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Not all types of depressed patients who persist with their antidepressant treatment improve in side effect complaints: A comparison of treatment completers and dropouts in the STAR*D trial

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Abstract

Introduction: There is a "traditional belief" that antidepressant side effect complaints improve with medication persistence; however, support for this theory has remained inconclusive. We aimed to examine if side effect complaints improved over time by modeling the relationship between side effect complaints and time at dropout for patients receiving citalopram during the first level of acute treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.

Methods: We categorized the 2833 patients into five patterns by week of dropout. We used pattern-mixture modeling to model change in side effect complaints (frequency, intensity, and burden) over the 12-week course of treatment, while accounting for attrition and depressive severity. Using post-hoc linear contrasts, we compared the attrition patterns with the completers' pattern for severity of side effect complaints at each respective last visit prior to dropout as well as averaged side effect complaints across the duration of treatment. We also reported frequencies and tolerability of side effects for nine organ/function systems over the course of treatment.

Results: Patients who dropped out early exhibited worsening side effect burden and patients who dropped out later showed improvements in side effect frequency and intensity. Treatment completers improved in all side effect complaints over the course of treatment. Early attrition patterns had more severe side effect complaints for both tests of post-hoc linear contrasts than later attrition patterns and completers.

Conclusions: Side effect complaints from antidepressant treatment improve over time, but only for some types of patients. As a precaution for early dropout, clinicians should monitor patients who exhibit worsening and more severe side effect complaints—especially in the first 6 weeks of antidepressant

Thomas T. Kim and Colin Xu contributed equally to this work.

treatment. In addition, clinicians may want to consider changing the type of treatment early on for these patients, rather than encouraging them to persist with their current medication.

KEYWORDS

antidepressant persistence, SSRI side effect symptoms, SSRI side effect tolerability, STAR*D

1 | INTRODUCTION

Antidepressants have been recommended as a first-line treatment for patients with more severe depression.[1] While they have been shown to be efficacious in the reduction of depressive severity, they have also been associated with side effects.[2,3] For example, the international Study to Predict Optimized Treatment for Depression (iSPOT-D), a real-world clinical trial in which outpatients with non-psychotic major depressive disorder (MDD) were randomized to one of three antidepressant arms, found that only 41.3% of patients reported experiencing no side effects at the end of the 8-week treatment course.[4] In addition, the iSPOT-D observed that greater side effect burden at week two predicted poorer treatment prognosis amongst treatment completers.[4,5]

Patient attrition during a course of treatment lowers the probability of a patient with MDD from experiencing an efficacious outcome; within psychiatric treatment for MDD, the inability to tolerate side effects has been the most common reason for patients discontinuing treatment.[6,7] Furthermore, there is a "traditional belief that, if patients can "endure" side effects initially, then the tolerability of an antidepressant will gradually improve, leading to a decrease in the rate of premature treatment discontinuation owing to intolerance."[8] This theory remains inconclusive: while Uher et al.[9] found that treatment completers' side effect complaints improved over the course of antidepressant treatment, Lin et al.[10] observed similar rates of attrition by intolerable side effects between patients who dropped out early versus later on during antidepressant treatment (see also Reference 11).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is the largest treatment study to date in evaluating antidepressant effectiveness for outpatients with MDD.[12] Within the STAR*D trial, patients provided measurements of not only depressive severity, but also side effect complaints (i.e., frequency, intensity, and burden of the entire side effect profile) over their course of treatment. Warden et al.[13] found that, amongst patients who received a course of citalopram during the first level of treatment in the STAR*D trial, patients who dropped out reported greater depressive severity—and surprisingly, lower side effect complaints—at the last measurement prior to dropping out than patients who did not drop out. However, their analysis did not consider heterogeneity in patients' patterns of time at dropout (i.e., every patient who provided data for at least one postbaseline visit but dropped out before the 12-week cutoff of the treatment trial was classified as "later attrition subjects").

Significant outcomes

- Side effect complaints from antidepressant treatment improved over time, but only for some types of patients.
- As a precaution for early dropout, clinicians should monitor patients who exhibit worsening and more severe side effect complaints—especially in the first 6 weeks of antidepressant treatment.
- In addition, clinicians may want to consider changing the type of treatment early on for these patients, rather than encouraging them to persist with their current medication.

Limitations

- Our analyses only examined side effect complaints for citalopram and not for other types of antidepressant medications.
- The STAR*D trial did not include a placebo condition (for comparative analyses).

