

Brief Report**Role of Patient Experience in Antidepressant Adherence: A Retrospective Data Analysis**Mark Vanelli, MD, MHS^{1,2}; and Marcelo Coca-Perraillon, MA³¹*Adheris, Inc., Burlington, Massachusetts;* ²*Department of Psychiatry, Beth-Israel Medical Center, Harvard Medical School, Boston, Massachusetts;* and ³*Health Care Policy Department, Harvard Medical School, Boston, Massachusetts***ABSTRACT**

Background: In a previous study, we found that past medication use was associated with medication adherence in patients prescribed atypical antipsychotics.

Objective: The present study aimed to determine whether past medication experience was associated with adherence in patients prescribed selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.

Methods: Deidentified computerized pharmacy records of patients from 1157 pharmacies throughout the United States were used to select patients who were dispensed extended-release venlafaxine, controlled-release paroxetine, sertraline, fluoxetine, escitalopram, and/or citalopram between October 1, 2003, and March 31, 2004. Patients who were dispensed an antidepressant during this enrollment period were stratified into 2 groups. One group consisted of patients to whom an antidepressant medication had not been dispensed in the 180-day period prior to the index date. The other group was composed of individuals who had been dispensed an antidepressant during that period. *Discontinuation* was defined as being ≥ 30 days late for a scheduled refill. Adherence was measured using Kaplan-Meier analysis during a 360-day follow-up period.

Results: Of 211,565 patients analyzed, 38.5% had not received an antidepressant previously; 74.0% of the total sample were women. The mean age was 50.5 years. The median times to medication discontinuation were 67 days in patients not previously dispensed an antidepressant and 184 days in those who were. Discontinuation in the first 30 days was observed in 38.8% of patients not previously dispensed an antidepressant and in 18.8% of those who were.

Conclusions: Prior antidepressant receipt rather than the use of a particular medication was associated with antidepressant adherence in this analysis. Patients without prior antidepressant receipt faced twice the risk for discontinuation during the first 30 days of treatment. (*Clin Ther.* 2008;30:1737-1745) © 2008 Excerpta Medica Inc.

Key words: adherence, medication discontinuation, antidepressant adherence.

INTRODUCTION

Depressive disorders increase the risk for school failure,¹ divorce,² unemployment,³ suicide,⁴ and all-cause mortality⁵ and are the second-leading cause of lost productive years of life in the world today.⁶ Episode recurrence occurs in ~85% of patients diagnosed with unipolar depression, while in bipolar disorder, recurring depressive episodes are common and may occupy 32% to 50% of the days lived with the illness.^{7,8} Depressive recurrence in turn increases the likelihood that future episodes may be more severe, frequent, and difficult to treat.⁹ Sustained antidepressant use over a 12- to 36-month period may decrease the risk for depressive relapse in unipolar depression by 70% relative to antidepressant discontinuation,¹⁰ while ongoing use of atypical antipsychotics and mood-stabilizing agents over similar periods of time may help to reduce the risk for depressive relapse in bipolar disorder.¹¹⁻¹³ Consequently, identifying fac-

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tors that can reduce the risk for premature antidepressant discontinuation continues to be an important clinical and public health goal.

Anxiety disorders, which include panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, and social phobia, similarly impair quality of life and are associated with levels of workplace disability on par with cardiovascular disease, arthritis, and depression.¹⁴ Antidepressants are also widely used to treat anxiety disorders, although we know far less about their role in preventing recurrence. Despite treatment, symptom recurrence and ongoing symptoms often occur in patients with anxiety disorders.¹⁵ The extent to which poor medication adherence may contribute to the ongoing or breakthrough symptoms commonly experienced in patients with depressive or anxiety disorders receiving routine care remains unanswered.

