

The Failure of Evidence-Based Medicine to Guide Treatment of Antidepressant Nonresponders

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Depression is one of the world's greatest health problems,¹ and prompt recognition and vigorous treatment to remission are the best means to reduce the global illness burden, increased mortality, and untold suffering associated with depressive disorders. As I have reviewed elsewhere, dozens of randomized controlled trials (RCTs) have documented that antidepressant pharmacotherapy, the most widely used treatment for depression, has limited efficacy.²⁻⁵ Such findings are not an anomaly of RCTs: Trivedi and colleagues⁶ found that depressed patients had no more than a 50-50 chance of responding to up to 12 weeks of pharmacotherapy with citalopram in the first level of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Physicians treating depressed patients thus need to be well versed in the alternate strategies for antidepressant nonresponders and—at least in theory—the principles of evidence-based medicine (EBM) should provide the best means to weigh the merits of the most promising treatment options. Regrettably, as Ruhé and colleagues⁷ report in this issue of the *Journal*, the state of the evidence on second-stage strategies for selective serotonin reuptake inhibitor (SSRI) nonresponders is so meager that it is essentially futile to apply EBM to this important problem. In this commentary, I will explore the causes of the failure of EBM to guide selection of therapeutic alternatives for SSRI nonresponders and make several modest suggestions for future research.

Why are there so few relevant RCTs for such a common problem as treatment-resistant depression (TRD)? A small part of the problem is that EBM approaches tend to favor older, more established therapies, and Ruhé et al.⁷ limited their review to patients who did not respond to an SSRI. Had Ruhé et al.⁷ taken a broader view, they would have concluded that lithium augmentation, thyroid aug-

mentation, and switching to a monoamine oxidase inhibitor are established “A-level” therapies for nonresponders to tricyclic antidepressants (see, for example, Thase⁸). Nevertheless, the SSRIs are hardly new therapies and, as tens of millions of patients worldwide have been treated with these medications in the nearly 20 years that have transpired since fluoxetine was introduced, the dearth of RCTs is not from lack of opportunity. Moreover, the older therapies were studied in STAR*D, and it was found that both lithium and thyroid augmentation,⁹ as well as switching to either nortriptyline¹⁰ or tranylcypromine,¹¹ hardly set the world on fire for patients who had not responded to at least 2 sequential trials of newer antidepressants.

A more salient explanation is that studies of TRD are both difficult to conduct (see, for example, Rush et al.¹²) and difficult to obtain funding for. At the root of the former problem is the undeniable fact that, because antidepressants have modest effects, very large RCTs need to be undertaken in order to have adequate statistical power to make meaningful comparisons. Even in the STAR*D study, which is the largest study of TRD ever undertaken, only between-group differences of greater than or equal to 15% in response or remission rates could be detected with 80% power. As the mean drug-placebo difference in contemporary antidepressant RCTs is only about 10% (e.g., Thase et al.^{2,4}), STAR*D, in retrospect, was underpowered. If one accepts a 10% difference in outcomes as the acceptable “margin” of incremental benefit,¹³ perhaps as many as 1600 patients would have to begin an initial course of SSRI therapy in order to enroll the 700 to 800 patients necessary to conduct an adequately powered, 2-arm, controlled trial contrasting one novel therapy with placebo. That said, such a labor-intensive and expensive trial would provide no information about the relative efficacy of that novel intervention, and, even if the novel therapy was significantly more effective than placebo, the study would fall short of the evidentiary standard employed by the U.S. Food and Drug Administration (FDA), which requires at least 2 positive, well-controlled RCTs for an indication. It truly is a challenge to prove that a particular treatment is effective when standard options have failed.

There are also significant ethical concerns about the appropriateness of using a placebo control for patients

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who have not responded to standard therapies, and alternate control conditions—such as continuing the ineffective medication or switching to a closely related medication—are not without interpretative issues.^{8,12} In my view, the most useful control groups are (1) for augmentation studies, continuing the ineffective medication and adding an identically appearing placebo and (2) for switch studies, switching to a second SSRI. By these standards, it is not certain if either of the augmentation strategies tested in STAR*D would have been more effective than placebo, and neither of the across-class switches offered a 10% advantage over the within-class switch from citalopram to sertraline.^{14,15}

Another possibility would be to treat patients with a history of antidepressant nonresponse with interpersonal psychotherapy (IPT) or cognitive-behavioral therapy (CBT), randomizing only those who remain depressed at the midphase therapy to double-blind treatment with an active drug or placebo. Both IPT and CBT have antidepressant efficacy and are typically conducted over 12 to 16 weeks, which would permit an adequate amount of time for a 2-stage RCT. However, I recognize that this is an, as of yet, unproven strategy and would be nearly as costly as the earlier example.

