Attitudes of Patients With Schizophrenia Toward Placebo-Controlled Clinical Trials

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Background: Despite the fact that the efficacy of antipsychotic treatment in patients with schizophrenia has been demonstrated in numerous double-blind studies, placebo-controlled studies are still commonly performed. Although much is known about the opinions of professionals concerning this issue, so far nothing is known about the opinions of patients who are most affected by the realization of placebo-controlled clinical trials.

Method: In a cross-sectional study from June 2000 to January 2001, 100 inpatients and outpatients with ICD-10 schizophrenia or schizophreniform disorder were investigated by using a questionnaire specifically developed to survey patients' attitudes concerning possible participation in placebo-controlled clinical trials. Psychopathology and side effects were physician-rated.

Results: 56% of patients would not be willing to participate in a placebo-controlled clinical trial. On the other hand, only about 16% of the patients are against clinical trials in principle. Gender, treatment, severity of psychopathology (Positive and Negative Syndrome Scale), adverse events (UKU Side Effect Rating Scale), and attitude toward medication (Drug Attitude Inventory) had no statistically significant influence on the decision. Most of the patients (76%) stated that they would not lose trust in their physician if asked to participate in a placebo-controlled clinical trial.

Conclusion: The opinions and fears of patients who are most affected by the debate need to be considered when deciding whether a placebo-controlled clinical trial is necessary.

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Despite the fact that the efficacy of antipsychotic treatment in patients with schizophrenia has been demonstrated in numerous double-blind studies, placebo-controlled studies are still commonly performed. During the past decade, the question as to whether placebo-controlled clinical trials in schizophrenia are ethical and/or necessary has been raised increasingly. Experts' and ethical committees' opinions on this issue are divided.[1–8]

Ethical concerns can be based on the most recent version of the Helsinki Declaration, which states that "the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."[9(p4)] Yet, the same document also states that this does not exclude the use of placebo or no treatment in studies in which no prophylactic, diagnostic, or therapeutic method exists.

Another concern regarding placebo-controlled clinical trials is associated with increased risk of harm, as there is consensus that placebo-controlled trials are unethical if patients risk death or irreversible serious morbidity as a result of having standard treatment withheld. It is yet unclear whether withholding or discontinuing antipsychotic medication in patients with schizophrenia causes greater long-term morbidity. While patients have been reported to become more difficult to treat following relapses, a common complication of antipsychotic withdrawal,[10–12] the only study that has to our best knowledge investigated the data of a placebo group of an antipsychotic trial[13] has been unable to confirm concern about a worse outcome for these patients. Clearly, from a purely epidemiologic perspective, patients who stop taking antipsychotics following adherence problems represent a much more clinically relevant group than the small number of patients who discontinue antipsychotic treatment in order to enter placebo-controlled clinical trials.

In addition, supporters of placebo-controlled trials argue that a placebo control is necessary to define the "absolute" effect of a product and as an internal validation of the trials.[1] If the test drug and standard drug perform equally in an experiment not controlled by a placebo, such findings would show that the 2 drugs are indeed equal but would fall short of proving that either drug is effective.[14]

Table 1. Attitudes Toward Participation in Placebo-Controlled Clinical Trials Among 100 Patients With Schizophrenia or Schizophreniform Disorder

Question	Yes (%)	No (%)
1. Would you be willing to participate in a placebo-controlled clinical trial? *If yes, please go to 2; if no, please go to 3.*	44.0	56.0
2. I would participate in a placebo-controlled clinical trial because[a]		
a) I want to support the development of new drugs	79.1	20.9
b) I would have the possibility of remaining unmedicated (ie, free of antipsychotics)	72.1	27.9
c) I would receive more medical care	65.9	34.1
d) I would be able to talk to my physician more often	50.0	50.0
e) I would be guaranteed to be treated in this hospital	58.1	41.9
f) My experience with clinical trials has always been positive	20.9	79.1
g) My family/friend/legal advisor wants me to participate	7.1	92.9
h) To please my doctor	41.5	58.5
3. I would not be willing to participate in a placebo-controlled clinical trial because[b]		
a) I fear that not receiving medication might worsen my condition or slow improvement	76.8	23.2
b) I know that long-term drug treatment is necessary	72.7	27.3
c) My doctor has informed me of the necessity of drug treatment	71.4	28.6
d) I am in principle against clinical trials	16.4	83.6
e) I want to know whether I am really receiving medication	70.9	29.1
f) I don't want to have to make such decisions	29.1	70.9
g) I have had bad experience with clinical trial	9.1	90.9
h) It would be too much effort	29.1	70.9
i) My family/friends/legal advisor do not want me to participate	10.9	89.1
4. Would you lose your trust in your physician if he/she asked you to participate in a placebo-controlled clinical trial although he/she has educated you of the necessity of drug treatment?	24.0	76.0

