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Keeping Our Eyes on STAR*D

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> "Keep your eyes on the stars, and your feet on the ground."
>
> —Theodore Roosevelt

Only 30% of patients with major depressive disorder achieve remission with initial treatment, and many patients with depression undergo serial treatment trials to improve response. Unfortunately, the literature has provided limited guidance on what sequences of such trials are most likely to result in timely remission for these patients.

The STAR*D project is a 6-year, $35 million study examining "next best" steps for patients with major depressive disorder who do not benefit from initial and subsequent treatments. In this issue, Nierenberg et al. and McGrath et al. present results from the last of the series of STAR*D practical medication trials, the Level 3 augmentation trial comparing lithium and T_3 and the Level 4 trial comparing tranylcypromine and the combination of extended-release venlafaxine and mirtazapine.

STAR*D was designed for applicability to practice, and the sample was selected to be generalizable to the patients we are likely to encounter in practice. All STAR*D participants received the Level 1 treatment, which was monotherapy with citalopram. Patients whose depression did not remit with citalopram were encouraged to proceed with additional trials until remission was achieved. Those who moved on to STAR*D Level 2 could undergo randomized assignment to as many as seven different treatments, depending on their preferences for medication versus psychotherapy and for the broader strategies of switching to another agent versus augmenting citalopram with another agent. There were four switch options (monotherapy with sustained-release bupropion, sertraline, extended-release venlafaxine, or cognitive therapy) and three augmentation options (citalopram plus sustained-release bupropion, buspirone, or cognitive therapy).

Patients who did not remit with Level 2 medication treatments could undergo randomized assignment to up to four Level 3 treatments: two switch options, in which patients switched to monotherapy with nortriptyline or mirtazapine, and two augmentation options, in which patients continued taking their current antidepressant along with either lithium or T_3. Patients whose depression still did not respond adequately and who moved on to Level 4 underwent randomized assignment to either tranylcypromine or the combination of extended-release venlafaxine and mirtazapine.

Results of the Level 1 trial were published in January 2006 (1). The results of the Level 2 trials followed in March, and the results of the Level 3 "switch" options were published in July 2006 (2–4).

In this issue, Nierenberg et al. report findings on the Level 3 augmentation trial. They found no significant differences in remission rates between patients receiving lithium and those receiving T_3; 15.9% of patients receiving lithium and 24.7% of patients receiving T_3 augmentation met remission criteria by the end of the 12–14 week trial. However, patients taking lithium were more likely to report side effects and to exit the trial because of side effects.

Also in this issue, McGrath et al. report findings the Level 4 trial. Here too, there were no significant differences in remission rates between the two treatments; 6.9% of patients receiving tranylcypromine and 13.7% of patients receiving venlafaxine and mirtazapine remitted. Patients receiving tranylcypromine experienced less symptom reduction on a secondary outcome measure and were more likely to exit the trial because of side effects.

Nierenberg et al. recommend that after two failed trials, T_3 augmentation be considered before lithium augmentation because of its more favorable side effect profile. McGrath et al. recommend that after multiple failed treatments, combination treatment with venlafaxine and mirtazapine be considered before treatment with tranylcypromine for the same reasons.

What should clinicians make of these STAR*D findings? What aspects of the findings can we usefully bring to our practices?

Clearly, one take-home message is that after patients with depression fail to obtain adequate benefit from two or more treatment trials—and this applies to more than 40% of patients with major depression—only modest responses can be expected from each subsequent treatment trial. None

of the late-sequence STAR*D options emerged as a miracle intervention for patients with treatment-resistant depression. Clearly, we urgently need more effective treatments for depression.

Other take-home messages are necessarily narrow in scope because of the study design. The STAR*D trials were not placebo controlled. Because few patients consented to be randomized across switching and augmentation strategies, STAR*D investigators could not conduct planned head-to-head comparisons of switching versus augmenting treatment options (5).

Also, the STAR*D investigators' selection and placement of medication treatments within the sequence of trials was based on what drugs were "safest, easiest to take, and most frequently used" in addition to the drugs' reported efficacy in placebo-controlled trials. The sequencing of treatments on the basis of what "clinicians are using" ensures that study results are immediately germane to clinical practice, but this approach has drawbacks when popular treatments have unproven benefit and are not compared with placebo or better-established treatments. Unless a drug produces a very large benefit, its placement later in a trial sequence frames much of the subsequent discussion. Drugs used later can be discussed only in the context of "down-line" options.

Keeping these issues in mind, the modest Level 3 augmentation results do not issue a clarion call for reviving the often recommended, but seldom used, lithium and T_3 augmentation treatments. However, they also do not consign these treatments to "last resort" status. Although there are a few negative studies, lithium is still the augmenting strategy with the most evidence for efficacy in placebo-controlled trials.

STAR*D results also do not tell us where lithium and T_3 should be placed in the overall sequence of treatment trials. After one treatment failure, 30% of Level 2 patients receiving bupropion or buspirone augmentation remitted, a finding that has been given considerable attention in clinician publications. However, these agents have only weak or mixed evidence of efficacy in placebo-controlled trials. In the STAR*D study, these augmentation options were not compared with placebo or with better-supported options, such as lithium and T_3 augmentation. Lithium and T_3 might have had higher response rates if administered in Level 2.

Finally, even the narrow conclusion that T_3 is superior to lithium after two failed trials may be problematic, given the manner in which lithium was administered in the study. Lithium doses were capped at 900 mg/day, and blood levels were not routinely tested. Among tested patients, only half had levels ≥0.6 meq/liter. While low lithium doses have been used in some augmentation studies, a meta-analysis indicates that higher doses are associated with greater efficacy (6). Lithium is also one of the few drugs with evidence for a specific antisuicide effect, an important consideration when treating patients with major depressive disorder (7).

The narrow recommendation from the Level 4 study—that after multiple failed trials venlafaxine/mirtazapine would be preferable to tranylcypromine—appears to be warranted, although, as the authors point out, tranylcypromine may have been placed at a disadvantage by the required 2-week washout period. The broader question of where these "fourthline" treatments might be placed in an optimal sequence of trials remains unanswered.

Investigators from the National Institute of Mental Health-sponsored Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) are now reporting the results of their practical trials comparing the effectiveness of antipsychotic medications for patients with schizophrenia and patients with Alzheimer's dementia and psychosis. The CATIE study has produced more surprises than STAR*D, possibly because investigators included a placebo arm in the trial for patients with Alzheimer's dementia and an older antipsychotic comparison agent in the trial for patients with schizophrenia (8). When ethically possible, including placebo control subjects and directly comparing popular newer treatments and older therapies may produce more definitive and more striking results.

Researchers involved in the STAR*D project can be proud of carrying this enormous effort to completion. All clinicians should pay close attention to the results of these well-executed trials. While the STAR*D project could not address all complex treatment sequencing decisions, it has provided important evidence applicable to clinical decision making by ordering treatments by relative efficacy or tolerability at specific therapeutic junctures. Future studies must build on these trials, evaluating additional sequencing options and directly comparing important treatment alternatives, such as switching versus augmentation.

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