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Early Adverse Events and Attrition in SSRI Treatment: A Suicide Assessment Methodology Study (SAMS) Report

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Abstract

Adverse events during selective serotonin reuptake inhibitor (SSRI) treatment are frequent and may lead to premature treatment discontinuation. If attrition is associated with early worsening of side effects or the frequency, intensity, or burden of side effects, interventions to maximize retention could be focused on patients with these events. Outpatient participants (n=265) with nonpsychotic major depressive disorder entered an 8-week trial with an SSRI. At baseline and week 2, specific side effects were evaluated with the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry, and at week 2 the Frequency, Intensity, and Burden of Side Effects Rating globally assessed side effects. Attrition was defined by those participants who left treatment after week 2 but before week 8. No specific week 2 side effect, either treatment emergent or with worsening intensity, was independently associated with attrition. Global ratings of side effect frequency, intensity, or burden at week 2 were also not associated with subsequent attrition. Neither global ratings nor specific side effects at week 2 were related to patient attrition during SSRI treatment. Other factors appear to contribute to patient decisions about continuing with treatment.

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Keywords

attrition; adherence; adverse events; antidepressant; depression

Introduction

Attrition or premature discontinuation during antidepressant treatment compromises outcomes in both clinical trials and routine clinical settings, since even the most efficacious medications will not work if patients do not take them. Up to two-thirds of patients discontinue antidepressants in the first 3 months.^{1, 2} Not surprisingly, those who discontinue are less likely to reach remission.³⁻⁵

Selective serotonin reuptake inhibitors (SSRIs) are currently the most frequently used antidepressants^{6, 7}; however, adverse events are commonly reported among SSRI users^{8, 9} and have been associated with discontinuation of antidepressants in both clinical trials and naturalistic settings.^{10, 11}

SSRIs increase the availability of serotonin (5-HT) at the synaptic cleft.^{12, 13} Central and peripheral serotonin receptors mediate multiple functions including sleep, arousal, appetite, sexual functions, gut motility, and smooth muscle tone.¹³⁻¹⁹ Many side effects may therefore be attributed to serotonergic effects, among which gastrointestinal disturbances such as nausea, vomiting, and diarrhea are frequently reported^{9, 20, 21}; as are activating side effects like insomnia, anxiety, and agitation; sedating side effects such as drowsiness²⁰; sexual dysfunction¹³; headache, cholinergic side effects such as sweating, dizziness⁹; and malaise.²¹

In a meta-analysis of 95 randomized trials with over 10,000 patients, 12% discontinued SSRI treatment reportedly due to side effects.⁶ Similarly, in a survey of 672 patients in naturalistic treatment, 15% discontinued an SSRI in the first 3 months of acute treatment, reportedly due to side effects.²² The incidence of side effects is the highest at the onset of treatment,²³ with side effects typically appearing within the first 2 weeks.²⁴ In a naturalistic setting, the most common side effects in the first 3 months of treatment with SSRIs were drowsiness (38%), sexual dysfunction (34%), dry mouth (34%), headache (23%), dizziness (23%), insomnia (22%), anxiety (19%), nausea (18%), and weight gain (17%), with all symptoms except weight gain appearing within the first 2 weeks 64-85% of the time. All side effects except dry mouth were considered bothersome by 33-67% of those reporting them.²⁴ In a second naturalistic study, patients were more likely to discontinue SSRIs when side effects emerged, generally in the first or second week after treatment initiation.²² Others have noted upper gastrointestinal complaints such as nausea and vomiting,^{20, 25} usually appearing in the first or second week,^{26, 27} as most commonly related to discontinuation.