With respect to research funding, we must come to terms with the fact that the manufacturers of antidepressants, who fund the large majority of RCTs, generally should not be counted on to fund large, pragmatic studies of TRD. There are a few exceptions pertaining to augmentation strategies (modafinil,^{16,17} olanzapine augmentation of fluoxetine^{18,19}), although—at least to date—these efforts have not led to any FDA indications for medications for TRD.

Barring some unforeseen change in regulatory practices, the focus of the pharmaceutical industry will continue to be on the research necessary to bring a novel compound to the market, with the hopes that these medications will become first-line therapies. Whether valid or not, there is a widely held perception within the pharmaceutical industry that a medication that was shown to be effective for TRD would be pigeonholed as a second-line or third-line therapy.

As illustrated by Ruhé et al.,⁷ when postmarketing studies of new medications as treatments for SSRI nonresponders are conducted, the manufacturers are much more likely to employ a prospective, open-label case series design. Such studies have some value, especially when the observed response rates are very high (i.e., “Looks promising—further research is needed.”) or low (i.e., “Don’t bother!”). However, the observed response rates in these studies are typically intermediate and, hence, indeterminate. Even when moderately high response rates are reported, as exemplified by 3 studies that I led,^{20–22} caution in interpreting the results is needed because open-label case series capitalize on expectation

bias, particularly when the preceding SSRI nonresponse was not established prospectively.

As one of the STAR*D investigators, I am proud that our efforts illustrate that large practical studies of TRD can be conducted in collaboration with the National Institute of Mental Health (NIMH) and that this research can be conducted with “real world” patients, including those who receive their care in primary care clinics and community mental health centers. It is also true that a number of pharmaceutical manufacturers contributed hundreds of thousands of dollars to defray the cost of study medications, with no strings attached.

STAR*D left many questions unanswered, however, and there is much work to be done. As Ruhé et al.⁷ have confirmed meta-analytically, more research is needed in order to answer even relatively basic questions facing physicians treating depressed patients every day, such as “Do I switch or do I augment and, either way, with what strategy?” And, alas, although a Depression Treatment Network has been established to carry on the work of STAR*D, even the most optimistic among us expects that federal funding will be available to test no more than one or 2 questions at a time.

If neither the pharmaceutical industry nor the NIMH can be counted on to pay the bill, then who will fund the studies necessary to bring the evidence base for management of depression to a level that is on par with other chronic medical disease states? We are the only likely candidates—psychiatrists who treat depressed patients and who share the common belief that clinical research can lead to better outcomes for patients. Wouldn’t it be nice if the American Psychiatric Institute for Research and Education (APIRE), a component of the American Psychiatric Association, could be lured into the business of conducting large practical studies on TRD? The APIRE Web site states that their Practice Research Network has more than 800 participating psychiatrists and that for a number of years, they have been conducting descriptive studies. As the patients treated by the Practice Research Network psychiatrists are seen on a fee-for-service basis, the project might require only a modest level of funding for data management and administrative support—an amount that would be neither the ruination of the NIMH nor outside of the range of many foundations. Although there are legitimate reservations about asking “paying customers” to accept random assignment to treatment, this is not an ethical issue with proper informed consent. Alternative designs, such as randomizing doctors, rather than patients, to rotating blocks of strategies might also be considered (i.e., Dr. Smith’s random assignment is to treat 10 consecutive consenting patients with a second SSRI, followed by 10 consecutive consenting patients with medication X.). The analytic approach needed for this type of design is a bit more complicated, but there are excellent biostatisticians available who would be more than able to work out the kinks.

As in other areas of medicine, there needs to be an ongoing commitment to conducting the kind of large-scale pragmatic studies that are needed to help inform day-to-day practice.²³ If one takes into account the billions of dollars that depression costs the U.S. economy each year, continued investment in research aimed at improving the outcomes of individuals with difficult-to-treat depression provides strong justification for continuing collaboration among academia, industry, government, and practicing psychiatrists.

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