Speed of Improvement in Sleep Disturbance and Anxiety Compared With Core Mood Symptoms During Acute Treatment of Depression in Old Age

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Objective: *The objective of this study was to examine the relative speed of improvement in sleep disturbance and anxiety symptoms compared with core mood symptoms in acute treatment of late-life major depression.* **Method:** *The authors conducted secondary analysis of acute treatment data in 470 older patients treated in three federally funded studies. The authors compared rates of improvement in three Hamilton Rating Scale for Depression symptom clusters after stratification by study.* **Results:** *Anxiety symptoms improved more slowly with antidepressant monotherapy and with combined pharmacotherapy/psychotherapy, whereas sleep symptoms improved at a similar rate as core mood symptoms.* **Conclusions:** *Anxiety symptoms tend to persist in patients with late-life depression.* (Am J Geriatr Psychiatry 2006; 14:550–554)

Key Words: Depression, geriatric, treatment, symptoms, sleep, anxiety, mood

In the first weeks of acute treatment, the "pre-response" phase, depressed patients are at risk for noncompliance and treatment discontinuation. The clinician's ability to convey realistic expectations of symptom improvement is critical in helping the patient to remain in treatment. Should one expect all symptoms of depression to improve at a similar pace, or do some symptoms improve more quickly than others?

Older studies suggest that neurovegetative or somatic symptoms of depression, particularly sleep disturbance, improve early with antidepressant treatment. For example, studies of tricyclic antidepressants[1,2] found a rapid improvement in sleep in the first 1–3 weeks of treatment. However, the effect on sleep can be attributed to the nonspecific sedative action of tertiary amine tricyclics and seems to vary according to the degree of sedation produced by the antidepressant. Moreover, it may not be observed at all with some newer agents.[3]

Although we have reported a rapid resolution of suicidality in most older depressed patients treated with nortriptyline or paroxetine,[4] data are less consistent with respect to improvement of other depressive symptoms, in particular with newer antidepressants. To address this gap, we performed a secondary analysis of data from a large group of patients who participated in treatment studies of late-life depression, examining the temporal pattern of improvement across the following clusters of symptoms: core mood symptoms, sleep disturbance, and anxiety in a study of antidepressant monotherapy and two studies of combined pharmacotherapy/psychotherapy. We hypothesized that sleep symptoms would improve faster than core mood symptoms but that anxiety symptoms would resolve more slowly.

METHODS

We examined the course of improvement in three clusters of depressive symptoms using acute treat-

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ment phase data from three federally funded studies of late-life major depression with a total of 470 participants: 1) maintenance therapies in late-life depression (MTLD-1), a study of maintenance treatment in persons with recurrent major depression;[5] 2) MTLD-2, a study of maintenance therapies in persons aged 70 and older with major depression, recurrent or single-episode;[6] and 3) the nortriptyline–paroxetine (NT/PX) study, a double-blind, randomized comparison of nortriptyline and paroxetine.[7] Data from the first 12 weeks of treatment were used, because the shortest study (nortriptyline–paroxetine) lasted 12 weeks.

Participants

The three studies, which have been described in detail elsewhere,[5,7,8] included somewhat different populations: younger, less cognitively impaired and less physically ill participants in MTLD-1 compared with participants in MTLD-2 and NT/PX. Most participants in MTLD-1 (82%) and MTLD-2 (91%) were outpatients, whereas in NT/PX, half (51%) were inpatients. To be included, participants were required to have a pretreatment score of 15 or higher on the 17-item Hamilton Depression Rating Scale (HAM-D). All participants in these three studies were considered for inclusion in this analysis. Because 18 patients participated in more than one study, we included only data from the most recent trial, allowing for older age at the time of data acquisition. Patients with unstable medical conditions and active substance use were excluded from the trials, yielding a final group of 470 participants included in the present analysis.

The same study personnel at the University of Pittsburgh conducted the three studies. All participants (or their authorized representative) provided written informed consent after the goals and procedures of the study were explained to them.

