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Beyond Efficacy: The STAR*D Trial

(Reprinted with permission from the American Journal of Psychiatry 2006; 163:5–7)

Psychiatrists have a range of treatments to offer patients with depression. Randomized controlled trials have demonstrated the efficacy of tricyclic antidepressants, SSRIs, cognitive behavior therapy, and interpersonal therapy. For each of these interventions, one can say with some confidence that at least 40% of a cohort with depression will show statistically significant reductions in unbiased ratings of depression. This information, while entirely commendable in the world of research, is far from satisfactory in the world of practice where an individual clinician needs to make treatment decisions to help an individual patient. The practical questions that the clinician might ask include: For this specific patient, what is the best of the available treatments? What magnitude of response can my patient realistically expect in 4 or 6 weeks? And what should I do if my patient is not sufficiently better in this period: continue or switch treatments? If the first treatment does not work, what is the next best option?

Trivedi and colleagues have addressed these questions in a landmark study, part of which is published in this issue of the *Journal*. Their results from the first phase of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial signify a new approach to clinical trials as part of an NIMH effort to support research with direct, practical value to clinicians. These trials, variously called "practical trials" or "effectiveness trials", differ from traditional efficacy trials in several ways (1, 2). Whereas traditional efficacy trials have strict inclusion criteria, usually compare a drug against placebo, and limit outcome to rating scales, effectiveness trials include a broad spectrum of patients (including suicidal patients in depression trials), compare active treatments rather than active treatment against placebo, and focus on real-world outcomes such as measures of functioning. In addition, these new trials often test effectiveness with self-declared patients in primary care settings where most depressed patients receive treatment. Traditional efficacy trials generally study symptomatic volunteers recruited via advertisements, and the setting is either in academic health centers or commercial clinical research organizations.

The STAR*D trial enrolled 4,041 outpatients with nonpsychotic depression at 23 psychiatric and 18 primary care sites. All patients began with a 12-week course of the SSRI citalopram, administered according to a treatment manual that allowed individualized management of doses within a preplanned schedule. The STAR*D trial focused specifically on achieving remission from depression rather than partial improvement. Phase 1 examined this first 12 weeks of treatment to identify those who achieved remission. Among the patients who did not achieve remission or could not tolerate citalopram, Phase 2 compared several different strategies that entailed either replacing citalopram with a different treatment or augmenting citalopram with an additional treatment, including cognitive therapy. Those without sufficient improvement were offered up to two additional levels of treatment. Those who achieved an adequate response were followed for 1 year to evaluate long-term outcomes with these various treatments.

So what does this approach tell us? This first report of the STAR*D trial includes only Phase 1 results (N=2,876) but already provides important, practical answers. First, only about 30% of patients met criteria for remission during citalopram treatment. For remission, the mean dose of citalopram (41.8 mg/day) was higher and the mean duration of treatment (47 days with 5.5 visits) was longer than might have been expected on the basis of current clinical practice. This rate and timing of response was approximately the same in specialty care and primary care sites. Who responds? In general, response was best in highly educated, currently employed Caucasian women with few complicating psychiatric or medical disorders. Most important, this study demonstrates that for at least 70% of patients, appropriate treatment with an SSRI is not enough. What is the next best step for this 70%? The results of Phase 2 should answer that question.

Aside from the specific results, the report from Trivedi et al. is important for demonstrating that research in ecologically valid settings works. The STAR*D trial may be one of the first psychopharmacologic studies to merge the disease management approach to the demands of a clinical trial.

Disease management, an important new trend in caring for patients with chronic illness (3), enlists the patient as a collaborator by providing tools for self-monitoring symptoms, side effects, and adherence. In this study, simple self-ratings were used to guide the dose increments. As we are seeing with other chronic illnesses, these ratings may be a practical adjunct to guiding depression treatment in routine practice outside of a research study, analogous to self-monitoring glucose for the management of diabetes.

In some diseases, such as pediatric cancers, cystic fibrosis, and a number of rare neurologic disorders, every patient becomes a research subject. But in psychiatry, as in most areas of medicine, there has been a gulf between research and practice. This has led to the unfortunate current state where too many research studies have little immediate relevance to practice, and too little practice is based on research evidence. NIMH has developed several practical trials such as STAR*D to bridge this gap between research and practice by studying patients in real-world settings and asking questions with practical relevance.

Other recent NIMH practical trials include the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which compared the newer "atypical" antipsychotic medications with one another and with the older conventional antipsychotic medications in terms of reduction of symptoms, ability to resume functioning, and side effects. In two different components of the trial, various antipsychotics were evaluated in people with schizophrenia (4) and in people with Alzheimer's disease who were also experiencing psychosis or agitation (5). Another practical trial, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), was designed to determine the most effective long-term and acute therapies for people with bipolar disorder, including SSRIs, mood-stabilizing medications, and atypical antipsychotics as well as various types of psychosocial interventions (6).

These trials match the NIMH vision of developing personalized care. Personalized care, whether in cancer or depression, will be based on a thorough understanding of risk and resilience of each individual as well as a deep understanding of the pathophysiology of the disorder. By beginning to identify which particular treatment benefits which patient, the STAR*D trial takes us a little closer to realizing this vision for nonpsychotic depression. From Phase 1 it appears that the SSRI citalopram is only sufficient for a minority of patients, particularly high functioning, well-educated women with few comorbid psychiatric or medical problems. Since there was no placebo control group, we do not know how many of these patients would remit without active drug treatment, so even for this 30%, can we be certain of the value of the drug? This trial was not designed to test efficacy of citalopram treatment, for which comparable remission rates with SSRIs in placebo-controlled, 8-week, randomized, controlled trials had already been reported. But the bigger question is how to choose the treatment for the other 70% of patients. With the forthcoming Phase 2 results, we should soon know even more about how to choose treatments for those who do not respond to the first trial of an SSRI.

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