In Defense of the Traditional Efficacy Trial

The randomized controlled clinical trial is still a relatively new technology for assessing therapeutic interventions, yet innovations in the design and analysis of clinical trials in psychiatry have lagged behind other areas of the biomedical sciences. This delay in the advancement of the science and practice of psychiatric clinical trials is due in part to the inability, dating back to the 1950s, to solve the problem of the unreliability of psychiatric diagnosis and to the inability of psychiatric researchers to develop common agreed-upon outcome measures. Even though advances have been made in diagnosis and measurement, the existence of these and other methodological problems continues to contribute to the limited success of acute-phase efficacy trials in psychiatry. For example, in depression, Thase (1999) notes that

At least one third of the published clinical trials of approved antidepressants are negative for efficacy, which can be partly explained by the clinical and neurobiological heterogeneity of the depressive disorder and partly because of methodological inadequacies. Unfortunately, too little attention is given to ensuring the reliability of diagnosis and dependent measures, sample sizes are seldom large enough to detect modest yet honestly significant differences, and too many trials are pursued before dose-response characteristics are fully understood.

If it is true, as in depression, that “no currently approved medication obtains intent-to-treat response rates of better than 60%—actually, intent-to-treat rates of 40% to 50% are commonplace—and 10% to 20% of antidepressant trials are ended prematurely because of adverse effects” (Thase 1999), then it is not surprising that these treatments do not generalize well into clinical practice, since even in the most controlled settings we do not have very effective first-line interventions. Recently, as pressure has mounted for treatments that work in real world settings, it seems that more attention has focused on perceived inadequacies of the traditional efficacy trial (e.g., Norquist et al 2000) than on our continued inability to understand and characterize the heterogeneity of mood disorders (Hyman and Shore 2000), to identify appropriate outcome measures (Rush et al 2000), and to address methodological inadequacies such as the ones noted above. Innovations in the design of clinical trials alone will not solve the problem of the lack of effective clinical interventions, but multidisciplinary collaborations that consider the challenges as a whole and build on existing experience in the science and practice of clinical trials hold great promise for advancing our ability to identify and optimally administer effective treatments.

Design Considerations: Evaluating Treatment Strategies

When first- and second-line treatments are available and have been shown to be effective, a challenging question then is how to design a clinical trial to determine the best treatment strategy that will inform clinicians whether or not and when to move a patient from the first-line treatment to the second-line treatment. Two articles are presented in this issue that are concerned with this question, specifically in the context of treatment for bipolar disorder. Lavori et al (2000), in a very interesting and carefully reasoned review, draw upon their considerable experience with the science and practice of clinical trials to propose an innovative adaptive (within-patient) threshold-based strategy for clinical decision making and illustrate ways to design randomized clinical trials to compare such treatment strategies. A notable feature of this article is the careful specification of the clinical questions of interest, the assumptions being made, and the criteria that will be used to identify the best treatment strategy.

In an equally scholarly and thought-provoking article, Rush et al (2000) are concerned with a similar question, and in this same context discuss practical problems in the development and evaluation of effective acute treatments for bipolar disorder. They propose designs to study treatment-resistant patients who need additional medication. Specifically, they consider “add-on” designs to evaluate the utility of a new intervention as adjunct to whatever baseline treatment(s) patients are receiving, as well as discontinuation designs. It should be noted that there is accumulating evidence to suggest that for patients who respond to a treatment, subsequent changes to that treatment could have detrimental effects. Therefore, clinical trials to study such treatment strategies must include randomized comparison groups that consist of the full complement of treatment strategies, including patients who continue on their initial treatments without changes (see, e.g., Greenhouse et al 1991).
Methodological Considerations

As noted above, there are clearly important methodological problems that need to be solved to help advance the practice of clinical trials in psychiatry. In addition, there is a great deal of experience and wisdom in the science and practice of clinical trials in the other biomedical sciences that will help as well. Interestingly, both Lavori and colleagues and Rush and colleagues acknowledge the contributions from research experiences in cardiovascular disease and epilepsy, respectively, to their proposed new designs. Similarly, hybrid studies that by design simultaneously include experimental and observational data are being used in other areas of biomedical research, and are creating exciting opportunities for answering questions about interventions in more general settings and interesting challenges to statisticians to develop methods for the design and analysis of such studies. (See, for example, the study of the effectiveness of breast conservation therapy versus mastectomy in day to day medical practice using results from randomized clinical trials and administrative database records for breast cancer patients treated outside randomized studies [U.S. Government Accounting Office 1994].)

In considering statistical methods that will contribute to advancing the practice of clinical trials in psychiatry, it is useful to place intervention studies into the wider context of scientific discovery. Although the scientific method provides a systematic approach for gathering evidence and is predicated on learning, previous results and knowledge are not explicitly incorporated in the standard statistical analysis used to assess evidence. There is a statistical approach, however, that does provide a formalism for scientific learning through applications of Bayes theorem. Although the Bayesian approach to statistical problems has been considered by many to be theoretically appealing but of unproven benefit in practice, with the advent of modern computational techniques Bayesian methods have begun to emerge as powerful tools for analyzing data in complex settings, such as clinical trials and longitudinal data analysis (Brophy and Joseph 1995; Goodman 1999a, 1999b; Greenhouse 1992).

Why Bayesian methods for clinical trials? As we have seen, the implementation and analysis of randomized controlled clinical trials is rarely easy. Although in theory the conduct of a trial should be relatively straightforward, the complexity of doing a trial in practice arises in part from the need to balance the ethics of human experimentation with the principles of scientific design. Procedures for monitoring clinical trials, for example, developed out of a desire to minimize the number of patients exposed to a potentially inferior or harmful treatment. Yet, these procedures often require relatively sophisticated mathematical and statistical methods for their implementation. Interest in the application of Bayesian methods in clinical trials has grown, in part, because these methods can in fact be conceptualized as familiar multistage, hierarchic models (e.g., random regression models), and because these methods offer an approach for dealing with many of the difficult practical problems that arise in the conduct and analysis of such studies. Some of the features of the Bayesian approach include the ability to utilize relevant historical information regarding the magnitude of the treatment effect of interest, the ability to monitor a trial without the need for adjustments according to the number of looks at the data, the ability to make inferences from a trial based on posterior probabilities of clinically meaningful outcomes, and the ability to measure and report evidence in a scientifically more meaningful way (Greenhouse and Wasserman 1995; Speigelhalter et al 1994).

Much work is needed to begin to use Bayesian methods in psychiatric research, but the effort promises to be worth it. Nevertheless, to develop and implement robust interventions for psychiatric disorders that will be effective in real world settings, it still will be necessary to develop methods that can better identify homogeneous diagnostic categories and can identify prognostic factors for treatment response, to develop meaningful and well-specified outcome measures, and to utilize designs and methods that answer clinical questions of interest.

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References


