The STAR*D Study: A Four-Course Meal That Leaves Us Wanting More

This issue of the *Journal* features an article by Rush and colleagues that provides an overview of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. The STAR*D study is the largest prospective study of a sequential series of treatments for depression ever conducted. In this study, 3,671 patients entered treatment at 41 sites, 18 of which were primary care facilities. The study included a variety of baseline and outcome measures that provide a wealth of information about the characteristics of the patients and their response.

The STAR*D study differs from typical clinical trials. Subjects were identified as they came for treatment. Symptomatic volunteers were not included. Inclusion criteria were generous. Although psychotic and bipolar patients were excluded, most other psychiatric disorders were allowed. Most clinical trials in depression exclude patients with recent active substance abuse. STAR*D only excluded patients likely to need inpatient detoxification. Of the patients entering the first treatment step, 61.5% had a concurrent psychiatric disorder. As the result of broad inclusion criteria, the STAR*D study is more representative of patients in clinical practice.

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The study confirms that about one-third of patients achieve remission with initial treatment and that remission rates decline with successive treatment failures (1). Remission rates were 36.8%, 30.6%, 13.7%, and 13% after treatment steps 1 through 4. The authors note that remission rates drop more substantially after two failed treatments. This might support the developing notion that treatment-resistant depression is defined by two prior treatment failures.

Higher remission rates during the initial trial were seen in patients who were female, Caucasian, employed, or had higher levels of education and income (2). Alternatively, patients who required more treatments were more severely depressed and had more concurrent psychiatric and medical disorders.

It is tempting to speculate about reasons for the declining remission rates. The most obvious reason is that the remaining patients were less responsive to antidepressants or cognitive behavior therapy. An alternative hypothesis is that the portion of response associated with the nonspecific effects of patient care—attention, reassurance, and education, otherwise referred to as "placebo response"—was declining. In an analysis of 52 randomized, placebo-controlled drug trials, Khan and associates found that about 73% of the decrease in Hamilton scores in the drug group could be accounted for by these nonspecific effects (3). It would seem clinically understandable if after two failed treatment trials lasting about 6 months, nonspecific interventions lost their effectiveness.

The study provides very interesting information about relapse. Consistent with prior data, patients who achieve remission are less likely to relapse than patients who have only responded (i.e., persistent symptoms despite 50% or greater improvement in their rating) (4). To my knowledge, however, no previous report has provided information on rates of relapse after successive treatment trials. In the STAR*D study, rates of relapse ascend with each treatment step. Among those achieving remission, relapse rates were 33.5%, 47.4%, 42.9%, and 50.0% after the four treatment steps. Relapse rates were even higher in patients who improved but did not achieve remission (range=59% to 83%). It is particularly worrisome that at steps 3 and 4, in addition to low remission rates (13.7%

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and 13.0%), nearly half of those remitting relapsed. Treatment in the relapse phase was naturalistic: patients were encouraged to remain on their last treatment, but treatment changes or other treatments were allowed. But regardless of that, from step 2 on, less than half of those responding and remitting remained well.

The study also found that intolerance increased after each treatment step: 16.3%, 19.5%, 25.6%, and 34.1%. Readers should remember that the term "intolerance" includes dropouts *for any reason* during the first 4 weeks, or side effects after that. One might expect that side effect rates would decline with each step (once those prone to side effects drop out). Perhaps patients that drop out are becoming demoralized with each failure and are giving up.

The investigators are to be applauded for their emphasis on remission and their inclusion of the relapse data. Together these data start to inform us about sustained recovery in depression. In my opinion, the authors have cited the positive side of the coin here. They note that after four treatments the cumulative remission rate is 67%. But this does not account for relapse. If the goal of treatment is sustained recovery, relapse should be considered. I found a cumulative sustained recovery rate of 43% after four treatments, using a method similar to the authors but taking relapse rates into account. This calculation does not take into account what happens to "responders" (who might remit later), and neither the author's cumulative remission rate or my sustained recovery rate takes into account the ascending number of patients who discontinue treatment prematurely.

This paints a less hopeful picture for the treatment of depression, but it may be consistent with the "real world" patients included in this study. More than 75% of the STAR*D patients had recurrent or chronic depression, 61.5% had a concurrent psychiatric diagnosis, and 83% had received previous treatment for their current episode (N= 3,057 of 3,671). In these STAR*D patients, achieving and sustaining complete recovery is a challenge.

The greatest disappointment of the study—depending on your perspective—was that patients were not randomly assigned to all treatments at level 2, and as a result comparisons between treatment strategies were limited. Patients were given the option of declining or accepting certain treatments. Patients who agreed to augmentation or switching strategies were randomly assigned within those groups. The authors decided on this design to mimic real practice and to improve recruitment and retention. They discovered, however, that patients have their own opinions. Only 21 of 1,439 patients (1.5%) agreed to randomization to all of the treatment choices at level 2. As a consequence, it is not possible to compare augmentation with switching or with cognitive therapy. And as the authors note, patients selecting these options were different. Those who switched to a new medication had more severe illness than those who received augmentation or cognitive therapy. The lower entry score in the cognitive therapy and the augmentation groups may explain the higher remission rates. Note the apparent mean change in all groups at step 2 was about the same: 3 points on the QIDS-SR.

One of the surprises of the study was the finding that among patients who switched to another drug, a second SSRI (sertraline) was just as effective as a drug with a different mechanism (bupropion) or a "dual-action" agent (venlafaxine) (5). Does this mean longer duration is just as important as the drug chosen? This study was not placebo controlled, and it is not possible to determine what portion of response was associated with nonspecific factors (which would tend to obscure true drug differences). Regardless of these limitations, this study remains the largest to randomize and compare three switches after a prospectively documented treatment failure. While treatment was open label, the expected bias would seem to favor bupropion or venlafaxine. The findings challenge commonly held beliefs.

The study also highlights what we do not know about depression treatment. While a variety of augmentation, switching, and psychotherapy strategies have been described,

the "evidence-base" is mainly limited to comparisons with placebo. Few studies have compared alternative strategies. Few studies have examined predictors of response to different treatments. And the majority of the previous augmentation and switching studies only required that patients had failed one current treatment trial. Few studies have identified patients with depressions that are truly treatment resistant.

The STAR*D study provides a wealth of data about treatment of depression. It offers hope to patients that successive treatments will increase their chance for remission. Overall, the study provides "benchmarks" for the field in terms of the effectiveness of current treatments for depression. Yet the relapse data are sobering. The lack of difference between switching strategies at level 2 will no doubt stimulate much debate. Perhaps most disconcerting, the lack of differences between treatments at levels 2, 3, and 4 leaves us without a roadmap to guide treatment selection and leaves us wanting more.

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Dr. Nelson reports receiving lecture honoraria from GlaxoSmithKline and Pfizer and serving as a consultant/advisor to Abbot, Biovail, Bristol-Myers Squibb, Corcept, Eli Lilly, GlaxoSmithKline, Orexigen, Organon, Pfizer, Sepracor, and Shire. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.