Randomized controlled trials: still somewhat immature

Gabor Keitner
Division of Psychiatry and Human Behaviour, Brown University, Providence, RI, USA

Dr. Thornicroft's article on the maturation of randomized controlled trials (RCT) in mental health provides both good news and bad news. The good news is that there is growing awareness and acceptance of RCTs in seeking evidence based practices in psychiatric care. The bad news is that we are at an even more immature stage of methodologic development than Dr. Thornicroft suggests that we are. The obstacles to sound RCTs are many and daunting. Some of these obstacles are so central as to be unresolvable.

The conflict between the design of efficacy trials that give a reasonably sound answer to a very narrow question addressing a very limited population and the design of effectiveness trials that evaluate complex questions in a more heterogeneous and "real world" population is one example. The former provides a relatively clear answer to a question so narrow as to

Correspondence:
Professor G Keitner,Division of Psychiatry and Human Behaviour, Brown University, Providence, RI 02912-G, USA.
email: gkeitner@lifespan.org

have limited clinical utility. The latter provides more applicable and generalizable answers but without any precision as to the active ingredients.

In a recent report, for instance, it was noted that fewer than fifteen percent of patients who applied to participate in clinical trials were found to be eligible for recruitment to those studies.[1] Looking at this issue from another perspective, fewer than fifteen percent of unselected patients attending a psychiatric outpatient department clinic met eligibility criteria for inclusion into clinical trials.[2,3] Results from clinical trials are nonetheless routinely interpolated to the universe of patients with similar but not identical diagnoses and problems. A call to give greater weight to data derived from RCTs without educating the professions and the public to the significant methodologic problems and limitations of RCTs may by creating a false sense of security. By raising expectations it may also lead to unsupportable clinical practices. The recent increase in polypharmacy in the treatment of most psychiatric disorders may be, partly, a reflection of this tendency to generalize from unrepresentative studies giving rise to unrealistic expectations of effectiveness.

Dr. Thornicroft notes that clinical trials allocating individual patients to a simple trial of a single or sequential intervention is most common and presumably easier to design and implement than studies of groups and systems of care. Yet even "single" clinical trials are fraught with many variables that are difficult to control for or at worst are easily manipulated to conform to pre-existing biases.

Patients can be chosen who are more or less likely to respond to the treatments studied. Patients who have comorbidity, have an illness that is too severe and difficult to treat, who are "too young," "too old," who cannot read and cooperate with the consenting process, whose illness is characterized by frequent or infrequent recurrences can be included or excluded based on desired outcomes.

Outcome measures can also be chosen to increase or decrease the likelihood of a particular result. Many RCTs use multiple outcome measures for the same set of symptoms and focus on the ones that yield the most desirable results. Even more disturbing is the trend to altering definitions of response and remission so as to make a treatment appear better than it really is. Definitions of treatment response range from 50% to 40% to 30% of change from baseline scores.

True placebo response rates are becoming increasingly difficult to ascertain. Many RCTs have placebo response rates in the range of 30 – 70% due to a tendency to pick patients with lower severity of illness, without comorbidity, or history of treatment failures and patients who will cooperate with the treatment protocols.

Studies that attempt to evaluate the effectiveness of psychotherapies alone or in conjunction with medications face even greater hurdles. This is especially so when multiple sites are used. This is often the case as it is very difficult to obtain sufficient numbers of subjects at any one site. In these studies additional problems relate to trying to control for non-specific treatment factors, establishing and monitoring therapeutic fidelity and adherence tot he treatment studied and maintaining blindness on the part of raters to the therapies being compared.

Conducting methodologically sound studies is very expensive, adding to the difficulty of arriving at meaningful data that can be reliably accepted as guideposts for clinical practice. Because of the expense of the studies it is difficult to conduct studies with large enough numbers to have adequate power to answer the questions being asked. The source of funding for the studies also appears to have some impact on the results obtained.

None of the above concerns are meant to undermine Dr. Thorncroft's attempt to draw attention to the importance of empirical testing of treatments and his assertion that RCTs are "a gold standard for answering questions about treatment efficacy." In this he is clearly correct. He is also correct in identifying the early developmental stage that we are in in understanding and using RCTs. We need to mature both in the development of more rigorous well-designed and analyzed studies and we need to mature in our ability to recognize and accommodate to data emanating from studies that do not meet such standards.

The reality is that we are unlikely to have large numbers of well-conducted studies on large numbers of patients that address many of the daily clinical questions that practitioners need answers for in order to provide competent care. This places considerable burden on clinicians to review the methodology sections of RCTs in order to determine how much of the information presented is valid and reliable as well as relevant to their practice.

For the foreseeable future, even with the increasing recognition of the value and importance of RCTs, most clinicians will, in addition, continue to rely on their own clinical experience and the experience of their colleagues to guide their clinical decision making. The challenge will be to blend these different sources and types of information into meaningful and clinically useful guidelines.

References

1. *Keitner GI, Posternak MA, Ryan CE. How many subject with major depression meet eligibility requirements of an antidepressant efficacy trial? J Clin Psychiatry 2003; 64:1091-1093.*
2. *Zimmerman M, Mattia JI, Posternak, MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 2002; 159: 469-473.*
3. *Posternak MA, Zimmerman M, Miller I, Keitner G. A Reevaluation of the Exclusion Criteria Used in Antidepressant Efficacy Trials. American Journal of Psychiatry 2002; 159:191-200.*