Six or more months of antidepressant use is generally recommended to treat episodes of major depression and anxiety disorder and to prevent recurrence.^{16–21} As a practical matter, however, identifying nonadherence in outpatient practice remains difficult because it cannot be directly monitored. Studies have found that adherence self-reported by patients and reported by providers correlate poorly with objective measures of medication use (pill counts, electronic monitoring).^{22,23} The following questions thus arise: How can health care providers better understand when antidepressant discontinuation is most likely, and who is most at risk?

Pharmacy data provide a powerful tool to help clinicians understand when antidepressant discontinuation is most likely in routine care. The benefits of these data include the ability to objectively and inexpensively capture patterns of medication use that prevail across a range of geographies, provider types and sites, insurance carriers, and socioeconomic groups. In a previous study²⁴ that used national retail pharmacy data (N = 406,032), we found that the rate of antipsychotic medication discontinuation was higher in patients not previously dispensed an antipsychotic medication in the prior 180 days than in those previously dispensed an antipsychotic during this period (median days to discontinuation, 125 vs 34; $P < 0.05$ [log-rank test]). This risk was greater in the first 30 days of treatment than during any other monthly interval during the 360-day follow-up period. After 30 days, 48.8% of patients without previ-

ous medication experience discontinued treatment, compared with 24.0% of patients in the group with previous medication experience. We speculated that episodes of illness recurrence tied to medication discontinuation, or improvement associated with product use, might promote adherence through fear-conditioned or emotional learning, a type of learning that is not subject to forgetting and extinction.²⁵ Patients without prior medication or illness experience would be unable to draw on this type of learning and thus might be at a greater risk for medication discontinuation.

An unanswered question is whether a lack of recent medication or illness experience is associated with an increased risk for medication discontinuation in other medication classes. The primary objective of this brief report was to determine whether a lack of recent antidepressant receipt was associated with an increased risk for medication discontinuation in a large, nationally representative sample of patients.

MATERIALS AND METHODS

Deidentified computerized pharmacy records from pharmacies that were part of a national retail pharmacy chain across the United States were used to select data from patients who were dispensed extended-release (XR) venlafaxine, controlled-release (CR) paroxetine, sertraline, fluoxetine, escitalopram, and/or citalopram from October 1, 2003, to March 31, 2004. All health-protected information was removed from the data set prior to analysis. The use of data was in accordance with the US Department of Health and Human Services' Health Insurance Portability and Accountability Act. The New England Institutional Review Board approved the study and its methods. Complete prescription histories were analyzed for all patients regardless of the health care plan, insurer, or self-pay status.

The available data elements included medication brand; dosage; quantity dispensed; date dispensed; number of refills prescribed; and the age, sex, and zip code of the recipient. Birth date, sex, and zip code were data elements entered by pharmacy personnel at the point of sale.

Eligible patients were stratified into 1 of 2 groups. One group was composed of patients to whom no medication-in-class had been dispensed in the 180 days preceding the index date (the date on which the medication was first dispensed). The other group consisted

of patients to whom a medication-in-class was dispensed during the 180-day period prior to the index date (Figure 1).

The Master Drug Database (Medi-Span Inc., Indianapolis, Indiana) was used to classify drugs as antidepressants. Patients were defined as having discontinued therapy once they were ≥ 30 days late for a scheduled refill. Those who were switched from the index antidepressant to another antidepressant were considered to have continued with therapy. Individuals prescribed ≥ 2 antidepressants were classified according to the first antidepressant dispensed. Patients' incomes were estimated using US Census data from 2000, by ZIP code. To exclude patients for whom medication was prescribed for short-term (nonmaintenance) use, we excluded data from patients without prior medication experience whose index-days' supply was < 30 .

Because we used only pharmacy data in this analysis, adverse-events data were unavailable.

Statistical Analysis

Adherence was evaluated using Kaplan-Meier curves to compare the time-to-discontinuation between the 2 groups during a 360-day period after the index date. *Adherence* was defined as the number of days until the medication was discontinued. Differences in Kaplan-Meier curves for both groups were compared using log-rank tests.

