

Effect of Study Criteria on Recruitment and Generalizability of the Results

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Objective: Clinical trials are indispensable to drug approval process. This research examined the effect of a specific study criteria on recruitment and generalizability of the results.

Methods: The following were reviewed: (a) the usual inclusion and exclusion criteria for the antipsychotic trials performed at the Institute; (b) epidemiologic data, to determine the effect of study criteria on the target population; and (c) the recruitment procedures/strategies used to identify potential candidates. A survey was conducted to determine the percentage of schizophrenic patients in a conventional outpatient psychiatric clinic conforming to the usual enrollment criteria for antipsychotic trials.

Results: Intensive recruitment efforts in a general population of 3.6 million would have been expected to yield only 632 eligible subjects out of 36,000 suffering from schizophrenia. Out of 632, only 50 contacted the research site after an intensive recruitment effort. From those 50, 30 were excluded during a telephone interview. Of the 20 remaining, 6 were excluded for a variety of reasons during a face-to-face interview. Thus, only 14 subjects out of a population of 3.6 million met the study criteria.

Conclusions: These results emphasize the rarified nature of patients-volunteers who enter a clinical trial. Inclusion and exclusion study criteria can severely restrict the number of eligible subjects, dictate recruitment strategies, and in turn affect generalizability of the results.

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Clinical trials are an indispensable part of the FDA drug approval process. They are vital to the effective and safe use of new drugs.¹ Billions of dollars are spent annually in the process of developing and marketing new therapeutic agents. It is critical that the findings of a particular clinical efficacy study be generalizable to the projected treatment population. Therefore, finding appropriate research subjects is of paramount importance.

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The purpose of this article is to show how inclusion and exclusion criteria affect the enrollment of subjects in a clinical trial and how that, in turn, affects the generalizability of the results.^{2,3} This article examined how the inclusion and exclusion criteria for a specific study can dramatically reduce on the percentage of a population that will be eligible for a specific clinical trial.⁴ The specific study was an open-label, multiple-dose trial investigated the effect of concurrent administration of donepezil HCl with risperidone on the pharmacokinetics and safety profile of both drugs.⁵

METHODS

For this article, the authors reviewed the following:

- (a) The usual inclusion and exclusion criteria common to antipsychotic clinical trials performed at the research institute.
- (b) The effect of specific inclusion and exclusion criteria for a specific study which included:
 - Only participants with schizophrenia
 - Monotherapy with risperidone, at stable doses of not <2 mg/d for at least 2 months prior to screening
 - Males only
 - Weight range within 20% of ideal weight, as specified in the “1983 Metropolitan Life Insurance Height and Weight Tables”
 - No heart rate of <55
 - No acute exacerbation of schizophrenia in the last 60 days
- (c) The literature, specifically epidemiologic data, to determine the effect of specific inclusion and exclusion criteria on the size of the target population relative to the general population.^{6,7}
- (d) Chart review was conducted for all the schizophrenic patients at a general psychiatric outpatient clinic to evaluate what percentage of schizophrenic patients are only on one antipsychotic medication.
- (e) Two surveys were conducted to assess the means used for recruitment:
 - Survey #1 (for details of the survey visit the website for the journal at www.psychopharmacology.com) was to evaluate the attitude of physicians toward clinical

research trials. That survey composed of a questionnaire, given to healthcare professionals, mostly psychiatrist and primary care physicians, at the psychiatric grandrounds. About 70 physicians filled out their questionnaire completely.

- Survey #2 (for details of the survey visit the website for the journal at www.psychopharmacology.com) was conducted at a general psychiatric outpatient clinic to see how many psychiatric patients choose to read newspaper, watch TV, or listen to the radio. A questionnaire was given to 100 outpatients to evaluate the recruitment efforts through the media.

Other methods used to reach the target population for the study were:

1. Letters to all psychiatrists in the target area (5 cities with the total population of 3.6 million) informing them about the nature of the study.
2. Newspaper advertisement placed in major newspapers covering all 5 cities.
3. Information about the study sent to local support groups like the National Alliance for Mentally Ill (NAMI) and Mental Health Association (MHA).

