Reading Reports of Clinical Trial Results

John M. Kane, M.D.

The ASCP is particularly concerned about enhancing the knowledge base and the success of knowledge transfer in clinical psychopharmacology. Given the number of clinical trials being published and the amount of trial data available to clinicians, we discuss some key elements of trial design, analysis, and reporting.

The goal of clinical trials in psychopharmacology is to characterize the ***efficacy*** and ***safety*** properties of the treatment being studied. No single trial, no matter how well-designed and conducted can succeed in fully meeting these goals. Therefore, issues relating to design apply not only to an individual trial but to a whole series or program of trials that are iterative: *What is learned in early trials should influence the design of subsequent trials*. To expect that once a medication receives regulatory approval everything will be known as to how a drug should be used is unrealistic. This issue is highlighted by the ongoing uncertainty as to optimum doses of many compounds, even after marketing, and is particularly apparent in the antipsychotic drug arena. Striking shifts in dosing recommendations and clinical practice have occurred long after antipsychotic agents have gone through the formal regulatory process.

Dosage

Important dosage issues in clinical trials are whether a broad range of doses was studied and whether dosages were fixed or flexible. ***Flexible dosing*** means that the clinician investigator had the option to change the dose (even when blind to the actual treatment assignment) based on therapeutic response and/or adverse effects. A problem with flexible dosing is that patients who are poorly responsive to medication in general or to the study drug in particular can end up receiving higher doses, making it difficult to establish a dose-response relationship. Documenting the decision-making process that leads to dosage adjustments can also be difficult.

Fixed-dose trials can be particularly important for medications that have long elimination half-lives or during maintenance treatment trials. In these situations, the result of a dosage manipulation will not occur until some future point in time, which makes it difficult to establish dose-response relationships. It can be difficult, however, to conduct studies with as many fixed-dose arms as one would like, and flexible dosing more closely mimics how medications will be used by clinicians in the real world.

A design that provides some flexibility is the ***fixed dosage range*** strategy. This allows dosages to be changed within specified nonoverlapping ranges if side effects occur or the patient's condition worsens. In reviewing data on new medications, determining what evidence is available regarding dose-response relationships for particular adverse as well as clinical effects is important.

Whether different dosage titration schedules lead to differences in response or time course of response are other important questions. In a competitive marketplace, pharmaceutical companies are often eager to demonstrate that a particular compound has a rapid onset of action; however, doses likely to bring about rapid response might also be associated with a higher rate of adverse effects. These relationships are not always readily apparent in early trials or even when a compound is marketed.

When a new compound is compared to an established comparator, the dosage of the established drug is critical in determining relative efficacy and tolerability. Much debate regarding the results of trials is based on the choice of comparator and the dosage(s) involved. Even with widely used established medications, debate about optimum dosing in general (e.g., haloperidol) and in particular populations (e.g., first-episode schizophrenia patients) can continue for years. As a rule, controlled active-active comparisons might have multiple dosage arms for the new compound but only a single arm for the established comparator. An inadequate or excessive dose of the control drug can lead to the appearance that the new agent is more effective or better tolerated.

Response

Another important consideration is how response is measured in a clinical trial. Is the measure clinically meaningful or is any statistically significant difference in response between 2 compounds clinically meaningful? For example, in many trials of antipsychotic medication, a 20% improvement criterion is used in assessing response. If the question is what proportion of patients has at least some degree of response, then the 20% improvement criterion is an appropriate metric. If the question is how many patients achieve a relatively asymptomatic state (in remission) or how many patients respond such that a clinician would see no need to alter the treatment, then a different metric is required.

Many patients who receive treatment with an "appropriate" dose of medication do not achieve an adequate response as measured by no perceived need to change the treatment. When most medications are marketed (and long after), how such patients should be managed is unclear. Should the dosage be increased, and if so, how high should the dosage be? Should another medication be tried, and if so, which one? Should an adjunctive medicine be added, and again, if so, which one and at what dosage? The question, "For how long?" then applies to all of these strategies. In establishing the efficacy of any of these possible strategies, having some proportion of the original subjects remain on the original treatment with no change in dosage is critical. This constant dosage controls for the passage of time and the "halo" effect of entering into a trial.

Unfortunately, pharmaceutical companies have relatively little interest in pursuing these questions since they focus on patients who have had an inadequate response to their compound. So-called "switch" studies are frequently conducted by the pharmaceutical industry but usually without optimum design or control groups. Pharmaceutical sponsors do not usually want to see their compound used as an adjunctive treatment, though this is gradually changing. As a result of these issues, we have remarkably few data on how to manage poor or partial responders, who, in the case of schizophrenia, represent a substantial proportion of patients. A consequence of this lack of information is a high prevalence of antipsychotic polypharmacy with few data supporting the practice.

Dropout

Another important element to examine in clinical trials is the dropout rate. The higher the dropout rate, the more difficult it can be to draw meaningful conclusions when comparing different active compounds or when comparing an active compound to placebo. Conducting clinical trials is an enormous challenge, and there are many legitimate reasons why patients do not complete the full trial. Although trial analysis will often distinguish between observed cases and last observations carried forward, neither of these is adequate. More sophisticated techniques are now widely used but, again, do not substitute for high completion rates.

ASCP Corner offerings are not peer reviewed and represent the opinion of the author. This discussion represents a brief overview of a few important issues to consider in evaluating clinical trials. Many other elements are worth considering, and some will be discussed in subsequent columns. We welcome your feedback and suggestions for future topics. Send e-mail to jrusso@lij.edu.