[a]Percentages are based on all patients who answered question 1 with yes (N = 44).
[b]Percentages are based on all patients who answered question 1 with no (N = 56).

Secondly, a test drug may turn out to be inferior to a standard drug it is compared to. Without a placebo control, however, it will be impossible to say whether the test drug has any activity at all, a question that may, at times, be worth answering. Furthermore, in placebo-controlled trials, side effects due to a product can be distinguished more reliably from disease-related events or carryover effects. Therefore, researchers and ethicists in favor of placebo-controlled clinical trials submit that such trials are necessary and ethically acceptable, provided that patients receiving placebo are not at risk for serious harm and give informed consent.[15]

Although much is known about the opinions of professionals concerning this issue, nothing is known about patients' opinions. As this group is most directly affected by the realization of placebo-controlled clinical trials, we attempted to get information about the willingness of patients to take part in a placebo-controlled clinical trial.

METHOD

We investigated inpatients and outpatients between the ages of 19 and 65 years in a cross-sectional study conducted June 2000 to January 2001. The diagnostic criteria for schizophreniform disorder or schizophrenia according to ICD-10[16] served as the basis for study inclusion. Only patients capable of giving written informed consent to participation in a clinical trial were studied. Psychopathologic symptoms and side effects were rated by a physician involved in the treatment of the patients. The rating instrument used to evaluate the severity of psychopathology was the Positive and Negative Syndrome Scale (PANSS).[17] The UKU (Udvalg for Kliniske Undersogelser)[18] was employed to rate adverse events. A score of 1 (0 = no or doubtful symptoms) or higher on any UKU item indicated side effect "cases." Additionally, demographic and current treatment data were gathered.

Furthermore, patients were asked to complete a questionnaire specifically developed to survey patients' attitudes concerning possible participation in placebo-controlled clinical trials. This questionnaire is based on the authors' experience of common questions, comments, and concerns expressed by patients who have participated in clinical studies in the past. In addition to the questionnaire (Table 1), written information about such studies was provided that was based on informed consent forms for placebo-controlled clinical trials approved by the local ethical review board. Furthermore, the physician informed patients that the question whether they would be willing to participate in a placebo-controlled clinical trial was merely hypothetical and would have no consequences for further treatment.

The patients' subjective response to antipsychotics and their attitudes toward medication were assessed by means of the Drug Attitude Inventory (DAI).[19] It is divided into 7 factors: (1) subjective positive feelings related to antipsychotics, (2) subjective negative feelings attributed to the drugs, (3) patients' model of health, (4) patients' confidence in physician, (5) patients' attitude toward the locus of control in taking medication, (6) patients' belief in the effect of antipsychotics in forestalling relapse, and (7) concerns with potential toxic effects.

Table 2. Sociodemographic Data and Their Effect on the Decision Whether or Not to Participate in a Placebo-Controlled Clinical Trial

Variable	Patients Would Be Willing to Participate: Yes	No	p Value
Gender, N (%)			
Male	34 (50.0)	34 (50.0)	.088
Female	10 (31.2)	22 (68.8)	
Age, y[a]	35.0 ± 9.5	35.6 ± 10.1	NS
Outpatients, N (%)	17 (37.8)	28 (62.2)	NS
Inpatients, N (%)	23 (52.3)	21 (47.7)	
Duration of illness, y[a]	8.3 ± 8.3	9.8 ± 7.5	NS
Frequency of past inpatient treatments[a]	1.69 ± 1.1	2.05 ± 0.8	.094

[a]Values are mean ± SD.