RESULTS

Most of the clinical studies for schizophrenia/schizoaffective disorder shared a lot of inclusion and exclusion criteria in common but that specific study was even more restrictive.

This review found that the inclusion criteria common to most clinical trials of novel antipsychotic medications include:

1. Subject must have a primary diagnosis of schizophrenia or schizoaffective disorder.
2. Age range between 18 and 65.
3. Females should be non-childbearing potential and not breastfeeding.
4. Subject should be free from acute exacerbation of psychosis for at least 6 months.
5. Subject must be willing to discontinue all psychotropic medications during washout.
6. Subject must be in good health with normal laboratory findings except for minor deviations determined to be nonclinically significant by the investigator.
7. Subject's electrocardiogram (EKG) must show normal sinus rhythm and must be without clinically significant abnormalities at screening and baseline.
8. Urine drug screen must be negative for illicit drugs.
9. Subject should be at least 80% of the lower weight limit and not greater than 140% of the upper limit of ideal weight for gender, age, height, and frame as established in the "1983 Metropolitan Life Insurance Height and Weight Tables."
10. Baseline PANSS of >60 and <120.

This review also found that the following exclusion criteria were common to most clinical trials of novel antipsychotic medications:

1. Subject resistant to neuroleptic treatment.
2. Subjects with DSM-IV defined psychoactive substance abuse/dependence in the preceding 3 months.
3. Subjects with mental retardation, organic mental syndrome or disorders, brief psychotic disorder, or mood disorder with psychotic features.
4. Subjects who are currently on or who have been given depot neuroleptic medication within 8 weeks of baseline.
5. Subjects receiving lithium, mood stabilizers, or anti-convulsants within 2 weeks of screening.
6. Subjects receiving fluoxetine within 5 weeks of baseline.
7. Subjects who received investigational drug during the 4 weeks immediately preceding the baseline visit for the study.
8. Subjects judged by the investigator as being at imminent risk of suicide or homicide.
9. Women of childbearing potential, pregnant, or nursing mothers.
10. Subjects with serologic evidence of acute or chronic hepatitis B or C.
11. Subjects known to be HIV positive.
12. Subjects with a history of clinically significant and/or currently hematologic, renal, hepatic, gastrointestinal, endocrine, pulmonary, dermatologic, oncologic, or neurologic disease.
13. Subjects with a history of clinically significant cardiovascular disease.
14. Subjects with a history of true allergy to any neuroleptic or neuroleptic malignant syndrome.

The effect of those specific inclusion and exclusion criteria on the size of the potential volunteer pool was as follows:

Inclusion criteria #1: Only participants with schizophrenia

Because the lifetime prevalence of schizophrenia is about 1% of the general population,^{8,9} only 36,000 individuals out of a general population of 3.6 million would meet this criterion (Table 1).

Inclusion criteria #2: Must be on specific monodrug therapy

A chart review was done at a general psychiatric outpatient clinic which sees about 25 to 30 patients with schizophrenia every month to determine how many of clinic patients with schizophrenia were on risperidone alone. Only 8% of all patients with schizophrenia in that clinic were on risperidone of at least 2 mg/d. Hence, this requirement of monodrug therapy narrowed down further reduced the target population by another 92 %, from 36000 to 2880 (Table 1).

TABLE 1. The Effect of Study Inclusion and Exclusion Criteria on Reducing the Size of the Target Population

Criteria	Target Population	Reduction by %	Remaining Population
Only schizophrenia	3.6 million	99	36,000
Monodrug therapy	36,000	92	2880
Only males	2880	50	1440
No drugs/alcohol	1440	35	936
No obesity	936	30	655
No hepatitis B/HIV	655	3.5	632

General available population, 3,600,000; Kansas City MSA, 1,073,725; Oklahoma City MSA, 1,038,999; Tulsa MSA, 776,906; Wichita MSA, 544,343; Topeka MSA, 165,348 [From the United States Census Bureau of 1998].

Inclusion criteria # 3: Must be male

The lifetime incidence of schizophrenia is essentially the same for both sexes^{8,9} so this reduced our target population by 50% from 2880 to 1440 (Table 1).