RESULTS

Data from 1157 pharmacies throughout the United States were included (South, 40%; Midwest, 38%; West, 13%; and Northeast, 9%). The distribution of patients in the sample ($N = 211,565$) was as follows: sertraline, 58,388 patients; fluoxetine, 43,412; escitalopram, 37,582; venlafaxine XR, 28,983; citalopram, 22,904; and paroxetine CR, 20,296. Patients without receipt of an antidepressant in the 180 days before the index fill composed 38.5% of the sample. Women composed 74.0% of the sample. The mean age was 50.5 years. The mean income was \$51,487. Population characteristics of the 2 groups are shown in the table.

The median number of days to discontinuation was 67 in patients not previously dispensed an antidepressant and 184 in those who were (Figure 2). The rate of medication discontinuation in the first 30 days was 38.8% in patients not previously dispensed an antidepressant and 18.8% in those who were. At 180 days, the discontinuation rate was 74.9% in patients not previously dispensed an antidepressant and 48.3% in those who were. The mean monthly rate of antidepressant discontinuation after the first 30 days was 4.6% in patients with prior antidepressant receipt and 4.2% in those without.

The median (95% CI) days to discontinuation in patients not previously dispensed an antidepressant, by antidepressant, were as follows: sertraline, 66 (65–67);

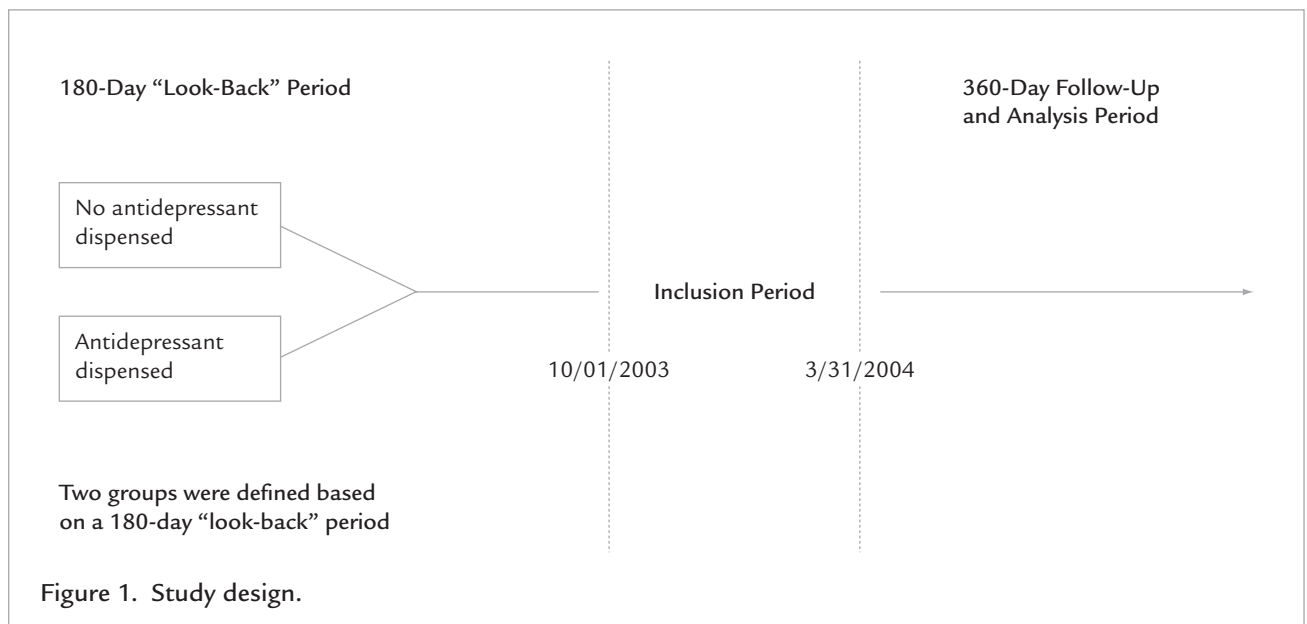


Table. Demographic characteristics of the study population. Values are % of patients.