1.1 | Aims of the present study

Therefore, using data from patients who received citalopram during the first level of acute treatment in the STAR*D trial, we conducted an exploratory analysis to examine if side effect complaints improved over time for each of the attrition patterns by modeling the relationship between side effect complaints and time at dropout. We then compared the trajectories of side effect

complaints between treatment completers and each attrition pattern.

2 | METHODS

2.1 | STAR*D research design

The STAR*D trial aimed to provide guidance for clinicians and patients in selecting the best next-step treatment for the many "real-world" patients who fail to gain sufficient relief from their first, and/or subsequent antidepressant treatment.[12,14] Within the study, patients who experienced an unsatisfactory clinical outcome from their course of treatment had the option to enter the subsequent step and receive a different type of treatment. Each step consisted of 12 weeks of treatment, with an additional 2 weeks for patients deemed close to remission. Further details of the STAR*D rationale, design, and description of treatment settings can be found elsewhere.[12]

2.2 | Participants

Patients enrolled in the STAR*D trial were 18–75 years old, diagnosed with nonpsychotic MDD, and seeking care at 18 primary and 23 psychiatric care clinical sites across the United States.[14] As described by Warden et al.[14]:

> A pretreatment score ≥14 on the 17-item Hamilton Depression Rating Scale (HAM-D) was required for study entry. Broad inclusion and minimal exclusion criteria were used to ensure a comprehensive representative cohort of "real world" patients to maximize the generalizability of findings...patients with most psychiatric and medical comorbidities could be enrolled as well as patients who were suicidal or abusing substances. Patients with a clear history of intolerance to the medications used in the first two levels of treatment were excluded as well as patients with a lifetime history of bipolar disorder, psychotic disorder, current anorexia nervosa, or a current primary diagnosis of bulimia or obsessive compulsive disorder (OCD). Patients were excluded if they were receiving antipsychotics, anticonvulsants, mood stabilizers, CNS stimulants, or nonstudy antidepressant medications or if they were breastfeeding or pregnant.

2.3 | Treatment

Patients enrolled in the STAR*D trial first received citalopram treatment.[12] The protocol recommended treatment sessions at baseline and at weeks 2, 4, 6, 9, and 12.[14] The recommended starting dose of citalopram was 20 mg/day, with doses increasing to 40 mg/day by week 4 and 60 mg/day by week 6.

2.4 | Measures

The 16-item Quick Inventory of Depressive Symptomatology-Self-Rated (QIDS-SR) scale,[12,15] a measure of depressive severity, was completed at baseline and at weeks 2, 4, 6, 9, and 12.[16] Beginning at week 2 (and then at weeks 4, 6, 9, and 12), patients completed the Patient Rated Inventory of Side Effects (PRISE) scale,[12,16] an assessment of the presence of side effects in the following nine organ/function systems: gastrointestinal, nervous system, heart, eyes/ears, skin, genital/urinary, sleep, sexual functioning, and other. If patients indicated the presence of a side effect, they were asked to rate the tolerability of the side effect, with judgments ranging from 0 to 2 (scores of 0 = "no side effect"; 1 = "tolerable side effect"; and 2 = "distressing side effect").

After completing the PRISE, patients were asked to fill out the Frequency and Intensity of Side Effects Rating and Global Rating of Side Effect Burden (FIBSER) scale.[12,16] Patients provided judgments on three domains: frequency (frequency of side effects of medications taken within the past week for depression); intensity (intensity of side effects due to medications taken within the last week for depression); and burden (degree to which antidepressant medication side effects over the last week interfered with day-to-day functions). Each domain was rated on a seven-point scale, which ranged from "No side effects" to "Present all the time" for frequency; "No side effects" to "Intolerable" for intensity; and "No burden" to "Unable to function due to side effects" for burden (see Wisniewski et al.[16] for psychometrics and more information of the FIBSER scale).

2.5 | Statistical analyses

We used the pattern-mixture modeling approach described by Hedeker and Gibbons[17] to model changes in side effect complaints while accounting for patient attrition. Pattern-mixture modeling has been shown to provide more accurate estimates of patient outcomes compared to traditional multiple imputation techniques

for missing data, especially for clinical trial data in which outcomes may be related to the likelihood of attrition.[18] For our models, we applied the last wave specification of pattern, in which patients are grouped by their last observation in the study.[17] Thus, patients were categorized into five patterns: week 2 dropouts (i.e., patients whose last observation was in week 2), week 4 dropouts (i.e., patients whose last observation was in week 4), week 6 dropouts (i.e., patients whose last observation was in week 6), week 9 dropouts (i.e., patients whose last observation was in week 9), and completers (i.e., patients who had observations in week 12).