Side effect burden has also been associated with SSRI discontinuation. At week one, 58% of 85 patients receiving SSRIs reported at least one moderately severe side effect with a mean number of 3.5 events.²⁸ Many studies identify associations between side effects and dropout through spontaneous patient report, physician report, retrospective interview, or do not specify how side effect data were gathered or how it was determined whether they were related to medication discontinuation.^{6, 22-24, 29}

We previously reported that patients' concern or ambivalence about continuing in treatment if they were to experience side effects was related to attrition, whether or not side effects actually occurred.⁵ To the best of our knowledge, however, there are no studies evaluating

the relationship between prospective, objective, patient self-report ratings of the emergence or worsening of a comprehensive list of specific adverse events in the first weeks of acute treatment and attrition during the course of that treatment. If attrition is associated with early worsening of any specific adverse events or with the overall frequency, intensity, or burden of side effects, interventions to maximize retention could be tailored for patients with these events and used early in the course of treatment.

This report utilizes data from the Suicide Assessment Methodology Study (SAMS) to address the following questions:

1. Is the emergence/worsening of specific adverse events early in treatment associated with attrition? Independently associated with attrition?
2. Is the frequency, intensity, or burden of adverse events early in treatment associated with attrition?

The relationship between early symptom improvement and attrition was also explored.

Materials and Methods

Study Description

SAMS was designed to develop easy-to-use patient- and clinician-rated measures of suicidality and associated symptoms for use at initiation and dose escalation of SSRIs.

The study was part of the National Institute of Mental Health's Depression Trials Network. It was conducted in accordance with the Declaration of Helsinki and was overseen by the National Coordinating Center (NCC) (The University of Texas Southwestern Medical Center), Data Coordinating Center (DCC) (Epidemiological Data Center at the University of Pittsburgh), and 15 Regional Centers. The Institutional Review Boards at all these locations approved and oversaw the study protocol. A Data Monitoring and Safety Board (DSMB) evaluated the protocol and consents prior to study enrollment and monitored patient safety throughout the study.

In all, 265 outpatients, 18-75 years old, with nonpsychotic major depressive disorder (MDD) and a baseline 17-item Hamilton Depression Rating Scale (HRSD₁₇) score of ≥ 14 ^{30, 31} provided written informed consent and were enrolled at 6 primary and 9 psychiatric care sites nationally. Inclusion criteria were broad and exclusion criteria minimal to maximize the generalizability of findings. All participants were treated for up to 8 weeks with one of the following SSRI antidepressants at the discretion of the clinician: citalopram, escitalopram, fluoxetine, paroxetine, paroxetine-CR, or sertraline.

The 16-item Quick Inventory of Depressive Symptomatology Clinician rated version³²⁻³⁴ (QIDS-C₁₆) based on the nine DSM IV TR criteria for a major depressive episode to evaluate symptoms of depression was collected at baseline, each clinic visit, and by phone in the weeks in which there was no clinic visit. The Systematic Assessment for Treatment Emergent Events – Systematic Inquiry³⁵ (SAFTEE-SI), a 55-item self-report that rates the side effects most commonly reported with the study medications as not present, mild, moderate or severe was collected at baseline and each study visit. The SAFTEE also includes one item rating how much all these side effects were bothersome or interfered with daily activities. The Frequency, Intensity, and Burden of Side Effects Rating³⁶ (FIBSER), a three-item self-report measure which rates the frequency, intensity, and overall burden or amount of interference in day-to-day activities and function due to the side effects attributable to the medications was collected at clinic visits after baseline.

Further description of study methods and assessments is reported elsewhere.⁵

Treatment

Protocol visits were to occur at weeks 0, 2, 4, 6, and 8. Clinical decisions and dose adjustments were made using Measurement-Based Care (MBC) guidelines.³⁷⁻³⁹ MBC utilizes the assessment of depressive symptom severity based on the QIDS-C₁₆ and tolerability based on the SAFTEE and FIBSER at each visit to guide treatment decisions and dose selection.

Attrition and Adverse Event Definitions

For the analysis of the association of adverse events and attrition, attrition was defined as leaving the study at any time after the week 2 visit.

Worsening of adverse events was defined by a one point or greater increase in severity on the SAFTEE from baseline to week 2. This included both emergence of an adverse event not present at baseline and worsening of an event already present at baseline. Frequency, intensity, and burden of side effects were scored from the FIBSER at week 2.

