Patients Excluded From an Antidepressant Efficacy Trial

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Background: The impact of exclusion criteria on antidepressant trials is rarely investigated and poorly understood. We describe specific reasons for exclusion from a double-blind comparative trial and analyze the selection procedure and its impact on treatment outcome.

Method: A 6-week randomized double-blind trial for depressive disorders recruited patients through outpatient psychiatric services, private offices, and health care centers. Of the 612 consecutive patients interviewed for a diagnosis according to DSM-III-R, 209 (34%) finally entered the trial.

Results: 86% of the included patients had no comorbid psychiatric disorder, whereas a third of those excluded had at least one ($p < .00001$). Patients were excluded for having chronic alcohol or drug misuse (17%), receiving antidepressant drugs (15%), or having physical problems precluding their ability to take either of the drugs studied (14%). Some patients could not be included because of a referral to other modes of treatment (19%) or organizational difficulties (16%). The excluded patients less often suffered from major depressive disorder than those who were included in the trial. In particular, patients excluded because of suicidal thoughts or intent more often had a history of previous major depressive episodes ($p = .006$) compared with the included patients. The most important sociodemographic factors related to exclusion from the trial were male sex and unmarried status.

Conclusion: Patients with previous depressive episodes or comorbid disorders were more likely to be excluded from the antidepressant efficacy trial. Data on the efficacy of antidepressant drugs on this patient population are still only infrequently obtained.

(J Clin Psychiatry 1996;57:572–575)

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The authors thank Mr. Olli Kiviruusu for technical help in data processing and F. Hoffmann-La Roche Ltd. for material support in providing the drugs investigated.

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Despite the recognition of selection bias in antidepressant trials, the literature has rarely reported specific reasons that can hamper representative enrollment of patients or detailed justifications for exclusions. It is generally agreed that only patients suffering from depressive illness as assessed using internationally accepted diagnostic and severity criteria should be enrolled in antidepressant efficacy trials.[1] Inclusion and exclusion criteria are utilized to equalize the study and control groups for comparison and to decrease the variance within groups. They also guide the selection of patients for studies that evaluate the effectiveness of antidepressants as treatments for a spectrum of disorders.[2] Exclusion criteria used to assess the subject's eligibility can vary considerably from study to study, but certain criteria are common to most trials. Patients are usually excluded if they have psychotic symptoms, a specified type of personality disorder, substance abuse, risk of suicide, unstable medical conditions, or concomitant medications.[3] Finally, randomization is usually done to minimize the bias caused by a selection procedure.

Two previous studies have shown that the reporting of important features of design and analysis is often omitted even in some of the leading general medical journals.[4,5] Some information about eligibility criteria is usually provided by authors, but it is frequently inadequate. There may thus be difficulties in generalizing the results of a trial to patient groups other than the selected subjects themselves. We conducted a nationwide study in which the sample population was representative of depressive patients attending psychiatric services. In addition, we used several measures to estimate the efficacy of two antidepressant drugs, fluoxetine and moclobemide.[6] In the present report, we describe specific reasons for excluding subjects and other reasons for noninclusion in this double-blind comparative trial, and we analyze the selection procedure and its impact on treatment outcome.

METHOD

We carried out a randomized, double-blind, comparative antidepressant trial in six regions covering all the university hospital catchment areas in Finland, between April 1991 and August 1992. Finland's population is stable at approximately five million and is homogenous in

ethnicity. The 27 research sites involved were mostly outpatient psychiatric services, private offices, and health care centers, but some psychiatric hospitals also took part in the recruitment. Before the trial began, training sessions for investigators were organized in each area to increase the interrater reliability and minimize the variability between sites. The study complied with the Declarations of Helsinki and Tokyo, and it was accepted by the local ethics committee of each region. Informed consent was given by the patients. Subjects and assessors were kept unaware of the treatment received.