Inclusion criteria #4: Must not have alcohol/drug abuse/dependence

Alcohol/drug abuse/dependence is a common problem with psychiatric patients. Thirty-five percent of patients with schizophrenia have problems with drugs and/or alcohol.^{5,9} This requirement reduced the potentially eligible population by 35%, from 1440 to 936 (Table 1).

Inclusion criteria #5: Weight range within 20% of ideal weight

An estimated 97 million adults are overweight or obese in the United States.¹⁰ According to National Heart, Lung and Blood Institute/National Institutes of Health and the World Health Organization, overweight is defined as having a body mass index (BMI) of ≥ 25 kg/m² and obesity as having a BMI of ≥ 30 kg/m².^{10,11} According to literature, 25% of males are overweight.¹¹ Allison et al¹⁰ have studied obesity rates in patients with schizophrenia and found the rates to be at least as high, if not higher than in the general population. For all the above reasons, a conservative estimate is that at least 30% of male patients with schizophrenia are more than 20% of their ideal weight range. This requirement reduce our potential pool of subjects by another 30%, from 936 to 655 (Table 1).

Inclusion criteria #6: Subject with serologic evidence of acute/chronic hepatitis B or C and those who are HIV positive are excluded from the study

Only 3.5% of general population is at risk of having serologic evidence of hepatitis B and/or C and HIV (<http://www.cdc.org>). This requirement reduced the potentially eligible population by 3.5% from 655 to 632 (Table 1).

In summary, only 632 out of 3.6 million people would be expected to meet the criteria for this study as a result of

the general and the specific inclusion and exclusion criteria for this study.

To reach this potentially eligible population, various methods were used as mentioned in the Methods section.

- Letters mailed to psychiatrists as well as primary care physicians generated only 3 referrals. This is consistent with the results of Survey #1, which found that only 50% healthcare professionals, including psychiatrists, felt comfortable in referring their patients for schizophrenia research trial.
- Newspaper advertisement placed in 8 different newspapers in 5 different cities produced only 7 calls in response. This is consistent with Survey #2 results, which showed that only 65% of the patients with schizophrenia read newspaper no more than once a week.
- Efforts like personal visits by research staff to sites where there were potentially eligible subjects, letters to case managers and social workers informing them of the study produced 4 referrals but only one was eligible.
- Information about the study to all local support groups such as NAMI and MHA produced no referrals.
- Public announcement at a general psychiatric outpatient clinic generated only one referral, who was eligible but was not taking antipsychotic of interest for long enough duration as required by the protocol.

An intensive recruitment effort produced 50 potential eligible candidates who contacted the site. Reasons why 50 out of 632 potential subjects contacted the research site are as follows:

- Only 65% patients with schizophrenia read newspaper no more than once a week.
- Family/friends did not tell the potential subjects because of their own fears about clinical trials.
- Only 50% healthcare professionals felt comfortable in referring their patients for clinical trials.

Out of those 50, 30 were screened out for a variety of reasons listed below:

- Concomitant medications not allowed by the protocol took away 9/30.
- Subjects changed their mind to participate excluded 6/30.
- Less than 2 months on the antipsychotic of interest took away 5/30.
- Current drug/alcohol problems took another 6/30.
- Severity of illness did not allow them to give informed consent took away 2/30.
- History of seizure disorder excluded 2/30.

Of the 20 potential volunteers identified from the telephone screening, 6 were screened out during a face-to-face interview for:

- Positive urine drug screen—2/6
- Abnormal electrocardiogram—1/6
- Abnormal liver function test—2/6
- Severity of illness—1/6

Thus, only 14 eligible subjects were recruited from a population of 3.6 million people.

DISCUSSION

Finding only 14 subjects from a population of 3.6 million illustrates the effect the specific study inclusion and exclusion criteria can have on the size of the eligible population relative to general population.^{2,12} Although the sequential application of percentages of patients eliminated with each criteria may be misleading as it assumes they are randomly associated which is not the case all the time (eg, substance abuse or HIV positive may be greater in men than in women).