For each side effect complaint, we specified a linear pattern-mixture model, with side effect complaint as the dependent variable. Week, attrition pattern, and the week-by-pattern interaction were entered as fixed effect predictors. We also entered depressive severity (i.e., the QIDS-SR score) and severity-by-week interaction as fixed effects to control for depressive severity. A random intercept and random slope of week was modeled for each patient. Thus, our final model was the following:

$$y_i = b_{0i} + b_{1ij}\,\text{week} + b_{2ij}\,\text{pattern} + b_{3ij}\,\text{week} \times \text{pattern} + b_{4ij}\,\text{QIDS} + b_{5ij}\,\text{week} \times \text{QIDS} + e_{ij}.$$

We ran this model three times for each side effect complaint (intensity, frequency, and burden), and generated estimates of outcomes for the five timepoints in each of the five patterns.

In order to model the slope of change in side effect complaints and time at dropout, we extracted the linear contrast for each of the patterns while controlling for depressive severity. Note that we did not model the slope of change for week 2 dropouts as there were no observations beyond week 2 in this pattern.

We also conducted two post-hoc contrast analyses to compare the four attrition patterns with the treatment completer pattern. In our first analysis, we tested if patients who dropped out experienced greater side effect complaints than completers at their last visit prior to dropping out. We ran linear contrasts of the modeled side effect complaint score at the last visit prior to dropout between each attrition pattern and the completer's pattern. For example, to test if there was a significant difference in side effect burden between completers and week 6 dropouts, we ran a contrast between the modeled side effect score at week 6 for both week 6 dropouts and completers. Thus, we ran the following four contrasts: week 2 side effect scores between week 2 dropouts and completers; week 4 side effect scores between week 4 dropouts and completers; week 6 side effect scores between week 6 dropouts and completers; and week 9 side effect scores between week 9 dropouts and completers.

In our second analysis, we tested if patients who dropped out experienced greater averaged side effect complaints across the duration of their treatment than completers. We ran linear contrasts of the modeled averaged side effect complaint score between each attrition pattern with the completer's pattern. For example, to test if there was a significant difference in side effect burden between completers and week 6 dropouts, we ran a contrast between the modeled averaged side effect score of weeks 2, 4, and 6 for both week 6 dropouts and completers. Thus, we ran the following four contrasts: averaged side effect scores of weeks 2 and 4 between week 4 dropouts and completers; averaged side effect scores of weeks 2, 4, and 6 between week 6 dropouts and completers; and averaged side effect scores of weeks 2, 4, 6, and 9 between week 9 dropouts and completers. Note that we did not run a contrast for the averaged side effect score of week 2 between week 2 dropouts and completers because it would be identical to the test conducted in our first analysis for week 2 dropouts.

Because of the large number of post-hoc tests (seven contrasts for each of the three side effect complaints), we only interpreted comparisons that met an adjusted threshold of $p < 0.00238$, which we arrived at by dividing 0.05 by 21 (i.e., a Bonferroni correction[19]). All linear contrasts were conducted using the general linear hypothesis test function (glht) in package multcomp.[20]

3 | RESULTS

Table S1 presents the demographics and clinical characteristics of our sample. Our sample of 2833 patients comprised 1212 completers, 769 patients with a last observation at week 9, 381 patients with a last observation at week 6, 231 patients with a last observation at week 4, and 240 patients with a last observation at week 2. Table 1 presents the frequencies and tolerability of side effects for nine organ/function systems across the five timepoints; Table 1 also reports the average FIBSER scores across the five timepoints. We found that 3.2% of patients reported not experiencing any side effects at week 2, whereas 3.6% of patients reported experiencing every side effect at week 2. Note that the most endorsed side effects were the following: dry mouth; headache; difficulty sleeping; loss of sexual desire; anxiety; poor concentration; restlessness; fatigue; and decreased energy.

3.1 | Change in side effect complaints over time

After controlling for depressive severity, side effect frequency significantly increased over time for week

TABLE 1 Side effects over the course of treatment (not accounting for dropout): Frequency and tolerability of side effect symptoms in nine organ/function systems, and mean FIBSER scores.

