Predictors of Nonadherence to Continuation and Maintenance Antidepressant Medication in Patients With Remitted Recurrent Depression

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Objective: To identify predictors of nonadherence to continuation and maintenance antidepressant medication among patients with remitted recurrent depression.

Method: We used data of 91 remitted, recurrently depressed patients (at least 2 major depressive episodes as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders) treated with continuation and maintenance antidepressant medication in a 2-year prospective study. Patients were recruited at psychiatric centers and through media announcement from February 2000 through September 2000. Adherence was assessed with the Medication Adherence Questionnaire. Nonadherence on this scale indicates that patients missed 20% or more of their antidepressant medication. We determined nonadherence point prevalences at the 7 assessment points. Based upon these 7 assessments, we found nonadherence percentages ranging from 39.7% to 52.7% with a mean of 46.5% over 2 years. We examined a set of potential risk factors (patient-related, disease-related, and treatment-related) measured at baseline.

Results: In univariate analysis using a stringent significance level ($p \leq .005$), we found no independently related predictors of nonadherence over a 2-year period. In a multivariate analysis with backward elimination, the baseline predictors for nonadherence over a 2-year period were a higher level of personality pathology and a higher level of education.

Conclusion: There are no clear predictors of nonadherence to antidepressants in the continuation and maintenance phases in remitted, recurrently depressed patients. Further research should focus on the process of becoming nonadherent to antidepressants in the longest phase of antidepressant use to maximize the potential protective effect of these medications.

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Major depressive disorder (MDD) is a common mental disorder with large economic and societal costs. Around 50% of patients with a first episode will have further episodes. The recurrence rate of MDD rises to 80% to 90% in patients with 3 or more episodes.[1,2]

International guidelines[3,4] recommend that recurrently depressed patients (at least 2 previous episodes) who remit while taking antidepressants should be maintained on this medication for another 4 to 5 months (referred to as the continuation phase, American Psychiatric Association guidelines[4]) to 2 years (National Institute for Clinical Excellence [NICE] guidelines[5]). Prolonged use of antidepressants (referred to as maintenance therapy) ranges from at least 2 years (NICE guidelines[5]), to an unspecified period,[4] to even life-long antidepressant use to prevent relapse of recurrent MDD.

However, poor adherence to treatment of chronic diseases (somatic and psychiatric) is a worldwide problem of striking magnitude.[6] We found nonadherence rates in recurrently depressed patients ranging from 39.7% to 52.7% with a mean of 46.5% over 2 years.[7] This finding is in line with studies of adherence in other chronic diseases.[8]

Since suboptimal dosage and duration of antidepressant treatment increases the risk of relapse and chronicity, nonadherent behavior is of clinical, economic, and public health concern. Unfortunately, clinicians are only 50% accurate in their identification of potentially nonadherent patients.[9] It would be helpful if doctors could more accurately assess the risk for nonadherence in patients to discuss nonadherence and/or adjust their treatment.

Just as for other (somatic and psychiatric) diseases, risk factors for antidepressant nonadherence as presented in previous literature are inconsistent.[10,11] There is, however, consensus that adequate use of antidepressants is at least partly determined by complex physician, patient, and physician/patient interaction characteristics.[8,12]

In MDD, most predictive studies for antidepressant nonadherence are predominantly assessed in the acute phase of treatment. These results may not generalize to the remitted phase in recurrent depressive disorder. First, the depression state itself is a risk factor for nonadherence. In the remitted phase, patients may assume that they are "no longer in need of antidepressants" or may become less willing to continue tolerating previously acceptable antidepressant side effects (for example sexual side effects) and may not feel the direct consequences of stopping antidepressants.[13]

Second, in general, adherence rates are typically higher in acute conditions as compared to chronic conditions.[8] In the continuation and maintenance phase, patients are relatively more affected by fears of potent long-term cumulative or insidious adverse effects of antidepressants, such as personality change, addiction, or toxicity.[13]

