RESEARCH

Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans

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ABSTRACT

BACKGROUND: Generic antidepressants offer significant prescription drug cost savings compared with brand-name antidepressants, but critics of managed care interventions promoting generic medication use suggest that some generic antidepressants are not as safe or effective as the brand alternatives.

OBJECTIVE: To assess (a) rates of discontinuation of the initially dispensed medication and (b) disease-specific and total health care costs and pharmacy costs, comparing patients who initiated therapy with brand versus generic selective serotonin reuptake inhibitors (SSRI) or selective norepinephrine reuptake inhibitors (SNRI).

METHODS: Antidepressant users aged 18 to 64 years with no pharmacy claims for an SSRI/SNRI in the 180 days prior to the start of SSRI/SNRI therapy (baseline) were identified in the MarketScan database between July 1, 2005, and June 30, 2007, and were followed for 180 days (follow-up). All study patients met the following criteria: (a) continuously eligible from baseline through follow-up; (b) at least 1 medical claim with a primary or secondary diagnosis of major depressive disorder (ICD-9-CM codes 296.2 or 296.3) in either the baseline or follow-up period; and (c) no pharmacy claims for antipsychotic medications in the baseline period. For brand versus generic antidepressant initiators, logistic regression was used to determine the odds of 6-month therapy discontinuation, defined as no medication refills or absence of a refill for the initially dispensed medication within 1.5 times the days supply dispensed, adjusted for important covariates. Costs were measured as total plan allowed charges including member cost share. Adjusted mean (least squares means holding covariates at mean values) all-cause medical costs, disease-specific (claims with a ICD-9-CM diagnosis code for major depressive disorder in the primary or secondary diagnosis field) medical costs, all-cause pharmacy costs, and SSRI/SNRI antidepressant costs were compared for brand versus generic initiators using generalized linear regression models, also adjusted for baseline covariates.

RESULTS: Of 16,659 new SSRI/SNRI users, 47.8% (n = 7,955) initiated a brand-name medication and 52.2% (n = 8,704) initiated a generic product. Of the 7,955 who initiated a brand-name antidepressant, 46.8% (n = 3,723) discontinued the initially dispensed drug within 180 days, compared with 44.2% (n = 3,843) of the 8,704 who initiated a generic. The adjusted odds of discontinuation among generic and brand drug users did not significantly differ (odds ratio [OR] = 1.09, 95% CI = 0.98-1.22). Adjusted all-cause 6-month average health care costs in patients initiating therapy on a generic antidepressant were $3,660 (95% CI = $3,538-$3,787) compared with $4,587 (95% CI = $4,422-$4,757) for patients initiating on a brand-name antidepressant. Adjusted average 6-month SSRI/SNRI antidepressant costs were 43.7% lower in patients initiating on a generic drug ($174 vs. $309).

CONCLUSIONS: The likelihood of discontinuation was similar for patients who initiated therapy with brand or generic antidepressants, and short-term health care costs and pharmacy costs were lower in patients starting a generic SSRI/SNRI. The results suggest that the use of generic antidepressants as first-line agents in the treatment of major depressive disorder is associated with continuation rates similar to initiation with brand antidepressants but with lower health care costs.

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What is already known about this subject

- Evidence suggests that generic selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) provide cost savings over brand-name medications. An observational study by Dunn et al. showed that a step-therapy edit requiring patients to use a generic antidepressant prior to use of a brand-name medication resulted in drug cost savings of $1,880,562 ($0.36 per member per month) in 2005 dollars in the first year of implementation of the program, but the authors did not look at the impact on health outcomes or medical costs.
- Despite evidence of cost savings, some case reports and bioequivalence studies suggest a disadvantage in efficacy and tolerability of generic medications compared with brand-name equivalents. Further, observational reports have provided mixed evidence of safety and efficacy among brand and generic SSRIs and SNRIs. These studies are of varying quality, adding lack of clarity to the debate.

What this study adds

- Comparing patients initiating antidepressant therapy with a brand versus generic medication, there was no significant difference in the likelihood of discontinuation of the initially dispensed medication during the first 180 days of SSRI or SNRI therapy. Health care costs were lower among patients starting a generic SSRI/SNRI, even after adjustment for measurable factors that may affect costs, such as age and comorbidity.
- The discontinuation rate within 180 days of initiating antidepressant drug therapy among patients starting on a generic medication was 44.2%, compared with 46.8% among patients initiating therapy on a brand medication ($P = 0.006$). However, the adjusted odds of discontinuation among generic users did not significantly differ from those of brand drug users (OR = 1.09, 95% CI = 0.98-1.22).

