

Subject Selection for the Placebo- and Comparator-Controlled Trials of Neuroleptics in Schizophrenia

PAVEL MOHR, MD*†, AND PÁL CZOBOR, PHD*‡

*Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York; †Prague Psychiatric Center, Prague, Czech Republic; ‡New York University Medical Center, Department of Psychiatry, New York, New York

It has been suggested that inclusion of a placebo treatment arm in controlled clinical trials might bias the selection of study subjects. Presumably, patients in the placebo-controlled studies are more stable, but there are no data available to support such an assumption. The authors tested the hypothesis in a set of randomized trials of neuroleptics in treating schizophrenia by comparing placebo-controlled (PCTs) and comparator-controlled trials (CCTs) in terms of basic patient characteristics. The results, based on a total of 296 studies, showed that the patients in PCTs, compared with those in CCTs, were older ($p < 0.002$), had a longer duration of illness ($p < 0.001$), and a lower initial symptom severity ($p < 0.02$). No difference was found in the number of subjects per treatment arm or in the proportion of female subjects. However, investigation of studies which used same-gender study subjects revealed that female-only populations were more likely to be tested in PCTs ($p < 0.03$) than in CCTs. To investigate current trends in psychopharmacologic research, the authors tested separately a subset of trials of new atypical antipsychotics. The results indicated a significantly smaller number of females participating in the latest PCTs ($p < 0.0003$). Moreover, our findings suggest that the characteristics of patients in the current controlled trials are rather uniform; thus, the generalizability of new study findings for certain groups of patients with schizophrenia (e.g., with early or late onset or brief duration of illness) may be compromised. (*J Clin Psychopharmacol* 2000;20:240-245)

ONE OF THE MAJOR ISSUES in clinical research is the extent to which study subjects are representative of the whole population of interest.^{1,2} This concern

applies particularly to psychiatry, as documented by several authors who described a selection bias in schizophrenia studies. For example, patients with paranoid schizophrenia were less likely to participate in clinical research studies.^{3,4} Those patients with schizophrenia who refused to volunteer were older, white, less educated, female, and spent less time in a hospital.³⁻⁶ An insufficient representation of women in epidemiologic studies of schizophrenia was also described by Hambrecht and colleagues.⁷ Obviously, selection bias in controlled drug trials can influence study outcome and compromise the generalizability of the results. A potential solution would be to test new treatments in a variety of well-defined subgroups of psychiatric patients or to conduct studies that are more representative of the general patient population. Unfortunately, in recent years there is no trend toward the use of this approach. In our historical analysis of double-blind, randomized trials of neuroleptics for the treatment of schizophrenia (Mohr and Czobor, unpublished data), we have found a strikingly narrow age range represented by the subjects participating in the newer trials.

Somewhat surprisingly, reviews of clinical research articles do not discuss other factors that might influence the selection of study subjects. For example, in many cases, the subject selection is a matter of convenience: study participants are drawn from the pool of patients at a particular site. If the studies were carried out at V.A. centers, then male subjects would be over-represented; study subjects participating in the trials at state psychiatric facilities would be mostly patients with chronic illnesses who have been hospitalized for long periods of time.

One of the most important factors to be considered in reviewing the results of clinical research is study design. New compounds tested in double-blind clinical trials are being compared with a previously established standard treatment and/or an inactive substance, a placebo. The use of a placebo as a standard in the clinical trials of new psychotropic drugs is ubiquitous, especially in the

United States, where it seems to be a standard method approved by the Food and Drug Administration (FDA). On the other hand, most of the European trials do not use placebo controls.^{8,9} In addition to all of the ethical controversy and theoretical assumptions regarding the role of placebo controls in the study of therapy for schizophrenia,¹⁰⁻¹² it is important to investigate empirically whether subject selection for studies in which one group of subjects would be without active treatment is biased. Henn and colleagues⁹ suggest the possibility that stable patients with schizophrenia are more likely to be included in placebo-controlled treatment studies. Intuitively, investigators would tend to give an inactive substance to patients who are less likely to become a management problem, i.e., those who are older, less violent and agitated, and less severely and more chronically ill.