Treatment

Participants received open treatment with nortriptyline (target plasma level 80–120 ng/mL) in MTLD-1 and with *10–40 mg of paroxetine per day* in MTLD-2. In NT/PX, participants were randomized to blinded treatment with nortriptyline (target plasma level 80–120 ng/mL) or with *20–40 mg of paroxetine per day*. In MTLD-1 and MTLD-2, patients also received weekly interpersonal psychotherapy. Adjunctive lorazepam treatment up to 3 mg per day was given to 44% of participants in MTLD-1, 46% in MTLD-2, and 49% in NT/PX.

Assessments

Comparable assessment and treatment procedures were followed for the three studies; all participants were rated weekly with the HAM-D. Raters' training, measurements of interrater reliability for the HAM-D, and reviews of diagnoses were performed regularly.

Symptom Clusters

We used HAM-D items to construct the three symptom clusters: core mood symptoms (depressed mood, guilt, suicidality, work/interests), sleep disturbance (early, middle, late insomnia), and anxiety (agitation, psychic and somatic anxiety, hypochondriasis). These clusters are based on 1) findings of an exploratory factor analysis conducted in the pooled sample of 470 patients from the three studies; 2) previously published factor analyses of the HAM-D[9]; and 3) Hamilton's original grouping of items. To ensure the validity of comparison, we examined psychometric characteristics of the clusters. For interrater reliability, intraclass correlation coefficients were 0.95 (core mood symptoms), 0.92 (sleep disturbance), and 0.82 (anxiety); for internal consistency, Cronbach alpha coefficients at baseline were 0.42 (core mood symptoms), 0.45 (sleep disturbance), and 0.45 (anxiety); and for proportion of variance explained, eigenvalues for HAM-D factors, from which the clusters were derived, were 1.63 (core mood), 1.58 (sleep), and 1.54 (anxiety).

Statistical Analysis

We examined summary scores for items in each cluster against time. To make the cluster scores comparable, we transformed raw scores by dividing cluster scores (calculated by adding the relevant item scores) by the maximum observed score for the cluster and then multiplying by 100. We used these transformed scores in the analyses.

We used mixed-effect models to examine the improvement in cluster scores over 12 weeks of treatment stratified by study collapsing the nortriptyline and paroxetine branches of the NT/PX trial (because

no difference in response between drugs was found).[7] We included intercept and slope over ln-transformed week as random effects. Natural logarithm transformation of time was used for better linearization of the relationship. Cluster was included as a within-subject term. We parameterized the model to compare the sleep and anxiety clusters with the core cluster. A significant interaction with time indicated that the cluster had a different slope compared with the core cluster. Satterthwaite degrees of freedom were used in the tests of the mixed model parameter.

RESULTS

Rate of Symptom Improvement Across Studies

The rate of improvement in core mood symptoms and anxiety clusters differed significantly across studies as indicated by the group by time interaction (core mood symptoms: $F = 9.98$, $df = 2, 417$, $p < 0.0001$; anxiety: $F = 16.54$, $df = 2, 421$, $p < 0.0001$). The rate of improvement in sleep disturbance was similar across the studies ($F = 0.57$, $df = 2, 433$, $p = 0.57$). Because the rates of improvement in core mood and anxiety clusters differed between studies, we stratified the comparisons by study.

Sleep Disturbance versus Core Mood Symptoms

Symptoms of the sleep disturbance cluster improved at a similar rate compared with the core mood symptoms cluster in two studies (MTLD-1: $t = 1.06$, $df = 5041$, $p = 0.29$; MTLD-2: $t = 0.51$, $df = 5045$, $p = 0.61$) and more slowly than the core mood symptoms in the NT/PX study ($t = 5.25$, $df = 2612$, $p < 0.0001$).