Thus far, the only study of nonadherence in patients suffering from recurrent depression could not identify differences in demographic and clinical variables between adherent and nonadherent patients.[14] However, that study was possibly biased because it derived from a medication trial with an intervention that aimed to create an alliance between treatment team, patient, and family in order to improve adherence.[14]

The present study examines a set of potential risk factors for nonadherence in patients with remitted recurrent depression taking continuation and maintenance antidepressants. To our knowledge, this is the first study of risk factors for nonadherence in this kind of population. To improve external validity of our findings, we used a seminatural cohort, which is a unique population for evaluating medication use because of the monitored noncontrolled use of antidepressants during the 2-year follow-up period of the study.

METHOD

Participants

Participants (N = 172) were remitted patients with a diagnosis of recurrent depression who took part in a clinical trial to assess the effect of cognitive-behavioral therapy on relapse prevention.[15] They were recruited at psychiatric centers and through media announcement in the Netherlands from February 2000 through September 2000. The study protocol was approved by the relevant institutional ethics review committees, and all subjects provided written informed consent.

Participants all met the following criteria: (1) at least 2 major depressive episodes in the last 5 years defined according to DSM-IV[16] and assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders[17] by trained evaluators; (2) current remission status according to DSM-IV criteria > 10 weeks and ≤ 2 years ago; (3) a 17-item Hamilton Rating Scale for Depression[18] (HAM-D) score < 10; and (4) no current mania, hypomania, history of bipolar illness, psychotic disorder (current and previous), organic brain damage, alcohol or drug misuse, predominant anxiety disorder, recent electroconvulsive therapy, recent cognitive treatment or receipt of cognitive therapy at the start of the study, or current psychotherapy with a frequency of more than 2 times per month. There was no restriction on use of pharmacotherapy. Every 3 months and at 2 years' follow-up, we collected information on the use of antidepressants. More details about participants, recruitment, and inclusion and exclusion criteria and medication use are available in Bockting et al.[15,19]

Of the original study sample (N = 172), we excluded 41 patients (22% male, mean ± SD HAM-D score = 4.3 ± 2.9) who were not treated with antidepressants at the moment they entered the study and 24 patients (28.2% male, mean ± SD HAM-D score = 3.6 ± 2.8) because they did not take antidepressants at any of the 7 adherence assessment points. Sixteen patients were excluded because of missing data on antidepressant use over the follow-up period. Therefore, the analyses were performed with 91 patients.

The 16 patients who were excluded because of missing data on antidepressant use over the follow-up period were comparable to the 91 included patients except for severity of last depression (excluded cases experienced less often a mild last depression: 0% vs. 10.1%, more often a moderate depression: 62.5% vs. 28.6%, and less often a severe last depression: 37.5% vs. 60.4%, $\chi^2 = 7.670$, df = 2, p = .022). They also had a slightly higher baseline HAM-D score (t = –1.73, df = 105, p = .09; excluded cases: mean = 4.8, SD = 2.7; completers: mean = 3.5, SD = 2.8).

Study Measures

Dependent variable. Nonadherence was assessed with the Medication Adherence Questionnaire (MAQ).[20] Nonadherence on this scale indicates that patients missed 20% or more of the doses of their antidepressant medication.[21] We determined nonadherence point prevalences at the 7 assessment points. Based upon these 7 assessments, we classified 30.8% of the patients (28/91) as always adherent (adherent at all assessments) and 69.2% (63/91) as nonadherent (not adherent at all assessments) over 2 years.