What this study adds *(continued)*

- Total adjusted average 6-month health care costs in patients initiating therapy on a generic drug were $3,660 (95% CI = $3,538-$3,787), 20% less than the average $4,587 (95% CI = $4,422-$4,757) for patients initiating on a brand-name drug ($P < 0.001$). Average SSRI/SNRI antidepressant costs in patients initiating therapy on a generic drug were $174 (95% CI = $169-$180), 44% less than the average $309 (95% CI = $300-$319) for patients initiating on a brand-name medication ($P < 0.001$).

Brand-name selective serotonin reuptake inhibitors (SSRIs), such as Lexapro (escitalopram; Forest Laboratories) and Paxil CR (paroxetine controlled release; GlaxoSmithKline), and brand-name SNRIs, such as Cymbalta (duloxetine HCl; Lilly), are often prescribed as first-line medications by physicians for the treatment of some mental health disorders, such as major depressive disorder. Decisions to prescribe brand-name medications rather than generic therapeutic equivalents may be made on the basis of perceived clinical effectiveness or tolerability[1] but also may be influenced by the marketing efforts of pharmaceutical companies.[2,3] However, there is mixed evidence of treatment continuity and cost-effectiveness when comparing brand and generic antidepressant therapies.

Multiple meta-analyses of randomized controlled trials have found that treatment of adults with major depressive disorder with second-generation antidepressants is generally efficacious and safe, with more recent evidence suggesting greater efficacy for sertraline compared with other second-generation drugs.[4-8] A 2009 multiple-treatments meta-analysis of 12 new-generation antidepressants, which included both single-source brand and generically available agents, concluded that clinically meaningful differences in efficacy and tolerance among the medications favored escitalopram and sertraline; the authors noted that sertraline had the most favorable balance between costs, benefits, and acceptability among patients.[8] Nonetheless, a comparative effectiveness review sponsored by the Agency for Healthcare Research and Quality cautioned that such studies were not intended to test variation in individual responses to individual drugs,[4] and case reports of symptom relapse following generic substitution have emerged in the literature.[9,10] Investigations by the U.S. Food and Drug Administration into reports of this type, comparing brand versus generic buproprion, found minor differences in pharmacokinetics that did not fall outside of accepted boundaries for bioequivalence.[11] A *Carlat Psychiatry Report* on the issue (2009) noted that the preponderance of evidence suggesting that generic drug substitutions result in failure was found in "single cases or very small case series, virtually all written by authors who are also paid consultants for pharmaceutical companies."[12] Still, concerns about generic substitution of antidepressants have persisted.[13] Observational comparisons and bioequivalence studies of patients treated with brand versus generic second-generation antidepressants have produced mixed findings.[13-15]

As part of containing the rising cost of health care in general, and prescription medications specifically, managed care organizations, employer groups, and other plan sponsors are increasingly adopting intervention programs that are designed to encourage efficient use of pharmaceuticals, including step therapy. Step-therapy programs work by requiring that patients attempt the use of first-line medications prior to receiving pharmacy benefit coverage for other prescription drugs in the same therapy class.[16] The first-line medications are often lower-cost generic drugs that can offer the same health benefits as the more expensive brand-name drugs originally prescribed by physicians. Because the value of the brand-name SSRIs/SNRIs has not been unequivocally demonstrated, generic antidepressants may offer cost savings without an increase in adverse health outcomes, as is intended in step-therapy programs.

Studies have examined the impact of obligatory generic antidepressant step-therapy programs on pharmacy costs and utilization[17] or have estimated the economic impact of cost control programs among patients with a single diagnosis,[18] but no published research identified through a Medline search has evaluated multiple outcomes associated with the initial prescription of different generic SSRIs or SNRIs compared with brand medications in patients with major depressive disorder. Although the outcomes of a utilization management program requiring first-line use of a generic medication were not directly measured, the purpose of this study was to answer questions about potential treatment failure by assessing discontinuation rates and health care costs, comparing patients who initiated therapy with a generic versus a brand-name SSRI or SNRI. The study was conducted by a pharmacy benefits management (PBM) company.

Methods

Study Cohort and Data Source

A cohort study design was used to compare discontinuation rates and health care utilization costs among patients using brand versus generic SSRI or SNRI antidepressant therapy. Data from the MarketScan Commercial Claims and Encounters dataset (Thomson Reuters, New York, NY) for the period of January 1, 2005, to December 31, 2007, were used. These data include commercial (e.g., not Medicare or Medicaid) health insurance claims (inpatient and outpatient medical, and outpatient pharmacy) as well as enrollment data from large employers and health plans across the United States that provide private health care coverage for more than 45 million employees, their spouses, and dependents, all of whom are younger than age 65 years. This administrative

claims database includes a variety of fee-for-service, preferred provider organization, and capitated health plans.