A physician not involved in the treatment of the patients provided the questionnaire and the DAI in order to avoid biased answers, as most patients enrolled in the survey had been long-term patients of an outpatient clinic of our hospital, treated by the same doctors for years.

Statistics

Analyses were conducted using SPSS 8.0 for Windows (SPSS Inc., Chicago, Ill.). Group comparisons were performed using the chi-square test (Fisher exact test), when the dependent variable was nominal (dichotomous). The Mann-Whitney U test was used to compare 2 groups of continuous or ordinally scaled data.

RESULTS

We investigated 100 patients with schizophrenia or schizophreniform disorder; 68% of patients were male, 32% female. The mean ± SD age was 35.4 ± 9.8 years. At the time of investigation, 93 patients were treated with antipsychotics, 82 (88.2%) with second generation and 11 (11.8%) with traditional antipsychotics.

Fifty-six percent of patients stated that they would not be willing to participate in a placebo-controlled clinical trial (Table 1). The reasons most often given were (1) the fear that not receiving medication might worsen their condition or slow improvement, (2) the awareness that long-term pharmacologic treatment is absolutely necessary, and (3) being informed by their doctor of the necessity of drug treatment. The reasons most often given by patients who would be willing to participate in such a study (44%) were (1) the wish to support the development of new drugs, (2) the possibility of remaining unmedicated, and (3) the desire to receive more medical care.

When analyzing the influence of sociodemographic data (Table 2) on this decision, we found that patients who had been treated as an inpatient more often in the past tended to be reluctant to participate in such a trial (p = .094). Fifty percent of the male patients in contrast to only 31.2% of the females would hypothetically participate in such studies (p = .088). Family status and place of living had no influence on the willingness to participate in a placebo-controlled trial.

Regarding psychopathology, patients had relatively few positive symptoms (mean ± SD PANSS = 14.1 ± 6.7) and low-to-moderate negative symptoms (mean ± SD PANSS = 19.9 ± 7.7); the mean ± SD PANSS total score was 66.4 ± 22.6. Neither the PANSS total score nor any of the subscores had a statistically significant effect on the decision.

The side effect most often found was concentration difficulties (> 60% of patients). Asthenia, sedation, failing memory, depression, tension, increased duration of sleep, weight gain, and diminished sexual desire were observed in more than 40% of patients. Neither the UKU total score nor any specific side effect showed an influence on the patients' decisions.

The attitude toward medication as assessed by the DAI did not influence this decision either. Generally, the subscales describing positive aspects of antipsychotics (general positive feelings = 49.35; confidence in physician = 89.97; prevention = 88.75) received much higher scores than subscales characterizing negative aspects (general negative feeling = 29.98; health/illness-dependent drug intake = 41.77; control = 12.37; harm = 33.26).

Most of the patients (76%) stated that they would not lose trust in their physician, if asked to participate in a placebo-controlled clinical trial.

DISCUSSION

Despite the fact that only about 16% of the patients reported to be against clinical trials in principle, more than 55% would not be willing to participate in a placebo-controlled clinical trial. This difference can be considered an indicator that patients are skeptical about such studies. This is also reflected by the fact that more than 75% would not be willing to participate in a placebo-controlled clinical trial because they fear that not receiving medication might worsen their condition or slow improvement. Unfortunately, we cannot directly answer the question whether patients not willing to participate in a placebo-controlled clinical trial would be willing to participate in a psychopharmacologic trial employing an active control drug. Indirectly, one can infer from the fact that only 16.4% of patients were opposed to clinical trials in general that the rest, namely 83.6%, would be willing to participate in such a study. We recommend the addition of a specific question in future studies addressing this issue.

