Clinical Trial Design Issues in Schizophrenic Research

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Research studies are an indispensable tool in the Food and Drug Administration approval process. Becoming familiar with different research study designs helps one to understand and interpret the results of clinical trials. Research studies are undertaken with 2 major goals in mind: (1) to get a drug into registration (regulatory needs) and (2) to understand the clinical application of medicines (clinical application needs). This article discusses the 2 major goals of research studies, the design issues associated with those goals, and the design features of several recent comparative studies of atypical antipsychotics.
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Research studies are an indispensable tool in the Food and Drug Administration approval process. Becoming familiar with different research study designs helps one to understand and interpret the results of clinical trials. Study designs are intimately linked with the goals of a study, and, conversely, the goals of a study should be married to the design. Research studies are undertaken with 2 major goals in mind: (1) to get a drug into registration (regulatory needs) and (2) to understand the clinical application of medicines (clinical application needs). Registration of a drug requires at least 2 adequate and well-controlled studies that provide a minimum definition of the safety and efficacy of a medicine; this is accomplished by conducting highly structured, randomized controlled trials (RCTs). An advantage of regulatory requirements is that bias is controlled as much as possible; a disadvantage is that the design may not reflect the needs of patients in actual real-world settings. Many clinical application studies, on the other hand, represent real-world situations and contribute to guiding medical practitioners in clinical practice. This article will discuss the 2 major goals of research studies, the design issues associated with those goals, and the design features of several recent comparative studies[1–5] of atypical antipsychotics.

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STUDY DESIGNS

Randomized Controlled Trials

An RCT requires prospectively defined hypotheses and outcome measures that support the goal of detecting a statistically significant treatment effect. In almost all cases, patients are randomly assigned to treatment conditions, and a placebo or comparator drug (or both) is used as a reference compound. The patient sample is well defined; that is, specific inclusion and exclusion criteria are used, and blind assessments of efficacy and safety are carried out. Drug dosing is usually controlled with fixed, flexible, or combined fixed/flexible dosing schedules. Dosing manipulations and the duration of a trial are tailored to the unique diseases or disorders of the patient sample. According to the Third Consensus Conference on the Methodology of Clinical Trials With Antipsychotic Drugs,[6] the placebo-controlled, parallel-group trial is the design of choice to test the efficacy of an antipsychotic drug. Placebo-controlled studies can give an estimate of the extent of changes due to spontaneous remission and other nonspecific factors, as well as provide a measure of the magnitude of specific pharmacologic effects. The duration of a research trial is another important design issue, and research studies are classified as acute trials (4 to 8 weeks), medium-term trials (2 to 6 months), and long-term trials (6 to 24 months). The length of the trials is dependent on the type of study, but most antipsychotic clinical trials are 4 to 8 weeks in duration. Placebo-controlled trials should be as short as possible; for example, 4 to 6 weeks for an acute study and 1 year for a long-term study.

If an RCT is to influence clinical practice, it must address an area of clinical uncertainty.[7] If there is consensus (on the basis of trustworthy evidence) that a treatment is effective, there is little point in conducting a trial. The

more common the dilemma, the more relevant the RCT. Clinical uncertainty is related to the ethical justification for randomization; that is, if clinicians are uncertain about the most effective treatment, then randomization becomes an ethical option or even a requirement.

Advantages of RCTs include the elimination of a number of potential biases.[8] Randomization minimizes baseline variability, and blindness controls bias in patient and rater outcome evaluations. Moreover, blindness controls bias in how the treatment is administered. Disadvantages of RCTs include a subject pool that is limited to patients who are eligible for and agree to participate in a double-blind clinical trial. Randomization usually means that patients are assigned to a drug or dosage group with no consideration of prior history. This means that patients who may be deriving benefit from adjunctive medicines—for example, a mood stabilizer—may not be allowed to take the medicine during a clinical trial; thus, some eligible patients may elect to forego enrollment.

Clinical Guidance Studies

Since the designs of RCTs are so highly structured, they may fail to provide information about the clinical applications of medicines. Thus, investigators also need to conduct research studies to gain information for providing clinical guidance to complement studies done to fulfill regulatory needs. Studies that reflect real-world conditions, involve representative samples, and evaluate effectiveness over long treatment periods include multiple research designs that provide useful data to guide medical practitioners. In addition to RCTs, other study designs used for clinical guidance needs include open-label, retrospective, or use-pattern (effectiveness) studies.

