Identifying Risk for Attrition during Treatment for Depression

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Key Words

Attrition · Adherence · Depression · Antidepressant · Attitudes

Abstract

Background: Understanding patients' ambivalence about treatment persistence may be useful in tailoring retention interventions for individual patients with major depressive disorder. **Methods:** Participants (n = 265) with major depressive disorder were enrolled into an 8-week trial with a selective serotonin reuptake inhibitor. At baseline and week 2, the participants were asked about their intent to return for the next visit, complete the study and continue in the study should they experience side effects or no improvement. Dropouts were defined as participants who discontinued attending clinic visits before completing the trial. **Results:** Participants who at baseline reported an uncertain/negative intent to continue if they experienced side effects or no improvement dropped out at a significantly higher rate by weeks 6 and 8. Uncertain/negative intent at week 2 predicted attrition at all following visits. Dropouts without side effects were more likely to have reported an uncertain/negative intent to attend at both baseline and week 2, while dropouts who experienced side effects were more likely to

have reported an uncertain/negative intent to attend only at baseline. Positive intent to continue was associated with greater symptom improvement in both dropouts and completers despite the possibility of lack of efficacy. **Conclusions:** Participants' pretreatment concerns about continuing antidepressant treatment in the presence of side effects signals challenges to the completion of a full 8-week acute phase treatment, even if the participant does not develop side effects. Individualized review of concerns and tailoring appropriate interventions may be necessary to reduce attrition.

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Introduction

Attrition, or leaving treatment prematurely, is a substantial problem in the treatment of major depressive disorder (MDD) [1]. The attrition rates in the first 12 weeks of treatment can be as high as 65% in naturalistic settings [2–4] and 36% in clinical trials [5], and as many as 15% of the patients never begin a prescribed antidepressant [6]. These high attrition rates are disturbing given that patients who leave treatment are less likely to reach remission [7–9], have poorer functioning [10] and are more

likely to relapse [11]. Clearly, it would be beneficial to develop interventions to reduce attrition. The recent focus on personalized medicine [12] highlights the importance of asking not what is best for the hypothetical typical patient, but rather what is best for each individual [13] so that interventions may be tailored to meet the needs of each patient. Unfortunately, there is currently a dearth of strategies for identifying specific patients at risk for attrition early in antidepressant treatment based on potentially modifiable factors.

Specific beliefs and attitudes about illness and medications – such as concerns about overuse, harmfulness or side effects – have been associated with a lack of adherence to dosing recommendations or persistence in treatment [14–17]. Attitudes about treatment are specific to individuals and may also be modifiable during treatment, making attitudes a potentially useful data source for the identification of patients at risk for attrition.

Explicitly asking patients about their intent to continue in treatment may be the most direct method for obtaining data on patient attitudes [18, 19]. If intent to attend future visits is related to attrition, this factor could be used as a covariate in statistical analyses to reduce outcome and treatment group bias [18]. More importantly, patient-specific intent to continue coupled with the identification of possible reasons for future discontinuation could be used to tailor evidence-based interventions to retain individual patients.

Side effects and lack of efficacy are common and are primary reasons for dropping out of antidepressant treatment trials that last 6 weeks or longer (dropout rates of 3.7–19.8 and 2.1–9.9%, respectively [5, 20]). In a naturalistic setting, 55% of the patients on serotonin reuptake inhibitors reported at least 1 bothersome side effect within about 3 months of starting treatment and these patients were about 3 times more likely to drop out [6].

This report evaluates participants' intent to attend future treatment visits overall and in the context of side effects or not getting better. It uses data from the Suicide Assessment Methodology Study of the Depression Trials Network of the National Institute of Mental Health to address the following questions: can attrition be predicted using participants' self-reported intent to (a) attend the next treatment visit, (b) remain in the study until completion, or (c) remain in the study if experiencing side effects or lack of efficacy?

We anticipated that participants who report a negative or uncertain intent to continue in the study in response to these questions are more likely to drop out. We also

explore how the actual experiences of side effects or lack of efficacy during the study are related to participants' earlier reported intent to remain in the study.

Methods

Study Description

The primary objective of the Suicide Assessment Methodology Study was to develop easy-to-use clinician- and patient-friendly measures of suicidality and associated symptoms. The Institutional Review Boards at the National Coordinating Center (the University of Texas Southwestern Medical Center), the Data Coordinating Center and each of 15 regional centers approved and oversaw the study protocol. The participants provided written informed consent prior to study enrollment.

