STAR*D: What Have We Learned?

STAR*D represents a 7-year effort by literally hundreds of people and thousands of patients. Future reports will 1) compare longer-term outcomes of the various randomized treatments (e.g., does cognitive therapy prevent relapse better than medication as either a switch or augmentation strategy?); 2) identify which patients benefit from which treatments (e.g., do different patients [defined by different clinical features or genetic polymorphisms] respond differently to different treatments?); and 3) determine whether different treatment sequences (in steps 1 to 4) are preferred for some but not other patients (1). At this point, however, we can ask, "What have we learned so far?"

This highly representative clinical sample of depressed outpatients has revealed that major depression is often chronic, severe, and associated with substantial general medical and psychiatric comorbidity. Two-thirds of patients had at least one concurrent general medical condition; two-thirds had at least one other psychiatric disorder; nearly 40% had their first depressive episode before age 18; over half reported a mood disorder in at least one first-degree relative; and over half met criteria for anxious features (2, 3). In addition, patients in primary care and psychiatric settings with major depression did not differ clinically except for slightly higher rates of general medical conditions in primary care settings, and slightly higher rates of prior suicide attempts in psychiatric settings (4).

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In terms of treatment tactics, STAR*D developed and implemented easily applied methods to enhance the quality of care in both daily practice and in clinical trials in representative groups of patients. This so-called "measurement-based care" entailed the routine use of simple paper-and-pencil symptom and side effect measures at each treatment visit, along with guidance based on these measures to recommend timely dose or treatment changes. A likely consequence of this high-quality, consistent care was that outcomes in primary care and psychiatric settings were not different (5).

Longer times than expected were needed to reach response or remission. In fact, one-third of those who ultimately responded did so after 6 weeks (and half of those who ultimately remitted did so after 6 weeks) (5). These results suggest that stopping a vigorously dosed treatment for patients who report little benefit by 6 weeks is ill-advised. Itemized symptom measures (as opposed to a global judgment) might well detect a benefit (e.g., 25%–45% reduction in baseline symptom severity) that many patients may not report if asked for their global impression. If a modest improvement (e.g., ≥20% reduction) is present, a dose increase (if tolerated) at 6 weeks or simply further exposure (up to 10 weeks) may help a sizable number of patients to at least respond, if not achieve remission, by 12 weeks.

As for treatment strategies, we found that patients had clear preferences about their acceptance of augmentation versus switching at both the second and third levels in STAR*D (6). Those who fared better in the prior step and who evidenced minimal intolerance preferred augmentation, while those with little benefit or substantial intolerance with the prior treatment preferred to switch. Whether augmentation is best even if the initial treatment is minimally effective could not be evaluated in the STAR*D design.

As for specific medications at the second step, results suggest that either a within-class switch (e.g., citalopram to sertraline) or an out-of-class switch (e.g., citalopram to bupropion-SR) is effective, as was a switch to a dual-action agent (e.g., venlafaxine-XR). While bupropion-SR and buspirone were not different as augmentation options in the

second-step treatment according to 17-item Hamilton Rating Scale for Depression scores, secondary measures (e.g., tolerability, symptom change from baseline to exit in the 16-item, clinician-rated Quick Inventory of Depressive Symptomatology) recommended bupropion-SR over buspirone. Thus, substantial pharmacologic differences between the second-step medications did not translate into substantial clinical differences in efficacy.

The cognitive therapy findings at the second step were both encouraging and disappointing. There was no difference between cognitive therapy as a switch or as augmentation strategy versus medication as a switch or augmentation strategy (7). Yet cognitive therapy may well be treating a group that is not particularly medication responsive (8). However, far fewer patients than expected elected randomization that included cognitive therapy—perhaps because of the need for additional copayments, the fact that some patients were already seeing a therapist, or the need to visit yet another provider at another site. Thus, future work to enhance the delivery and convenience of obtaining cognitive therapy is needed. Much as 7-Eleven has found, convenience sells. Inconvenience is an obstacle.

In the third medication step (Level 3), a medication switch was far less effective than was a medication switch at the second step according to scores on the 16-item, self-reported Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$). In addition, a change in presumed mechanism of action at the third medication switch step (mirtazapine versus a third reuptake blocker, nortriptyline) did not produce different outcomes.

At the third medication augmentation step (Level 3), T_3 augmentation did as well or better than lithium, suggesting that T_3 deserves stronger consideration than many expected and confirming the value of T_3 (9) in less resistant patients. Higher doses of lithium might have been more effective, but even at the doses used, tolerability was an issue.

Finally, in the fourth medication step (Level 4), we expected a better result than we obtained with tranylcypromine—perhaps because the Level 3 medication had to be discontinued for a washout period before tranylcypromine could be started or because lower than desired tranylcypromine doses were used (although tolerability was an issue with tranylcypromine). In these rather treatment-resistant Level 4 patients, results also provided the first evidence of tolerability and at least modest efficacy with the combination of venlafaxine-XR plus mirtazapine.

Finally, subject attrition was substantial, despite the extra staffing provided by the Clinical Research Coordinators, patient education, and the availability of cost-free treatment. Most patients who left the study were not in remission. Methods to enhance retention and to achieve earlier remission in more patients are clearly needed.

Our initial follow-up findings (10) revealed: 1) remission at entry into the follow-up phase was consistently associated with a better prognosis than was simple improvement at entry into the follow-up phase after the first, second, and third treatment steps; 2) patients and clinicians are less willing to push for remission in patients with greater levels of resistance, since more patients at follow-up entry were *not* in remission after more prior unsuccessful acute treatment trials; and 3) regardless of remission status at follow-up entry, higher relapse rates were found among those who required more acute treatment trials (i.e., for those with greater levels of resistance).