Inclusion criteria required that the patient: (a) had a pharmacy claim for an SSRI or SNRI during an identification period from July 1, 2005, through June 30, 2007, identified by mapping National Drug Code (NDC) numbers provided in the MarketScan dataset to generic product identifier (GPI, Medi-Span, Inc., Indianapolis, IN) codes beginning with 5816 or 5818; (b) was a new user of an SSRI or SNRI, defined as the absence of a pharmacy claim for an SSRI or SNRI in the 180 days prior to the date of the first observed SSRI/SNRI claim in the identification period (index date); (c) did not have pharmacy claims for antipsychotic medications (GPI codes beginning with 59) in the 180 days prior to the index SSRI/SNRI claim; (d) was aged 18 years or older as of the index pharmacy claim date; (e) was continuously enrolled in a prescription drug benefit plan for 180 days prior to the index pharmacy claim and 180 days after the index pharmacy claim; (f) did not have claims with a negative days supply, duplicate claims, or reversed claims with negative cost values in the 180 days prior to or after the index pharmacy claim; and (g) had at least 1 claim with a primary or secondary diagnosis of single-episode or recurrent major depressive disorder as indicated by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 296.2 and 296.3 in the 180 days prior to or after the index pharmacy claim, as these are patients who may require longer term therapy.[19] Brand versus generic status for each SSRI/SNRI pharmacy claim was determined by mapping the NDC number in the MarketScan file to an internal PBM file that indicated brand or generic status.

Exposure and Covariates

The exposure of interest was the occurrence of a new pharmacy claim for a generic SSRI or SNRI. Pharmacy and medical claims were evaluated for the 6-month time periods before (baseline) and after (follow-up) the index date. Exposure could occur at any point on or after July 1, 2005.

Patient age category (in years: 18 to 25, 26 to 40, 41 to 55, 56 to 64) as of the date of the index pharmacy claim was included as a potential covariate because age may be associated with antidepressant treatment outcomes.[20,21] Gender may also place patients at increased risk for developing certain types of psychiatric disorders such as depression,[22] and differences in adverse effects and time-to-response to different therapies have been reported between male and female antidepressant users.[23,24] Based upon the apparent differences in response to therapy, gender was also included as a potential confounder, with female gender as the reference group.

The risk for therapy discontinuation may also increase with some comorbidities.[25] A Charlson Comorbidity Index (CCI) score based on the 180 days prior to and after the index pharmacy claim (baseline and follow-up) was calculated for all members of the sample. The CCI is a validated measure of the burden of chronic illnesses that has been adapted for use with ICD-9-CM codes found in administrative claims data over a 12-month period.[26] The CCI was included as a potential confounder and measured as a categorical variable (scores of 0, 1 to 2, 3 to 5, and 6 or more). In addition, the medical costs incurred by patients with some mental health illnesses can be an indication of symptom severity.[27] The summed all-cause medical costs (total plan allowed amounts for outpatient and inpatient hospital and for physician services, not including pharmacy costs) incurred by patients in the baseline period were also measured, and analyzed as a categorical variable based on quartiles ($1-$178, $179-$657, $658-$2,402, and $2,403 or more).

Depression has been successfully managed in the primary care setting,[28] but therapy discontinuation may be more likely among patients who are receiving specialized psychiatric care, such as psychotherapy.[29] Thus, receipt of inpatient or outpatient psychiatric medical care, indicated by Current Procedural Terminology (CPT) codes 90801-90829 (psychiatric interviews and psychotherapy) and 90862-90899 (other psychiatric services or procedures, such as pharmacologic management, electroconvulsive therapy, and hypnotherapy) in the baseline period, was examined as a potential confounder. Recent evidence also suggests that some SSRIs may be associated with an increased risk of bleeding,[30] which could theoretically suggest that patients beginning anticoagulant therapy may be more likely to discontinue therapy. A binary variable indicating a pharmacy claim for an anticoagulant (GPI codes beginning 8310 [heparins], 8320 [coumarin anticoagulants, including warfarin], or 8333 [thrombin inhibitors]) in the baseline period was also measured.

Finally, primary or secondary diagnosis of a comorbid mood disorder during either the baseline or follow-up period, including anxiety state (ICD-9-CM codes 300.0x), bipolar disorder (ICD-9-CM codes 296.0, 296.4, 296.5, 296.6, 296.7, 296.8) or obsessive compulsive disorder (ICD-9-CM codes 300.3, 301.4) was also assessed. Each comorbid mood disorder was measured as a separate binary variable. Both time periods were included because diagnosis prior to the initiation of an SSRI or SNRI may have affected which medication was prescribed, and diagnosis after the initiation of therapy may have affected the decision to discontinue or augment therapy.