Now this article will look into the reasons for having those specific inclusion and exclusion criteria requirements for the specific study, and then will discuss their impact on generalizability of the results.

Inclusion Criteria #1: Only Schizophrenics

The decision to include only schizophrenic participants in the study was related to the primary objective, which was to determine the pharmacokinetic profiles of donepezil HCl and risperidone, following the administration of multiple doses donepezil HCl during the steady state of risperidone.⁵ Patients with schizoaffective disorder are frequently also on antidepressants or mood stabilizers because of their affective symptoms.^{8,9} Therefore, the chances are better on finding a schizophrenic patient on stable doses of risperidone monotherapy for at least 2 months than with schizoaffective disorder.

Inclusion Criteria #2: Must be on Specific Monodrug Therapy

If the participants had been allowed to take other medications beside risperidone and donepezil HCl during the study, it could have confounded the attempt to assess any possible pharmacokinetic interactions between them.⁵

Inclusion Criteria #3: Must be Male

There are gender differences in drug pharmacokinetics that can affect results.¹³ Given a small study population, the inclusion of both males and females could potentially increase interindividual variability. Drug concentration and distribution can differ in women versus men for a number of reasons including:

1. Lower acidic environment increases absorption of drugs in females.¹⁴
2. Slower transit time in the small intestine of females delays drug absorption and lower peak blood concentration.^{8,9}
3. Protein binding is lower in women than in men, which results in increased free fraction of the drug.^{13,14}
4. Estradiol and progesterone reduce specific CYP enzyme (CYP2D6) activity in females.¹⁴

5. Women have a larger volume of distribution for lipid-soluble drugs as a result of having high percentage of adipose tissue, thus providing a relatively larger reservoir to store psychotropic drugs.^{9,14}

Inclusion Criteria #4: Must Not Have Alcohol/Drug Abuse/Dependence

Acute alcohol ingestion has complex effects on the metabolism of drugs.¹⁵ Acute ingestion of alcohol can reduce first pass metabolism and thus increase plasma drug concentration.^{9,15} Chronic alcohol ingestion can cause cirrhosis, reducing hepatic CYP enzyme concentration and liver mass and result in portacaval shunting.¹⁶ These effects will increase plasma drug levels if the dose is not adjusted to compensate for the decrease in clearance. Chronic alcoholics also have numerous medical problems like gastritis, gastric ulcer, anemia, hypertension, pancreatitis, cirrhosis, persistent impotency, and insomnia.^{9,15} These conditions can alter the metabolism and/or complicate the patient's response to a variety of drugs.

Drug abuse/dependence in subjects also pose the risk of having medical problems including AIDS as a result of intravenous drug abuse.^{8,9} Drug abuse/dependence can also produce symptoms suggestive of psychotic disorders like schizophrenia as can be seen in subjects addicted to amphetamine or cocaine.^{9,15} Drug abuse/dependence can produce changes in laboratory values, EKGs, and in rating scales.¹⁵

Inclusion Criteria #5: Weight Range Within 20% of Ideal Weight

The reason for this requirement is because the absolute and the relative size of the body's fat compartment changes with morbid obesity.^{9,10} The relative percentage of total body water and protein content decreases in morbidly obese patients as well as in the elderly.⁹ Conversely, their percentage of fat content increases, resulting in a relatively larger reservoir to store psychotropics.^{10,11} Hence, the drug's effect can persist, for a longer duration in a manner proportional to the size of the adipose compartment.^{8,9} Inclusion of volunteers who differ markedly in terms of their lean body mass can increase interindividual variability in pharmacokinetics, which in turn could interfere with the primary objective of the specific study.

