

Dose Selection and Comparator Drugs in Schizophrenia Research

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Dose selection and comparator drugs are important methodological issues in the evaluation of clinical data. Investigators rely heavily on dose selection in schizophrenia research, particularly when making comparisons between and across groups of compounds. In reality, however, the criteria for selecting a dose of drug in research trials are rather crude. Dosing and comparator issues vary enormously, depending on several factors. This article will discuss some of the dose-selection issues in schizophrenia research and the doses of antipsychotic drugs used in 5 recent comparative clinical trials.

(*J Clin Psychiatry* 2001;62[suppl 9]:29–32)

Dosing and comparator drug issues are important in the evaluation of clinical data in schizophrenia research. Despite 30 years of widespread use and numerous clinical trials—including a study¹ using 3 different doses of haloperidol in a fixed-dose design—physicians are still debating the optimal dose of haloperidol. Part of the problem is a tendency on the part of clinicians to want to prescribe a drug in its simplest fashion; that is, one size fits all. A drug that has one recommended dose is generally easier to use. Additionally, there is an element of naivete or reluctance on the part of researchers to even attempt to search for the optimum dose of a new drug to suit all the numerous purposes for which psychotropics are used. This article will discuss some of the dose-selection issues in schizophrenia research and the doses of antipsychotic drugs used in 5 recent comparative clinical trials.

FACTORS IN DOSE SELECTION

Investigators rely heavily on dose selection in research studies, particularly when making comparisons between and across groups of compounds. In reality, however, the criteria for selecting a dose of drug in research trials are rather crude, and dosing and comparator issues vary enormously, depending on several factors (Table 1).

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Presented at the symposium "Evaluating Clinical Trial Data From Schizophrenia Research," which was held March 17, 2000, in Washington, D.C., and supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

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Patient Selection Criteria

Diagnostic and inclusion criteria of the study population are important factors in determining the dose of drug in schizophrenia research trials. One of the hard lessons learned by physicians in the psychiatric field is that first-episode, drug-naive schizophrenic patients respond to lower doses of antipsychotics than patients who have recurrent illness.² Interventions made during the early stages of schizophrenia can have a critical impact on the long-term course and outcome of the disease. The age of the patient and acuity level of the illness should also be taken into account; elderly patients frequently need lower doses of medication than younger patients. Advancing age can have an unfavorable impact on the metabolism of antipsychotics and the development of side effects, which can affect compliance and dropout rates.³ Other factors in dose selection are potential drug interactions, washout periods, and the carryover effect from previous treatment. Since most patients who enroll in clinical trials have been previously treated with antipsychotics, the duration of washout is significant. Johnson and Johnson⁴ pointed out that a 1-week washout period is of little value in patients who have been continuously treated, particularly with depot injections, for weeks or months. Because of ethical reasons, however, a longer washout period is not permitted in some countries that participate in multicenter trials. There has been rather consistent reporting of antiparkinsonian medication use in placebo groups in new drug development trials, which is probably due in large part to a carryover effect from prior antipsychotic treatment.

Titration Schedule

Some drugs can be titrated more rapidly than others; consequently, a drug that can be titrated rapidly may have a faster effect than another drug requiring slower titration. Because the time course of response is so variable

Table 1. Factors in Dose Selection

Patient selection criteria (eg, first-episode, age, acuity level)
Washout duration
Titration schedule
Fixed- vs flexible-dose design
Concomitant medication
Evidence of dose-response relationship
Domains of efficacy
Specific adverse effects
Novel compounds

in psychiatric disorders, there is nothing to titrate against. It is extremely difficult to decide on an effective dose for any patient on a given day when the time course of response in acute schizophrenia is likely to be several weeks. Even after a patient has been completely discontinued from medication, the time course to relapse may be many months. Furthermore, judgments about effective dosage levels change with time and clinical experience, and the proper maintenance dose may not become apparent during short-term studies. Thus, whether titrating up (acute treatment) or down (maintenance treatment), there is no clear target for response, which makes it difficult to arrive at conclusions.

Methods of administering antipsychotic medication are also somewhat primitive. One could argue that drugs should be given on a milligram-per-kilogram basis and that the relationship between dose response and blood drug levels should be used more often. However, interest in these practical guides for establishing a basis for treatment has waned in recent years.

