The STAR*D Trial: Revealing the Need for Better Treatments

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STAR*D (Sequenced Treatment Alternatives to Relieve Depression) continues to stimulate debate. The landmark trial demonstrated the feasibility of large-scale, community-based studies conducted without pharmaceutical company support. The results provided insight into nonresponse to initial treatment with selective serotonin reuptake inhibitors and alternatives for second- and third-line treatment options and suggested opportunities for personalized approaches to depression care. However, initial and one-year remission rates (28% and 70%, respectively) suggest that important goals for treatment of this disabling disease remain out of reach and that the bar for antidepressants has been set far too low. (*Psychiatric Services* 60:1466–1467, 2009)

Depression is the largest source of medical disability for Americans between 15 and 44 years of age (1). The National Comorbidity Survey Replication reported an annual prevalence of 6.6%, with half of the cases classified as "severe" or "very severe" (2). Although more people are receiving treatment for mental disorders such as depression, there is no evidence that either the morbidity or mortality of these disorders has substantially changed in the past two decades (3–5). Although there may be multiple influences on the rates of disorders and suicide, this point bears repeating: despite extensive marketing of antidepressants—more than 232 million prescriptions in 2007 (6)—public awareness campaigns, and abundant research data, we know of no evidence that shows a meaningful decrease in the rates of suicide or disability from depression.

Of course, antidepressants are used for many other disorders, and suicides are not limited to persons with depression. However, for other heavily used medications, such as antibiotics and statins, the public health outcomes are demonstrably better. These concerns about the value of current depression treatments come at a challenging time, with the United States facing both increasingly constrained resources and growing demands for more economical health care.

Is the problem the complexity of the disorder or the poor effectiveness of the treatments? For us, STAR*D demonstrates that treatment for depression may be less effective than advertised. After 14 weeks of citalopram (average dosage of 41.8 mg per day), 28% to 33% of participants experienced remission. A total of 50% achieved remission after a subsequent switch to or augmentation with another antidepressant. An additional 13% to 14% experienced remission after additional trials with other antidepressants or augmenting strategies. At the end of 12 months, with up to four treatment steps, roughly 70% of participants were in remission. These results are positive, especially for a population with moderate to severe depressive symptoms and substantial comorbidity. However, most placebo-controlled trials report response rates of roughly 30% among depressed persons in placebo groups. It should be noted that remission rates in such placebo groups are lower than 30%. In addition, depressive episodes frequently last from six to 12 months, suggesting that some episodes among STAR*D participants could have been self-limiting even without treatment. Furthermore, many STAR*D participants who achieved remission subsequently relapsed. In the absence of a placebo control group, one could argue that the results of STAR*D demonstrate weak, transient effects of antidepressant treatment.

Nevertheless, let's assume that the results are due to medication effects and not placebo effects or nonspecific influences. Should we accept 28% remission rates after 14 weeks as success? Is a 70% remission rate at one year sufficient? How high should we set our goals for this disabling and often deadly disease? For us, the results of STAR*D suggest that important goals remain out of reach.

Rapid response

In most disorders characterized by acute pain and suffering, patients seek treatments that work in hours not weeks. Electroconvulsive treatment is effective in days, not weeks with a higher response rate than achieved in STAR*D. A research trial

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with ketamine reported antidepressant response, including remission in some cases, within hours (7). Although ketamine is not practical as an antidepressant, these rapid responses provide the proof of principle that we have set the bar for antidepressants far too low—or at least that their effects are far too slow. Research funded by the National Institute of Mental Health continues to investigate whether existing treatments can be used to speed recovery, such as starting with a combination of treatments. Clearly, the next generation of treatments needs to focus on remission in hours or days not weeks and months.

Personalized care

Patients with depression are not looking for effectiveness in a population, they are looking for what will be most effective for themselves. STAR*D provided some demographic evidence for who is most likely to respond or achieve remission, but it did not yield the personalized data we need for helping clinicians and patients choose which medication, psychotherapy, or combination will be best for an individual. Some have used the STAR*D results for pharmacogenomic studies (8,9). Although such studies are laudable for their scale and scope, the absence of a placebo arm means that the data will be helpful only for predicting nonresponse or toxicity. On the basis of the effect sizes observed in genomic studies of STAR*D data, pharmacogenetic tests do not seem quite ready for translation into clinical practice (10). The next generation of trials will likely need to identify other moderators so that such information that can be combined with genetic test results to better predict who will achieve remission with which treatment. Genomics may help, but imaging, family history, and clinical characteristics will also contribute (11).

Effective treatments

One of the strengths of STAR*D was its use of remission as a primary outcome variable. By this measure, current medications may be necessary but not sufficient for the treatment of depression. Psychosocial treatments, such as cognitive-behavioral therapy (CBT), are important, but in the STAR*D trial relatively few participants chose CBT. We need a new generation of antidepressant treatments, both medical and psychosocial. These treatments need to be based on a more thorough understanding of the biology of this illness, and they need to be developed with consideration of the economics and feasibility of delivering health care. CBT is clearly an effective treatment for many with major depressive disorder, but there are too few clinicians trained in CBT and generally inadequate quality control of psychosocial treatments.

In terms of medical treatments, we are facing a crisis in drug discovery, because many biotechnology and pharmaceutical companies will either collapse or become even more risk averse during this economic downturn. Although recent research on deep brain stimulation is extraordinary in its implications for the biology of depression (12) and the Food and Drug Administration has recently approved regional transcranial magnetic stimulation for depression as well as deep brain stimulation for obsessive-compulsive disorder (www.fda.gov/medicaldevices), we do not know whether these experimental interventions will have a substantial public health impact for the millions of people with major depressive disorder.

Conclusions

STAR*D was an important study. It demonstrated the feasibility of large-scale trials across many settings that are independent of support from pharmaceutical companies. The results dispelled several myths in the treatment of depression, including the advantage of a dual-action switch agent for patients who do not respond to selective serotonin reuptake inhibitors (SSRIs) and the futility of using a different SSRI for those who do not respond to citalopram. The study also documented the frequency of relapse, especially among those who were not in remission. But perhaps most of all, STAR*D reminds us that we have a long way to go in the treatment of this common, disabling illness. In 2007 in the United States more prescriptions were written for antidepressants than for any other class of medication, at a cost of nearly $12 billion (6). Research needs to move beyond simply investigating the comparative effectiveness of current medications to pursuing the development of better treatments that will reduce the burden of illness from depression.

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