Evaluating Characteristics of Patient Selection and Dropout Rates

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Patient selection and dropout rates can affect the results of a clinical trial. Long lists of exclusions in the selection of patients for clinical trials reduce the possibility of examining treatment responses for heterogeneity and make recruitment difficult. In many cases, a pool of 100 potential subjects may yield only 2 or 3 qualified participants, a fact that raises the issue of generalizability of results. Dropouts should be carefully defined in advance and can be used as dependent variables for the comparison of different treatments. This article discusses some of the sampling characteristics (gender, age, diagnosis, inpatient/outpatient status, prior neuroleptic use, and symptom severity) and dropout rates in 5 recent comparative clinical trials of atypical antipsychotics. *(J Clin Psychiatry 2001;62[suppl 9]:11–14)*

Patient (or subject) selection and dropout rates can affect the results of a clinical trial. Long lists of exclusions in the selection of subjects reduce the possibility of examining treatment responses for heterogeneity and make recruitment difficult.[1] Inclusion criteria define the subjects who have the appropriate diagnosis within such predetermined limits as age and other factors.[2] Subjects who meet the inclusion criteria constitute the target sample and are drawn from the source population, such as patients admitted to a particular hospital or subjects within a catchment area. Because of subsequent exclusion criteria, only a small fraction of the target sample may actually proceed to randomization. For example, Schreiber et al.[3] evaluated patients who had been selected for referrals for admission to a National Institute of Mental Health clinical research unit. Of 399 patients selected from referrals received between February 1983 and December 1986, only 53 (13.3%) were ultimately admitted to the unit. Patients were excluded for behavioral reasons (substance abuse or destructive behaviors) as well as for medical problems, diagnostic uncertainties, and age. In a recent study[2] of treatment for mania, only 27 (17%) of 164 patients who had met the inclusion criteria were recruited. Thus, a pool of 100 potential subjects may yield only 2 or 3 qualified participants, a fact that raises the issue of generalizability of results.[4]

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Dropout rates should also be considered when evaluating the results of clinical trials. Sample attrition can lead to serious methodological problems.[5] This article will discuss some of the sampling characteristics (gender, age, diagnosis, inpatient/outpatient status, prior neuroleptic use, and symptom severity) and dropout rates in 5 recent comparative clinical trials of atypical antipsychotics.

CHARACTERISTICS OF PATIENT SELECTION

The main purpose of the sampling procedure is to achieve a representative sample of the patient population in question.[5] Well-defined inclusion and exclusion criteria should be carefully selected in advance of every research undertaking, regardless of the study design.

The diagnosis of patients enrolled in a study should be registered and documented.[5] Inclusion and exclusion criteria as well as information on the number of patients screened must be specified to gain an impression of whether the sample is representative of the patient population in question and how far the results can be generalized. The most severely ill patients may be excluded because of concern about the risk of further clinical worsening.[6] Likewise, patients who are responding to medications may be excluded because of a fear of jeopardizing their fragile clinical stability. Five recent comparative studies[7–11] of atypical antipsychotics demonstrate commonly used sampling characteristics in the current research of psychosis.

Diagnosis

A diagnosis of schizophrenia was the primary inclusion criterion for entry into all 5 comparative clinical studies reviewed in this article (Table 1).[7–11] Related psychotic disorders, such as schizophreniform disorder and schizoaffective disorder, were also allowed. All patients in the Conley et al.[10] and Ho et al.[9] studies had DSM-IV diagnoses of

Table 1. Sampling Characteristics in 5 Comparative Antipsychotic Trials[a]