In all, 265 adult outpatients with nonpsychotic MDD, 18–75 years of age, were enrolled at 6 primary and 9 psychiatric care sites across the USA and were self- or professionally referred. The results are therefore more generalizable to real-world clinical settings than those from typical efficacy studies. Nonpsychotic MDD was diagnosed clinically and confirmed with the Psychiatric Diagnostic Screening Questionnaire [21, 22] and an MDD checklist from the Diagnostic and Statistical Manual of Mental Disorders – fourth edition – text revision [23]. The participants were treated with a selective serotonin reuptake inhibitor (SSRI) antidepressant and monitored for 8 weeks. The SSRIs used were at the discretion of the treating physician and could include citalopram, escitalopram, fluoxetine, paroxetine, paroxetine-CR or sertraline. The participants received medications and doses that are routinely received in clinical practice for a duration of time that reflects consensually recommended preferred practices. Clinical research coordinators (CRCs) at each clinical site supported participants and clinicians.

To provide appropriately vigorous yet tolerable dosing, clinical management was informed by critical decision point dosing tables and measurement-based care [24–26]. Measurement-based care included measurement at each clinic visit of (1) depressive symptom severity with the Quick Inventory of Depressive Symptomatology – Clinician-rated (QIDS-C₁₆) [27–29] and (2) side effects and medication tolerability using the Systematic Assessment for Treatment-Emergent Events – Systematic Inquiry [30], a 55-item self-report that rates the most commonly reported side effects expected with the study medications, the 3-item Frequency, Intensity and Burden of Side Effects Rating (FIBSER) [31], a self-report measure which provides global ratings of frequency, intensity and overall burden due to side effects attributable to the antidepressant treatment, and a self-rated medication treatment adherence questionnaire to assess compliance with the prescribed antidepressant. Measurement-based care was used successfully in clinical practice settings in the Sequenced Treatment Alternatives to Relieve Depression trial [32, 33].

Protocol visits were to occur at weeks 0, 2, 4, 6 and 8. In addition, the QIDS-C₁₆ and FIBSER were collected by phone at weeks 1, 3, 5 and 7. The participants were also contacted by telephone on Mondays, Wednesdays and Fridays during the first 2 weeks following medication initiation and following a dose increase (week 4 or later) to evaluate the presence of suicidal ideation and emergence of associated symptoms.

Table 1. Baseline characteristics of the sample

Race	
White	170 (64.2)
Black	64 (24.1)
Other	31 (11.7)
Gender	
Male	77 (29.1)
Female	188 (70.9)
Employment	
Unemployed	95 (36.0)
Employed	155 (58.7)
Retired	14 (5.3)
Marital status	
Never married	85 (32.2)
Married	99 (37.5)
Divorced/separated	70 (26.5)
Widowed	10 (3.8)
Insurance	
Private	115 (44.4)
Public	50 (19.3)
None	94 (36.3)
Hispanic	
No	234 (88.3)
Yes	31 (11.7)
Age at onset (≥ 18 years)	
No	96 (36.6)
Yes	166 (63.4)
Family history of alcohol/drug	
No	144 (54.5)
Yes	120 (45.5)
Family history of suicide	
No	256 (97.0)
Yes	8 (3.0)
Number of depressive episodes (≥ 2)	
No	79 (33.8)
Yes	155 (66.2)
Chronic depression (≥ 2 years)	
No	174 (71.0)
Yes	71 (29.0)
Anxious features	
No	90 (34.0)
Yes	175 (66.0)
Age, years	265 [41.2 $\pm$ 13.5]
Education, years	264 [13.5 $\pm$ 2.8]
HRSD ₁₇ (without SI item)	264 [21.5 $\pm$ 4.5]
QIDS-C ₁₆ (without SI item)	265 [14.8 $\pm$ 3.2]
GMC severity	264 [3.2 $\pm$ 3.7]

Figures are numbers of cases with percentages in parentheses and means $\pm$ SD in square brackets. HRSD₁₇ = 17-item Hamilton Rating Scale for Depression; QIDS-C₁₆ = Quick Inventory of Depressive Symptomatology (clinician-rated); GMC = general medical condition.