Characteristic	No Prior Antidepressant (n = 81,474)	Prior Antidepressant (n = 130,091)
Age group		
≤50 y	57.7	47.3
51–60 y	17.3	23.3
61–70 y	10.4	13.6
>70 y	14.6	15.8
Sex		
Female	72.0	74.9
Male	28.0	25.1
Copayment*		
<\$1	24.0	18.0
\$1–<\$15	30.4	37.3
\$15–<\$30	27.2	28.2
\$30–<\$60	8.6	7.8
≥\$60	9.7	8.7
Region		
South	40.0	40.0
Midwest	37.8	38.6
West	13.0	12.3
Northeast	9.2	9.1
Median income*		
<\$35,000	32.4	30.5
\$35,000–<\$50,000	47.3	48.1
≥\$50,000	20.3	21.5

*Percentages may not total 100% due to rounding.

fluoxetine, 72 (69–75); escitalopram, 67 (65–69); venlafaxine XR, 76 (72–81); citalopram, 64 (62–67); and paroxetine CR, 60 (60–61). Among patients previously dispensed an antidepressant, these values were sertraline, 175 (170–179); fluoxetine, 210 (204–213); escitalopram, 151 (149–154); venlafaxine XR, 214 (210–221); citalopram, 198 (192–206); and paroxetine CR, 177 (169–182) (Figure 3). Over the study period, the rates of patients who were switched from one antidepressant to another were 6.5% in patients not previously dispensed an antidepressant and 11.8% in those who were. For every patient who was switched to another medication in the class, 7.9 stopped using their antidepressant medication outright in both groups combined.

DISCUSSION

Three conclusions emerge from this study. First, prior antidepressant use and illness experience rather than receipt of a specific medication were associated with improved adherence. Previous studies of antidepressant adherence have associated elevated rates of adherence with specific antidepressants and their underlying efficacy and tolerability profiles without considering the confounding effects of prior patient medication or illness experience on adherence. One retrospective analysis of pharmacy claims from primary care patients enrolled in a commercial health maintenance organization (N = 21,636) found that venlafaxine, fluoxetine, and sertraline had the lowest rates of premature discontinuation among commonly