Anxiety versus Core Mood Symptoms

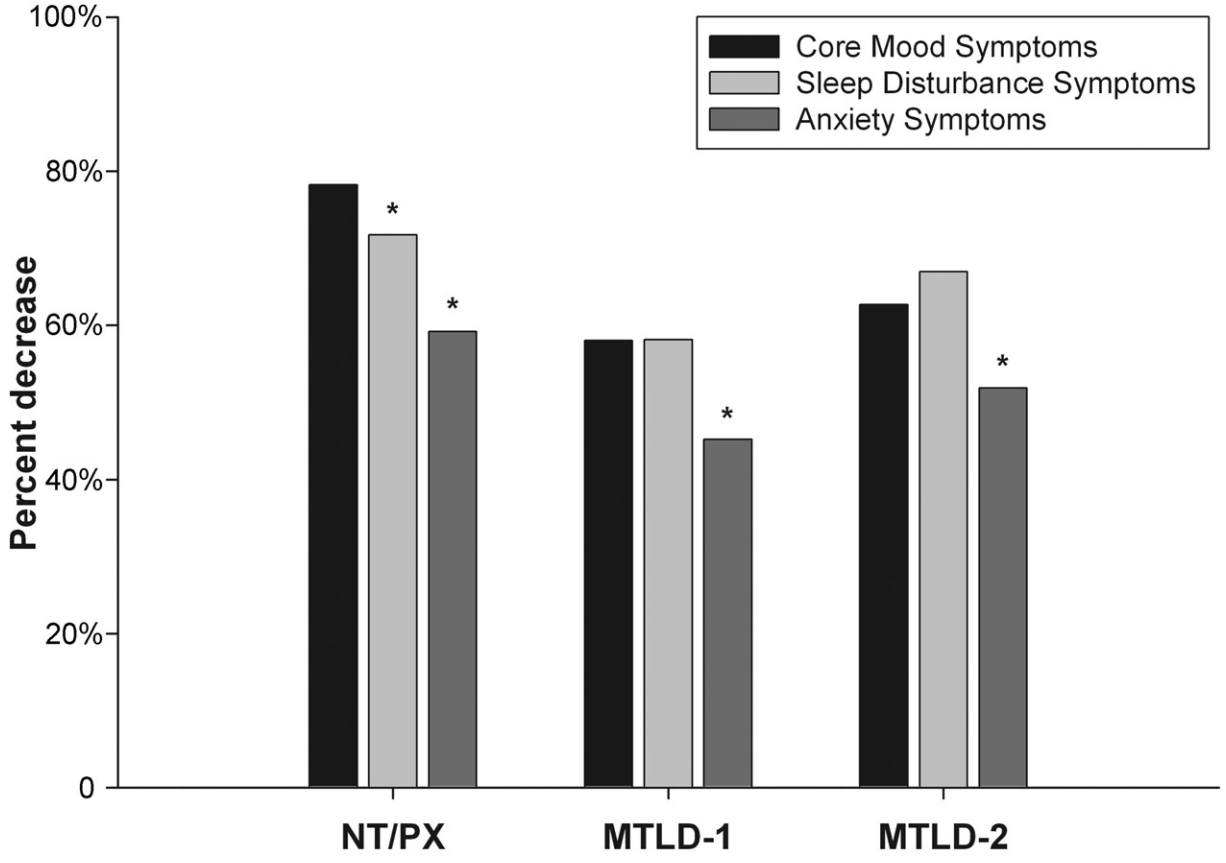
As shown in Figure 1, the rate of improvements in core mood symptoms and anxiety clusters differed significantly across studies as indicated by the group by time interaction (core mood disorders: $F = 9.98$, $df = 2, 417$, $p < 0.001$; anxiety: $F = 16.54$, $df = 2, 421$, $p < 0.001$). In all three studies, the improvement in the anxiety cluster symptoms was significantly slower than improvement in core mood symptoms (NT/PX: $t = 8.58$, $df = 2612$, $p < 0.0001$; MTLD-1: $t = 8.81$, $df = 5041$, $p < 0.0001$; MTLD-2: $t = 5.76$, $df = 5045$, $p < 0.0001$). As a sensitivity analysis of the robustness of our findings, we calculated within-group effect sizes (ES) dividing the estimates of change in scaled scores by the standard deviation.[10] All ES were large, ranging from 0.97–2.19. The rankings of ES were as follows: MTLD-1, core mood symptoms (1), sleep disturbance (2), anxiety (3); MTLD-2, core mood symptoms (1), anxiety (2), sleep disturbance (3); NT/PX, core mood symptoms (1), anxiety (2), sleep disturbance (3).