However, there are no data supporting this presumption. To investigate this issue, we conducted a meta-analysis of published double-blind, randomized, controlled trials of antipsychotic drugs used in the treatment of schizophrenia. The results may contribute much needed information to the ongoing debate on the scientific merit of placebo treatment controls. The objective was to compare study populations in placebo-controlled (PCTs) and comparator-controlled trials (CCTs). We hypothesized that study subjects in PCTs would be older, less severely and more chronically ill than those studied in CCTs and that such patients would also be more likely to be included in longer randomized trials. Based on previously published findings,^{4, 5, 7} both types of trials would use a higher proportion of male subjects. Because the contrast (effect size) between a tested compound and a placebo is presumably greater than that between a new and a standard treatment, we expected that the number of study subjects per treatment arm would be smaller in PCTs. To investigate the current practice (in our earlier analysis, we observed changes in controlled trials over the years; P. Mohr and Czobor, unpublished data), we separately analyzed a subset of trials testing new atypical antipsychotics.

Methods

Selection of the trials

Double-blind studies of neuroleptics with published results were identified via MEDLINE and through the relevant references. The subject "schizophrenia" and generic names of the antipsychotic agents currently approved for treatment of schizophrenia in the United States or Europe were used for the search. Included trials were randomized and double-blind, having parallel-treatment cells and a the primary outcome of efficacy

and/or safety. Excluded were trials that were (1) open-label, single-blind, crossover, maintenance, withdrawal, and short-term (fewer than 7 days); (2) comparing different dosage regimes of one drug without another control; (3) investigating combined or adjunctive treatment; and (4) using prevailing diagnoses other than "schizophrenia" or "schizoaffective disorder," or not separately analyzing patients with schizophrenia.

Variables

Variables describing basic design features and population characteristics were extracted from the articles for the purpose of the analyses. Study design was characterized by the following variables: type of trial (PCT or CCT), planned duration of postrandomization treatment, and the number of study subjects in each treatment arm. Population characteristics included the following variables: percentage of men and women, mean age, mean age at onset of illness, and mean duration of the illness. The initial score on the Clinical Global Impressions (CGI) scale,¹³ the most commonly used measure, was selected as an index of severity of illness.

Statistical analysis

Analysis of variance (ANOVA) was used to examine the difference between CCTs and PCTs in terms of mean age, duration of illness, age at onset of illness, severity of illness measured by CGI, number of subjects per treatment arm, and gender distribution (percentage of male subjects), according to the type of trial (PCT or CCT). An identical analysis was done in a subset of trials that tested the four new atypical neuroleptics¹⁴⁻¹⁷ (Table 1).

To further explore subject selection according to gender, a subset of all studies that used same-gender study populations (female or male subjects only) was analyzed. In this subset, χ^2 analysis was applied to test for a relationship between type of trial and gender of the study population. ANOVA was used to test differences in mean age, duration of illness, and severity of illness measured by CGI between trials with female-only and male-only populations. Associations between mean age, duration of illness, age at onset of illness, initial severity of illness, and gender distribution (used as dependent variables) with the duration of active treatment (an independent variable) were tested using bivariate linear regressions.

Results

Data

Altogether, we collected 296 double-blind randomized trials of neuroleptics: 98 PCTs and 198 CCTs. The