Study	N	Mean Age, y	Male, %	Schizophrenia, %	Outpatients, %	Prior Neuroleptic Use	Baseline Symptom Severity	
							PANSS	BPRS
Tran et al[7] (1997)	339	36.2	64.9	81.7	58.1	…		
Risperidone							95.7	36.2
Olanzapine							96.3	36.7
Conley, Mahmoud, et al[8] (1999)	407				…	Yes		
Risperidone		41.0[b]	72.3	86.6			80.7	
Olanzapine		38.9	73.0	85.2			81.2	
Ho et al[9] (1999)	42			100	100[c]	No		
Risperidone		29.6	76.2					46.3
Olanzapine		33.5	76.2					43.9
Conley et al[10] (1999)	372			100	100	Yes	…	
Risperidone		38.6	59.0					
Olanzapine		40.1	63.0					
Clozapine		37.2	61.0					
Decanoates (haloperidol or fluphenazine)		39.0	63.0					
QUEST[11] (1999)	751	35–70[d]	50.0		100	…		
Risperidone				34.0			72.6	
Quetiapine				35.0			74.3	

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale, … = unknown.
[b]$p < .05$.
[c]All patients started on treatment as inpatients and followed as outpatients.
[d]Age presented as range.

schizophrenia. In the Tran et al. study,[7] 81.7% of the patients had a diagnosis of schizophrenia. Comorbid disorders and Axis I disorders other than schizophrenia, schizophreniform disorder, or schizoaffective disorders were exclusion criteria in the Tran et al. study along with the failure to show at least minimal clinical response to 3 antipsychotics in 3 chemical classes dosed at ≥ 800 chlorpromazine equivalents per day or clozapine dosed at ≥ 400 mg/day for at least 6 weeks. Additionally, pregnant or lactating women and patients with serious medical illnesses in which pharmacotherapy posed a substantial clinical risk or confounded diagnoses were excluded in the Tran et al. study.[7]

A total of 86.6% of patients in the risperidone group and 85.2% in the olanzapine group had a diagnosis of schizophrenia in Conley, Mahmoud, et al.[8] The remainder of the patients had a diagnosis of schizoaffective disorder. Subjects were excluded if they were refractory to risperidone or olanzapine treatment or had received clozapine treatment. In contrast, the QUEST trial[11] had substantially fewer schizophrenic patients (quetiapine 35%, risperidone 34%) than the other studies. Subjects who had a rather unusual assortment of disorders (for a clinical study of schizophrenia) were also included in the QUEST trial. In addition to schizoaffective disorder, patients who had diagnoses of bipolar I disorder, major depressive disorder, delusional disorder, Alzheimer's dementia, and other unspecified diagnoses were enrolled. Patients were excluded from the study if there was evidence of medically significant disorders, a past history of nonresponse to clozapine, current clozapine treatment, or a history of drug-induced agranulocytosis. Generally, the results of a clinical trial are easier to interpret if the diagnostic criteria for inclusion are clearly specified and relatively narrow. The broad diagnostic criteria of the QUEST trial make it more difficult for the clinician to interpret the results.

Gender and Age

Schizophrenia is a heterogeneous disorder in which individuals present with a range of symptoms that may change over time. Historically, most clinical studies of schizophrenia have focused on chronic, treatment-resistant, male patients. Men are frequently selected for clinical trials because they have an earlier onset of illness, poorer response to neuroleptics, and poorer outcomes.[12] As for age, the wealth of data from clinical trials in young schizophrenics may not translate to older subjects who require polypharmacy due to both schizophrenia and chronic medical illnesses.[13] Thus, gender and age restrictions may limit the applicability of study results from randomized patients to a wider population.

In the 5 studies reviewed, the only statistically significant between-group difference in age occurred in Conley, Mahmoud, et al.[8]; the olanzapine group (mean ± SD age = 38.9 ± 0.8 years) was slightly younger than the risperidone group (41.0 ± 0.8 years, $p < .05$) (see Table 1), but the difference was probably not clinically meaningful. A preponderance of men (risperidone 72.3%, olanzapine 73.0%) was also noted in Conley, Mahmoud, et al. In the Tran et al. study,[7] the majority of patients were men (64.9%), and the mean ± SD age of the patient population was 36.21 ± 10.73 years. The mean ± SD age at onset of illness was 23.7 ± 8.0 years, so most patients had been sick for about 13 years.