We were surprised that we were not able to find an influence of psychopathologic symptoms, side effects, and attitude to drug treatment on our research questions. This may be due to the fact that we investigated a fairly homogeneous sample of stable schizophrenia patients with

little variance between the investigated variables. As number of previous hospitalizations did have an impact on the willingness to participate in such studies, one may assume that patients who had been hospitalized more often, most likely due to a more active episode of the disorder, may have more often received a strong recommendation to stay on medication treatment. This in turn could have driven their reluctance to hypothetically discontinue medication treatment in a placebo-controlled study. It should also be noted that 93 of these patients investigated were currently taking antipsychotics, therefore representing a somewhat selected population. The 7 remaining patients were not taking antipsychotic medication at the timepoint of investigation for different reasons (i.e., washout period). Whether or not current treatment status has an influence on the attitudes we have investigated cannot be answered from the study. Roberts[20] found that consumers, who in general are quite willing to participate in research, express the unwillingness to suspend the medication regimen, which often took quite some time to optimize, as their biggest cause for hesitation or concern. In this context, it should be emphasized that most patients do not discontinue medication for the purpose of participating in a placebo-controlled clinical trial. Generally, they are asked to participate in randomized clinical trials after relapsing due to having discontinued medication on their own.

Not only patients, but also relatives have raised their doubts about the necessity of placebo-controlled clinical trials. They argue that, following the development of many new medications with fewer side effects and perhaps greater effectiveness, discontinuing or withholding such effective drugs is ethically more questionable.[21]

Considering the reasons why patients would be willing to participate, the hope that they would get better treatment (e.g., I would receive more medical care, I would be able to talk to my physician more often, I would be guaranteed to be treated in this hospital) seems to be an important motivator. This triggers the question whether patients who expect better treatment can be justifiably included in placebo-controlled studies.

Not only the hope to improve their own treatment but also the wish to contribute to society by participating in biomedical research motivates many humans. In our study, about 80% of patients argued that they wanted to support the development of new drugs. This wish may include hope for some future benefit for themselves or for their families.

As a considerable number of schizophrenia patients, at some points in their lives, suffer from impaired capacity to adequately process information and subsequently reach informed decisions, it has been suggested that persons with schizophrenia should be declared a vulnerable population meriting special protection, including requiring a guardianship to authorize research participation.[22–24] This determination of competence is highly stigmatizing. Research suggests that approximately 75% of patients with schizophrenia incorporate information and make decisions similar to comparison groups when dealing with consent issues.[25] On the other hand, many patients seem to have problems in understanding the term *placebo*. Mattocks and Horwitz[26] have reported that patients had been happy to be randomized into the placebo group. They believed that they would get a treatment that they would not have received had they refused participation. Despite the fact that in our study the patients were given written information explaining the term *placebo*, it was necessary to give additional extensive narrative explanations to make the term *placebo* plausible. In this context, Carpenter et al.[7] have emphasized that the investigator must ensure that the participant understands that placebo assignment involves risk without the potential benefit of the experimental drug.

Furthermore, the fact that more than 50% of patients would not be willing to give consent to a potential placebo-controlled study also raises doubts about the generalizability of data obtained by these studies. Not only the willingness of patients but also the readiness of physicians to include patients seems to cause a selection bias. A study by Mohr and Czobor,[27] which tested the hypothesis that inclusion of a placebo-treatment arm in controlled clinical trials might bias the selection of study subjects, showed the following results based on a total of 296 studies: patients in placebo-controlled trials, compared with those in active comparator-controlled clinical trials, were older ($p < .002$), had a longer duration of illness ($p < .001$), and had a lower initial symptom severity ($p < .02$). In addition, Fleischhacker et al.[28] have reported that the dropout rate in studies including a placebo group is higher than in comparator-controlled clinical trials. If the dropout rate in the placebo group is higher than in the active treatment group, an artificially enhanced drug/placebo difference might be found. Volavka[8] has also indicated that data from early in the study for those taking placebo will be compared to data obtained much later in the study for those treated with the active compound, if last-observation-carried-forward-analysis is used. All of these findings add to the complexity of trying to interpret results from placebo-controlled clinical trials in patients with schizophrenia.

Our results provide additional support to the view that such studies should not only be discussed from the point of view of ethical concerns. Methodological problems, such as selection bias, also need to be taken into account. Hopefully, alternative study design will obviate the need for conducting and interpreting comparative clinical trials in the future.

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