TABLE 1. Controlled trials of new atypical neuroleptics

Study	Tested Drug	Control	N
Arvanitis and associates ¹⁴	Quetiapine	Placebo, haloperidol	361
Beasley and associates ¹⁵	Olanzapine	Placebo, haloperidol	335
Beasley and associates ¹⁶	Olanzapine	Placebo	152
Borison and associates ¹⁷	Risperidone	Placebo	36
Borison and associates ¹⁸	Quetiapine	Placebo	109
Chouinard and associates ¹⁹	Risperidone	Placebo, haloperidol	135
Fabre and associates ²⁰	Risperidone	Placebo, haloperidol	12
Marder and Meibach ²¹	Risperidone	Placebo, haloperidol	388
McEvoy and associates ²²	Sertindole	Placebo	38
Small and associates ²³	Quetiapine	Placebo	286
van Kammen and associates ²⁴	Sertindole	Placebo	205
Zimbroff and associates ²⁵	Sertindole	Placebo, haloperidol	497
Beasley and associates ²⁶	Olanzapine	Haloperidol	431
Blin and associates ²⁷	Risperidone	Haloperidol	62
Bondolfi and associates ²⁸	Risperidone	Clozapine	86
Češková and Švestka ²⁹	Risperidone	Haloperidol	62
Claus and associates ³⁰	Risperidone	Haloperidol	44
Hoyberg and associates ³¹	Risperidone	Perphenazine	107
Huttunen and associates ³²	Risperidone	Zuclopenthixol	98
Klieser and associates ³³	Risperidone	Clozapine	59
Min and associates ³⁴	Risperidone	Haloperidol	35
Peuskens ³⁵	Risperidone	Haloperidol	1,362
Tollesfson and associates ³⁶	Olanzapine	Haloperidol	1,996
Tran and associates ³⁷	Risperidone, olanzapine	—	339

list of publications is available from the authors upon request. The sample size available for the analyses varied with the individual measures.

Subject selection

The results are summarized in Table 2. We found a statistically significant relationship between the type of trial and the mean age of its subjects ($p < 0.002$; $F = 9.68$; $df = 1,227$); PCTs used older study subjects than did CCTs. A similar relationship, confirming that the patients in PCTs were more chronically ill than those in CCTs, was also found between the type of trial and the mean duration of illness ($p < 0.001$; $F = 11.35$; $df = 1,101$). Moreover, we observed a statistically significant difference between the two study types in the severity of illness indexed by the initial score of the CGI ($p < 0.02$; $F = 5.81$; $df = 1,55$): PCTs used patients who were less severely ill as subjects. No significant relationship was detected be-

tween the type of trial and the mean age at onset of illness, the mean number of subjects per treatment arm, and the gender distribution, respectively.

In the set of trials of new atypical antipsychotics (Table 3), we found a significant effect of the type of trial on gender representation: fewer women participated in the PCTs ($p < 0.0003$; $F = 20.36$; $df = 1,18$). A small but statistically significant difference between the two types was also observed in the mean age of the subjects at onset of illness ($p < 0.03$; $F = 5.60$; $df = 1,15$). No significant difference according to study type was found in the mean age, duration of illness, or initial severity of illness. The difference in the mean number of subjects per treatment arm (PCTs = 47.1; CCTs = 144.8) failed to reach statistical significance.

Analysis of the subset of all trials that used only male or female subjects (Table 4) revealed that female-only samples were more likely to be tested in the PCTs than

TABLE 2. Comparison of the study subjects in placebo- and comparator-controlled trials*

	Placebo-Controlled Trials		Comparator-Controlled Trials		ANOVA	
	N	Mean (SD)	N (studies)	Mean (SD)	F	p Value
Age (yr)	76	40.0 (8.1)	153	36.8 (6.9)	9.68	<0.002
Duration of illness (yr)	42	14.7 (5.3)	61	10.9 (5.8)	11.35	<0.001
Age at onset of illness (yr)	17	23.9 (2.1)	28	23.4 (4.0)	0.22	<0.6
Initial severity of illness (CGI score)	25	4.6 (0.5)	32	5.1 (0.8)	5.81	<0.02
No. of study subjects (mean no. per treatment arm)	98	30.4 (33.1)	197	36.2 (75.8)	0.52	<0.5
% of male subjects	78	58.5 (36.4)	159	61.2 (24.7)	0.45	<0.5

*ANOVA, analysis of variance; CGI, Clinical Global Impressions Scale.