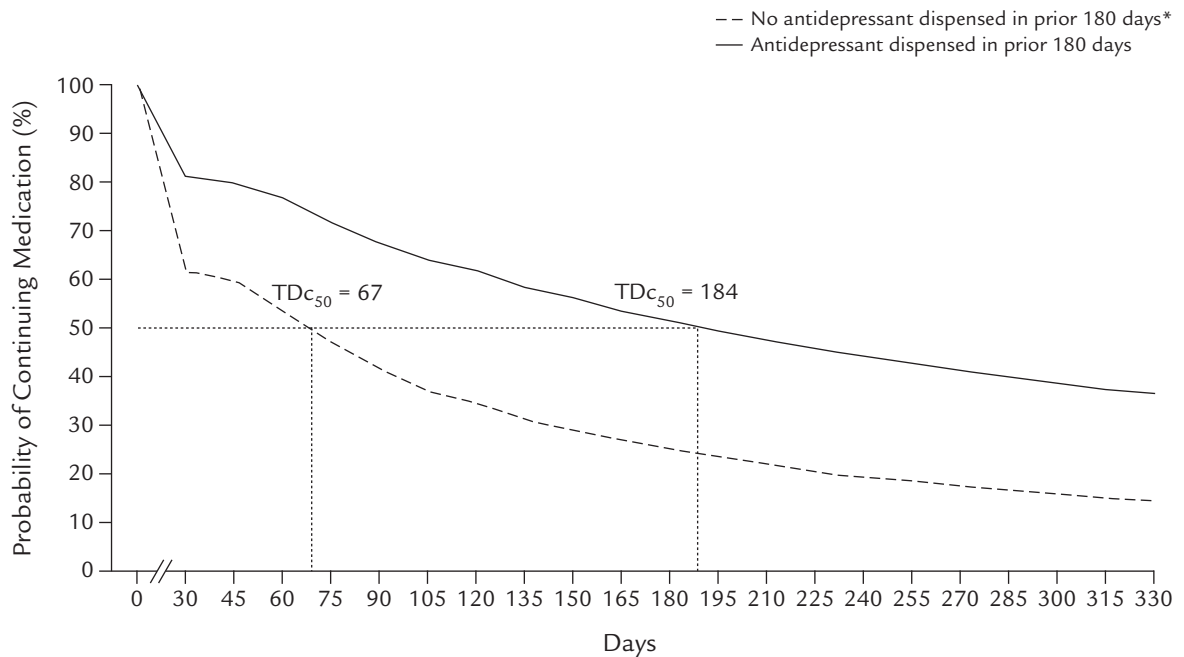


Figure 2. Kaplan-Meier estimates of risk for antidepressant discontinuation (defined as being ≥ 30 days late for a scheduled refill). TDC_{50} = median time to discontinuation. *Patients in whom no antidepressant was dispensed in the prior 180 days included previously treated patients whose treatment was restarted after a lapse in antidepressant use of ≥ 180 days, as well as newly diagnosed, treatment-naïve, “first-episode” patients.

prescribed antidepressants. To increase the prevalence of patients receiving an adequate antidepressant trial, the authors suggested that providers increase the use of medications specifically associated with low rates of discontinuation.^{26,27} Here, however, we found that the greatest differences in antidepressant adherence were observed in patients who received the same antidepressant but had different levels of prior medication experience, not among patients prescribed different antidepressants. Such data suggest that modifiable factors associated with patient knowledge, attitude, and practice—not the receipt of a specific medication—are the appropriate focus for efforts designed to improve antidepressant adherence and treatment outcomes. The results from the present study also suggest that researchers need to be alert to the effects that prior medication or illness experience have on adherence and how such increases may be unrelated to the efficacy or tolerability profile of a medication.

Second, these findings underscore the importance of selectively reengineering the process of care to pa-

tients who have not been dispensed an antidepressant prescription in the prior 6 months, especially during the first 30 days of treatment. Thirty-nine percent of such patients discontinued use of medication in the first 30 days; this rate was 8.4-fold greater than the mean monthly rate of 4.6% that subsequently prevailed. Patients in this category would include newly diagnosed, first-episode patients and previously diagnosed and treated patients who had lapsed and restarted treatment. While National Committee for Quality Assurance depression guidelines currently recommend ≥ 3 provider contacts during the first 12 weeks of outpatient treatment,²⁸ our findings suggest that frequent provider follow-up for such patients may need to take place during the first 4 weeks of treatment.

Increased patient follow-up and education at the onset of treatment may help to improve antidepressant adherence and treatment outcomes. In a 12-month trial of 217 primary care patients with unipolar depression, Katon et al²⁹ randomized patients into a

