

# Compliance With Antidepressants in a Primary Care Setting, 1: Beyond Lack of Efficacy and Adverse Events

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**Background:** Treatment guidelines recommend antidepressant treatment be continued for at least 6 months to ensure maximal improvement and to prevent relapse. Naturalistic studies show that the average length of treatment is shorter than 6 months and that dropout rates are high. Factors leading patients to discontinuation of therapy are not well understood. This study investigates when and why patients stop treatment and whether they inform their doctors. **Method:** Patients (N = 272) receiving antidepressant therapy due to an episode of major depressive disorder (DSM-IV) were asked to complete an antidepressant compliance questionnaire. Patients were then telephoned monthly while they continued on antidepressant therapy, up to 6 months. During each call, patients were asked standard questions. **Results:** By endpoint, 53% of patients had discontinued antidepressant treatment. The most common reason given was "feeling better." However, different dropout reasons were prevalent at different times after initiation of therapy. Overall, 24% of the patients did not inform their physician about stopping the antidepressant medication. The likelihood of patients' informing their physicians differed according to the patients' reasons for discontinuation and according to the patients' perceptions of their relationship with their physicians. **Conclusion:** These results provide new guidelines for improving compliance. Strategy should be adapted to the stage of treatment, as patients' reasons for discontinuation vary as treatment progresses. The attitude of the physician and the information provided by the physician significantly influence whether patients inform the physician when they discontinue antidepressant therapy.

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Current treatment guidelines recommend that patients maintain antidepressant treatment for at least 6 months.<sup>1-3</sup> This length of therapy has been strongly associated with prevention of relapse<sup>4</sup> and with greater improvement in depressive symptoms.<sup>5,6</sup> Maintaining therapy for a longer time has also been shown to be important for occupational functioning, which improves more slowly than depressive symptoms.<sup>7</sup>

Length of treatment in a naturalistic (primary care) setting is short and dropout rates are high.<sup>8</sup> The factors leading to patients' discontinuing their therapy are not well understood. Often clinical trials allow for only 2 reasons/categories for patients who discontinue therapy: lack of efficacy and adverse events.<sup>9</sup> However, a small study by Maddox et al.<sup>10</sup> revealed that the reasons for dropping out are different in a naturalistic setting. In that study, feeling better was the most frequent reason given, followed by adverse events, other reasons, physician's instructions, and medication having no effect. In addition, Maddox and colleagues found that 63% of patients had not informed

their physicians that they had stopped antidepressant treatment.<sup>10</sup>

Thus, the aim of the present study was to investigate the dropout phenomenon in a routine general practitioner physician (GP) practice: when and why patients prematurely stop treatment and if they inform their doctors about stopping.

## MATERIALS AND METHOD

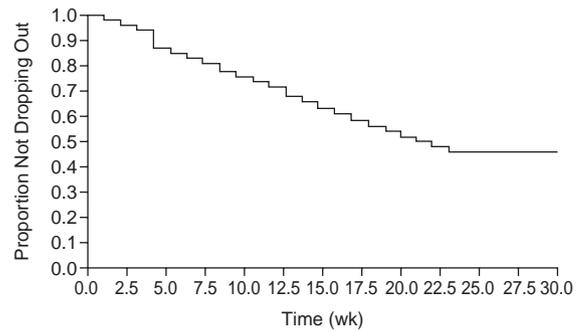
After receiving informed consent of the patient, participating GPs (N = 91) sent the principal investigator (K.D.) a file for each patient, indicating the DSM-IV criteria for major depressive disorder, patient name and contact information, and the antidepressant prescribed for that patient (fluoxetine, 221 patients; citalopram, 14 patients; paroxetine, 12 patients; sertraline, 9 patients; fluvoxamine, 5 patients; trazodone, 2 patients; venlafaxine, 2 patients; and moclobemide, 1 patient; missing values in 6 patients). Patients with major depressive disorder for whom an antidepressant was indicated were consecutively enrolled. Inclusion criteria were an episode of major depressive disorder and being at least 18 years old. The mean age of the patients was  $43 \pm 13$  years; 72% were women.

