What Can Large Simple Trials Do for Psychiatry?

An article in this issue by Strom and colleagues (1) on the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) trial nicely illustrates the promise and the limitations of large simple trials (LSTs). LSTs may be unfamiliar to some readers of the *Journal* because they are rare in psychiatry. Briefly, LSTs are pragmatic randomized clinical trials that are narrowly focused on clearly defined outcomes that are important to patients as well as clinicians. Their goal is to detect modest but meaningful differences between treatments on important outcomes in typical clinical situations (2). Procedures and data collection are greatly simplified compared with typical randomized trials. A large sample is usually needed to detect differences between treatments that would be missed in smaller trials because of inadequate statistical power (3). To enhance generalizability, participants in LSTs are recruited from a variety of clinical sites and are meant to represent typical patients receiving routine care. To enroll large numbers of typical patients, LSTs need the collaboration of clinicians who care for many patients. Simple procedures mean that routine clinical practice is minimally disrupted, which helps keep costs down so that many patients can be enrolled.

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ZODIAC

The U.S. Food and Drug Administration (FDA) approval letter for ziprasidone, dated February 5, 2001, reminded the drug's maker of its "postmarketing study commitments," including "a study of sudden unexpected death with ziprasidone and other atypical antipsychotics" (4). The commitment resulted from concern that ziprasidone's known risk of prolonged cardiac repolarization, measured by the electrocardiographic QTc interval, might cause an increased rate of potentially fatal arrhythmias (e.g., torsade de pointes).

The ZODIAC study carefully adhered to the major conventions of LSTs—a huge number of participants, a simple protocol with minimal data collection, and an important and well-defined outcome measure (nonsuicide mortality). The study was well designed, conducted, and reported. The authors' conclusions are cautiously worded to reflect proper statistical inferences. A plain-language interpretation is that rates of nonsuicide mortality were similar for patients taking ziprasidone and olanzapine over 1 year, but the finding is imprecise because mortality rates were low over the study period. However, it is important to remember that people using antipsychotics are at increased risk of sudden cardiac death compared with those not taking such medications, and that this risk is dose-related (5).

Readers may see ZODIAC, the largest prospective randomized study of patients with schizophrenia yet conducted, as a missed opportunity to learn much more about effects of antipsychotic drugs on other outcomes of interest, including functioning, symptoms, weight, and extrapyramidal side effects. This is the major trade-off in an LST—to obtain a reliable answer about a single outcome, a huge number of patients must participate, but extensive data are not collected. Nevertheless, important effectiveness information is included in the ZODIAC report. Time to treatment discontinuation for any cause was longer for people assigned to olanzapine than for

those assigned to ziprasidone. Psychiatric hospitalizations were significantly more likely for those assigned to ziprasidone. Thus the ZODIAC study confirms effectiveness findings from earlier randomized trials and meta-analyses (6–9).

As illustrated by the Method section of the ZODIAC report and the study timeline, even though procedures at clinical research sites are minimal, LSTs can be enormously complex undertakings that require extensive planning and years to conduct. Surely, 7 years (the time from FDA approval for ziprasidone until ZODIAC was first publicly presented) is too long to wait for the results of a study addressing an increased risk of mortality. Because of this, LSTs are not the optimal way to examine the risk of rare but serious adverse events.

Postmarketing randomized controlled trials such as ZODIAC provide information about longer-term drug safety, but better, faster, and cheaper ways to get this information are desperately needed. One promising new program is the FDA's Sentinel Initiative, which aims to build a national automated health care data system to monitor the safety of FDA-regulated products "continuously and in real time" (10). The Sentinel Initiative has already begun multiple projects that will shape an "active surveillance" system that will augment existing systems that rely on external sources to report potential adverse events (11).

Role for Large Simple Trials in Psychiatry

LSTs can and should have an important role in assessing the effectiveness of newly approved drugs compared with standard treatments in psychiatry (12). Little is known about the long-term effects of new drugs when they come to market. The relatively small and brief trials conducted to achieve regulatory approval are carefully designed to show short-term efficacy and safety but are clearly not concerned with long-term adverse effects. Even major safety problems, including increased risk of sudden cardiac death, may be undetected when a new drug is first available. The widespread use of patented new drugs in preference to existing treatments, based only on results from short-term registration trials and with minimal long-term safety data, is expensive and potentially dangerous.

As prospective and randomized trials, LSTs represent the gold standard of comparative effectiveness research and can provide the most reliable information possible about the real-world effectiveness of new medications. By keeping goals simple and costs low, LSTs may be affordable for public funders that need objective information. LSTs can help identify true advances and avoid costly adoption of new medications that offer no real advantage over old ones. LSTs can also be used to evaluate common but unproven practices, such as the simultaneous use of multiple antipsychotics for people with schizophrenia.

Some aspects of psychiatric practice do not fit easily into the LST model. Psychiatry generally lacks the commonly accepted, discrete, and clearly important outcomes that are the primary endpoints of LSTs. Recovery may be the most important outcome for mental disorders, but it is not simple to measure. Treatment discontinuation for any cause has many desirable properties, but its clinical significance is unclear to some. Hospitalization, relapse, and efficacy failure may be the best outcome measures for LSTs involving severe mental disorders.

An excellent recent example of a pragmatic or large simple trial in psychiatry is the U.K. Mental Health Research Network's Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation (BALANCE) trial (13). BALANCE compared lithium alone, valproate alone, and the combination of lithium and valproate for maintenance treatment of bipolar disorder. The primary outcome measure used to indicate relapse was time to new intervention for new mood episode. Because the use of a new intervention is important but occurs commonly, the study did not require a huge number of participants to judge a meaningful difference. Simple procedures meant that study costs were

not enormous. The study's important findings—namely, that combination therapy with valproate and lithium and lithium monotherapy are more likely to prevent relapse than valproate alone—should influence practice (13).

There is an important potential role for LSTs in psychiatry to evaluate the comparative effectiveness of new treatments and other common but unproven treatment strategies. LSTs can provide essential information for clinicians, patients, and policy makers at limited public expense. However, to ensure that drugs are safe and to provide adequate monitoring for rare but serious adverse events, the current active surveillance initiatives of the FDA are more likely to yield timely information.

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