Potential predictors. We examined a set of potential risk factors measured at baseline either by trained interviewers or self-rating scales. These potential predictors,

Table 1. Univariate Predictors of Nonadherence Over 2 Years Among Patients Who Continuously and Intermittently Took Antidepressants (N = 91)[a,b]

	Univariate				Multiple Regression			
Predictor	β	OR	95% CI	p	β	OR	95% CI	p
Patient factors								
Sex female/**male**	–0.761	0.467	0.155 to 1.408	.177*	–0.836	0.434	0.113 to 1.656	.222
Age	0.004	1.004	0.959 to 1.052	.853	…	…	…	…
Personality (PDQ-4+ total score)	0.033	1.034	0.998 to 1.070	.062*	0.037	1.308	0.978 to 1.101	.221
Marital status, living alone/**not alone**	0.034	1.035	0.409 to 2.617	.942	…	…	…	…
Education level (high/**other**)	1.099	3.000	0.921 to 9.773	.068*	1.558	4.747	1.052 to 21.428	.043
Familial psychiatric disease, yes/**no**	0.485	1.624	0.602 to 4.378	.338	…	…	…	…
Smoking, yes/**no**	–0.370	0.691	0.242 to 1.969	.489	…	…	…	…
Employed, yes/**no**	–0.419	0.658	0.268 to 1.612	.360	…	…	…	…
Comorbidity Axis I, yes/**no**	0.637	1.891	0.375 to 9.538	.440	…	…	…	…
Disease factors								
No. of previous episodes before T0	0.558	1.747	0.978 to 3.119	.059*	0.598	1.818	0.887 to 3.727	.103
Severity of residual symptoms T0	0.135	1.144	0.964 to 1.358	.122*	0.136	1.146	0.922 to 1.425	.219
Severity of last episode before T0 overall	…	…	…	.036*	…	…	…	.120
Medium vs low	–2.197	0.111	0.012 to 1.007	.051	–2.101	0.122	0.012 to 1.294	.081
Severe vs low	–1.123	0.325	0.038 to 2.803	.307	–1.154	0.315	0.032 to 3.136	.325
Duration of last episode before T0 overall	…	…	…	.331	…	…	…	…
> 2 mo and < 8 mo vs ≤ 2 mo	–0.459	0.632	0.216 to 1.847	.402	…	…	…	…
≥ 8 mo vs ≤ 2 mo	0.391	1.478	0.396 to 5.512	.561	…	…	…	…
Onset before age 21 y, yes/**no**	0.460	1.583	0.554 to 4.529	.391	…	…	…	…
Total DAS-A score at baseline	0.011	1.011	0.996 to 1.026	.161*	–0.002	0.998	0.973 to 1.760	.868
SCL-90 score at baseline	0.302	1.353	0.271 to 6.54	.713	…	…	…	…
BDI score at baseline	0.357	1.429	0.826 to 2.473	.202	…	…	…	…
Treatment factors								
Current treatment, specialty care, yes/**no**	–0.342	0.710	0.289 to 1.747	.456	…	…	…	…
Adequate fluoxetine equivalent T0, yes/**no**	0.634	1.886	0.753 to 4.718	.175*	0.553	1.739	0.568 to 5.323	.332

[a]30.8% (28/91) adherent over 2 years; 69.2% (63/91) nonadherent over 2 years.
[b]Bold refers to the reference category.
*p ≤ .2.
Symbol: … = no data.
Abbreviations: BDI = Beck Depression Inventory, DAS-A = Form A of the Dysfunctional Attitude Scale, OR = odds ratio, PDQ-4+ = Personality Disorder Questionnaire-4+, SCL-90 = 90-item Symptom Checklist.

categorized into 3 domains (patient-related, disease-related, and treatment-related), are presented in Table 1.

Personality. Personality was evaluated with the 99-item self-report Personality Disorder Questionnaire-4+[22] (PDQ-4+), which assesses DSM-IV personality disorders and has been widely used in personality disorder research. For this study, we used the PDQ-4+ total score.[22]