Subjects were selected from the 612 consecutive patients who attended the services over a set period. To be eligible, the trial participants had to be aged over 18 years, meet the criteria for a depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R),[7] and have a minimum score of 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[8] The severity of depressive symptoms was also rated with the 13-item Beck Depression Inventory (BDI).[9] Patients were excluded from the trial for the following reasons: having suicidal thoughts or intent, having current psychotic symptoms, receiving monoamine oxidase inhibitors (MAOIs) or serotonin selective reuptake inhibitors (SSRIs) within the 5 preceding days, participating currently in another trial, receiving current electroconvulsive therapy (ECT), having physical problems precluding their ability to take either of the antidepressant drugs, depressive symptoms lasting less than 2 weeks, chronic alcohol or drug misuse, epilepsy, severe liver dysfunction, pregnancy, or breast-feeding. Current psychotherapy was not a reason for exclusion. Exclusion criteria were not mutually exclusive, but assessment of multiple criteria, if necessary, was allowed for each patient.

We designed our protocol to meet closely the usual patterns of prescribing antidepressant medication in practice. We emphasized the study to be representative of clinical management of depressive patients. Therefore, we studied a whole spectrum of depressive disorders for which antidepressants are commonly indicated, including adjustment disorder. Patients who met the eligibility criteria were randomly assigned to receive either 300 mg of moclobemide or 20 mg of fluoxetine a day in a double-blind trial for 6 weeks. The methods of the trial and assessment of the antidepressant efficacy have been described in detail elsewhere.[6,10,11]

Our objective was to investigate whether patients who were included would be more severely depressed than those excluded from the trial. In addition, we explored the frequencies of specific criteria and nonspecific reasons for exclusion and were interested in whether the selection procedure would match clinical experience on recruitment strategies. For statistical analysis, the chi-square test with Yates' correction was used for categorical variables and the unpaired t test for continuous variables.

Table 1. Reasons for Exclusion From the Trial (N = 381)

Reason	N	%
Chronic alcohol or drug misuse	65	17
Receiving MAOIs or SSRIs within the 5 preceding days	58	15
Physical problems precluding the ability to take either trial drug	55	14
Current psychotic symptoms	42	11
Suicidal thoughts or intent	36	9
Current ECT	16	4
Participating in another current trial	3	1
Having depressive symptoms for less than 2 weeks	3	1
Epilepsy	3	1
Being pregnant or breast-feeding	3	1
Severe liver dysfunction	2	1

RESULTS

Of the 612 consecutive patients interviewed, 264 subjects (43%) met one exclusion criterion, and 117 (19%) two or more. The specific reasons for exclusion are presented in Table 1. In addition, some patients could not be included in the trial because of a referral to other modes of treatment (N = 74, 19%), organizational difficulties such as periods of leave (N = 60, 16%), a good response to other antidepressant drugs previously (N = 50, 13%), their refusal (N = 45, 12%), and their familiarity to a study team member (N = 11, 3%). Reasons for a referral to other modes of treatment were, among others, a need for immediate medication (N = 27) or ECT (N = 7), and a preference for psychotherapy (N = 4). Twelve generic compounds had been prescribed to patients having a history of good response to other antidepressant drugs. Three patients refused drug treatment, and informed consent was not obtained from a fourth. Twenty-seven patients were not eligible because of scoring low on the HAM-D. Altogether, 231 patients (38%) did not meet any exclusion criteria or other obstacles for entry into the trial. Among these, 21 subjects were subsequently found not to be in need of antidepressant medication and were thus ineligible for the trial. Contact was lost with 1 patient. Hence, 209 patients (34%) finally entered the trial. Forty patients (19%) dropped out during the 6-week trial.

In the population studied, the excluded patients were significantly younger than both those who were included and those who completed the 6-week trial (Table 2). There were significantly more men among the excluded than the included; in particular, men were excluded significantly more often than women because of suicidal thoughts or intent, or chronic alcohol or drug misuse. The excluded patients were significantly more often unmarried.

