STAR*D: Helping to Close the Gap Between Science and Practice

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Practical clinical trials, such as STAR*D (Sequenced Treatment Alternatives to Relieve Depression), extend the traditional randomized controlled trial to real-world settings. Consumers and clinicians should be encouraged by STAR*D's 70% remission rate and should realize that for many participants remission required medication switching and augmentation. Policy makers should recognize the importance of easy access to a full range of treatments. Researchers should be sobered by the high attrition rate and the 30% of participants who did not achieve remission. Although more such practical trials are needed, future work must more meaningfully involve consumers in design, analysis, and interpretation. (*Psychiatric Services* 60:1458–1459, 2009)

The continuing gap between knowledge and practice is one of the most vexing problems facing our health care system. The 17-year latency period before consistent application of new knowledge to ordinary practice likely proves fatal for thousands of people each year (1). The gap stems from persistent problems in the training and support of clinicians as well as in the organization and financing of services. Addressing these problems will be a core challenge in efforts to reform health care. It is critical that this gap be closed.

On Capitol Hill burgeoning political activity supports the use of systematic reviews and comparative effectiveness research to make decisions about policy and health care coverage. These efforts explicitly rely on rigorous and relevant scientific findings as well as on appropriate methods for synthesizing and interpreting scientific results.

One aspect of these approaches that is not frequently discussed is related to the ways in which information is generated, synthesized, disseminated, and implemented. Because of strong cultural traditions in most biomedical disciplines, the randomized clinical trial is held as the gold standard for scientific inquiry. Clearly, this method is preferred when we desire to strongly demonstrate that a particular intervention can reliably produce a specific effect under particular circumstances. For many reasons, these circumstances are typically quite constrained, often involving homogeneous samples of volunteers who are treated systematically over a relatively brief period. The target outcome is generally a particular clinical marker, often at the symptom level. Persons are assigned to treatments without regard for their treatment preferences. Although all of these controls increase the likelihood of detecting a causal signal, they do little to inform us about the effects of the intervention in more representative situations, which has led to the distinction between efficacy and effectiveness trials. Efficacy involves demonstrating the effect under optimal, controlled circumstances, whereas effectiveness trials attempt to replicate these findings in real-world situations.

STAR*D (Sequenced Treatment Alternatives to Relieve Depression) is one of several practical clinical trials that were launched by the National Institute of Mental Health (NIMH) to help remedy some of these concerns. From our perspective, STAR*D and its companion studies represent important advances in clinical research that enhance the results of both observational studies and randomized clinical trials. As such they are a critically important addition to our body of knowledge and have provided valuable information for consumers, clinicians, and policy makers. In this commentary we highlight some features and findings of STAR*D that have particular relevance for consumers seeking depression treatment in real-world settings and for advocates who work to ensure consumers' access to high-quality care.

Relevance of STAR*D for consumers and advocates

A few of the features of the STAR*D design are particularly noteworthy in regard to closing the gap between science and practice (2). STAR*D involved more than 4,000 participants, who were receiving care at 41 representative primary and specialty care clinical sites. The sample is more representative than the typical sample in a randomized clinical trial because min-

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imal exclusion criteria were employed, thus permitting more subgroup analyses than the typical trial. Using remission rather than response to treatment as the clinical target helped to sharpen our thinking about outcomes and allowed for a better understanding of the trajectory of recovery. Use of a 12-month follow-up and multiple outcome measures across clinical, functional, and quality-of-life domains provided a framework for better understanding of the overall, more enduring effects of treatment. The design also allowed participants to choose among various strategies for medication augmentation or switching when their symptoms did not remit during the initial trial of citalopram. These strategies included the choice of another selective serotonin reuptake inhibitor at the level 2 intervention. This feature allowed for modeling and better understanding individual preferences for treatment than would have been the case with a standard trial design.