Fixed/Flexible-Dose Design

The methodological advantages of fixed- versus flexible-dose designs and the criteria for changing dose can sometimes be confusing to clinicians. Fixed- and flexible-dose studies answer different questions, and each has advantages and disadvantages. A fixed-dose design can answer the question of how drugs compare in standard doses, and a flexible-dose design may answer the question of how drugs compare in optimal doses.⁵ Fixed-dose designs have the advantage of being standardized, but have the disadvantage of some patients being underdosed or overdosed, which may lead to decreased efficacy and increased dropout rates. In a flexible-dose design, given the variable time course of response and the tremendous heterogeneity of schizophrenia, the poor responders are likely to end up taking the highest dose of drug, which makes it difficult to draw meaningful conclusions about a dose-response relationship. Fixed-dose studies have been very valuable from that standpoint. A combined fixed- and flexible-dose design may allow adjustments to be made within a dose range, but the criteria for changing dose are often unclear.

The results of fixed-dose studies sometimes fail to be reflected in clinical practice. For example, the early findings of Marder and Meibach⁶ and Chouinard et al.⁷ were

reflected in the original package labeling that provided the initial recommended dose of risperidone. However, as the use of risperidone increased in the United States, clinicians observed that patients often responded to lower doses of the drug than originally recommended. Consequently, as a result of both the international trials and clinical experience, a lower dose of risperidone has since been recommended in the manufacturer's product information.⁸

Concomitant Medication

The issue of concomitant medication affecting dose selection applies not only to prescribed medications but also to drugs related to substance abuse. The prevalence of substance abuse among patients who have schizophrenia has increased enormously over the past 20 years. Cigarette smoking in schizophrenic patients can have a potential impact on blood antipsychotic levels, and alcohol and other substances of abuse may have direct or indirect effects on metabolism. Any compound has the potential for affecting the treatment response of patients taking antipsychotics at any given dose.

Dose-Response Relationship

Domains of efficacy. The trickiest task in dose selection is trying to establish the efficacy of single drugs across the broad domains of schizophrenia—especially when the dose-response relationship in the different domains may not be identical or even similar. Investigators must speculate about preclinical models having, for example, an impact on negative symptoms that require a different array of receptor pharmacology than models having an impact on positive symptoms or combined symptomatology. Drug effects may also take more time to evolve in one symptom domain than in another.⁵ Measuring efficacy across the various domains of schizophrenia is a serious problem, and it is naive to think that one dose of a single drug will behave optimally across all domains.

Specific adverse effects. The same dilemma applies to adverse effects; that is, there is great difficulty in establishing a dose-response relationship across a wide range of adverse effects. Even an entity as well defined as extrapyramidal side effects rarely demonstrates a clear-cut relationship with blood antipsychotic levels, which suggests that vulnerability may be the basis for development of motoric symptoms in some patients. On the other hand, some dose-response relationships are quite informative and provide useful clues to the future course of treatment.

Novel compounds. The fact that the binding profiles of novel antipsychotics affect a number of different receptors adds to the challenge of establishing a dose-response relationship. As the next generation of drugs emerges—some with partial agonist activity and others with combined agonist/antagonistic activity—dose-response rela-

Table 2. Mean Drug Doses in 5 Antipsychotic Trials

Drug	Study					
	Conley et al ¹⁰	Conley, Mahmoud, et al ¹¹	Tran et al ¹²	Ho et al ¹³		QUEST ¹⁴
				4 wk	5.2 mo	
Risperidone (mg/d)	4.8	4.8	7.2	5.7	4.5	4.4
Olanzapine (mg/d)	16.3	12.4	17.2	14.4	13.8	...
Clozapine (mg/d)	430.7
Quetiapine (mg/d)	253.9
Haloperidol decanoate (mg/mo)	181.5
Fluphenazine decanoate (mg/q 2 wk)	46.1

tionships may become quite complicated, and it will be difficult and laborious for researchers to tease apart all the connections.

COMPARATOR DRUGS

Another methodological issue in research design is choosing the proper dosage of the comparator drug to administer to trial subjects.⁹ The head-to-head comparison of clinical trial results is not always straightforward. For example, studies that use several dose ranges of the trial drug may use a single dose range of the comparator drug that may be less than optimal. An equal number of groups and dose ranges for both drugs is more informative. Likewise, using higher than adequate dosage of the comparator drug may bias the study in favor of the new drug. Because of side effects associated with the conventional antipsychotics that were commonly used as comparator drugs in the past, the atypical antipsychotics may soon become the gold standards for use as comparator drugs.