TABLE 3. Comparison of the study subjects in trials of new atypical neuroleptics^a

	Placebo-Controlled Trials		Comparator-Controlled Trials		ANOVA	
	N	Mean (SD)	N	Mean (SD)	F	p Value
Age (yr)	11	37.3 (1.6)	12	36.1 (1.7)	3.0	<0.1
Duration of illness (yr)	10	14.7 (1.2)	6	13.2 (2.3)	2.66	<0.1
Age at onset of illness (yr)	10	22.4 (0.7)	7	23.3 (1.0)	5.60	<0.03
Initial severity of illness (CGI score)	11	4.6 (0.5)	6	4.5 (0.6)	0.21	<0.7
No. of study subjects (mean no. per treatment arm)	12	47.1 (27.0)	12	144.8 (276.7)	1.48	<0.2
% of male subjects	9	81.1 (9.7)	11	62.4 (8.9)	20.36	<0.0003

^aANOVA, analysis of variance; CGI, Clinical Global Impressions Scale.

in the CCTs ($\chi^2 = 4.49$; $df = 1$; $p = 0.034$). Furthermore, in single-gender trials with female-only populations, subjects were older (age: $p < 0.004$; $F = 9.28$; $df = 1,53$) and more chronically ill (duration of illness: $p < 0.03$; $F = 5.23$; $df = 1,25$) than in trials involving only male patients. Overall, the male-only trials outnumbered the female-only trials by more than 2 to 1.

Study design and patient characteristics

For all studies, there was a significant positive relationship of moderate size between planned duration of postrandomization treatment and mean age of the study subjects ($r = 0.35$; $p < 0.0001$; $F = 32.15$; $df = 1,224$). Similarly, we found a positive association between the duration of treatment and the duration of illness ($r = 0.38$; $p < 0.0001$; $F = 17.28$; $df = 1,101$). The age at onset of the illness was not related to the duration of the trial. Although the subjects in longer trials tended to have a lower initial CGI score, the relationship between duration of treatment and severity of illness did not reach statistical significance. Furthermore, our analyses indicated that duration of treatment was not a function of an interaction of the study type with age or duration of illness.

In the PCTs alone, we observed that more severely ill patients were more likely to be put on shorter trials, but this association failed to reach statistical significance. A statistically significant relationship was found between gender distribution and duration of treatment in the CCTs ($r = 0.21$; $p < 0.009$; $F = 6.92$; $df = 1,154$), suggesting that longer trials used a higher number of male subjects.

Discussion

The fact that study samples of patients with schizophrenia participating in clinical trials differ in a systematic way from the general population of patients with schizophrenia has been described previously. Our findings suggest that the use of placebo controls can be a source of another selection bias. The results of our study essentially confirmed our expectations: study

subjects participating in PCTs were older, were more chronically ill, and had a lower initial severity of illness than those in the CCTs. An obvious explanation would be that because some subjects will inevitably be administered a placebo in PCTs, investigators tend to enroll those patients with schizophrenia who are less likely to become management problems when active treatment is withheld.

A selection bias for PCTs would have serious consequences for the generalization of the results obtained in these trials. Therefore, before we drew any conclusions about the potential practical implications, we separately analyzed 12 PCTs and 12 CCTs of the new atypical neuroleptics, which arguably exemplify the latest trends in clinical psychopharmacology.¹⁴⁻³⁷ The results, summarized in Table 3, showed that these CCTs and PCTs did not differ in the age, chronicity, or initial severity of illness of their study subjects. The difference in the age at onset of illness was only 1 year. Furthermore, the substantial difference between new PCTs and CCTs in the number of study subjects per treatment arm (that failed to reach statistical significance) is somewhat virtual; it can be attributed to the combined data from three large international multicenter trials.³⁵⁻³⁷

Hence, the findings from the small sample of 24 most recent trials of atypical neuroleptics suggest that the presence of a placebo arm, with the exception of a biased representation for female patients (see below), does not affect subject selection. However, inspection of the basic descriptive data also reveals a remarkably small variation in subject characteristics across studies. In particular, for age, duration of illness, and initial symptom severity, the standard deviations of the mean

TABLE 4. Placebo- and comparator-controlled trials with the same gender (female-only and male-only) population