Analytic Methods

The population was characterized with descriptive statistics such as percentages and measures of central tendency. The association between the emergence of adverse event symptoms and attrition was assessed using a Chi-Square test or Fisher's Exact Test. A stepwise logistic regression model was used to identify worsening symptoms (adverse events) associated with lack of remission. The following characteristics were used in the model to control for their potential confounding effect: baseline severity of depression, presence of anxious symptoms, antidepressant medication, chronic depression, race, time in study, and concomitant general medical condition (GMC) burden. The association between the frequency, intensity, and burden of side effects and attrition was assessed using Fisher's Exact Test. A t-test was used to compare the mean changes in symptom severity between those who did and did not drop out.

Results

Baseline characteristics of the sample are reported elsewhere.⁵ Frequency of use and dosing of each SSRI are in Table 1. About 69% of the week 2 sample was female, 20% black, and 11% Hispanic with a mean age of about 42. The sample had substantial recurrent depression (68%), chronic depression (30%), and had on average three concomitant GMCs. Of the original study sample (n=264), 12 participants (5 %) dropped out before the week 2 visit and 44 (17 %) after the week 2 visit. Of those dropping out after week 2, 5 % (n=14) dropped out between weeks 2 and 4, 6% (n= 15) between weeks 4 and 6, and 6 % (n=15) between weeks 6 and 8.

Frequency of worsening of side effects from baseline to week 2 is shown in Table 2. Side effects reported most frequently at week 2 included decreased appetite (27%), dry mouth (26%), delayed orgasm (20%), stuffy nose (20%), loss of sexual interest (19%), drowsiness (19%), and nausea/vomiting (19%).

In bivariate analyses without controlling for potential confounding factors, weight loss was associated with dropout and sweating excessively with remaining in treatment (Table 3). No other specific adverse events or the general bothersome nature of side effects as measured by the SAFTEE were associated with attrition. Controlling for baseline depression severity, anxious symptoms, antidepressant medication, chronic depression, race, concomitant GMC burden, and time in the study, no specific adverse event was associated with attrition after week 2.

Frequency, intensity, and burden of side effects as measured by the FIBSER at week 2 were not associated with attrition after week 2 (Table 4). There were limited numbers of patients reporting severe intensity or burden of side effects.

Change in symptom severity scores on the QIDS-C₁₆ between the baseline and week 2 visits did not differ between dropouts and treatment completers (-4.57 (4.63) vs. -4.37 (4.01); $p=0.8081$).

Discussion

While conventional wisdom suggests that side effects are common, appear early in treatment, and are associated with treatment discontinuation, the current findings suggest otherwise. Although 41 of the most expected SSRI side effects (gastrointestinal, activating, sedating, cholinergic, and sexual symptoms) were reported as worsening by 4-27% of the sample that returned for the week 2 visit, none of the 55 symptoms queried by the SAFTEE were independently associated with attrition during the remainder of the 8-week acute treatment. Overall side effect frequency, severity, and burden as experienced by patients at week 2, based on either the SAFTEE burden item or the FIBSER, were also not related to attrition.

Although side effects have been linked to attrition,^{6, 10, 22, 28, 40} attrition in this study was independent of the prospectively measured presence, frequency, severity, or burden of side effects at week 2, the time typically associated with the appearance of side effects.^{24, 26, 27} This is despite 25% of participants reporting side effects of at least moderate intensity and 14% reporting at least moderate burden. There were few participants, however, who reported severe intensity or burden of side effects. Since bothersome or severe side effects have been associated with treatment discontinuation,^{10, 22} the low frequency of severe side effects in this sample could account for the failure to find an association between global severity or burden of side effects and attrition.

Since there was no difference in early symptom change between dropouts and completers, early lack of efficacy does not provide an alternate explanation for attrition in this sample.