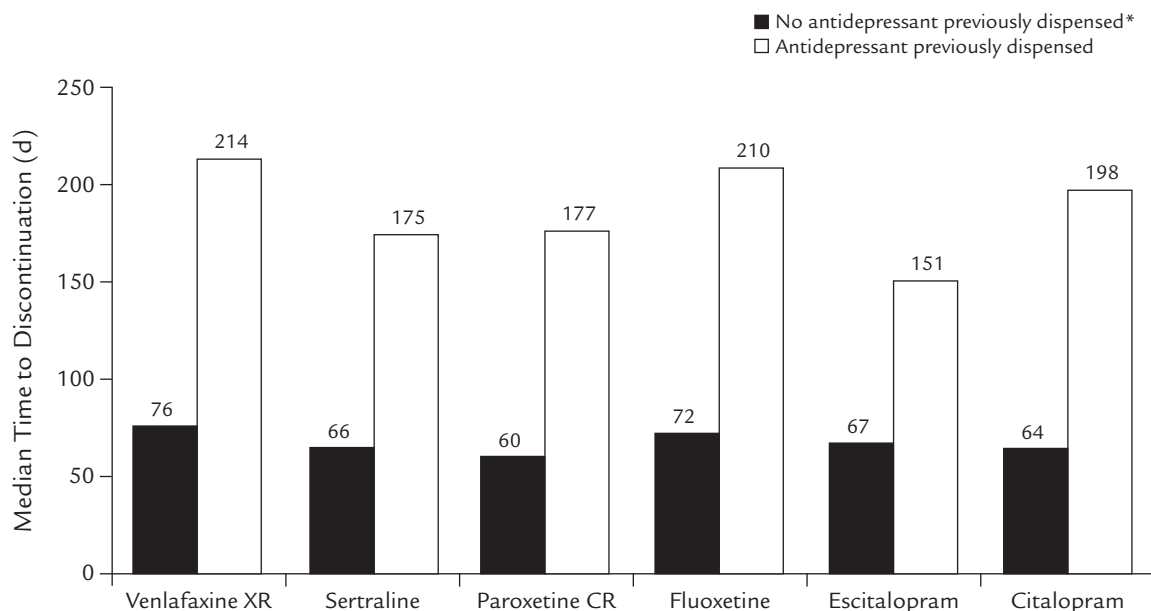


Figure 3. Median time to antidepressant discontinuation (defined as being ≥ 30 days late for a scheduled re-fill), based on patient experience. XR = extended release; CR = controlled release. *Patients in whom no antidepressant was dispensed in the prior 180 days included previously treated patients whose treatment was restarted after a lapse in antidepressant use of ≥ 180 days, as well as newly diagnosed, treatment-naïve, “first-episode” patients.

control group and an intervention group that received weekly follow-up during the first 4 weeks of treatment as well as educational materials and ongoing follow-up during the continuation and maintenance phases of treatment. Intervention patients were more likely to receive an adequate dose of antidepressant for 90 days or more (75.5% vs 50.0%), rate antidepressant medications as very helpful (88.1% vs 63.3%), and show a decrease of 50% or more in depressive symptoms (74.0% vs 43.8%).²⁹ One strategy that might be tested is to “front-load” follow-up and educational interventions in high-risk patients during the first 30 to 45 days of treatment, after which the frequency and intensity of visits could be decreased. Given the shortage of psychiatrists in many areas, nurses, social workers, and case managers might provide much of the needed follow-up and education.

Third, lack of recent medication or illness experience may be a risk factor for medication discontinuation among patients with chronic illnesses in general, with different median times to discontinuation being characteristic of a drug class. In a prior study, we

found that the median time to discontinuation in patients previously dispensed an antipsychotic was 3.7-fold longer relative to those who were not (125 vs 34 days).²⁴ In this study, the median time to discontinuation was 2.7-fold longer in patients previously dispensed an antidepressant relative to those who were not (184 vs 67 days). We speculate that this increase in the median time to discontinuation reflects the presence of a learning curve. Patients prescribed antidepressant and antipsychotic medications commonly begin medication use when they experience symptoms and discontinue when they feel better or experience intolerable adverse effects. Frequent cycling on and off of medications may help patients to learn the value of adherence through personal experience. Empirical support for such a hypothesis is suggested in a study of the factors associated with good versus poor compliance in patients with euthymic bipolar disorder (N = 200) who were followed up over a 2-year period.³⁰ In this study, a greater number of total illness episodes (15.8 vs 9.1) and a greater number of prior depressive episodes (7.4 vs 4.5) were as-

sociated with good versus poor compliance. A pattern of medication adherence tied to the painful consequences of medication discontinuation may be a type of patient learning common to different medication classes.³¹

Better reporting and dissemination of data that can summarily suggest the presence of problems with the effective use of medication in populations are needed. Absent such data, providers may be unaware of the kinds of patients, types of medication, and points in therapy at which medication discontinuation and treatment failure are most likely. Organizations with access to population-based data, such as managed care organizations, insurers, and government agencies, might take to reporting median discontinuation times with different medication classes so that providers can better target follow-up and education in those patients and medication classes in which the risk for medication discontinuation is greatest.