Axis I comorbidity. Axis I comorbidity was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Number of previous episodes before baseline (first study assessment; T0). Number of previous episodes was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Severity of residual symptoms. The 17-item HAM-D[18] was used to assess participants' baseline levels of depressive symptomatology. The HAM-D, administered by psychologist/research assistants blind to treatment condition, is a widely used semistructured clinical interview that covers a range of affective, behavioral, and biological symptoms and has acceptable psychometric properties.[23] Scores can range from 0 to 52. Our 4 interviewers (psychologist/research assistants) second rated 17 of the participants' interviews. The intraclass correlation was 0.94, indicating high agreement. Further, the 21-item self-report Beck Depression Inventory[24] was used to assess baseline depression symptomatology in the past week. Scores may range from 0 to 63.[24]

Severity of last episode before T0 overall. Severity of last episode was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Duration of last episode before T0 overall. Duration of last episode was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders.[17]

Level of psychopathology. The 90-item Symptom Checklist[25] was used to assess the total baseline level of psychopathology in the past week.

Dysfunctional attitudes. Dysfunctional attitudes (baseline) were assessed with the Dutch adaptation of the Dysfunctional Attitude Scale (DAS).[26] The DAS is a 40-item scale that assesses excessive and rigid beliefs, hypothesized by Beck[27] to be vulnerability factors for depression. Participants rate their agreement with each belief on a 7-point Likert scale ranging from "totally agree" to "totally disagree." Scores range from 40 to 280, with higher scores indicating greater levels of dysfunctional attitudes. Form A of the DAS, which has been shown to have good psychometric properties, was used.[28]

Medication. Every 3 months, information on antidepressant medication (type and dosage) over the previous months was monitored with the Trimbos/IMTA Self-Report Questionnaire for Costs Associated With Psychiatric Illness.[26,29]

Other patient-related and treatment-related potential predictors. Semistructured interviews were used to provide other (not mentioned above) potential predictors such as sociodemographic characteristics, psychiatric history, and disease management.

Statistical Analysis

For the analyses, we had to take into account the fact that half of our sample received an additional psychological intervention that prevented recurrence. The effect of this treatment depended on the number of previous depressive episodes.[15] One way to take this fact into account is to restrict all analyses to the control group, which of course would lower the power of these analyses considerably. An alternative approach is to assess whether the intervention had an effect on the relation between the predictor and nonadherence or not. In the first case, the analyses should be restricted to the control group; in the latter case, the analysis can be performed on the pooled experimental and control group data with a considerable gain in statistical power.

In a preliminary logistic regression analysis, we assessed for each potential predictor separately whether treatment condition in combination with number of previous episodes had a modifying and/or confounding effect on the relation between potential predictor and nonadherence. The modifying effect was assessed by the 3-way treatment by number of previous episodes by potential confounder interaction and the 2-way treatment by potential confounder interaction. In case of no effect modification, the confounding effect was assessed by examining the change of the regression coefficient for each potential confounder when treatment condition was added to the model. A 10% change in the regression coefficient was considered an indication for confounding.

Given the relatively lower power of the test for interaction compared to tests for main effects, we used an α level of .10 for all tests for interaction to guard against type II error. Since the distribution of number of previous episodes was skewed, and the minimum number of previous episodes was 2, we used the following formula $P = \ln(p - 1)$, with p the actual number of previous episodes and P the transformed variable used in the analysis.

For none of the potential predictors did treatment condition or the combination of treatment condition and number of previous episodes modify the relation between the predictor and nonadherence, neither did treatment condition confound this relation. Consequently, all analyses were based on pooled data, and treatment condition was not entered into the analysis.

In order to assess the effect of predictors on nonadherence, we used a 2-step procedure proposed by Hosmer and Lemeshow.[30] In the first step, for each of the potential predictors, the effect on nonadherence was assessed in a univariate logistic regression analysis with nonadherence as the dependent variable and the potential predictor as the independent variable. Given the effect on type I error of the number of tests, we used a relatively stringent significance level of $p \leq .005$ for the interpretation of the univariate results. In the second step, all potential predictors related to nonadherence (using a more lenient significance threshold of $p \leq .20$) were entered into a multivariate logistic regression model. A final prediction model was established using a stepwise procedure with backward elimination. Both odds ratios (ORs) and 95% confidence intervals (CIs) are presented. The Hosmer-Lemeshow goodness-of-fit statistic and Nagelkerke R^2 are used to assess the fit of the final model with the observed data. All analyses were performed using SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago, Ill.).