Outcomes

Two primary outcomes were measured during the follow-up period: discontinuation of the initial GPI-10 coded medication, including its brand or generic status, and health care costs. During the 180 days after initiation of therapy, patients could discontinue the initially dispensed therapy (i.e., either switch to a different antidepressant drug or terminate antidepressant therapy altogether) or continue on the index

medication. A 6-month follow-up time period was chosen for this study, which is consistent with the National Committee for Quality Assurance recommendations for effective management of major depressive disorder treated with an antidepressant medication.[31] A discontinuation date was considered as the date of the last pharmacy claim for the initial medication plus the days supply dispensed for the last pharmacy claim, and a study completion date was defined as the index pharmacy claim date plus 180 days. Patients were considered to have discontinued therapy if the index pharmacy claim was not refilled within 1.5 times the days supply dispensed (e.g., 45 days on a 30 day supply, 135 days on a 90 day supply).[32] A switch from the initial medication to another medication with a different GPI-10 was considered a discontinuation, as was a switch between the brand and generic formulations of the same medication. Medication switches were counted as discontinuations to measure change to the initially prescribed medication, addressing the concern that the initial prescription of a generic medication is associated with greater proportions of patients who discontinue or otherwise fail therapy. Once a patient was defined as discontinued, re-initiation of the index medication was not considered.

Total health care costs included the plan allowed charges, including member cost share, for all inpatient and outpatient medical services claims and for all outpatient pharmacy claims in the 180-day follow-up period. Costs were further categorized as disease-specific (charges incurred for medical claims with an associated primary or secondary diagnosis of major depressive disorder as indicated by ICD-9-CM codes or pharmacy claims for any SSRI or SNRI) and all-cause (charges incurred for any claims—not dependent on ICD-9-CM diagnosis codes or therapeutic classes).

Older antidepressants, such as tricyclic antidepressants, are still used alone and in conjunction with newer SSRIs and SNRIs because some patients respond differently to different mechanisms of action.[33] As response or nonresponse to other antidepressants may affect continuation of SSRIs or SNRIs, and as failure to respond to SSRIs or SNRIs may be reflected by new treatment with an older antidepressant, augmentation of therapy with a non-SSRI/SNRI antidepressant (GPI codes beginning 5812 [modified cyclics, including nefazadone and trazadone], 5820 [tricyclic antidepressants], and 5830 [miscellaneous antidepressants, including buproprion) in the 180-day period after the index pharmacy claim was also considered as a secondary outcome.

Statistical Analysis

Each variable that could potentially affect the relationship between the exposure and discontinuation was entered into a logistic regression model. Variables with a *P* value of less than 0.1 in bivariate screening were entered into full models, and variables with a *P* value of less than 0.05 were retained in the final model. The variables used in specifying the logistic regression model included patient age category, gender, CCI category, baseline medical cost category, receipt of psychiatric medical care in the baseline period, indication of anticoagulant therapy in the baseline period, indication of a comorbid mood disorder diagnosis in either the baseline or follow-up period, and an indicator of which SSRI or SNRI was initially prescribed.

To assess the impact of augmentation of SSRI/SNRI therapy with a non-SSRI/SNRI antidepressant after initiation of therapy, a stratified analysis compared the relationship between the initial exposure to a generic or brand SSRI/SNRI and therapy discontinuation in a subsample of patients who filled a prescription for a non-SSRI/SNRI antidepressant in the follow-up period versus a subsample of patients who did not. The odds ratios of the final logistic regression models were compared in the subsamples.

Generalized linear models (GLM) were constructed to measure the relationship between exposure status and health care costs. Models were specified with a gamma distribution and log link function to satisfy the assumptions of homoskedasticity and a normal distribution.[34] The summed all-cause total health care costs, disease-specific total health care costs, all-cause pharmacy costs, and SSRI or SNRI antidepressant costs measured in the follow-up period were each evaluated. The associations of health care costs and pharmacy costs with generic drug status were assessed, controlling for covariate effects with a *P* value of less than 0.1 in bivariate screening. Variables with a *P* value of less than 0.05 were retained in the final models.

Least squares mean costs holding covariates at their mean values were calculated for patients initiating brand-name versus generic medications. For each least squares mean, t-type 95% confidence intervals (CIs) were constructed using the SAS (SAS Institute Inc., Carey, NC) LSMEANS option in the GENMOD procedure. All variables were checked for missing data. Statistical analyses were performed using SAS version 9.2. The a priori alpha value was 0.05.