Study Population

A total of 265 eligible outpatients provided written informed consent and were enrolled and treated from July 2007 through February 2008. Eligible participants had a score ≥ 14 on the baseline 17-item Hamilton Rating Scale for Depression [34, 35]. Participants with general medical conditions (GMCs) were eligible as long as their GMCs did not contraindicate the use of an SSRI. Patients were ineligible if they had bipolar disorder; schizophrenia; schizoaffective disorder; MDD with psychotic features (lifetime); a current primary diagnosis of anorexia nervosa, bulimia nervosa, or obsessive-compulsive disorder; current substance abuse or dependence; required inpatient treatment at the time of study entry; or had a well-documented history of nonresponse (in the current major depressive episode) to two adequately delivered SSRI treatments. Patients were also ineligible if they were breast-feeding, pregnant, or intending to become pregnant, had taken an antipsychotic medication within 4 months of study entry, or had taken antidepressants in the 2 weeks prior to screening (4 weeks for fluoxetine and 6 weeks for MAOIs). Suicidality was acceptable as long as inpatient treatment was not indicated at the baseline visit.

Assessments

At the screening/baseline visit, CRCs collected clinical and sociodemographic information and completed the 17-item Hamilton Rating Scale for Depression. At baseline, the participants also completed a 125-item forced-choice (symptom present or absent) self-report DSM-IV axis I screening questionnaire, the Psychiatric Diagnostic Screening Questionnaire and the Self-Administered Comorbidity Questionnaire [36], a 40-item self-report that assesses the presence of a range of common medical conditions. During all clinic visits, including baseline, the CRCs also collected the QIDS-C₁₆, FIBSER and Systematic Assessment for Treatment-Emergent Events – Systematic Inquiry.

At baseline and at the week 2, 4 and 6 clinic visits, the participants responded to the following questions in a self-report format: (1) How likely is it that you will come back for the next treatment visit? (2) How likely is it that you will complete all 8 weeks of the study? (3) If your depression is not getting better, how likely are you to stay in the study? (4) If you are experiencing bothersome side effects, how likely are you to stay in the study?

Each question was rated on a Likert-type scale with 5 possible responses ranging from very unlikely to very likely. Questions 1 and 2 were derived from the approach suggested by Leon et al. [18] and Demirtas and Schafer [19].

Remission was defined as a score of ≤ 5 on the last available QIDS-C₁₆. The presence of side effects was determined by a FIBSER score of ≥ 3 , reflecting a moderate burden of side effects.

Definition of Attrition

Dropouts were defined as participants who discontinued attending clinic visits at any point after the baseline visit. Those who left treatment for medical reasons, such as development of a medical condition that contraindicated the study medication, were not considered dropouts.

Analytic Methods

Descriptive statistics, means and standard deviations for continuous variables, and percentages for discrete variables, were used to characterize the sample. χ^2 tests and Fisher's Exact Test

Table 2. Responses to intent-to-attend questions at baseline (n = 264) and at week 2 (n = 213)

Response	Likely to attend next visit, %		Likely to complete 8 weeks, %		Stay if not improving, %		Stay if having side effects, %	
	baseline	week 2	baseline	week 2	baseline	week 2	baseline	week 2
Very likely	84.5	86.4	81.1	85.0	53.0	60.1	34.9	50.7
Likely	13.3	10.8	14.8	12.6	24.2	24.4	28.8	23.9
Not sure	1.5	1.4	3.4	1.9	21.2	12.7	28.4	22.1
Unlikely	0.0	0.5	0.0	0.0	1.2	2.3	6.4	1.9
Very unlikely	0.7	0.9	0.7	0.5	0.4	0.5	1.5	1.4

were applied to test the equality of the probability of attrition among those who provided positive and uncertain/negative responses to the assessment of the intent to attend future visits. χ^2 tests were also used to evaluate the association of attrition, the presence of side effects and intent to continue with side effects, as well as attrition, symptom improvement and intent to continue if not improving. All tests were conducted with a 2-sided alternative hypothesis.

Results

The characteristics of the sample are reported in table 1. About a fifth of the sample dropped out (56/264); 4.6% (n = 12/264) by week 2, 9.9% (n = 26/264) by week 4, 15.5% (n = 41/264) by week 6 and 21.2% (n = 56/264) by week 8. Remission was significantly less likely for dropouts (23%) than for completers (47%) ($p = 0.0013$).

Given the frequency distribution of responses to the questions about future intent (table 2), the positive responses 'very likely' and 'likely' to stay were collapsed to the category 'positive' and the uncertain/negative responses 'not sure,' 'unlikely' and 'very unlikely' to stay were collapsed to the category 'uncertain/negative' for analysis.