The rate of early medication discontinuation observed in the present study was similar to rates reported by Olfson et al³² and Mullins et al.²⁷ In a retrospective analysis of data from the Medical Expenditure Panel Survey for 1996–2001 in adults who initiated antidepressant therapy (N = 810), Olfson et al found that the rate of antidepressant discontinuation during 30 days of therapy was 42.4%. In a retrospective analysis of claims data from 1999–2002 in adult health maintenance organization members prescribed paroxetine, sertraline, or citalopram (N = 14,915), Mullins et al found a 30-day discontinuation rate of 46.6%. In our study, the 30-day rate of antidepressant discontinuation during 2003–2004 was 38.5% in patients who were not dispensed an antidepressant in the prior 6 months.

Limitations associated with this study included a lack of collateral diagnostic information. Because the data were deidentified information from pharmacy prescription records, the diagnostic mix of patients and the intended duration of antidepressant use could not be established. Patients may have appropriately discontinued use of antidepressant medication due to short-term use (eg, for premenstrual dysphoria) or off-label use. Excluded from the analysis were patients without prior medication experience who received <30 days of medication. However, patients initiating therapy might receive <30 days of medication as part of an initial titration to confirm tolerability. Because patients new to therapy are likely to have poorer rates

of adherence relative to experienced patients, their exclusion might serve to overestimate adherence should an aggregate rate of adherence be calculated for the new and experienced groups as a whole. It is unknown what the effect on adherence results might be if we were to have excluded from this analysis newly diagnosed patients who received short-term prescriptions (such patients typically receive more frequent provider follow-up as part of the titration) relative to those who received ≥ 30 days' supply. This topic is worth further study. Patients may also have received instructions to use medication at a lower dose than written on the prescription (eg, when a pill splitter is used to cut a tablet in half, the quantity dispensed is doubled), which might have artificially increased persistence. Reasons for treatment discontinuation might have included hospitalization or a change in residence. Patients might have migrated from one pharmacy to another or switched from a retail to a mail-order pharmacy. Differences in insurance coverage might have affected the results. Although all of these factors might have affected the absolute rates of adherence, it is not clear whether such factors would have affected the relative rates of adherence between groups of patients receiving the same medication and who differed only in whether they previously had been dispensed an antidepressant. Refill rates from closed pharmacy systems are known to provide good measures of overall adherence,^{33,34} but the data from the present study were from retail pharmacy chains. However, the rate at which patients migrate into and out of such chains is estimated to be 0.5% per year.³⁵

CONCLUSIONS

In these patients prescribed selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, medication discontinuation was 2-fold as likely in the first 30 days of treatment in patients who were not dispensed an antidepressant in the prior 180 days across all of the antidepressants studied. Past antidepressant use, rather than the receipt of a specific medication, was associated with medication adherence. Given that mean rate of medication discontinuation was elevated in patients who had not been dispensed an antidepressant in the previous 180 days, irrespective of the specific antidepressant prescribed, such patients might merit increased follow-up and education at the onset of therapy.

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Dr. Vanelli owns stock in Adheris, Inc.; has served as a consultant or member of the speakers' bureaus at AstraZeneca Pharmaceuticals LP, Wilmington, Delaware; Eli Lilly and Company, Indianapolis, Indiana; Schwarz Pharma AG, Monheim, Germany; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; and Janssen Pharmaceutica, Titusville, New Jersey; and has received grant support from Abbott Laboratories, Abbott Park, Illinois. Mr. Coca-Perraillon owns stock in Adheris, Inc.

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