RESULTS

Table 1 summarizes the results of the univariate logistic regression analyses. Using a conservative significance level of $p \leq .005$ to guard against an inflated type I error because of the relatively large number of significance tests, none of the potential predictors were significantly related to nonadherence.

However, in relatively small samples (as in our case), lack of statistical significance is not equivalent to no effect. It can also be an indication of insufficient power. For this reason, we will also discuss the effect of potential confounders focusing on effect sizes (the ORs). In terms of effect sizes, male gender, higher education level, family history of psychiatric disease, Axis I disorder, more previous episodes, and low severity of psychiatric episode are relatively strong predictors for nonadherence.

Variables that were univariately associated with nonadherence at the $p \leq .20$ level were entered into a multiple logistic regression model (see multiple regression in Table 1). These variables were gender, education level, PDQ-4+ total score, number of previous episodes, severity of residual symptoms, severity of last depressive episode, number of dysfunctional episodes, and adequate dose of antidepressant. The strength and direction of the relation of the potential predictors in this multiple regression model are comparable to the strength of the univariate relations with nonadherence.

Finally, we tried to find the most parsimonious prediction model using more stringent significance levels ($p \leq .05$) and a stepwise procedure with backward elimination. This resulted in a model with only 2 risk factors (Table 2). The PDQ-4+ total score (increasing PDQ-4+ total score means increasing likelihood for nonadherence)

Table 2. Multivariate Logistic Regression for Nonadherence Over 2 Years[a,b]

Predictor	β	OR	p	95% CI
Personality (PDQ-4+ total score)	0.048	1.049	.014	1.010 to 1.090
High education level, yes/no	1.358	3.889	.034	1.111 to 13.617

[a]30.8% (28/91) adherent over 2 years; 69.2% (63/91) nonadherent over 2 years.
[b]Nagelkerke R^2 of the model was 14.8%.
Abbreviations: OR = odds ratio, PDQ-4+ = Personality Disorder Questionnaire-4+.

and education level (higher education level means increasing likelihood for nonadherence). This final model explained approximately 15% of the variance in nonadherence (Nagelkerke R^2 = 14.8%).

DISCUSSION

To our knowledge this is the first study that explores a set (patient-related, illness-related, and treatment-related) of potential predictors for nonadherence to continuation and maintenance antidepressant use in remitted recurrently depressed patients in a seminatural cohort. In a univariate analysis using a stringent significance level ($p \leq .005$), we found no independent predictors of nonadherence over a 2-year period. In a multivariate analysis, the baseline predictors for nonadherence over a 2-year period were a higher level of personality pathology and a higher level of education.

Personality pathology and personality characteristics have been found to be predictors of nonadherence in other studies as well. For example, Cohen et al.[31] explored the relation of personality characteristics and nonadherence with antidepressants in patients with acute MDD and reported a significant relation between extraversion and nonadherence. Tedlow et al.[32] reported an association between lower rates of narcissistic-histrionic personality disorders and better adherence. In our sample, however, we found no relation between specific personality pathology and specific personality symptom clusters as assessed with the PDQ-4+ and adherence, which makes it delicate to set up a hypothesis on this subject. In general, personality pathology is thought of as behavior patterns with limited adaptive capability.[16] Building further on this assumption, it may be that patients with more personality pathology are, because of less adaptive capability, less able to adapt to their doctor's advice.