Uncertain/negative responses to the questions about coming back for the next treatment visit or completing the study predicted attrition at several time points, but very few participants (2–4%) responded in this manner (table 3). However, a substantial number of participants were willing to signal negative/uncertain intent at baseline (23–36%) and at week 2 (15–25%) in response to the questions about side effects or lack of efficacy. An uncertain/negative response at baseline to either of these questions was associated with attrition at weeks 6 and 8, while an uncertain/negative response to either of these questions at week 2 predicted attrition at weeks 4, 6 and 8.

There was no association between baseline severity and attrition ($p = 0.9235$). The odds ratio for the QIDS-C₁₆ with a 5-unit increase was 1.02, and using the goodness of fit test, the model fits well.

Dropouts who experienced side effects were 3 times more likely to have reported uncertain/negative rather than positive intent about staying in the study with bothersome side effects at baseline (7 vs. 2%). Dropouts who did not report side effects were still twice as likely to have reported uncertain/negative rather than positive intent at baseline about staying in the study with side effects (20 vs. 10%) and 3 times as likely to have reported uncertain/negative rather than positive intent at week 2 (20 vs. 7%). Completers, whether or not they actually experienced side effects during treatment, showed little difference in uncertain/negative versus positive intent to continue at either baseline or week 2.

Among both dropouts and completers, participants who reported an uncertain/negative intent to continue with lack of improvement had significantly less improvement in symptom severity by the QIDS-C₁₆ than those who reported a positive intent to continue (23 vs. 38% change in dropouts and 43 vs. 56% change in completers). There was about a 2-point difference in improvement on the QIDS-C₁₆ in both of these comparisons, a clinically meaningful difference.

Discussion

Our results indicate that self-reported intent to continue if experiencing side effects and intent to continue even with a lack of initial efficacy are very good markers for attrition. A substantial percentage of participants were willing to express concern or ambivalence at baseline about continuing to attend with side effects (36%) or

Table 3. Associations between intent to attend and attrition

Response		n	Attrition by treatment week							
			week 2		week 4		week 6		week 8	
			%	p value	%	p value	%	p value	%	p value
<i>Likely to attend next visit</i>										
Baseline	No	6	0.0	0.5887	0.0	0.4128	16.7	0.9380	16.7	0.7829
	Yes	258	4.7		10.1		15.5		21.3	
Week 2	No	6	–	–	16.7	0.0622	16.7	0.3115	50.0	0.0067
	Yes	207	–		2.9		6.3		12.1	
<i>Likely to complete 8 weeks</i>										
Baseline	No	11	18.2	0.0266	27.3	0.0476	36.4	0.0513	36.4	0.2092
	Yes	253	4.0		9.1		14.6		20.6	
Week 2	No	5	–	–	20.0	0.0339	40.0	0.0023	60.0	0.0017
	Yes	208	–		2.9		5.8		12.0	
<i>Likely to stay if not getting better</i>										
Baseline	No	60	8.3	0.1091	15.0	0.1276	30.0	0.0004	36.7	0.0009
	Yes	204	3.4		8.3		11.3		16.7	
Week 2	No	33	–	–	12.1	0.0020	21.2	0.0002	30.3	0.0015
	Yes	180	–		1.7		3.9		10.0	
<i>Likely to stay with bothersome side effects</i>										
Baseline	No	96	7.3	0.1054	13.5	0.1279	24.0	0.0043	31.3	0.0026
	Yes	168	3.0		7.7		10.7		15.5	
Week 2	No	54	–	–	7.4	0.0493	14.8	0.0047	24.1	0.0059
	Yes	159	–		1.9		3.8		9.4	
No = Uncertain/unlikely to continue; Yes = likely to continue.										

lack of efficacy (23%). An uncertain/negative response to either of these questions at baseline and at week 2 predicted attrition, with improved prediction at week 2 for both questions.

Since 58% of the patients experience at least moderate side effects as early as 1 week after SSRI initiation [37], this improved prediction at week 2 with either the side effect or lack of improvement question may be due to participants basing their retention predictions on actual experience with side effects with the current treatment and/or a beginning perception of the drug's efficacy.

Since only 2–4% of the participants expressed a negative or uncertain intent to continue with treatment when asked the more general questions (i.e. likely to attend next visit, likely to complete 8 weeks), questions addressing specific concerns as opposed to general ambivalence are more likely to be useful in clinical practice. Participants may have good intentions at treatment initiation to complete treatment or may be concerned about disappointing their clinicians by expressing a general lack of commitment. Patients who actually experienced side effects prior

to dropping out were more likely, at baseline, to have reported an uncertain/negative response about continuing with side effects. Even more strikingly, however, dropouts who did not report side effects were still twice as likely at baseline and 3 times as likely at week 2 to have reported they were uncertain or negative about continuing treatment. In addition to predicting attrition, uncertain or negative responses to the question about continuing to attend if not improving were also associated with a meaningfully lower rate of symptom improvement in both dropouts and completers. This result may be similar to studies that found positive expectations of treatment effectiveness to be associated with improved treatment outcomes in depression [38–40] as well as a possible mechanism in the placebo effect [41].