When 2 drugs are compared in clinical trials, response rates of each drug may vary depending on the dose; a reported improvement at one dose level may not be present at other dose levels.⁹ Conversely, a higher than adequate dose of a drug may obscure significant improvement at an adequate dose level. Researchers can provide a reasonable dosage range to clinicians, but one should not assume that every patient responds to the same dose of drug in the same way over time. We are always hopeful that the lag time between evidence-based medicine and its clinical implementation can be reduced, but such is not always the case. Excessively high doses of haloperidol were administered for years before researchers had any impact on changing the prescribing practices of clinicians. Much depends on the marketing phase of the drug and the information available at the time.

In the 1-year naturalistic design of the Conley et al. study,¹⁰ the mean modal dose of risperidone was 4.8 mg/day, olanzapine was 16.3 mg/day, and clozapine was 430.7 mg/day (Table 2). Although the particular dosage recommendations and philosophy of the various Maryland institutions are unknown, this treatment schedule provides a sense of real-world conditions. Certainly, haloperidol

decanoate, 181 mg once monthly, can be considered a sufficiently moderate-to-high dose, but there was an unexpectedly high 1-year relapse rate (50%). Most studies show a 1-year relapse rate of approximately 15% to 20% in patients taking haloperidol decanoate.¹⁵ My colleagues and I¹⁶ found a 1-year relapse rate

of 15% in patients receiving 200 mg/month of depot haloperidol. The dose-response curve for fluphenazine decanoate is imprecise, but 25 to 50 mg every 2 weeks would be considered a moderate-to-high dose.¹⁷ Studies also show a 1-year relapse rate of approximately 15% to 20% in patients taking 50 mg of fluphenazine decanoate every 2 weeks. In the Conley et al. study,¹⁰ the mean fluphenazine decanoate dose of 46 mg every 2 weeks would also be considered a reasonably high dose of drug; the 1-year relapse rate was 24%.

In Conley, Mahmoud, et al.,¹¹ the mean dose of risperidone was 4.8 mg/day and of olanzapine was 12.4 mg/day, whereas in the Tran et al. study,¹² higher doses of both risperidone (7.2 mg/day) and olanzapine (17.2 mg/day) were used. The downward shift of risperidone and olanzapine dosage in Conley, Mahmoud, et al. is of interest, but considering the many different factors associated with the various studies, it is unclear whether the lower dosage accounts for differences. As mentioned above, clinical experience with risperidone has resulted in a recommended dose that is lower than that used at the start of the Tran et al. study.¹²

While open-label studies tend to be viewed as reflecting real-world conditions, investigators may be titrating against a poor response or a moving target. In the Ho et al. study,¹³ a naturalistic study in which patients were treated by research psychiatrists, there were data available at 2 timepoints. At the end of 4 weeks, patients were taking a mean risperidone dose of 5.7 mg/day; at the end of 5.2 months, the mean dose had been lowered to 4.5 mg/day. Mean olanzapine dosage was 14.4 mg/day at 4 weeks and 13.8 mg/day at 5.2 months. In the open QUEST trial,¹⁴ patients were randomly assigned in a 3:1 ratio to treatment with quetiapine or risperidone. The mean dose of risperidone was 4.4 mg/day and of quetiapine was 253.9 mg/day. Because of the broad diagnostic criteria and the unknown age and phase of illness of the study population, the QUEST trial¹⁴ is somewhat difficult to interpret. The population reportedly consisted of outpatients; however, it is possible that some of those outpatients were individuals with chronic disorders living in the community or residents in day programs or adult homes.

CONCLUSION

Dose selection in clinical research trials of patients with schizophrenia should include various factors such as patient selection criteria, washout duration, titration schedule, fixed- versus flexible-dose design, concomitant medication, and dose-response relationship. Choosing the proper dose of the comparator drug is another methodological issue in designing the trial. Dosage recommendations derived from trial results sometimes fail to be reflected in clinical practice. Researchers can provide a reasonable initial dose range to clinicians, but one should not assume that every patient responds to the same dose of drug in the same way over time. Dose selection often depends on the marketing phase of the drug and the information available at the time. Because data from research studies project group needs, studies that target doses to specific patients' needs would provide added benefit to clinicians.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), 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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