The Ho et al.[9] study comprised a majority (76.2%) of male patients in both risperidone and olanzapine treatment groups. The age groups were comparatively young and ranged from a mean ± SD age of 29.6 ± 10.4 years in the risperidone group to 33.5 ± 10.6 years in the olanzapine group. In this study, the mean ± SD age at onset of first treatment was 26.6 ± 10.1 years for the olanzapine group and 24.7 ± 8.8 years for the risperidone group, so the patients had been sick for only 4 to 6 years prior to starting the study. The majority (59%–63%) of patients in the Conley et al. study[10] were also men, and the ages ranged from a mean ± SD age of 37.20 ± 9.19 years in the clozapine group to 40.11 ± 13.57 years in the olanzapine group. The male/female ratio in the QUEST trial was 50/50, and the age range was 35 to 70 years (Zeneca Pharmaceuticals, data on file).

Inpatient/Outpatient Status

The hospital status of the sample can also influence the results of clinical trials. Hospitalized patients may be experiencing serious illness—e.g., first-episode psychosis or chronic relapsing psychosis—compared with outpatients who may be responding to medication and functioning relatively well in the community. On the other hand, regular staff monitoring of medications may improve compliance in hospitalized patients.

All patients in the Ho et al. study[9] were started on treatment as inpatients and followed as outpatients (see Table 1). Conversely, all subjects in the QUEST trial[11] were outpatients. Subjects in the Conley et al. study[10] were outpatients who had been discharged from Maryland State Mental Health facilities and were identified from state databases and hospital pharmacy records. At baseline, 41.9% of the patients in the Tran et al. study[7] were inpatients. Patients could begin the study as inpatients or outpatients, and a change in hospitalization status during participation in the trial was permissible. Both outpatients and inpatients (hospitalized for < 4 weeks at screening) were included in Conley, Mahmoud, et al.[8]

Prior Neuroleptic Use

A key variable in patient selection is whether a subject has received prior neuroleptic treatment. There is general agreement that exposure to neuroleptics has confounded the interpretation of a number of putative biological findings in schizophrenic research.[14] A chronic nonresponder who has failed 3 previous trials of atypical antipsychotics may fail to respond to a trial of a new antipsychotic whereas a neuroleptic-naive subject may respond well.[4] As the use of atypical antipsychotics becomes more common, it is increasingly likely that a subject who enrolls in a clinical trial of a new atypical antipsychotic will have failed to respond to trials of earlier drugs.

Prior to entering the study, about one half of the patients selected for Conley, Mahmoud, et al.[8] had received atypical antipsychotics and about 15% had received conventional depot antipsychotics (see Table 1). In the Ho et al. study,[9] none of the subjects were taking neuroleptics at the start of the study. Either they (1) were neuroleptic-naive and were being evaluated for first-episode psychosis, (2) had discontinued neuroleptic treatment prior to hospitalization at the research center, or (3) were withdrawn from neuroleptic medication as part of a positron emission tomography study.

All patients in the Conley et al. study[10] had been previously treated with neuroleptics. A few patients had been hospitalized within the state system for long periods; thus, the length of time on medication before patients could be discharged was longer in the more treatment-resistant patients—i.e., in the clozapine and decanoate groups—than in the risperidone and olanzapine groups. The number of patients taking prior neuroleptics in the multicenter QUEST trial[11] and in the Tran et al. study[7] was not reported. However, monitoring of baseline extrapyramidal events in the QUEST trial and a washout period in the Tran et al. study suggest prior neuroleptic use.

Symptom Severity

Clinical rating scales are established tools that quantify the phenomenological features of schizophrenia. Investigators should always use the best available rating scales for measuring drug effects in the positive, negative, or disorganized symptom dimensions being studied; additionally, global assessment scales should be used.[5]

A minimum score on the Brief Psychiatric Rating Scale (BPRS) extracted from the Positive and Negative Syndrome Scale (PANSS) of at least 42 (items scored 1 to 7) was necessary for inclusion in the Tran et al. study.[7] However, in actuality, the baseline mean ± SD BPRS total score of the sample was 36.2 ± 9.0 for the risperidone group and 36.7 ± 9.6 for the olanzapine group (see Table 1). Baseline scores on the PANSS and its subscales, the BPRS, the Scale for the Assessment of Negative Symptoms (SANS), and the Clinical Global Impressions scale indicated that the patients had severe (and mixed) positive, negative, and depressive symptomatology.