Symptom	Week 2 ($n = 2498$)	Week 4 ($n = 2182$)	Week 6 ($n = 2144$)	Week 9 ($n = 1797$)	Week 12 ($n = 1212$)
Gastrointestinal					
Diarrhea	29.1%	24.7%	23.4%	18.9%	19.1%
Constipation	17.4%	15.7%	14.9%	13.2%	12.5%
Dry mouth	43.8%	40.9%	36.6%	34.7%	32.0%
Nausea/vomiting	24.1%	16.3%	13.5%	11.8%	9.7%
None	26.9%	34.0%	39.4%	44.2%	47.6%
	($n = 1829$)	($n = 1449$)	($n = 1310$)	($n = 1010$)	($n = 638$)
Tolerable?	85.9%	85.9%	87.7%	87.5%	87.3%
Distressing?	14.1%	14.1%	12.3%	12.5%	12.7%
Heart					
Palpitations	12.1%	10.7%	9.8%	8.8%	6.9%
Dizziness on standing	22.2%	20.7%	18.9%	16.3%	16.3%
Chest pain	9.5%	8.6%	9.1%	8.2%	6.8%
None	63.9%	68.0%	70.0%	72.5%	74.3%
	($n = 928$)	($n = 717$)	($n = 667$)	($n = 508$)	($n = 320$)
Tolerable?	83.8%	82.3%	82.9%	86.6%	87.2%
Distressing?	16.2%	17.7%	17.1%	13.4%	12.8%
Skin					
Rash	5.8%	5.6%	6.1%	5.8%	6.6%
Increased perspiration	20.2%	18.2%	17.3%	16.7%	17.6%
Itching	15.1%	17.3%	16.8%	16.7%	18.8%
Dry skin	19.2%	21.7%	22.4%	22.2%	21.6%
None	56.7%	54.9%	56.0%	58.5%	57.2%
	($n = 1094$)	($n = 997$)	($n = 948$)	($n = 752$)	($n = 519$)
Tolerable?	85.9%	86.6%	87.1%	87.2%	87.5%
Distressing?	14.1%	13.4%	12.9%	12.8%	12.5%
Central nervous system					
Headache	49.4%	46.0%	41.4%	39.7%	36.5%
Tremors	14.8%	13.5%	12.6%	10.9%	9.3%
Poor coordination	10.4%	11.0%	10.7%	10.3%	7.7%
Dizziness	22.4%	19.9%	17.7%	15.7%	13.9%
None	35.0%	38.7%	44.9%	48.0%	51.7%
	($n = 1629$)	($n = 1340$)	($n = 1190$)	($n = 940$)	($n = 586$)
Tolerable?	80.2%	79.4%	80.8%	79.3%	83.6%
Distressing?	19.8%	20.6%	19.2%	20.7%	16.4%
Eye/ear					
Blurred vision	21.7%	21.2%	18.9%	16.6%	16.7%
Ringing in ears	19.8%	20.4%	18.0%	18.8%	15.0%
None	64.5%	65.1%	68.4%	69.9%	71.9%
	($n = 895$)	($n = 776$)	($n = 689$)	($n = 553$)	($n = 348$)
Tolerable?	85.0%	85.3%	86.5%	86.8%	89.7%
Distressing?	15.0%	14.7%	13.5%	13.2%	10.3%

(Continues)

TABLE 1 (Continued)