There are a number of other possible explanations for the lack of association between side effects and attrition in this study, in contrast to findings from prior studies. First, side effects may be more prominent in decisions about continuing treatment for patients with limited concomitant disorders in randomized controlled trials since they may have less experience with treatment for chronic conditions and less tolerance for inconvenience. Second, studies often identify only one main reason for treatment discontinuation,²² such as side effects. It may be that patients consider multiple issues, weighing the benefits and psychological, physical, financial and other costs of treatment in making a decision about treatment continuation.⁴¹⁻⁴⁴ Side effects may be one cost, but other perceived costs or benefits for individual patients are not typically measured in studies or discussed in clinical practice. Third, in this study the CRC inquired each week via a structured assessment⁵ about the likelihood of retention and discussion and resolution of patient specific barriers to retention likely occurred. There was also a high frequency of contact with a CRC including phone contact three times a week for 4 of the 8 weeks of the study, and use of an algorithm that specifically requires that side effects be addressed if indicated based on the FIBSER burden score each week. Increased contact, use of an individual such as a coordinator to support the patient, objective measurement and feedback to patients, and explicit focus on attrition are similar to interventions associated with increased adherence in collaborative care studies,^{45, 46} and these interventions may have mitigated the valence of adverse events for patients in this study and/or reduced attrition.

The trajectory of what happens to side effects after their emergence may also be more important to keeping patients in treatment than the appearance itself or the overall frequency, intensity, or burden of the side effects. A small prior study found that dropouts and completers had the same frequency of adverse events; however, the completers habituated to the side effects more rapidly than the dropouts.²⁸ It may also not be the presence or burden of side effects that is related to discontinuation but the impact of the side effect on specific aspects of daily functioning.

Although adverse events are the rule rather than the exception,⁸ they may not be identified if clinicians do not ask about them directly. Adverse events often resolve in 2-4 weeks,²⁷ although for many patients they do not, suggesting a strong need to identify and treat side effects aggressively when they do emerge or worsen early in treatment. It is therefore important to use a systematic approach to identifying them at each treatment visit, such as the use of a scale like the FIBSER so they can be treated when they do emerge or worsen early in treatment.

Weight loss was associated with attrition in analyses that did not control for confounding factors such as depression severity. It is possible that worsening of appetite (reported by 27%) and weight loss (reported by 16%) in this sample were related to worsening of depression rather than an adverse event in response to medication. Depression severity has been associated with attrition.^{4, 47} The few significant findings in the bivariate analyses may also have been due to chance.

There are several limitations of this study. We did not evaluate worsening or emergence of side effects or symptom change later than the week 2 visit. We also do not have side-effect ratings for participants who left the study between baseline and week 2, or for participants who missed their week 2 clinic visit. Only 12 participants dropped out between baseline and week 2, but they may have experienced severe intensity or burden of side effects. The distribution of side effects and/or their association with attrition may have been different with a different SSRI distribution, with antidepressants from different classes, or in a blinded clinical trial that includes a placebo. The frequency of side effects of moderate or higher intensity or burden is lower than that reported in other studies.²⁸ We also do not have data in this study addressing patient perception of the costs and benefits of treatment or the relationship of adverse events to patient perception of these costs.

A further limitation of the study is having sufficient power to detect a moderate to small effect. For example, for a side effect that was relatively prominent, such as appetite decrease, which had an overall prevalence rate of 26.7% (in a sample of 206, 55 with appetite decrease and 151 without), there would be 80% power to detect a two-sided difference of 16%, 18% and 20%, assuming the rate of drop out in those without an appetite decrease was 10%, 15%, and 20%, respectively, with a type I error rate of .05. However, for a side effect that was relatively rare, such as drooling, which had an overall prevalence rate of 5.8% (in a sample of 206, 12 with drooling and 194 without), there would be 80% power to detect a two-sided difference of 31%, 34% and 36%, assuming that the rate of drop out in those without an appetite decrease was 10%, 15%, and 20%, respectively, with a type I error rate of .05.

In summary, this study does not support the commonly held belief that the presence, severity, or burden of side effects early in treatment with SSRIs is related to discontinuation of treatment, at least in patients who have frequent visits with their physician and are provided education and supportive medical management. By focusing on side effects, we may not be identifying the attitudes or issues of most importance to patients or how they are weighed in making a decision about treatment continuation. It may also be that what

happens to side effects after their emergence is more related to dropout than the emergence/worsening, intensity, or burden of side effects early in treatment. A consistent approach to identifying side effects and aggressive management of side effects may be helpful in keeping patients in treatment long enough to recover. However, further assessment of how patients make decisions to remain in treatment is important.