Results

There were 2,545,696 individual patients identified with a pharmacy claim for an SSRI or SNRI between July 1, 2005, and June 30, 2007 (Figure 1). From this sample, 951,605 were excluded because they were not new to SSRI/SNRI therapy; 148,600 were excluded because they had a pharmacy claim for an antipsychotic in the baseline period; 74,237 were excluded because they were younger than 18 years old; 742,271 were excluded for lack of continuous enrollment in the 180 days prior to and after the index pharmacy claim; 35,524 were excluded because of negative days supply of the index medication, single claims being counted multiple times, or negative cost values; and 576,800 were excluded because they did not have a primary diagnosis of major depressive disorder,

leaving 16,659 patients in the final sample. The decline in sample size resulting from excluding patients without a depression diagnosis has occurred in other observational studies using administrative claims databases.[15] There were no missing data in the analytic sample.

Therapy Discontinuation

The demographic and clinical characteristics of the patients were stratified by whether or not they discontinued therapy (Table 1). Within 180 days of initiating therapy on a brand or generic SSRI/SNRI, 7,566 patients (45.4%) discontinued the initially dispensed therapy. Of these, 2,916 (38.5% of those discontinuing, 17.5% of the sample overall) did not refill the initial prescription and 2,423 (32.0% of those discontinuing, 14.5% of the sample overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy, the mean (median) time until discontinuation was 50.8 (30) days (range 1 to 158 days); 68.8% of patients who discontinued did so in the first 60 days of therapy; and 84.0% discontinued within the first 90 days after initiating therapy (data not shown).

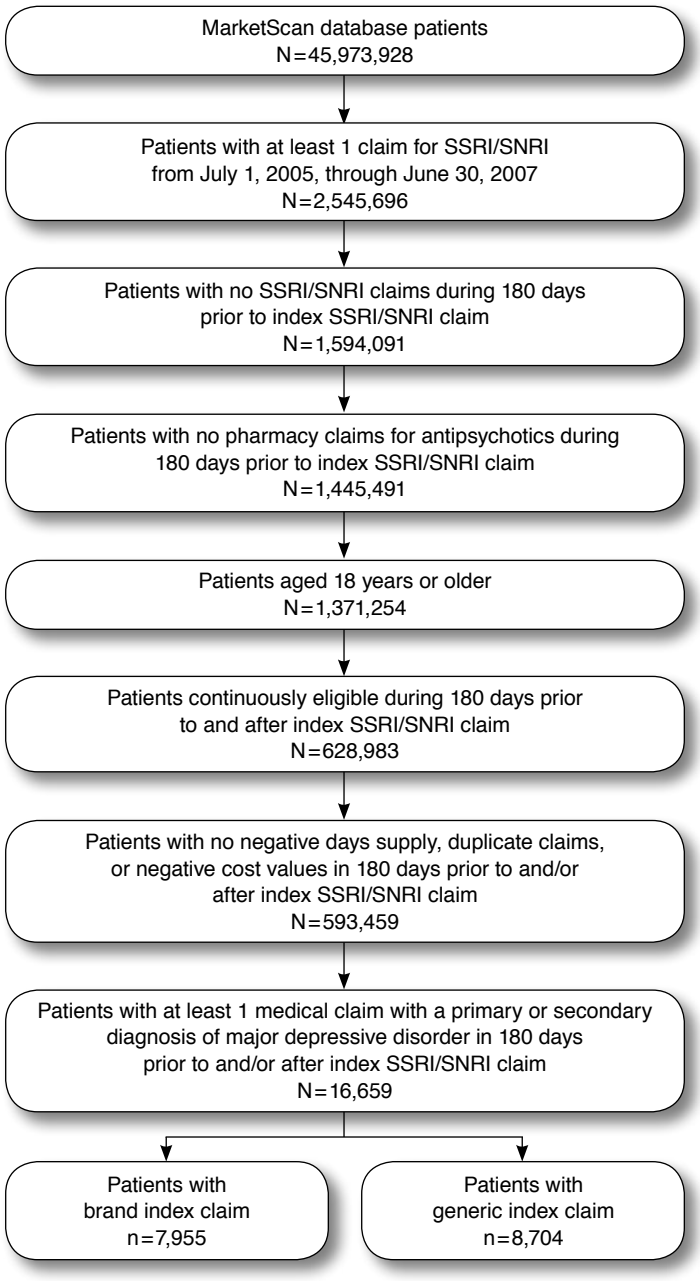
Of 8,704 patients who started treatment with a generic SSRI/SNRI, 3,843 (44.2%) discontinued the initially dispensed therapy during follow-up. Of those, 1,509 (39.3% of those discontinuing, 17.3% of generic users overall) did not refill their initial prescription, and 1,199 (31.2% of those discontinuing, 13.8% of generic users overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy after initiating therapy with a generic SSRI or SNRI, the mean (median) time until discontinuation was 51.2 (30) days (range 1 to 157 days); 68.0% of patients who discontinued did so in the first 60 days after the index pharmacy claim, and 84.4% discontinued therapy within the first 90 days (data not shown).