Because of this flexible and complex design, STAR*D has provided a great deal of rich information that is important for individuals seeking help for depression, as well as for clinicians, advocates, and public policy makers (3). Perhaps most important for consumers is the finding that nearly 70% of participants who continued in the trial achieved remission at 12 months. However, nearly half of the individuals who would ultimately achieve remission did not do so until the second, third, or fourth levels of the trial (4). In addition, a significant number of the individuals who achieved remission did not do so during the first six weeks of treatment. For consumers STAR*D results indicate that if they stay in treatment and if the clinician takes a measurement-based approach to care, the odds are good that they will recover. However, more than six weeks of treatment may be required to determine its ultimate effectiveness. Practical trials such as STAR*D may ultimately help us better predict individual treatment trajectories and preferences by using biological and psychosocial markers, thereby realizing the long-desired goal of specifying which treatments work best for which individuals to achieve which outcomes.

However, 30% of participants did not achieve remission after multiple interventions, and a large number of individuals dropped out of treatment (5). These results are cause for concern for advocates and researchers. The findings provide a strong rationale for additional research. Not only do we require basic and clinical research on prevention and treatment, but we clearly need services and implementation research to help us better design treatment approaches that increase participation and enhance quality. Practical clinical trails such as STAR*D provide an excellent format for addressing these services research questions.

For policy makers STAR*D holds several important lessons. Strong cost containment pressures often lead to restricted access to the full range of treatments. The STAR*D results show that engaging persons in continuing care is critically important. Access barriers frustrate participation. In addition, because nearly half of persons seeking care for depression will require multiple medication trials and augmentation strategies, a full range of treatments must be readily available. Although restricting access to care might reduce short-term expenditures, such an approach is likely to do so at the expense of health and functional status—thereby increasing societal costs overall.

Another policy-relevant finding involves the lack of any significant difference in outcomes between patients treated in the primary care or specialty care settings when a measurement-based treatment protocol is used (6,7). This is good news because most individuals seek care through the primary care sector. We must implement payment and regulatory strategies that create incentives for the use of measurement-based approaches in primary and specialty care. As in general health care, better health information technology holds great promise for improving the quality of care, which ultimately should reduce expenditures and improve health status.

Finally, and perhaps most important, the clinical and policy implications of the STAR*D findings argue for increased use of such real-world designs and of similar contract research mechanisms at NIMH. It is unlikely that this extensive and expensive multisite study would have been developed as an investigator-initiated project. It also would probably not have fared well in the traditional review process for research proposals. In the same vein, the collection and use of phase IV trial data must be improved to better inform treatment. Advocacy groups such as Mental Health America are promoting increased consumer-patient participation in the design of clinical trials to ensure that their preferences and the outcomes that they value are considered.

Conclusions

To inform practice we desperately need more timely, accessible, and trustworthy information from multiple, representative settings. The STAR*D trial is an example of a research approach that can help close the gap between knowledge and practice. The consequences of not investing in this type of research greatly outweigh the costs of implementing it.

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References

1. Institute of Medicine Committee on Quality of Healthcare in America: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC, National Academies Press, 2001
2. Rush AJ, Fava M, Wisniewski SR, et al: Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Controlled Clinical Trials 25:119–142, 2004
3. Rush AJ: STAR*D: what have we learned? American Journal of Psychiatry 164:201–204, 2007
4. Rush AJ, Trivedi MH, Wisniewski SR, et al: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. American Journal of Psychiatry 163:1905–1917, 2006
5. Warden D, Trivedi MH, Wisniewski SR, et al: Predictors of attrition during initial (citalopram) treatment for depression: a STAR*D report. American Journal of Psychiatry 164:1189–1197, 2007
6. Gaynes BN, Rush AJ, Trivedi MH, et al: Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. General Internal Medicine 23:551–560, 2008
7. Trivedi MH, Rush AJ, Gaynes BN, et al: Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. Neuropsychopharmacology 32:2479–2489, 2007