypothesized that in patients with melancholia, the efficacy of nortriptyline would be superior to that of sertraline, whereas among patients without melancholia, nortriptyline and sertraline would have equal efficacy.

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## METHODS

This study was a double-blind, randomized, 12-week clinical trial comparing nortriptyline with sertraline in depressed patients aged 45 years and older stratified by the presence of the melancholia subtype. Patients were recruited between August 1997 and July 2004 by radio and newspaper advertisements and/or through referral from other physicians. At the initial visit, a comprehensive psychiatric evaluation, including a Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV); 24-item HRSD; a Mini-Mental Status Examination (MMSE); Newcastle I scale for the assessment of melancholia; and a medical history, were performed. If the patient met inclusion criteria and signed an informed consent, a physical examination, electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed.

Inclusion criteria were as follows: (1) age 45 years and older; (2) major depressive disorder, single or recurrent, nonpsychotic, by DSM-IV criteria; (3) HRSD at least 16 at the initial visit and at the end of 1 week of placebo; and (4) willing and able to give informed consent. Exclusion criteria were as follows: (1) current or history of obsessive-compulsive disorder, psychotic disorder, or substance dependence (other than nicotine) within the past year by DSM-IV criteria; (2) judged to be a current suicide risk or serious suicide attempt within the past year; (3) status post-myocardial infarction, coronary artery bypass, or angioplasty with a positive history of angina or a positive stress test; (4) QRS interval greater than 0.12 seconds or Qtc interval at least 46 msec; (5) treatment with Coumadin, heparin, or Type 1 antiarrhythmic medications; (6) diagnosis of narrow-angle glaucoma;

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