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Disclosures

Diane Warden, Ph.D., M.B.A. has owned stock in Pfizer, Inc. within the last five years.

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Table 1**Medications and Dosing**

Study medications used	N (%)
At baseline	
Citalopram	98 (50.5)
Escitalopram	30 (15.5)
Fluoxetine	32 (16.5)
Sertraline	25 (12.9)
Paroxetine	8 (4.1)
Paroxetine CR	1(0.5)
At Week 2	
Citalopram	106 (51.7)
Escitalopram	31 (15.1)
Fluoxetine	34 (16.6)
Sertraline	25 (12.2)
Paroxetine	9 (4.4)
Paroxetine-CR	N/A
Study Medication Dose	Mean (sd)
At Baseline	
Citalopram	17.7 (4.3)
Escitalopram	10.0 (0.0)
Fluoxetine	18.5 (3.9)
Sertraline	48.6 (5.8)
Paroxetine	11.5 (4.7)
Paroxetine-CR	10.0 (--)
At Week 2	
Citalopram	21.1 (7.0)
Escitalopram	10.0 (0.0)
Fluoxetine	20.3 (5.6)
Sertraline	74.1 (29.0)
Paroxetine	15.6 (5.3)
Paroxetine-CR	N/A (--)

Table 2
Frequency of Worsening of Adverse Events at Week 2 (N=206)*

Adverse Event	%	Adverse Event	%
Appetite decrease	26.7	Trouble sleeping	12.1
Dry mouth	26.2	Blurred vision	12.1
Delayed orgasm	20.4	Constipation	11.7
Stuffy nose	19.9	Difficulty finding words	11.7
Loss of sexual interest	19.4	Muscle cramps	11.7
Drowsy	18.9	Trouble catching breath	11.2
Nausea/vomiting	18.5	Clenching of teeth	11.2
Trouble sitting still	18.0	Concentration	11.2
Sweating	17.0	Appetite increase	11.2
Strange taste in mouth	17.0	Hot flashes	11.2
Sleep disturbance	16.5	Numbness	10.7
Nervous	16.5	Feeling strange	10.2
Problems with sexual arousal	15.5	Abnormal sensations	10.2
Unable to sit still	15.5	Irritable	9.7
Stomach discomfort	15.5	Unsteadiness	8.7
Weight loss	15.5	Muscle twitching	8.3
Headache	14.6	Difficulty starting urination	8.3
Tremor	14.1	Diminished mental acuity	8.3
Weariness/fatigue	14.1	Hair loss	7.3
Poor memory	14.1	ringing in ears	7.3
Dizziness	13.6	Chest pain	6.3
General side effect bothersome	13.6	Bruising	6.3
Weight gain	13.1	Drooling	5.8
Heartbeat rapid	13.1		
Diarrhea	13.1		
Need to urinate	13.1		
Apathy	13.1		
Dizzy	12.6		

* As measured by the Systematic Assessment for Treatment Emergent Events – Systematic Inquiry (SAFTEE)