Of 7,955 patients who initiated treatment with a brand SSRI/SNRI, 3,723 (46.8%) discontinued the initially dispensed therapy during follow-up. Of those, 1,407 (37.8% of those discontinuing, 17.7% of brand users overall) did not refill the initial prescription and 1,224 (32.9% of those discontinuing, 15.4% of brand users overall) switched to a different antidepressant medication (data not shown). Among patients who discontinued therapy after initiating therapy with a branded medication, the mean (median) time until discontinuation was 50.3 (30) days (range 1 to 158 days); 69.9% of patients who discontinued did so in the first 60 days after the index pharmacy claim; and 83.7% discontinued therapy within the first 90 days (data not shown).

Patients who discontinued therapy were slightly younger on average than patients who did not discontinue (mean ages 39.3 years vs. 41.9 years, respectively, $P < 0.001$) and were more likely to have comorbid mood disorder diagnoses during the study period. Use of escitalopram or paroxetine HCl was more common among patients who discontinued therapy compared with those who did not discontinue (23.2% vs. 20.6%, respectively, and 11.2% vs. 7.9%, respectively, both $P < 0.001$).

Patients who initiated therapy on a generic SSRI/SNRI had similar odds of discontinuing the initially dispensed drug in the first 180 days of therapy compared with patients who initiated

FIGURE 1 Patient Selection Flowchart



SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

TABLE 1 *Profiles of 16,659 New SSRI/SNRI Users in the First 180 Days After Initiating Antidepressant Therapy in the 2005-2007 MarketScan Database*

	Continued Initially Dispensed Therapy n (%)	Discontinued Initially Dispensed Therapy n (%)	*P* Value[a]	Unadjusted Odds Ratio (95% CI)
	9,093 (54.6)	**7,566 (45.4)**		
Exposure				
Brand index pharmacy claim	4,232 (46.5)	3,723 (49.2)		Referent Category
Generic index pharmacy claim	4,861 (53.5)	3,843 (50.8)	0.006	0.90 (0.85-0.96)
Gender				
Female	6,005 (66.0)	4,880 (64.5)		Referent Category
Male	3,088 (34.0)	2,686 (35.5)	0.038	1.07 (1.00-1.14)
Age in years				
18 to 25	1,023 (11.3)	1,248 (16.5)		Referent Category
26 to 40	2,947 (32.4)	2,773 (36.7)		0.77 (0.70-0.85)
41 to 55	3,822 (42.0)	2,770 (36.6)		0.59 (0.54-0.65)
56 to 64	1,301 (14.3)	775 (10.2)	<0.001	0.49 (0.43-0.55)
Charlson Comorbidity Index[b]				
0	7,233 (79.5)	6,011 (79.4)		Referent Category
1 to 2	1,601 (17.6)	1,334 (17.6)		1.00 (0.93-1.08)
3 to 5	179 (2.0)	171 (2.3)		1.15 (0.93-1.42)
6 or more	80 (0.9)	50 (0.7)	0.239	0.75 (0.53-1.07)
Medical costs in U.S. dollars[c]				
$1-$178	2,239 (24.6)	1,928 (25.5)		Referent Category
$179-$657	2,316 (25.5)	1,849 (24.4)		0.93 (0.85-1.01)
$658-$2,402	2,336 (25.7)	1,826 (24.1)		0.91 (0.83-0.99)
$2,403 or more	2,202 (24.2)	1,963 (25.9)	0.008	1.04 (0.95-1.13)
Comorbid mood disorder				
Anxiety disorder[b]	1,303 (14.3)	1,230 (16.3)	0.001	1.09 (1.00-1.19)
Bipolar disorder[b]	69 (0.8)	112 (1.5)	<0.001	1.77 (1.29-2.42)
Obsessive-compulsive disorder[b]	57 (0.6)	50 (0.7)	0.785	0.85 (0.58-1.25)
Medical care				
Psychiatric medical care[c]	6,303 (69.3)	5,383 (71.1)	0.010	1.04 (0.97-1.10)
Anticoagulant use[c]	89 (1.0)	65 (0.9)	0.422	0.99 (0.72-1.37)
Specific SSRI/SNRI drug				
Fluoxetine[d]	1,964 (21.6)	1,317 (17.4)	<0.001	Referent Category
Citalopram[d]	1,459 (16.0)	1,104 (14.6)	0.010	0.89 (0.82-0.97)
Escitalopram[e]	1,873 (20.6)	1,756 (23.2)	<0.001	1.17 (1.08-1.25)
Fluvoxamine[d]	19 (0.2)	20 (0.3)	0.461	1.27 (0.68-2.38)
Paroxetine HCl[d]	721 (7.9)	844 (11.2)	<0.001	1.46 (1.31-1.62)
Paroxetine mesylate[e]	8 (0.1)	9 (0.1)	0.533	1.36 (0.52-3.51)
Sertraline[d]	1,829 (20.1)	1,493 (19.7)	0.594	0.98 (0.91-1.05)
Duloxetine[e]	541 (5.9)	473 (6.3)	0.417	1.05 (0.93-1.20)
Venlafaxine[d]	679 (7.5)	550 (7.3)	0.627	0.97 (0.86-1.09)