The only statistically significant between-group difference in baseline measures of the 5 studies reviewed was in the Tran et al. study; the SANS summary score was significantly ($p = .044$) higher in the olanzapine treatment group (12.2) than in the risperidone treatment group (11.6). This statistically significant difference in the baseline SANS summary score concerns me because a statistically significant difference at endpoint was also reported for the SANS without correction.

The inclusion criterion for symptom severity in Conley, Mahmoud, et al.[8] was a baseline total PANSS score ≥ 60 and ≤ 120. The baseline mean ± SD total PANSS scores in the sample were 80.7 ± 0.9 in the risperidone group and 81.2 ± 1.0 in the olanzapine group. These scores indicate

that the patients had less severe symptomatology than those in the Tran et al. study. In the Ho et al. study,[9] baseline assessments of psychopathology included negative, positive, and disorganized symptomatology measured by the total SANS/SAPS (Scale for the Assessment of Positive Symptoms) score and the BPRS. The mean baseline total BPRS score was 43.9 ± 13.5 in the olanzapine group and 46.3 ± 10.1 in the risperidone group, indicating a fairly ill population who probably required hospitalization.

In the QUEST trial, the baseline total PANSS score was 72.6 for the risperidone group and 74.3 for the quetiapine group (Zeneca Pharmaceuticals, data on file). These scores were considerably lower than the baseline psychopathology scores in the other studies, indicating a population that was less severely ill. Baseline assessments were not investigated in the Conley et al. trial.[10]

DROPOUTS

Dropout rates should also be examined when evaluating the results of clinical trials. Placebo-controlled studies traditionally have high dropout rates, since most patients receiving a placebo are nonresponders. Subjects are also reluctant to continue using an agent that either is ineffective or causes adverse effects. Dropouts should be carefully defined in advance and can be used as dependent variables for the comparison of different treatments.[5]

In the Tran et al. study,[7] a total of 178 (52.5%) patients completed the 28-week study (olanzapine, 57.6%; risperidone, 47.3%; p = .059), and the dropout rates were comparable for the 2 treatment groups. The reasons for withdrawal from the study included an early satisfactory response in some patients, adverse events, and lack of efficacy. In Conley, Mahmoud, et al.,[8] a large proportion of patients in the 2 treatment groups completed the study (risperidone, 72%; olanzapine, 77%; p = .21). Similar numbers of patients discontinued the study because of adverse events, and similar treatment duration was observed in the 2 treatment groups (risperidone: median = 55 days, mean = 46 days, range, 1–75 days; olanzapine: median = 56 days, mean = 49 days, range, 1–68 days). In the Ho et al. study,[9] the sample size at 6-month follow-up was approximately two thirds (N = 26) the size of the original sample (N = 42), and an equal distribution between treatment groups (risperidone, N = 13; olanzapine, N = 13) was demonstrated; reasons for discontinuation of the study were not given. Dropout rates were not reported in either the Conley et al. trial[10] or the QUEST[11] trial.

CONCLUSION

The sampling characteristics were similar in all 5 studies reviewed except for the QUEST trial. The majority of patients in 4 studies[7–10] had a diagnosis of schizophrenia. Only 35% of the patients in the QUEST trial[11] had a diagnosis of schizophrenia, but the percentage increased to just under 70% if patients who had a diagnosis of schizoaffective disorder were included in the sample. Subjects in the QUEST trial had lower PANSS scores than subjects in the other trials (indicating a less severely ill sample), all of the subjects were outpatients, and one half of the sample were women. Dropout rates were not consistently reported in the clinical studies reviewed.

Drug names: clozapine (Clozaril and others), 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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