Each patient was asked to complete and return an Anti-depressant Compliance Questionnaire (ADCQ) and the Sheehan Disability Scale<sup>11</sup> and to indicate the hour and day he or she preferred to get a monthly call at home. Patients were told they would receive a call each month for as long as they were on treatment, up to 6 months. During these phone calls, contact was limited to the administration of the Sheehan Disability Scale and some standard questions (Are you still taking the antidepressant medication? If not, when and for what reason[s] was the drug discontinued, and was the general practitioner informed about the discontinuation?). If patients gave multiple reasons for discontinuing antidepressant medication ("dropping out"), all reasons were recorded.

The ADCQ is a 50-item self-rated questionnaire assessing attitudes and beliefs about the causes of depression, the use of antidepressants, and the doctor-patient relationship. For each item, patients choose "mainly disagree," "rather disagree," "rather agree," or "mainly agree." A factor analysis based on the principal component method gives 4 factors explaining 30% of the variability. The first factor explains 15% and comprises the items on the relationship between patient and doctor. Since this article focuses on dropout reasons and on whether or not the patient informed the doctor about stopping treatment, only the items on the doctor-patient relationship are analyzed.

Results are expressed as means and standard deviations for quantitative variables and as frequencies for qualitative variables. Kaplan-Meier survival curves and the log-rank test were used to investigate and compare dropping-out time between subgroups of interest. The Mantel-Haenszel

Figure 1. Survival Plot of Time to Dropout Using the Kaplan-Meier Method for 272 Patients With DSM-IV Major Depressive Disorder<sup>a</sup>



<sup>a</sup>The graph shows the proportion of patients continuing on treatment with antidepressant medication over time.

chi-square test was used to study the correlation between 2 ordinal variables. All results were considered to be significant at the 5% critical level. Statistical calculations were carried out using the SAS package (SAS Institute, Inc., Cary, N.C., 1996).

## RESULTS

### Dropouts

The probability of not dropping out from antidepressant therapy was 0.88 after 4 weeks, 0.77 after 8 weeks, 0.68 after 12 weeks, 0.58 after 16 weeks, and 0.52 after 20 weeks (Figure 1). At the end of the study (6 months), 53% of the 272 patients had discontinued antidepressant treatment. The dropping-out process was not significantly related to the gender of the patient (log-rank test;  $p = .39$ ), to the gender of the doctor (log-rank test;  $p = .34$ ), or to the linguistic community, i.e., French- or Dutch-speaking patients (log-rank test;  $p = .56$ ). The age of the patient had no effect, either ( $p = .56$ ).

### Reasons for Dropping Out

The most frequently cited reasons for dropping out were "feeling better" (55%), "adverse events" (23%), "fear of drug dependence" (10%), "feeling uncomfortable with taking drugs" (10%), "lack of efficacy" (10%), "I have to solve my problems without drugs" (9%), and "my GP told me to stop" (9%). Patients were allowed to give multiple reasons for dropping out; 16% of patients gave 2 reasons, and 84% of patients gave 1 reason.

It is interesting to note that patients drop out for different reasons at different points in time. The patients who dropped out because of "adverse events" did so after a mean period of 6.5 weeks; because of "lack of efficacy," after 7 weeks; because of "fear of drug dependence," after 8 weeks; because "I have to solve my problems without drugs," after 10.5 weeks; because of "feeling better," after

11 weeks; because “my GP told me I could stop the treatment,” after 12 weeks; and because of “uncomfortable feelings,” after 13 weeks.

### Informing or Not Informing the Physician

Overall, 24% of the patients did not inform their physician about stopping the antidepressant medication. Again, informing or not informing the physician varied for each dropout reason. When the reason was “my GP told me I could stop the treatment,” 100% of the physicians were informed about stopping; for “feeling uncomfortable,” 82% were informed; for “feeling better,” 76% were informed; for “fear of dependence,” 60% were informed; for “adverse events,” 60% were informed; for “lack of efficacy,” 34% were informed; and for “I have to solve my problems without drugs,” only 25% of physicians were informed.

Patients who informed their physician about stopping medication agreed significantly more frequently with ACDQ items concerning doctor-patient relationship (assessed before the treatment started): “the GP understands perfectly how I feel” ( $p = .05$ ), “I am satisfied with the time the physician spends discussing my emotional problems” ( $p = .04$ ), “I am satisfied with the explanations the GP gives on the causes of my depression” ( $p = .04$ ), “my GP devotes enough time to listen to my problems” ( $p = .04$ ), and “my GP ensures that I am confident in the fact that antidepressants are the appropriate treatment” ( $p = .02$ ).