[a]*For categorical variables, P values were derived from Pearson chi-square tests. All tests compared patients who did versus those who did not discontinue therapy.*
[b]*Measured during a 12-month period including both the 180-day baseline and follow-up periods.*
[c]*Measured in the 180-day baseline period.*
[d]*Available in branded and generic formulations at given points between January 1, 2005, and December 31, 2007.*
[e]*Available only in a branded formulation between January 1, 2005, and December 31, 2007.*
CI = confidence interval; HCl = hydrochloride; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

therapy on a branded alternative (odds ratio [OR] = 1.09, 95% CI = 0.98-1.22; Table 2). Variables in the final model included generic status of the index pharmacy claim; age; gender; indicators for psychiatric medical treatment, comorbid anxiety disorder, and bipolar disorder; and specific SSRI/SNRI drug. In the analyses stratified by augmentation (i.e., in 2 subsample groups of patients who augmented therapy with a non-SSRI/SNRI antidepressant during follow-up vs. those who did not), patients who initiated therapy on a generic SSRI/SNRI were no more likely to discontinue therapy than patients who started a branded

TABLE 2 *Logistic Regression Analysis of Discontinuing the Initially Dispensed Antidepressant Therapy in 16,659 New SSRI/SNRI Users in the First 180 Days After Initiating Therapy in 2005-2007*[a]

	Adjusted Odds Ratio (95% CI) All Patients (C = 0.582)	Adjusted Odds Ratio[a] (95% CI) New Non-SSRI/SNRI (C = 0.638)	Adjusted Odds Ratio[a] (95% CI) No New Non-SSRI/SNRI (C = 0.579)
Brand index pharmacy claim	Referent category	Referent category	Referent category
Generic index pharmacy claim	1.09 (0.98-1.22)	1.45 (0.89-2.34)	1.08 (0.96-1.21)
Male	1.08 (1.01-1.15)	1.16 (0.89-1.51)	1.07 (1.00-1.15)
Aged 18 to 25 years	Referent category	Referent category	Referent category
Aged 26 to 40 years	0.76 (0.69-0.84)	1.00 (0.69-1.45)	0.75 (0.67-0.83)
Aged 41 to 55 years	0.58 (0.53-0.64)	0.63 (0.44-0.90)	0.58 (0.52-0.64)
Aged 56 to 64 years	0.47 (0.42-0.53)	0.44 (0.26-0.75)	0.47 (0.42-0.54)
Anxiety disorder[b]	1.10 (1.01-1.20)	1.22 (0.88-1.69)	1.09 (0.99-1.19)
Bipolar disorder[b]	1.80 (1.33-2.45)	3.33 (0.94-11.73)	1.67 (1.22-2.30)
Medical costs $1-$178[b]	Referent category	Referent category	Referent category
Medical costs $179-$657[b]	0.94 (0.87-1.03)	0.82 (0.57-1.17)	0.95 (0.87-1.04)
Medical costs $658-$2,402[b]	0.95 (0.87-1.04)	0.70 (0.49-1.00)	0.97 (0.88-1.06)
Medical costs $2,403 or more[b]	1.09 (0.99-1.19)	0.83 (0.58-1.20)	1.10 (1.01-1.21)
Psychiatric medical care[b]	1.06 (0.99-1.14)	0.92 (0.68-1.25)	1.06 (0.99-1.14)
Fluoxetine	Referent category	Referent category	Referent category
Citalopram	1.13 (1.01-1.25)	1.48 (1.00-2.20)	1.10 (0.99-1.23)
Escitalopram	1.50 (1.29-1.74)	3.57 (1.93-6.61)	1.42 (1.22-1.66)
Fluvoxamine	1.45 (0.77-2.75)	NA	1.31 (0.68-2.53)
Paroxetine HCl	1.79 (1.57-2.03)	2.67 (1.63-4.39)	1.74 (1.53-1.98)
Paroxetine mesylate	1.82 (0.69-4.79)	NA	1.40 (0.50-3.92)
Sertraline	1.24 (1.11-1.39)	2.52 (1.59-4.02)	1.19 (1.06-1.33)
Duloxetine	1.48 (1.24-1.78)	2.36 (1.11-5.04)	1.44 (1.19-1.73)
Venlafaxine	1.32 (1.11-1.57)	2.70 (1.34-5.46)	1.26 (1.05-1.50)