Symptom	Week 2 ($n = 2498$)	Week 4 ($n = 2182$)	Week 6 ($n = 2144$)	Week 9 ($n = 1797$)	Week 12 ($n = 1212$)
Genital/urinary					
Difficulty urinating	4.4%	4.6%	3.5%	4.1%	3.5%
Painful urination	1.9%	2.2%	2.0%	1.8%	2.1%
Menstrual irregularity	4.7%	5.3%	4.4%	4.9%	4.7%
Frequent urination	21.7%	22.7%	21.2%	19.1%	18.0%
None	70.6%	69.2%	72.2%	73.4%	74.5%
	($n = 761$)	($n = 690$)	($n = 617$)	($n = 490$)	($n = 319$)
Tolerable?	87.9%	87.0%	85.9%	89.8%	85.3%
Distressing?	12.1%	13.0%	14.1%	10.2%	14.7%
Sleep					
Difficulty sleeping	57.0%	54.7%	48.2%	43.2%	37.8%
Sleeping too much	19.0%	19.6%	18.3%	18.1%	18.0%
None	29.2%	31.4%	37.9%	43.4%	48.2%
	($n = 1773$)	($n = 1504$)	($n = 1340$)	($n = 1036$)	($n = 636$)
Tolerable?	57.5%	62.6%	67.4%	67.3%	69.8%
Distressing?	42.5%	37.4%	32.6%	32.7%	30.2%
Sexual functioning					
Loss of sexual desire	36.2%	34.9%	32.4%	28.8%	26.2%
Trouble achieving orgasm	20.2%	21.8%	21.4%	20.5%	18.8%
Trouble with erections	8.1%	8.2%	8.0%	7.7%	7.2%
None	50.1%	49.7%	51.2%	56.0%	59.7%
	($n = 1252$)	($n = 1113$)	($n = 1059$)	($n = 799$)	($n = 497$)
Tolerable?	60.9%	63.5%	65.0%	64.0%	64.0%
Distressing?	39.1%	36.5%	35.0%	36.0%	36.0%
Other symptoms					
Anxiety	48.0%	43.4%	39.9%	35.7%	32.2%
Poor concentration	44.0%	39.5%	35.0%	30.2%	25.0%
General malaise	19.7%	17.5%	13.9%	14.7%	12.0%
Restlessness	40.9%	38.9%	32.6%	28.8%	26.9%
Fatigue	51.6%	49.7%	44.4%	41.7%	37.6%
Decreased energy	47.4%	44.7%	39.7%	36.3%	31.9%
None	13.6%	16.9%	21.6%	26.0%	32.4%
	($n = 2146$)	($n = 1823$)	($n = 1679$)	($n = 1327$)	($n = 825$)
Tolerable?	62.0%	66.2%	69.3%	70.3%	73.1%
Distressing?	38.0%	33.8%	30.7%	29.7%	26.9%
FIBSER	**Week 2 ($n = 2492$)**	**Week 4 ($n = 2178$)**	**Week 6 ($n = 2140$)**	**Week 9 ($n = 1793$)**	**Week 12 ($n = 1212$)**
Frequency, mean (SD)	1.96 (1.86)	1.75 (1.83)	1.60 (1.80)	1.39 (1.71)	1.16 (1.57)
Intensity, mean (SD)	1.94 (1.64)	1.73 (1.60)	1.55 (1.58)	1.36 (1.52)	1.18 (1.44)
Burden, mean (SD)	1.33 (1.44)	1.16 (1.34)	1.07 (1.33)	0.95 (1.27)	0.81 (1.13)

Note: Tolerability frequencies were presented for only patients who experienced the side effect.

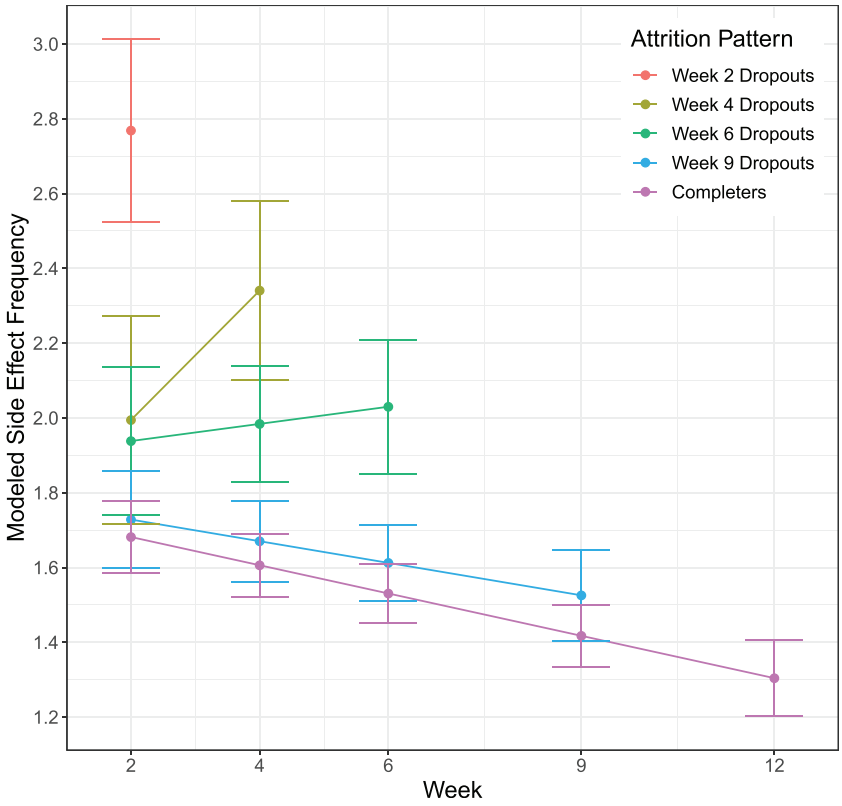

FIGURE 1 Modeled side effect frequency by attrition pattern. 0 = No side effects; 1 = Present 10% of the time; 2 = Present 25% of the time; 3 = Present 50% of the time; 4 = Present 75% of the time; 5 = Present 90% of the time; 6 = Present all the time. Error bars represent 95% confidence intervals.