The very nature of open-label trials tends to skew the results. An open-label trial is subject to biases since both patient and clinician know the treatment being administered. Only the responders are reported since nonresponders usually depart the study early in the trial. Many environmental factors can neither be identified nor controlled. Thus, open clinical trials must be planned and executed carefully to establish the validity of the results and to generate hypotheses for future double-blind studies. The Third Consensus Conference on the Methodology of Clinical Trials With Antipsychotic Drugs[6] agreed on the following guidelines for early open clinical trials. They are (1) to assess the safety of the administered new substances in patients, to describe the most common side effects or adverse effects, and to identify idiosyncratic effects; (2) to identify target symptoms or syndromes and discover new actions; (3) to observe the time course of major psychopathologic changes to determine the rating days of the double-blind studies; and (4) to estimate the therapeutic dose range. Retrospective studies are usually performed after the outcomes of interest have already occurred because the logic of the design leads from effect to cause.[9]

Table 1. Study Designs of 5 Comparator Studies

Study	N	Design	Duration, mo
Tran et al[1] (1997)	339	Randomized, controlled	7
Conley, Mahmoud, et al[4] (1999)	407	Randomized, controlled	2
QUEST[5] (1999)	751	Open, randomized	4
Ho et al[3] (1999)	42	Open, effectiveness	6
Conley et al[2] (1999)	372	Prospective, effectiveness	12

Effectiveness studies. Both internal validity (efficacy) and external validity (effectiveness) are critical aspects of evaluating therapeutic interventions. In contrast to efficacy studies that are conducted in a controlled research environment, effectiveness studies can be carried out in relatively uncontrolled environments in which mentally ill people actually function. In general, effectiveness studies aim at getting practical information on such outcome measures as quality-of-life status, work performance, rehospitalization rates, and cost effectiveness. The major limitation of most effectiveness studies is that they do not control bias, so that the reader must ultimately try to understand the limitations of that particular study. Notwithstanding, effectiveness research does not always mean uncontrolled research.[10] Well-planned studies can use random assignment procedures within naturalistic settings to produce unbiased estimates of the benefits of interventions.

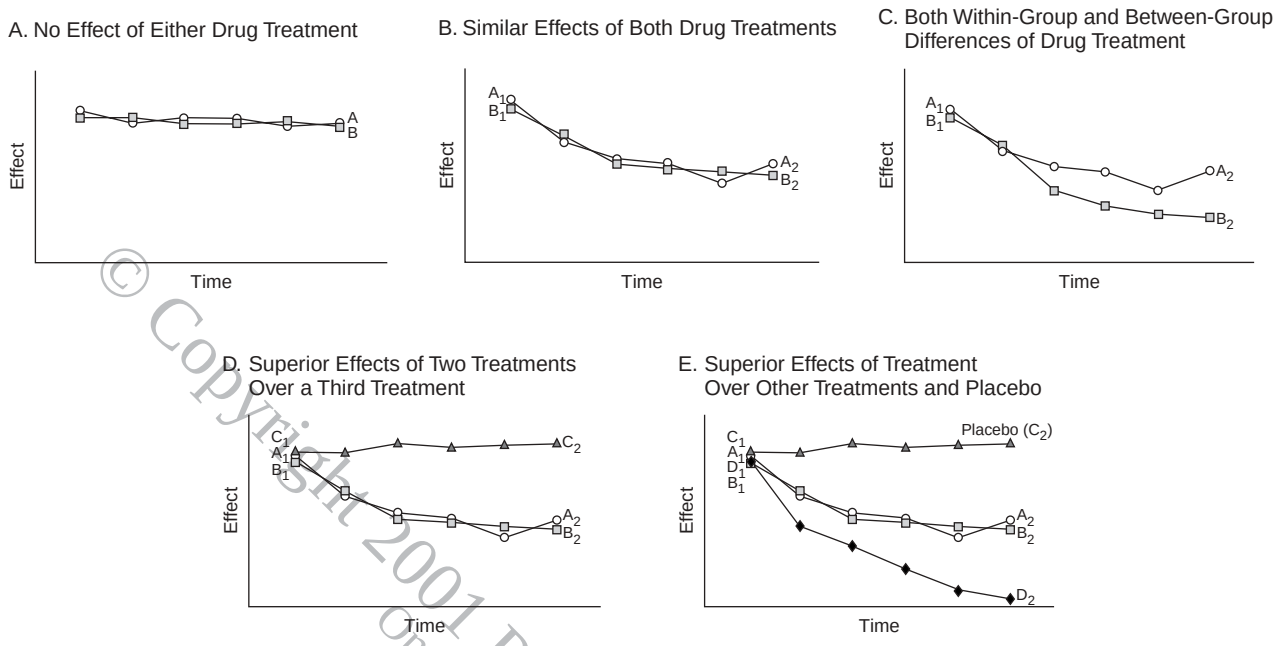
COMPARATOR STUDIES OF ATYPICAL ANTIPSYCHOTICS

Five recent comparative studies of atypical antipsychotics demonstrate certain design features of antipsychotic research (Table 1).[1–5] The studies of Tran et al.[1] and Conley, Mahmoud, et al.[4] are large, multicenter RCTs that compared the safety and efficacy of risperidone versus olanzapine treatment in both inpatients and outpatients. The duration of Conley, Mahmoud, et al. was 8 weeks, an acute study, and the duration of the Tran et al. trial was 28 weeks, a medium-term study.