Table 3
Percent of Participants With or Without Adverse Events That Dropped Out¹

Presence of Adverse Event	% Dropout ²	Presence of Adverse Event	% Dropout	Presence of Adverse Event	% Dropout
Appetite decrease		Poor memory		Numbness/tingling ^b	
No	13.3	No	15.3	No	16.3
Yes	18.2	Yes	10.4	Yes	0.0
Dry mouth		Dizziness/faintness		Feeling strange/unreal	
No	13.8	No	14.4	No	15.1
Yes	16.7	Yes	15.4	Yes	9.5
Delayed orgasm		Fluid retention		Abnormal sensations	
No	16.5	No	14.7	No	15.1
Yes	7.1	Yes	11.1	Yes	9.5
Stuffy nose		Weight gain		Irritable	
No	15.7	No	15.1	No	15.1
Yes	9.8	Yes	11.1	Yes	10.0
Loss of sexual interest		Heartbeat rapid		Unsteadiness	
No	16.3	No	13.4	No	16.0
Yes	7.5	Yes	22.2	Yes	0.0
Drowsy		Diarrhea		Muscle twitching	
No	13.8	No	15.1	No	15.3
Yes	18.0	Yes	11.1	Yes	5.9
Nausea/vomiting		Urinary frequency		Difficulty starting urination	
No	13.1	No	15.1	No	15.3
Yes	21.1	Yes	11.1	Yes	5.9
Trouble sitting still		Apathy		Diminished mental acuity	
No	16.0	No	14.5	No	13.8
Yes	8.1	Yes	14.8	Yes	23.5
Sweating excessively		Dizzy		Hair loss	
No	17.0	No	14.0	No	15.2
Yes	2.9	Yes	17.9	Yes	6.7
Strange taste in mouth		Trouble sleeping		ringing in ears	

Presence of Adverse Event	% Dropout ²	Presence of Adverse Event	% Dropout	Presence of Adverse Event	% Dropout
No	14.6	No	15.5	No	15.1
Yes	14.3	Yes	8.0	Yes	6.7
Nightmare/sleep disturbance		Blurred vision		Chest pain	
No	15.7	No	14.9	No	15.0
Yes	8.8	Yes	12.0	Yes	7.7
Nervous		Constipation		Bruising	
No	15.1	No	15.4	No	14.0
Yes	11.7	Yes	8.3	Yes	23.1
Problems with sexual arousal		Difficulty finding words		Drooling/increased salivation	
No	14.9	No	15.4	No	14.4
Yes	12.5	Yes	8.3	Yes	16.7
Unable to sit still		Muscle cramps		Menstrual irregularity	
No	15.5	No	14.8	No	16.3
Yes	9.4	Yes	12.5	Yes	14.3
Stomach discomfort		Trouble catching breath		Skin rash	
No	14.4	No	13.1	No	14.8
Yes	15.6	Yes	26.1	Yes	10.0
Weight loss ^a		Clenching of teeth		Slurred speech	
No	9.8	No	15.3	No	14.7
Yes	40.6	Yes	8.7	Yes	11.1
Headache		Trouble concentrating		Hearing/seeing things	
No	13.6	No	14.8	No	14.7
Yes	20.0	Yes	13.0	Yes	11.1
Tremor		Appetite increase		General side effect bothersome	
No	14.1	No	15.3	No	15.17
Yes	17.2	Yes	8.7	Yes	10.71
Weakness/fatigue		Hot flashes			
No	14.7	No	14.8		
Yes	13.8	Yes	13.0		

² Dropout rates for participants who did or did not report the adverse event. For example, among participants with an appetite decrease, 18.2% dropped out; among participants with no decrease in appetite, 13.3% dropped out.

² Dropout rates did not differ significantly for any adverse event except for weight loss^(a) ($p < .0001$). No participants reporting numbness/tingling^(b) dropped out; therefore, findings for this item are not interpretable.

Items from the Systematic Assessment for Treatment Emergent Events-Systematic Inquiry (SAFTEE-SI)

Table 4
Association of Frequency, Intensity, and Burden of Adverse Events with Attrition at Week 2

Frequency	N ¹	% Dropout ^{2,3}	Intensity	N ¹	% Dropout ^{2,4}	Burden	N ¹	% Dropout ^{2,5}
No side effects	71	14.1	No side effects	72	15.3	No impairment	110	14.6
10%	55	9.1	Trivial	35	5.7	Minimal impairment	40	15.0
25%	32	18.8	Mild	48	14.6	Mild impairment	27	7.4
50%	22	18.2	Moderate	37	18.9	Moderate impairment	20	15.0
75%	13	23.1	Marked	10	10.0	Marked impairment	5	20.0
90%	6	33.3	Severe	3	33.3	Severe impairment	3	33.3
All the time	7	0.0	Intolerable	1	100.0	Unable to function	1	100.0

¹Total number of participants in the category

²Percent of participants who dropped out

³p=0.4613

⁴p=0.1388

⁵p=0.2414

Items from the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)