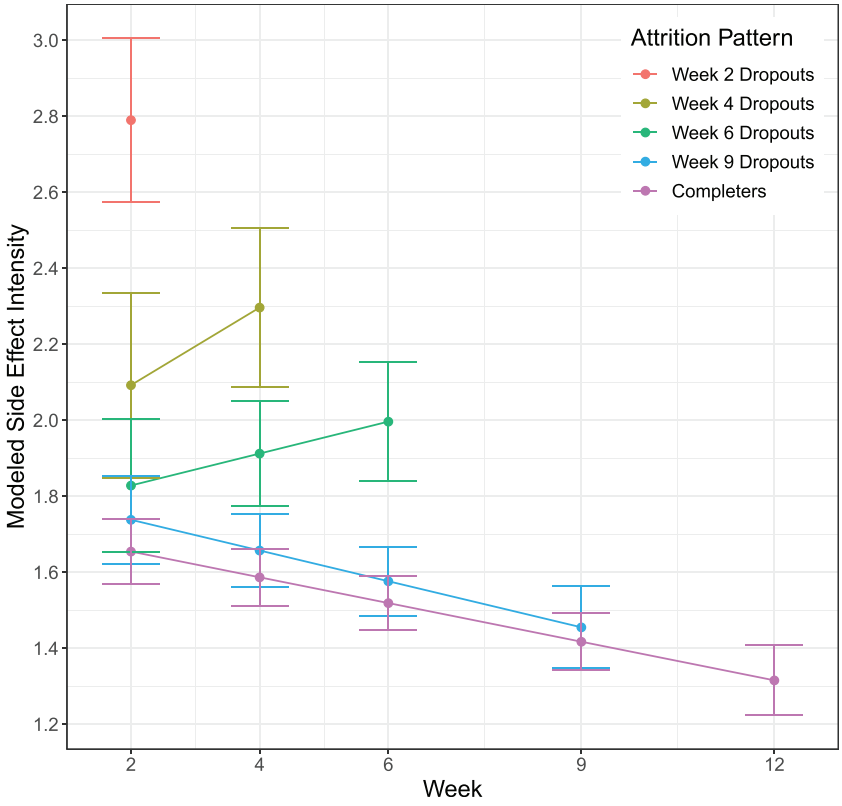

FIGURE 2 Modeled side effect intensity by attrition pattern. 0 = No side effects; 1 = Trivial; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe; 6 = Intolerable. Error bars represent 95% confidence intervals.

4 dropouts ($b = 0.16$, $p = 0.029$). Side effect frequency significantly decreased over time for week 9 dropouts ($b = -0.05$, $p = 0.002$) and completers ($b = -0.05$, $p < 0.001$). Side effect frequency did not significantly change over time for week 6 dropouts ($b = 0.01$, $p = 0.828$). See Figure 1.