The included patients more often suffered from major depressive disorder than those who were excluded from the trial. The excluded patients were significantly more likely to have psychiatric comorbid disorders, and they also significantly more often had a history of previous

Table 2. Demographic Characteristics and Diagnostic Categories Among the Patients*

Characteristic	Excluded Patients (N = 403)	Included Patients (N = 209)	Completed Patients (N = 169)
Age, mean (SE)	44.0 (0.7)	47.0 (0.8)[a]	47.2 (0.9)
Gender, N (%)			
Female	225 (56)	135 (65)[b]	104 (62)
Male	177 (44)	74 (35)	65 (38)
Marital status, N (%)			
Unmarried	99 (25)	30 (16)[c]	20 (13)
Married	208 (53)	107 (58)	88 (59)
Divorced	68 (17)	35 (19)	29 (19)
Widowed	21 (5)	14 (8)	13 (9)
DSM-III-R diagnosis, N (%)			
Major depressive episode	197 (49)	127 (61)[d]	105 (62)
Bipolar disorder, depressed	12 (3)	2 (1)	2 (1)
Depressive disorder NOS	75 (19)	22 (11)	16 (10)
Dysthymia	56 (14)	36 (17)	26 (15)
Adjustment disorder, depressed mood	53 (13)	22 (11)	20 (12)
Previous major depressive episode, N (%)	235 (59)	90 (49)[e]	79 (53)
Comorbid psychiatric disorders, N (%)			
None	272 (68)	180 (86)[f]	146 (86)
One	109 (27)	22 (11)	19 (11)
Two or more	22 (6)	7 (3)	4 (2)

*Comparisons are between the groups of excluded and included patients. Total group size varies due to incomplete data in certain categories.
[a]$t = -2.9$, df = 467.7, $p = .004$.
[b]$\chi^2 = 4.2$, df = 1, $p = .04$.
[c]$\chi^2 = 5.8$, df = 1, $p = .02$.
[d]$\chi^2 = 6.2$, df = 1, $p = .01$.
[e]$\chi^2 = 5.4$, df = 1, $p = .02$.
[f]$\chi^2 = 24.7$, df = 1, $p < .00001$.

major depression compared with the included. There was no difference in the presence of atypical symptoms of depression, or of bulimic symptoms, between any group of patients. The family history of depressive illness did not differ between any patient groups.

Patients excluded for suicidal thoughts or intent were younger, more often males, and more likely to have a history of previous major depressive episodes than the included ($t = -3.2$, df = 49.8, $p = .002$; $\chi^2 = 5.3$, df = 1, $p = .02$; $\chi^2 = 7.6$, df = 1, $p = .006$, respectively). Those excluded because of current psychotic symptoms or physical problems precluding their ability to take either of the antidepressant drugs more often had a history of previous major depressive episodes ($\chi^2 = 7.0$, df = 1, $p = .008$; $\chi^2 = 9.1$, df = 1, $p = .003$, respectively). The patients excluded for chronic alcohol or drug misuse were younger, more often males, and more often unmarried than the included ($t = -4.0$, df = 117.3, $p < .001$; $\chi^2 = 15.6$, df = 1, $p = .00008$; $\chi^2 = 8.2$, df = 1, $p = .004$, respectively). Patients who were not included because of a good response to other antidepressant drugs more often had major depressive episodes previously ($\chi^2 = 21.3$, df = 1, $p < .00001$). Patients whose first-degree relatives had depressive illness were more likely to refuse to take part in the trial ($\chi^2 = 4.4$, df = 1, $p = .04$).

Of the BDI items, mood ($t = -2.8$, df = 396.2, $p = .005$), pessimism ($t = -2.9$, df = 398.2, $p = .004$), lack of satisfaction ($t = -3.3$, df = 373.7, $p = .001$), guilt ($t = -2.6$, df = 380.8, $p = .009$), social withdrawal ($t = -2.9$, df = 400.8, $p = .003$), and indecisiveness ($t = -2.7$, df = 425.8, $p = .008$), as well as the total score ($t = -3.2$, df = 416.4, $p = .002$), were significantly lower among the excluded patients than among the included. Of the excluded, patients receiving ECT scored significantly higher ($p < .01$) on the BDI than the included patients. Among the excluded, those having suicidal intent, psychotic symptoms, or current alcohol or drug misuse scored significantly higher ($p = .009$, .022, and .023, respectively) on the BDI than the rest of that group.

DISCUSSION

The use of inclusion criteria guaranteed that clinically eligible patients were enrolled in the study. The included patients tended to suffer from more severe depression than the excluded. Specifically, there were more patients suffering from major depressive disorder among the included. The included patients also scored higher on the BDI items that specifically measured negative attitudes toward self. In examinations on its factor structure, the short form of the BDI has been demonstrated to represent one cognitively oriented symptom dimension.[12] Our study supported the view that the short form could be useful as a global measure of the severity of the cognitive aspects in depression.