## DISCUSSION

There was a linear increase in dropout rate over the 6-month study period, but almost half of the patients were still taking their antidepressant medication at the end of this study. This is a larger proportion than would be expected from comparisons to truly naturalistic studies.<sup>8,10</sup> Indeed, the present study was different in at least 2 aspects. First, there was possible selection bias. Physicians may have included patients they supposed to be highly compliant, or they may have included a greater proportion of patients with whom they had a good working relationship. Second, it is also possible that a monthly telephone call assessing how the patient feels improved compliance.<sup>12</sup>

The reasons patients gave for dropping out in this study give a different picture from that found in randomized clinical trials. In those trials, there are often only 2 main categories of dropout reasons found (lack of efficacy, adverse events).<sup>9</sup> The reasons patients gave in this study are comparable to those given in the study by Maddox and colleagues.<sup>10</sup>

Our data indicate that dropout reasons are different at different stages of treatments. Initially, lack of efficacy and adverse events are the main reasons; from 8 weeks on, psychological reasons become more important. Many randomized clinical trials last for only 8 weeks. Hence it is understandable that “lack of efficacy” and “adverse

events” are the major reasons for dropout in these trials. This time course gives us some important clinical guidelines for improving compliance; the strategy should be adapted to the stage of treatment.

In this study, 24% of the patients did not inform their physician about stopping the antidepressant medication. This is much lower than the 63% not informing their physician in the study by Maddox and colleagues.<sup>10</sup> There are a number of possible reasons for this difference. Maddox et al. included patients diagnosed with other indications for antidepressants such as anxiety disorders, eating disorders, and pain,<sup>10</sup> whereas this study focused on patients who were diagnosed with major depressive disorder. In addition, Maddox et al. assessed dropouts at only one time-point, 10 to 12 weeks after the patient was enrolled in the study, whereas we assessed dropouts monthly for 6 consecutive months.<sup>10</sup>

When carefully investigating the percentage of patients informing their physician about stopping for each particular reason of dropout, the following interpretation emerges. The more a dropout reason could hurt doctors' self-esteem, the lower the percentage of patients informing the doctors, and the more a dropout reason could please doctors, the higher the percentage of patients informing them. Indeed, it is more difficult to inform your doctor about “adverse events” (you gave me a medicine that causes side effects), about “lack of efficacy” (you gave me a medicine that is not effective), or about a desire “to solve my problems without drugs” (I do not agree that drugs should be a treatment option) than to inform the doctor about “feeling better” (you gave me an effective treatment).

Moreover, the 5 ADCQ items assessing the doctor-patient relationship are all predictive of the chance that patients will inform their physician that they have stopped taking their antidepressant medication. The better the information doctors gave and the more empathetic the doctors' attitudes were perceived to be, the higher the chance that patients informed their doctors. It is remarkable, however, that the doctor-patient relationship was not predictive of length of time patients continued to take antidepressant medication (K.D., et al., manuscript in preparation).

Taken together, these findings suggest that whether or not patients inform their physicians depends on the quality of the doctor-patient relationship and the estimated risk that a particular dropout reason could hurt or offend the doctor. Patients may have some reason to react in this way. In a study of physicians' attitudes toward noncompliance in their patients, 59% of physicians had ego-defensive reactions (medical threat, authoritarian, blaming the patient), 10% had avoiding reactions (altering the drug, withdrawal), and only 31% had task-oriented reactions (trying to determine the causes of noncompliance).<sup>13</sup>

Although these are clinically interesting findings, this study also has some important limitations. First, our finding that 24% of patients do not inform their physicians

about stopping antidepressant medication is only an estimate. Indeed, as a substantial part of the investigated patients did not inform their physician correctly about their compliance (having stopped treatment or not), we cannot be sure that these patients told us the truth on the telephone. Second, patients may not have been totally truthful about their reasons for dropping out. The reason given could be an attribution (socially desirable reason). Since this investigation demonstrates that informing the physician or not partly depends on the anticipated effect upon the physician, this phenomenon could also influence the nature of the reason that was communicated to us during the telephone calls. Third, since the physicians were informed about the aim of this study, there may have been a selection bias in the inclusion of patients that influenced our results.

*Drug names:* citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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