Anxious Depression and Response to Treatment

In this issue of the Journal, Fava and associates present data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrating that among 2,876 patients with major depression, those who were more anxious were less likely to respond and remit during citalopram treatment and were more likely to experience adverse events. Considering the magnitude of differences observed in recent placebo-controlled trials in depression and antidepressant comparison studies, the difference in response rates between anxious and nonanxious groups in the STAR*D sample—41.7% and 52.8%, respectively—is appreciable and an important finding.

*"How can the findings of STAR*D be reconciled with those of earlier large data sets?"*

In Level 2 of STAR*D, 1,292 patients who either had not remitted or were intolerant of citalopram switched to another antidepressant or received augmentation therapy. Again anxious patients were less responsive, and the difference in remission rates between the anxious and nonanxious patients was even greater. Level 2 included five different drug treatment options, but none was superior to any other for the anxious patients.

High levels of anxiety were also associated with significantly greater side effect frequency, intensity, and overall burden. A greater proportion of anxious than nonanxious patients discontinued treatment because of intolerance (19.2% and 14.6%, respectively). Serious adverse events and hospitalizations for general medical conditions were both more common in the anxious patients. Given the size of the STAR*D sample and the inclusion of both psychiatric and primary care sites, these data make a compelling case for the predictive value of anxiety.

The authors defined "anxious depression" according to a cutoff on the anxiety-somatization factor of the Hamilton Depression Rating Scale (HAM-D), and they compared this factor with other descriptors of anxiety. Anxious depression in all definitions was significantly associated with remission, but total score on the anxiety-somatization factor explained the highest proportion of the variance. Anxiety-somatization scores in the sample appeared to be normally distributed.

Clinicians may find the term "nonanxious" misleading. Most depressed patients report some anxiety even if it is not prominent.

Anxious depression is associated with other characteristics, which have been reported previously and in previous STAR*D publications. Anxious depression is associated with greater symptom severity, suicidality, and unemployment, less education, worse functioning, and poor prognosis.

Interest in anxious depression has a long history. In 1959, British psychiatrists West and Dally reported findings suggesting that iproniazid might be especially useful for these patients (1). Subsequently, two groups (2, 3) conducted studies comparing amitriptyline and phenelzine and obtained similar results; both drugs were effective, but phenelzine was slightly more effective for anxiety.

Studies of tricyclic antidepressants have had mixed results. I found 10 reports that included 24 clinical trials. In about one-third of the trials tricyclics were found to be less effective in anxious depression, and in two-thirds no difference was observed in the response of anxious and less anxious patients. For example, in a review of 14 trials with 788 patients and various tricyclics used as comparators, response rates were 62.7% and 62.1%, respectively, in anxious and less anxious patients (4). Anxious depression was defined in terms of various symptoms or based on the presence of panic disorder. Only

two of the tricyclic trials were placebo controlled. (For a detailed review, see the data supplement that accompanies the online version of this editorial.)

Results of second-generation antidepressant trials also have been conflicting. Fava et al. (5) reported less favorable outcomes in patients with major depression and any comorbid anxiety disorder than in patients without comorbid anxiety disorders after 8 weeks of open-label fluoxetine. Davidson et al. (6), in a pooled analysis of five venlafaxine-fluoxetine comparison studies that included 1,454 patients, found that response rates did not differ significantly between the groups with high and moderate anxiety levels (defined using the HAM-D psychic anxiety item). Remission rates, however, were lower in the group with high anxiety levels, but the drug-placebo differences appeared to be essentially the same for venlafaxine (19% and 18%, respectively) and for fluoxetine (10% and 11%, respectively) in the high and moderate anxiety groups. These data suggested that overall outcome was worse in patients with anxious depression but that the specific effects of drug treatment (drug-placebo differences) were maintained.

Three large reviews or meta-analyses that employed the HAM-D anxiety-somatization factor to define anxious depression failed to find an effect on outcome. Tollefson et al. (4) reviewed 19 double-blind, randomized trials of fluoxetine that included 3,183 patients with major depression. Five trials were placebo controlled, 12 were tricyclic comparisons, and two included both. Exclusion of comorbid anxiety disorders was not specified. Fluoxetine was superior to placebo in both the anxious and nonanxious groups. Mean response rates for fluoxetine did not differ significantly between anxious and nonanxious patients (55.7% and 60.7%, respectively). While response rates appeared slightly lower in anxious patients treated with fluoxetine, remission rates were significantly *higher* in anxious patients (38.3% compared with 29.5%). Discontinuations for adverse events did not differ significantly between anxious and nonanxious patients (15.0% and 14.6%, respectively).