Age and gender are important factors in the selection of patients for trials. Our results suggest that younger male patients formed a group likely to be excluded from the trial because of chronic alcohol or drug misuse, or suicidal thoughts or intent. These conditions were the reasons for exclusion in 26% of the excluded cases. Restricting the enrollment of women of childbearing potential in trials is another concern, since they represent a target population of interest for antidepressant drugs owing to their high lifetime prevalence rate of depressive disorders, ranging from 12% to 33%.[13] In our study, the excluded were more often not only younger but also male. Only 1% of the excluded were not included because of pregnancy or breast-feeding. These three subjects were 27, 29, and 36 years of age. In conclusion, women of childbearing potential were well represented in our patient population.

The included and excluded patients did not differ in the degree of suicidality as measured with the BDI items related to self-hate and self-punitive wishes. A small group of severely ill patients who were suicidal, had had major depressive episodes previously, or were receiving ECT was excluded from our trial. This meant that since suicidal patients were excluded by clinical judgment, our data on antidepressant efficacy were restricted to depressed individuals whose clinical picture was not charac-

terized by suicidal behavior. Hence, this particular feature of depressive illness was not able to be analyzed any further.

The exclusion of patients with previous major depressive episodes as well as psychiatric comorbid disorders resulted in chronically ill or otherwise difficult patients being more likely to be excluded from the trial. This finding is useful in everyday practice when considering antidepressant medication for a depressed patient. Since patients with comorbid disorders become easily excluded from antidepressant studies, data about the efficacy of antidepressant drugs on this patient population are infrequently obtained and thus guidelines on their management are difficult to pass on. These patients should therefore be monitored with particular care. In everyday practice, too, patients who suffer from major depressive disorder are more likely to complete a course of treatment than other depressed patients, who should thus be monitored carefully. We recommend that clinicians should initially assess their patients with well-defined diagnostic criteria and use that assessment as a basis for their decision about the treatment strategy and the care to be given. We suggest that special emphasis should be put on patients with recurrent major depressive disorder because of their relatively good compliance and potential treatment response to antidepressant drugs.

As a result of changing health care practices, hospitalized patients with depressive disorder are at risk of becoming less representative of the population treated with antidepressant drugs. Less severe depressive disorders are more commonly encountered in primary care settings than in mental health services, and thus such patients frequently avoid being included in antidepressant trials. We took account of some of these common pitfalls and paid special attention to the representativeness of our patient population. Twice as many women as men were enrolled in our trial, which is in agreement with the rates reported on prevalence by gender, but limits the conclusions that can be drawn from our results about male patients. However, our sample covered a large number of depressive patients attending both inpatient and outpatient psychiatric services in various parts of the country around the year. Moreover, most of the included patients were recruited from outpatient settings in which most depressed patients are in fact treated.

The questions arising from the recruitment method or selection procedure have rarely been tackled by previous studies.[14] The subjects and methods sections of antidepressant trial reports should be described more thoroughly. The reader would then be offered a better opportunity of evaluating the extent to which the reports on the drug efficacy refer to the drug effectiveness. There is also a growing need for antidepressant trials that would better reflect everyday practice. The efficacy of drugs can be verified in controlled conditions, but a clinician is usually working in more or less uncontrolled settings. Randomized clinical trials where diagnostics is based on well-defined criteria and accurate assessment are essential for confirming the antidepressant qualities of the drugs under consideration and exploring possible efficacy in additional clinical indications. However, these trials should give more information about the criteria guiding the selection procedure and should better match the requirements for reporting on the effectiveness of the drug(s) investigated.

In conclusion, our main finding was that patients with previous depressive episodes or comorbid disorders were more likely to be excluded from the trial. As patients with comorbid disorders seem to be readily excluded from antidepressant trials, data on the efficacy of antidepressant drugs on this patient population are infrequently obtained. We also found, as expected, that those who suffered from major depressive disorder more frequently entered the trial than were excluded and that current alcohol or drug misuse had the strongest excluding influence on the selection of patients.

Drug name: fluoxetine (Prozac).

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