These findings validate the importance of remission (not simply response) as a clinically meaningful endpoint, given the lower relapse rates for those who were in remission at entry into the follow-up phase than among those who had not achieved remission (10). These results also indicate that patients with treatment-resistant depression deserve very diligent follow-up care. These follow-up results also highlight the need to focus future trials on longer-term outcomes to examine the durability of earlier improvement and to identify the best treatments for patients who relapse over time.

The decreasing likelihood of remission with later treatment steps (14% and 13% after steps 3 and 4 versus 37% and 31% after steps 1 and 2, respectively) (10) has policy impli-

cations. Logically, primary care providers are well positioned—if given the time, staff support, and reimbursement support to deliver high-quality, measurement-based care—to conduct the first two treatment steps. Thereafter, more complex drug regimens are likely needed; the gains are likely to be lower; and the evidence base is truly sparse. Perhaps these steps are best left to specialists.

STAR*D results also raise important research design and treatment issues. Why not include more broadly representative patients in placebo-controlled efficacy trials that are used to develop treatments? Presently, symptomatic volunteers who are not fully representative of actual patients commonly populate these early efficacy trials. Unlike self-declared patients seen in practice settings, these subjects often have minimal medical or psychiatric comorbid conditions, nor are they chronically ill. Thus, efficacy trial findings may not generalize to actual practice. If we could protect patient safety and ensure internal validity in such efficacy trials, results would be more directly applicable to our patients, who are less likely to improve spontaneously than symptomatic volunteers. Such patients would reduce placebo response rates and thereby reduce the likelihood of failed trials.

From a treatment perspective, STAR*D results raise the question of whether combination (two antidepressants) or augmentation (one antidepressant and another agent to augment its effect) might be more effective (achieve remission faster in more patients) than several sequenced monotherapy steps. STAR*D found very reasonable safety and tolerability for several combination/augmentation options, but it did not compare such options (which are commonly used in practice) with monotherapies at different steps, except at Level 4. On the other hand, a large proportion of patients chose randomization to combinations/augmentations. Since remission must be the goal of treatment—a notion clearly supported by the STAR*D follow-up results—different combinations/augmentations at the first or second steps might well increase remission rates in more patients, either because different drugs target different patients or because the combination/augmentation is simply a pharmacologically more powerful and broader spectrum antidepressant.

The gap between what we do in practice and what we know is very large. We insist that remission is our goal, yet we do not routinely carefully measure symptoms in practice to determine if remission occurs. Yet we know that "better but not remitted" consistently leads to a worse prognosis than full remission. We often underdose or poorly titrate medication. Finally, we often combine treatments in practice, yet very few trials have assessed either safety or efficacy of these efforts. Analogous to treating hypertension, diabetes, or many other medical conditions, our patients deserve every chance to reach remission. "Less hypertensive" is not the goal of treatment of hypertension. Nor should "less depressed" be the goal for our depressed patients.

Finally, on a personal note, large efforts like STAR*D are the ultimate exercise in "delayed gratification." But at the end of the day, the journey—the process of working with outstanding investigators and committed staff and patients—is its own unique reward. No single trial can answer more than a few specific questions, but such efforts can develop new clinical or research methods and raise important questions for further study. I and all of my colleagues are extremely grateful for the chance to contribute a small bit in a large and challenging area. Most important, we wish to thank all of our patient participants and the clinical staffs for their commitment to making STAR*D a reality.

References

1. Murphy SA, Oslin DW, Rush AJ, Zhu J: Methodological challenges in constructing effective treatment sequences for chronic psychiatric disorders. Neuropsychopharmacology 2006; advance online publication, 8. Nov 2006; doi:10.1038/sj.npp. 1301241
2. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, Shores-Wilson K, Morgan D, Schwartz T, Balasubramani GK, Rush AJ: Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med 2004; 34:1299–1308

3. Fava M, Rush AJ, Alpert JE, Carmin CN, Balasubramani GK, Wisniewski SR, Trivedi MH, Biggs MM, Shores-Wilson K: What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. Can J Psychiatry 2006; 51:823–835
4. Gaynes BN, Rush AJ, Trivedi M, Wisniewski SR, Balasubramani GK, Spencer DC, Petersen T, Klinkman M, Warden D, Schneider RK, Castro DB, Golden RN: A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. Gen Hosp Psychiatry 2005; 27:87–96
5. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
6. Wisniewski SR, Fava M, Trivedi MH, Thase ME, Warden D, Niederehe G, Friedman ES, Biggs MM, Sackeim HA, Shores-Wilson K, McGrath PJ, Lavori PW, Rush AJ: Which second step treatments are acceptable to depressed outpatients and their clinicians? A STAR*D report. Am J Psychiatry (in press)
7. Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, Fava M, Nierenberg AA, McGrath P, Warden D, Niederehe G, Rush AJ: Cognitive therapy as a second-step treatment: a STAR*D report. Am J Psychiatry (in press)
8. Schatzberg AF, Rush AJ, Arnow BA, Banks PL, Blalock JA, Borian FE, Howland R, Klein DN, Kocsis JH, Kornstein SG, Manber R, Markowitz JC, Miller I, Ninan PT, Rothbaum BO, Thase ME, Trivedi MH, Keller MB: Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. Arch Gen Psychiatry 2005; 62:513–520
9. Joffe RT, Singer W, Levitt AJ, MacDonald C: A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 1993; 50: 387–393
10. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905–1917

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