It is important to resolve adverse events that occur early in treatment [37] and maximize the chances of rapid efficacy with aggressive treatment [42] to help reduce attrition. It is even more proactive, however, to inoculate patients who directly express concerns or ambivalence against discontinuation. Uncertain/negative intent to

continue with side effects or lack of efficacy may reflect concern about the treatment's possible harmfulness, consideration that depression is not serious enough to tolerate side effects, lack of awareness of the time needed to reach remission, prior negative experiences with side effects or any of a host of other possibilities. However, a noncommittal statement from a patient about continuing in treatment generally, or in the context of side effects or lack of treatment efficacy, is an excellent signal that indicates a potentially less resilient patient. With these patients, it may be helpful for clinicians to conduct an individualized review of patient-specific thoughts regarding side effects and lack of efficacy as well as other concerns about treatment or medication to personalize the focus of educational efforts.

There is evidence that such inoculation may be helpful. Studies have found that patients who discussed adverse events with physicians or pharmacists at the initiation of therapy and those told to continue medication for at least 6 months were less likely to discontinue antidepressant treatment [6], and patients told by their clinician that they might not see a benefit for 2–4 weeks were more likely to be taking their antidepressants 1 month into treatment [4]. These interventions may have modified patient beliefs or their intent to continue, or both. Studies of collaborative care or educational interventions indicate that the provision of educational or supportive interventions that can address topics such as what to do about side effects or the time expected to reach remission may be useful in improving adherence or persistence in taking medications as well as outcomes [4, 6, 43–46]. Personalized responses to each patient's own expressed concerns may be even more useful in retaining less committed, at-risk patients in treatment for a sufficient time to maximize the chances of reaching and sustaining remission with this often chronic or recurrent illness.

The current study has several limitations that may affect its generalizability. The participants received monitored dosing of medications while a CRC supported both clinician and patient. Side effects may not have been identified if they occurred following a visit but prior to dropout. Symptom improvement for completers and dropouts was based on the last available measurement occasion. Data about prior treatment experience were not available. We do not have retention data beyond 8 weeks. Some comparisons had small numbers, making generalizing from the findings difficult. The current study also did not address factors related to clinicians (e.g. experience), clinics (e.g. access and availability of appointments), medication (e.g. complexity of the regimen) or participants (e.g.

specific beliefs or attitudes about medication or treatment).

In summary, questions regarding intent to attend future antidepressant treatment visits in the context of side effects or lack of efficacy may be useful clinical tools. They may identify patients with concerns about these issues, as well as patients who may be less resilient to the challenges of completing a course of treatment or have other specific concerns that can be addressed. An individualized review of patient concerns and the individualized tailoring of educational or other interventions may reduce attrition and increase the chances for remission.

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D. Warden, PhD, MBA currently owns stock in Pfizer Inc. and has owned stock in Bristol-Myers Squibb Company within the last 5 years.

M.H. Trivedi, MD has been a consultant for Abbott Laboratories Inc., Akzo (Organon Pharmaceuticals Inc.), AstraZeneca, Bayer, Bristol-Myers Squibb Company, Cephalon Inc., Cyberonics Inc., Eli Lilly & Company, Fabre-Kramer Pharmaceuticals Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Johnson & Johnson PRD, Meade Johnson, Neuronetics, Parke-Davis Pharmaceuticals Inc., Pfizer Inc., Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals Inc., VantagePoint and Wyeth-Ayerst Laboratories. He has served on speaker bureaus for Abdi Ibrahim, Akzo (Organon Pharmaceuticals Inc.), Bristol-Myers Squibb Company, Cephalon Inc., Cyberonics Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Eli Lilly & Company, Pharmacia & Upjohn, Solvay Pharmaceuticals Inc., and Wyeth-Ayerst Laboratories. He has also received grant support from Bristol-Myers Squibb Company, Cephalon Inc., Corcept Therapeutics Inc., Cyberonics Inc., Eli Lilly & Company, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Merck, National Institute of Mental Health, National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer Inc., Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals Inc. and Wyeth-Ayerst Laboratories.

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