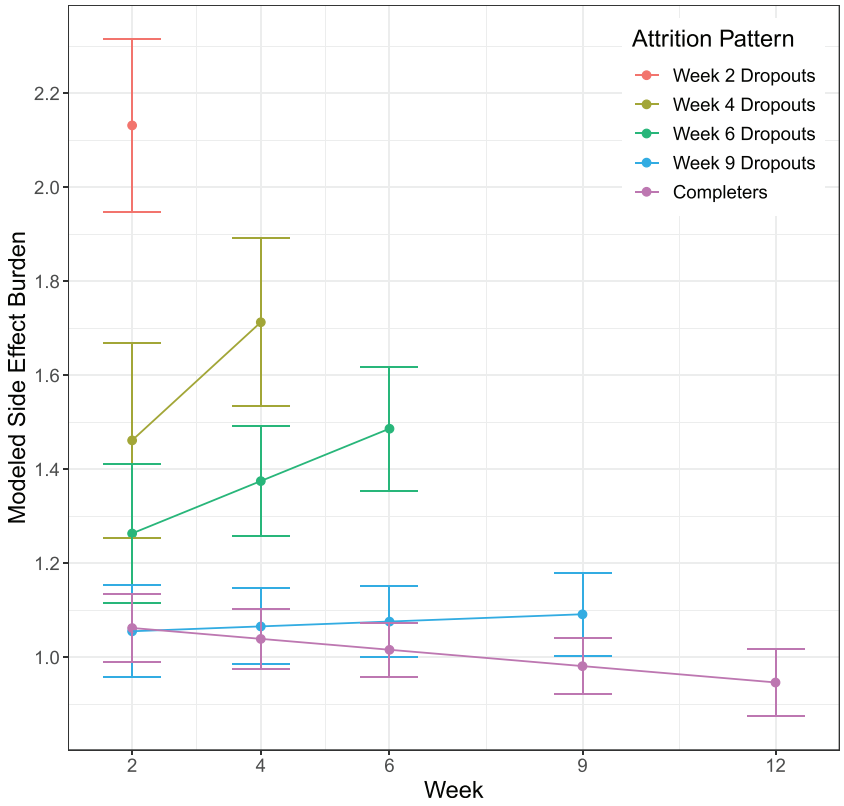

FIGURE 3 Modeled side effect burden by attrition pattern. 0 = No burden; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked; 5 = Severe; 6 = Unable to function due to side effects. Error bars represent 95% confidence intervals.

Side effect intensity significantly decreased over time for week 9 dropouts ($b = -0.06$, $p < 0.001$) and completers ($b = -0.05$, $p < 0.001$). Side effect intensity did not significantly change over time for week 4 dropouts ($b = 0.08$, $p = 0.181$) and week 6 dropouts ($b = 0.02$, $p = 0.388$). See Figure 2.

Side effect burden significantly increased over time for week 4 dropouts ($b = 0.12$, $p = 0.026$) and week 6 dropouts ($b = 0.05$, $p = 0.026$). Side effect burden significantly decreased over time for completers ($b = -0.02$, $p = 0.015$). Side effect burden did not significantly change over time for week 9 dropouts ($b = 0.00$, $p = 0.866$). See Figure 3.

3.2 | Contrasts of last visit side effect complaints between completers and dropouts

Compared to completers, weeks 2, 4, and 6 dropouts reported significantly greater last visit side effect frequency, intensity, and burden prior to dropping out (see Table 2). There was no significant difference in last visit side effect complaints between completers and week 9 dropouts.

3.3 | Contrasts of averaged side effect complaints across the duration of treatment between completers and dropouts

Compared to completers, weeks 2, 4, and 6 dropouts reported significantly greater averaged side effect frequency, intensity, and burden across the duration of treatment (see Table 2). There was no significant difference in the averaged side effect complaints across the duration of treatment between completers and week 9 dropouts.

4 | DISCUSSION

Using pattern-mixture modeling and data from patients who received citalopram in the first level of treatment in the STAR*D study, we found that both the change in side effect complaints over the course of treatment and the severity of side effect complaints predicted attrition. Specifically, the present study observed that attrition risk is especially elevated during the first 6 weeks of treatment for: (a) patients with worsening side effect burden; and (b) patients with more severe side effect complaints.

TABLE 2 Post-hoc linear contrasts of side effect complaints between treatment completers and attrition patterns.

		Frequency		Intensity		Burden	
Contrast type	**Attrition pattern**	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***
Last visit	Week 2	**1.09 (0.82–1.35)**	**<0.001***	**1.14 (0.90–1.37)**	**<0.001***	**1.07 (0.87–1.27)**	**<0.001***
	Week 4	**0.73 (0.48–0.99)**	**<0.001***	**0.71 (0.49–0.93)**	**<0.001***	**0.67 (0.48–0.86)**	**<0.001***
	Week 6	**0.50 (0.30–0.69)**	**<0.001***	**0.48 (0.30–0.65)**	**<0.001***	**0.47 (0.33–0.61)**	**<0.001***
	Week 9	0.11 (−0.04 to 0.26)	0.150	0.04 (−0.09 to 0.17)	0.572	0.11 (0.00–0.22)	0.041
Averaged across duration of treatment	Week 4	**0.52 (0.29–0.76)**	**<0.001***	**0.57 (0.36–0.78)**	**<0.001***	**0.54 (0.36–0.71)**	**<0.001***
	Week 6	**0.38 (0.20–0.56)**	**<0.001***	**0.33 (0.17–0.48)**	**<0.001***	**0.34 (0.20–0.47)**	**<0.001***
	Week 9	0.08 (−0.05 to 0.20)	0.255	0.06 (−0.05 to 0.18)	0.292	0.05 (−0.05 to 0.14)	0.331

Note: Bold indicates the contrasts that met the significance threshold.
*Significant at the Bonferroni corrected α of $p < 0.00238$.