Previous studies on adherence to antidepressant use found either no association with education or even better adherence in higher-educated patients.[33–37] These different findings might be (partially) explained by the fact that most of these prediction studies did not specifically focus on remitted, recurrently depressed patients. In other chronic diseases, like asthma, an association between higher education levels and nonadherence has also been found.[38]

It is possibly that higher-educated, remitted, recurrently depressed patients do not do what their doctor tells them to do when the disadvantages of antidepressants do not outweigh the advantages in their opinion in this phase of treatment. Cooper et al.,[39] for example, found in a community study that nonadherence to psychotropic medication is most likely to be a deliberate decision by patients who just do not think they need it or do not want to take it. Hunot et al.[40] reported concerns about antidepressants (such as dependency and side effects) and preference for nonpharmacologic treatments as predictors of nonadherence to antidepressants for any psychiatric condition (i.e., not only for depression) in primary care. Perhaps higher-educated patients are more affected by these concerns. However, further research is necessary to replicate this finding and to provide an idea about specific factors that contribute to the relation of nonadherence in highly educated patients.

In summary, both predictors of nonadherence that we found suggest that less adaptive capability and education level can be barriers to following a doctor's advice. Our results suggest too that factors other than the studied patient, illness, and treatment factors might play a key role in antidepressant nonadherence in remitted, recurrent depression. We consider that adherence in this maintenance phase of treatment also could be affected by (patient and treatment) features like doctor-patient communication style, treatment preference, and expectations and opinions about antidepressants.[40]

Side effects are also mentioned as possible predictors of nonadherence. However, this argument seems less plausible considering the stable adherence percentages over the last decades despite the use of newer antidepressants with fewer side effects.[39,41]

Limitations of the Study

Certain limitations must be considered when interpreting the findings of our study. First, we applied a prospective cohort approach to the data of patients who originally participated in a randomized, controlled cognitive therapy trial. Nevertheless, because the intervention neither modified nor confounded the relation between potential predictors and adherence, this should not have affected our findings.

Second, our data set did not include some other potential predictors of nonadherence like therapeutic alliance, patients' attitudes toward the illness, and the medication and side effects. These variables could be potential predictors of nonadherence in this phase of recurrent depression.

Third, given the relatively small sample size, the study may have lacked sufficient power to identify all

relevant predictors. Another limitation of the study is the potentially biased patient group (patients participating in a cognitive therapy trial), and the use of merely patient self-report adherence information instead of a multimethod approach. However, the MAQ is often used and well validated,[20,21] and our results are in line with studies on adherence in other chronic diseases.[8]

Strengths of the Study

We analyzed adherence data of a cohort of 172 patients with recurrent depression followed prospectively for 2 years after a remission. This cohort is unique because of its variety. It is a seminaturalistic cohort of recurrently depressed patients not participating in a medication trial (i.e., not controlling for antidepressant use) who at study entry were in remission and were receiving maintenance antidepressant therapy with diverse types of care (no care, primary care, and specialty care), suggesting that these findings are generalizable to remitted recurrently depressed patients using maintenance antidepressants.

Implications

We think that our findings are important for clinical management and further research. It is hard for doctors to recognize nonadherence in daily practice. Unfortunately, there is no specific patient profile that fully predicts nonadherence in remitted recurrently depressed patients. Based upon our findings, it is too early to assess these predictors in daily clinical practice. For the moment, doctors have to be continuously aware of this silent problem and should keep talking about it with their patients, not only in the acute phase, but also in the continuation and maintenance phases.

However, before we can conclude that there are no consistent predictors for nonadherence, qualitative research could be helpful (e.g., open patient interviews) to better understand nonadherent behavior and its underlying mechanisms.

In conclusion, we did not find univariate (patient-related, illness-related, and treatment-related) predictors of nonadherence, but we were able to construct a risk profile for nonadherence over a 2-year period (higher personality pathology and higher education). These predictors may suggest that a less adaptive capability (viewed as an important characteristic of personality pathology) and knowledge can be barriers in following a doctor's advice.

These results make clear that the process of becoming nonadherent is complex, and, thus, qualitative research must be done to understand nonadherence to antidepressants in the continuation and maintenance phases in recurrent depression in order to maximize the potential protective effect.

Drug name: fluoxetine (Prozac and others).

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