	Placebo	Comparator	All
Female-only ^a (%)	15 (71.4)	6 (28.6)	21 (100)
Male-only (%)	21 (43.8)	27 (56.2)	48 (100)
All (%)	36 (52.2)	33 (47.8)	69 (100)

^a χ^2 ; $p < 0.03$.

values in both PCTs and CCTs were small (Table 3). This finding indicates that the study samples were quite homogenous and that certain groups of patients were excluded. These groups, patients with early-onset and late-onset of schizophrenia, younger and elderly patients, and those with a brief duration of illness, may substantially differ in their treatment response.³⁸⁻⁴¹ The narrow age range of the subjects in new trials is consistent with earlier findings (Mohr and Czobor, unpublished data).

Our analysis revealed a similar representation of women in the two types of controlled drug studies in schizophrenia: 41% in PCTs and 39% in CCTs (i.e., the male-to-female ratio was approximately 1.5). Although this ratio is consistent with the prevailing theory that there is a somewhat higher incidence of schizophrenia among men, more recently, it has been argued that no such gender difference exists.^{42, 43} In the analysis of the subset of trials of new atypical neuroleptics, we found that women were underrepresented in those studies with a placebo arm (Table 3). This seems to be contradictory to another finding, that a female-only study population was more likely to be used in PCTs than in CCTs (Table 4). However, a closer look at our database unveils more information: all 12 new PCTs were conducted in North America (one with combined data from the United States and Europe),¹⁴⁻²⁵ and all 12 CCTs were European trials with international collaboration (Israel, South Africa, Latin America, Australia, Asia, and two in collaboration with the United States).²⁶⁻³⁷ The difficulties with enrollment of women for North American clinical trials have been noted previously by other authors as well.^{3, 5, 7} It seems that the low representation of women is a characteristic problem for recent U.S. schizophrenia research; the alternative interpretation, that the use of placebo controls itself (in the United States required by the FDA) biases gender distribution, is less likely. Moreover, this rationale is not at odds with the above-mentioned analysis of same-gender trials. The result simply implies that whenever a female-only study population is available, the investigators are more prone to use that population in PCTs. Perhaps these subjects might be perceived as those at a lower risk of becoming a management problem.

Results of the analyses of the relationship between planned duration of a trial and the patients' characteristics confirmed our hypothesis: older and more chronically ill, and probably also less severely ill, patients with schizophrenia received longer active treatment. This association may reflect the fact that older and more chronic patients are less likely to respond to treatment and therefore need a longer clinical trial to establish therapeutic efficacy. Conversely, younger, acutely ill patients with a higher severity of symptoms would require

shorter trials because they are expected to respond to antipsychotic treatment more favorably and with a shorter latency.⁴⁴

In conclusion, although our results indicated an overall bias in the patient selection for PCTs, this bias did not emerge for the study samples from the latest drug studies. We have observed, however, other potentially biasing patterns emerging. In the small sample of randomized clinical trials testing new atypical neuroleptics, we found a significantly smaller percentage of female subjects in PCTs compared with CCTs.

In addition, our results indicate that the demographic profile of subjects in the new studies is rather uniform. This uniformity poses a problem in the interpretation of the effect of drugs. The lack of new controlled trials for certain groups of patients with schizophrenia (e.g., with early onset, late onset, or brief duration of illness), together with the insufficient representation of women in a particular type of trial may compromise the generalizability of study findings. Of course, such a desirable generalizability might be limited by other factors, as well. Although their full account is beyond the scope of our article, we cite a few of them. For example, some authors^{3, 4} argue that higher ethical standards adopted over the years, such as mandatory informed consent, significantly influence patient selection. Furthermore, clinical drug trials have become a highly profitable business; there are numerous sites specialized solely in drug testing. However, no data on the mode of subject selection or other potential biases are available for these places. Because they can play a key role in clinical testing, any general conclusion inferred from their results has to be viewed with caution. We should be aware that our knowledge of new drug efficacy and safety is often based on a sample that is not representative of the whole patient population. All implications of current practices in clinical research and their changes should be closely scrutinized.

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