4.1 | Change in side effect complaints

Within psychiatric care for MDD, there is a "traditional belief" that side effect complaints improve with medication persistence[8]; however, support for this theory has remained inconclusive.[9–11] The results from the present study may explain these inconsistent findings. Uher et al.[9] concluded from their research that treatment completers' side effect complaints improved over the course of both nortriptyline (a tricyclic antidepressant) and escitalopram (an SSRI). We found a similar pattern: treatment completers improved in all three domains of side effect complaints (frequency, intensity, and burden) over the course of treatment, even after controlling for depressive severity. We also observed that patients who dropped out later (i.e., week 9 dropouts) showed improvements in side effect frequency and intensity, similar to completers. However, we found that not all types of patients improved in side effect complaints over time: patients who dropped out early (i.e., weeks 4 and 6 dropouts) exhibited worsening side effect burden. Thus, early worsening or lack of improvement may be a predictor of attrition, while an improvement in side effect complaints may be an indicator of medication persistence.

4.2 | Severity of side effect complaints

We found that early attrition patterns were associated with more severe side effect complaints. We observed that weeks 2, 4, and 6 dropouts had significantly greater side effect complaints at each respective last visit prior to dropout compared to week 9 dropouts and completers. Similarly, when comparing averaged side effect complaints across the duration of treatment, we found that weeks 2, 4, and 6 dropouts had worse scores than completers. Interestingly, our post-hoc contrasts revealed no significant difference in either last visit or averaged side effect complaint across the course of treatment between week 9 dropouts and completers. Thus, more severe side effect complaints predict attrition particularly early on in treatment, with the relative role of severity decreasing the longer a patient persists with their medication.

Contrary to Warden et al.'s[14] analysis of attrition within the STAR*D trial, we did not observe that patients who dropped out had lower side effect frequency, intensity, or burden at their last measurement prior to leaving the study than completers. Such a finding by Warden et al.[14] would paradoxically suggest that a patient who experiences higher side effect complaints is more likely to persist in antidepressant treatment and that a patient who experiences lower side effect complaints would be more likely to drop out. One explanation for the inconsistency between our findings and those of Warden et al.[14] is that they categorized patients who dropped out as one homogeneous group (i.e., any patient who dropped out between weeks 2 and 12 was considered a "later attrition subject"), whereas we classified each attrition pattern as its own distinct group.

4.3 | Presence of side effects for nine organ/function systems

We found that nearly all patients experienced at least one side effect early on in treatment. In the present study, the most endorsed side effects were consistent with prior research that examined common side effects of SSRI treatment for depression.[7,21,22] We also found that patients reported experiencing the most distress for symptoms within the sleep, sexual functioning, and other

(i.e., anxiety, poor concentration, general malaise, restlessness, fatigue, and decreased energy) systems.

4.4 | Limitations

Our analysis only examined side effect complaints for citalopram and not for other types of antidepressant medications. The STAR*D trial also did not include a placebo condition (for comparative analyses).

4.5 | Implications

The present study suggests that analyses that do not account for attrition pattern will likely find that side effect complaints improve with medication persistence; for example, we observed that the mean side effect complaints—without accounting for patient attrition—across weeks 2, 4, 6, 9, and 12 appeared to decrease monotonically over time (see Table 1). However, further analyses revealed that this improvement is partly attributed to patients with worsening and more severe side effect complaints dropping out, rather than a decrease in side effect complaints for all patients uniformly (see Figures 1–3).

In the STAR*D trial, patients were titrated to a targeted dose of 60 mg/day, on a schedule in which clinicians prescribed an initial dose of citalopram at 20 mg/day, with increases to 40 mg/day by week 4, and then to 60 mg/day by week 6.[23] Although clinicians were allowed some flexibility in time to titrate to the target dose, the target dose and titration dose amounts were standardized for all patients. Our findings suggest that clinicians should be cautious with increasing the medication dosage early on for patients with worsening and more severe side effect complaints, as this may not only worsen side effect complaints, but also increase the likelihood of attrition.

The present study found that not all types of patients who persist with their antidepressant treatment will experience an improvement in side effect complaints. Therefore, clinicians might want to consider changing the type of treatment early on (e.g., psychotherapy or a different antidepressant) for patients who exhibit worsening and more severe side effect complaints—rather than encouraging them to persist with their current medication.

4.6 | Future directions

Most patients who receive an SSRI treatment will first experience side effects within 2 weeks of treatment, with some patients even reporting the continuation of those side effects after 12 weeks of treatment.[22] It would be interesting for a future study to identify which types of side effect symptoms—as well as the tolerability—predicts attrition for each of the five patterns characterized in the present study.

The presence of side effects in the nine organ/function systems was assessed only after initiation of the medication treatment; a future study should ask patients about the presence of these nine systems even at pretreatment, as this may provide more information about the effect of medications on physical symptoms.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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