My colleagues Lon Schneider and Kevin Delucchi and I conducted a meta-analysis of 10 placebo-controlled studies of second-generation antidepressants in late-life major depression (7). We are now examining moderators of response, including anxiety defined by the HAM-D anxiety-somatization factor. Thus far we have obtained data from five studies with six contrasts in 2,443 patients (unpublished data). Response rates by meta-analysis were not significantly lower in anxious patients than in nonanxious patients (41.1% compared with 35.5%), and drug-placebo differences did not differ between the two groups.

Recently Papakostas et al. (8) presented data from a meta-analysis of 10 double-blind, randomized studies with 2,122 patients comparing bupropion with various selective serotonin reuptake inhibitors (SSRIs) in which patients with high levels of anxiety were identified with the HAM-D anxiety-somatization factor. The authors focused on SSRI-bupropion comparisons, but the data indicated very similar response rates in highly anxious patients and less anxious patients (62.3% and 63.3%, respectively). The SSRIs were slightly more effective in anxious patients, while bupropion was slightly less effective.

I have presented this brief review to illustrate trends and problems in the data. The tricyclic findings are mixed, but most trials found no difference in response in anxious and nonanxious patients. Different definitions of anxious depression were used. Often the exclusion of comorbid anxiety disorders was unclear. For second-generation agents, two reports of six trials presented evidence of poorer outcomes in anxious patients. On the other hand, three reviews or meta-analyses of trials using the HAM-D anxiety-somatization factor failed to find anxious depression predictive of outcome. The fluoxetine trials data set and the two meta-analyses cited above included 7,748 patients with 34 SSRI or serotonin-norepinephrine reuptake inhibitor contrasts, 11 bupropion contrasts, and 14 tricyclic contrasts; 20 contrasts were placebo controlled. In these trials, anxious depression was not associated with lower response rates or smaller drug-placebo differences. The review and the meta-analyses are particularly useful because they examine the anxiety predictor in all studies within a defined domain and are less vulnerable to ascertainment bias, that is, the tendency to identify and report positive rather than negative find-

ings. This is especially important because predictors are usually examined in retrospective secondary analyses, and secondary findings are less likely to be reported than primary outcomes, or only the positive associations are reported.

How can the findings of STAR*D be reconciled with those of earlier large data sets? One of the aims of STAR*D was to include patients with major depression typically found in psychiatric and primary care settings. While patients with bipolar and other psychotic disorders were excluded, nonpsychotic comorbid psychiatric disorders were allowed and were common. Prevalence rates for specific anxiety disorders ranged from 12% to 31% (9). Except for social phobia, all of these anxiety disorders predicted lower rates of remission, and the odds ratios indicated a stronger effect for comorbid anxiety disorders (odds ratios ranging from 0.65 to 0.80) than the anxious/nonanxious distinction (odds ratio=0.96) (9).

In contrast, the large fluoxetine review and the two meta-analyses cited included typical clinical trials. While methods of excluding anxiety disorders were not always well described, usually patients with a primary axis I disorder other than major depression were excluded. Patients with known obsessive-compulsive disorder or posttraumatic stress disorder would likely have been excluded. I suggest that the difference between the three large data sets and STAR*D is the high prevalence of comorbid anxiety disorders in STAR*D and that this may explain the association of anxiety and response. Symptoms of anxiety and presence of a comorbid anxiety disorder are related. The best way to disentangle the association of these two related variables with response would be to remove patients with comorbid anxiety disorders from the sample and then determine whether the HAM-D anxiety-somatization factor predicts poorer outcome. This is a crucial issue for DSM-V. If comorbid disorders are the major predictor, then the current diagnostic system may be satisfactory. If the anxiety-somatization factor score predicts outcome independent of comorbid anxiety disorders, then the STAR*D data would argue for including "anxious features" as a subtype of major depression.

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The author has consulted or served on advisory boards for Biovail, Bristol-Myers Squibb, Corcept, Eli Lilly, Forest, GlaxoSmithKline, Novartis, Orexigen, Organon, and Pfizer. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.