The Ho et al. study[3] is an example of an open-label effectiveness study of risperidone versus olanzapine treatment that focused on the outcome measures of symptom reduction, extrapyramidal side effects, and quality of life. A total of 42 inpatients were assessed in hospital prior to starting medicine, at discharge after 4 weeks treatment, and at follow-up after 6 months treatment. Within-group and between-group comparisons were done to show drug similarities and differences.

The Conley et al. study[2] is a prospective effectiveness study that compared the rehospitalization rates in 372 patients discharged from Maryland State Mental Health facilities while receiving atypical antipsychotics (risperidone, olanzapine, or clozapine) or conventional depot antipsychotics (haloperidol or fluphenazine decanoate).

Figure 1. Drug Effect Over Time



The subjects were followed by their regular clinicians, and the study was conducted over a 12-month period.

The QUEST study[5] is an example of an open, randomized, 4-month study that compared tolerability and efficacy in patients who were randomly assigned in a 3:1 ratio to either quetiapine or risperidone treatment. The sample population included patients with diagnoses of not only schizophrenia and schizoaffective disorder, but also bipolar I disorder, major depressive disorder, delusional disorder, and Alzheimer's dementia.

Detecting a Significant Treatment Effect

For regulatory purposes, a drug must demonstrate a treatment effect; that is, it must prove its superiority over another treatment under controlled conditions, while clinical guidance studies may show a treatment effect under uncontrolled conditions. Detecting a significant treatment effect is often a complicated task and may involve different presumed tiers of effect or some combination of models, such as comparisons of drug A versus drug B, placebo versus drug A, or low versus moderate versus high doses of drug.

Figure 1A demonstrates no treatment effect over time when making comparisons either between drug groups (drug A vs. drug B) or within drug groups (A_1 vs. A_2; B_1 vs. B_2). Studies that demonstrate no treatment effect are generally considered unsuccessful and seldom published. Figure 1B shows a treatment effect in which a decrease in a symptom score occurs by approximately the same amount in both treatment conditions (A_2 and B_2) over time. Since these findings demonstrate no substantial difference between treatments, this study would probably be inadmissable as a successful regulatory trial. However, in a clinical setting, a substantial improvement that occurs with drugs within a group is certainly a desirable outcome. Thus, even when the results of 2 or more drug treatments are the same, the conclusions may be different depending on the purpose for which the study is intended. How the results are to be interpreted is an important issue that should be addressed early in designing a study.

Figure 1C illustrates a meaningful difference between treatment outcomes as the 2 lines separate after a few epochs of treatments. Within-group differences are seen as A_1 progresses to A_2 and B_1 to B_2. Furthermore, there is a between-group difference in medicines A_2 and B_2 that would meet the regulatory standards of defining a treatment effect. The Conley et al. study[2] demonstrated substantially different rehospitalization rates between the atypical antipsychotics and conventional decanoates. Another model, Figure 1D, adds drug C (representing placebo) and shows that A_2 and B_2 are superior to C_2 over time. A placebo or reference arm is important for a study to demonstrate that it has the assay sensitivity to detect whether a treatment effect exists. Figure 1E shows a clearly superior treatment effect of drug D_2 over A_2, B_2, and C_2. Individual patients sometimes show an exceptionally robust response to a specific drug treatment, thus achieving the clinical goal of relief from the pain and suffering of psychosis. This last study design, represented by Figure 1E, is difficult to implement and takes immense re-

sources, but it is the best kind of trial to detect a significant treatment effect.

The Food and Drug Administration mandates that a manufacturer may not give indications for long-term use of a drug without long-term placebo-controlled trials of that drug.[8] However, many researchers question the ethics of a requirement that exposes part of a study group to placebo for long periods of time when effective treatment is available and have chosen to eliminate a placebo-control group from their study designs. Other researchers have raised the possibility of conducting studies that demonstrate equivalency rather than differences between drugs (see Figure 1B) in order to gain regulatory approval. However, equivalency studies cannot insure assay sensitivity and are unacceptable for regulatory purposes although they may provide valuable clinical information.

CONCLUSION

Because clinical trials are vital to the effective and safe use of new drugs, it is important to understand the issues raised by the trials, the population studied, and the questions answered by the trials. No single study design can address all the relevant questions about antipsychotic drug effects; the body of knowledge garnered from several studies best informs medical practitioners. In many studies of psychosis, the majority of patients conform to a diagnosis of schizophrenia or schizoaffective disorder, but other mental disorders may be present as well. The reality is that antipsychotics are beneficial to patients who have a variety of psychiatric illnesses in which psychotic symptoms occur, and it is important for physicians to have some knowledge of the research experience of a medicine when making clinical decisions.

Drug names: clozapine (Clozaril and others), fluphenazine decanoate (Prolixin Decanoate), haloperidol decanoate (Haldol Decanoate), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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