DISCUSSION

Our study examined the relative rate of improvement in three symptom clusters in the first 12 weeks of treatment of 470 older patients with major depression and found less improvement in anxiety symptoms than in core mood symptoms and no consistent difference in the rate of improvement in sleep symptoms as compared with core mood symptoms.

Our study groups included elderly in- and outpatients with nonpsychotic unipolar depression. Wide referral base, diagnostic homogeneity, protocolized treatment, and prospective, weekly, standardized assessment are strengths of this study. The use of the HAM-D items to create symptom clusters is an important limitation, because this scale lacks a consistent factor structure.[9] The sensitivity of HAM-D items to change[10] and their ability to discriminate across the entire range of depression severity have also been questioned. Another feature of the HAM-D, which may affect our comparison, is that different items are scored either on a 0–2 or a 0–4 scale, leading to a variable potential for change. To address this limitation and also as a sensitivity analysis of the robustness of our findings, we conducted the effect size analysis, which again demonstrated slower improvement in anxiety compared with mood symptoms. The lack of a placebo control represents another limitation, because we cannot rule out the possibility that this pattern characterizes the natural history of a depressive episode in late life as opposed to treatment effects. Finally, adjunctive lorazepam use might have resulted in a faster improvement in anxiety and sleep in some patients,

FIGURE 1. Improvement in Core Mood Symptoms, Sleep, and Anxiety From Baseline to Week 12 by Study (ü



Note: Bars represent the percent reduction in core mood symptoms (depressed mood, guilt, suicidality, work/interests), sleep disturbance (early, middle, and late insomnia), and anxiety (agitation, psychic and somatic anxiety, hypochondriasis) clusters of the 17-item Hamilton Depression Rating Scale from baseline to week 12. An asterisk marks clusters that vary significantly from the core mood symptom cluster.

potentially decreasing our ability to detect a difference in the speed of improvement.

The lack of earlier improvement in sleep disturbance contrasts with findings from studies of tertiary amine tricyclic antidepressants with strong sedative properties[1,2] or with more recent findings with trazodone[11] and does not support the notion that neurovegetative or "somatic" symptoms of depression are more responsive to treatment.

With antidepressant monotherapy (NT/PX) as well as with combined pharmacotherapy and psychotherapy (MTLD-1 and -2) and despite adjunctive lorazepam administration in almost half of the patients, we observed a slower improvement in anxiety symptoms. This pattern was seen in three studies with participants differing in age, medical burden, and the degree of cognitive impairment. This finding is thus not an artifact of treatment modality and is consistent with previously reported findings in primary care samples. In two large randomized, controlled trials of collaborative treatment of late-life depression in primary care, investigators reported a lower likelihood of remission in patients with high baseline anxiety levels[12] and delayed response to treatment in patients with comorbid posttraumatic stress disorder, but not panic disorder.[13] In subgroups of participants characterized here, we have previously found that those with a comorbid anxiety disorder had a longer time to response,[14] and higher levels of anxiety symptoms were a predictor of nonresponse.[15] Whether residual anxiety symptoms in this group represent manifestations of a major de-

pressive episode or comorbid chronic anxiety disorders remains to be examined. Furthermore, results of our other analysis in the same sample indicate that higher levels of anxiety may be associated with persistent or emergent suicidality in patients with late-life depression (Szanto et al., 2005, unpublished data), a link previously found in mixed-age samples.[16]

Future Directions and Clinical Implications

Persistent anxiety may put patients at risk for noncompliance, treatment discontinuation, and suicidality. Further research will need to address the nature of enduring anxiety symptoms and examine their differential response to alternative treatment strategies such as benzodiazepines or antipsychotics or anxiety-specific psychotherapy. At this time, we would suggest that the presence of such symptoms should prompt a repeated diagnostic evaluation for comorbid anxiety disorders after depressive symptoms have improved. Diagnosis of an anxiety disorder may lead to specific treatment such as anxiety-specific psychotherapy. In the absence of such a diagnosis, experts recommend increasing the dosage of a serotonergic antidepressant. [17]

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