Inclusion Criteria #6: Subjects With Serologic Evidence of Acute/Chronic Hepatitis B or C, and Those Who Are HIV Positive

Pharmacokinetics of a drug can change with acute/chronic disease states particularly diseases affecting the liver.⁹ Such diseases can decrease circulating protein binding resulting in an increase in the free drug fraction.^{8,9} Drug metabolism tends to decrease as a result of liver disease and

because of diminished hepatic blood flow, liver mass, and CYP enzyme content and activity. For patients who are HIV positive, their disease can alter the physiologic mechanisms subserving the various pharmacokinetic phases.^{5,9}

Because most of the studies exclude many participants with general medical and psychiatric comorbidities, generalizability is limited.^{2,17} The specific study chosen for this article was also limited for generalizability of the results because of the more restrictive inclusion and exclusion criteria.^{2,3} Difficulties in recruitment have been a major problem for investigators for many years.¹⁷ One of the concerns is the generalizability of clinical trial results to community practice, that whether participants recruited through advertisement according to a set inclusion and exclusion criteria are homogenous with those seeking treatment in a clinical setting. In other words, the effectiveness of established treatments in more representative clinical populations is not well established.^{2,7} Broad or less restrictive inclusion and exclusion criteria may increase generalizability of results.

Generalizability of research findings from clinical trials is a methodologic concern. Homogeneity between the sample population and the target population is necessary so that the results can be extrapolated.² There is little information regarding the best methods for subject recruitment especially for more restrictive inclusion and exclusion criteria.¹⁷ Data on the cost of these efforts are also lacking.

CONCLUSIONS

This article emphasizes the rarified nature of patients-volunteers who enter a clinical trial. Although inclusion and exclusion criteria are needed to produce a sufficiently homogenous population to permit rigorous and yet sensitive testing of the hypothesis, a price is paid in terms of the recruitment effort needed to identify an appropriate cohort of volunteers and in terms of the potential problems inherent in

trying to generalize the results to the larger population from which they were drawn.

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SURVEY #1**The University of Kansas Medical Center
School of Medicine–Wichita**

This survey is being conducted to assess the attitudes of health care professionals about clinical trial research. Thank you for taking your time to complete the questionnaire below:

1. Have you seen a television program critical of clinical research? Yes No
2. Have you seen such a program specifically critical of psychiatric research? Yes No
3. Rate your comfort level with clinical trials in the following disease states from 1 (most comfortable) to 10 (least comfortable):

___ Cancer	___ Schizophrenia
___ Hypertension	___ Major depression
___ Diabetes	___ Manic-depressive illness
___ Alzheimer's Disease	___ Upper respiratory tract infection
___ Epilepsy	___ Peptic ulcer disease
4. Would you, in general, be comfortable referring a patient to be evaluated for enrollment in:
 - a. a general medicine trial Yes No
 - b. a psychiatric clinical trial Yes No

If not, why not? List reason for each answer:

5. Please check the category which best describes your profession/position:

___ Psychiatrist	___ ARNP
___ Resident psychiatrist	___ PA
___ Nonpsychiatric physician	___ Social worker
___ Psychologist	___ Medical student
___ Nurse	___ Lay person

SURVEY #2

**The University of Kansas Medical Center
School of Medicine–Wichita**

Please answer the following questions to help us in our clinical research:

1. How often per week do you watch or listen to:

- | <u>Television</u> | <u>Radio</u> |
|---------------------------------|---------------------------------|
| <input type="checkbox"/> 7 days | <input type="checkbox"/> 7 days |
| <input type="checkbox"/> 6 days | <input type="checkbox"/> 6 days |
| <input type="checkbox"/> 5 days | <input type="checkbox"/> 5 days |
| <input type="checkbox"/> 4 days | <input type="checkbox"/> 4 days |
| <input type="checkbox"/> 3 days | <input type="checkbox"/> 3 days |
| <input type="checkbox"/> 2 days | <input type="checkbox"/> 2 days |
| <input type="checkbox"/> 1 day | <input type="checkbox"/> 1 day |

2. How often do you read the newspaper?

- 7 d/wk
- 6 d/wk
- 5 d/wk
- 4 d/wk
- 3 d/wk
- 2 d/wk
- 1 d/wk

3. Do you actively avoid watching television, listening to the radio, or reading the newspaper?

	<u>Television</u>	<u>Radio</u>	<u>Newspaper</u>
Yes	___	___	___
No	___	___	___

Diagnosis: _____

Resident: _____