[a]*MarketScan database; results stratified by whether patients initiated therapy on a non-SSRI/SNRI during the 180-day follow-up period.*

[b]*Comorbid anxiety disorder or bipolar disorder diagnosis measured in the 180-day baseline and follow-up periods; medical costs measured in the 180-day baseline period; psychiatric medical care measured in the 180-day baseline period.*

C = c-statistic (area under receiver operating characteristics curve); CI = confidence interval; HCl = hydrochloride; NA = not applicable; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

medication (Table 2). This finding suggests that while important, augmentation with a non SSRI/SNRI antidepressant does not affect the relationship between the generic status of the index pharmacy claim and discontinuation of therapy.

Health Care Costs

After adjustment for other factors associated with health care costs in patients with major depressive disorder, patients who initiated therapy on a generic drug had lower health care costs during the first 180 days after the index SSRI/SNRI prescription compared with brand drug users (Table 3). The adjusted average total health care costs (least squares mean costs) in the first 180 days after the index pharmacy claim among patients who initiated therapy on a generic SSRI/SNRI were $3,660 (95% CI = $3,538-$3,787) versus $4,587 (95% CI = $4,422-$4,757) among patients who initiated therapy on a brand medication. Least squares mean disease-specific health care costs were also lower in patients who initiated therapy on a generic medication compared to a brand medication ($803, 95% CI = $771-$836 vs. $1,125, 95% CI = $1,077-$1,175). All-cause pharmacy costs and SSRI or SNRI antidepressant pharmacy costs each were significantly lower among patients who initiated therapy with a generic medication compared with patients who initiated therapy with a brand medication ($761, 95% CI = $738-$785 vs. $965, 95% CI = $934-$998, respectively, for all-cause pharmacy costs; $174, 95% CI = $169-$180 vs. $309, 95% CI = $300-$319, respectively, for SSRI or SNRI antidepressant pharmacy costs).

Discussion

The principal objective of this study was to determine if there were differences in discontinuation rates and health care costs between patients who initiated antidepressant therapy on a generic SSRI or SNRI compared with patients who initiated therapy on a brand-name SSRI or SNRI medication. The adjusted comparison suggested there was no significant difference in the likelihood of discontinuation during the first 180 days of therapy, and the analysis of health care costs indicated

TABLE 3 Adjusted Least Squares Mean All-Cause and Disease-Specific Health Care Costs in 16,659 New SSRI/SNRI Users in the First 180 Days After Initiating Antidepressant Therapy in the 2005-2007 MarketScan Database

	Adjusted Least Squares Mean All-Cause Health Care Costs[a] (95% CI)	Adjusted Least Squares Mean Disease-Specific Health Care Costs[b] (95% CI)	Adjusted Least Squares Mean All-Cause Pharmacy Costs[c] (95% CI)	Adjusted Least Squares Mean SSRI/SNRI Antidepressant Pharmacy Costs[d] (95% CI)
Brand index pharmacy claim	$4,587 ($4,422-$4,757)	$1,125 ($1,077-$1,175)	$965 ($934-$998)	$309 ($300-$319)
Generic index pharmacy claim	$3,660 ($3,538-$3,787)	$803 ($771-$836)	$761 ($738-$785)	$174 ($169-$180)

[a]*Adjusted for age; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder or bipolar disorder in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.*

[b]*Adjusted for age; gender; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder, obsessive-compulsive disorder, or bipolar disorder diagnosis in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.*

[c]*Adjusted for age; Charlson Comorbidity Index score measured in the 180-day baseline and follow-up periods; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder or bipolar disorder diagnosis in the 180-day baseline and/or follow-up periods; psychiatric medical care in the 180-day baseline period; prescription claim for an anticoagulant in the 180-day baseline period; and specific drug*

[d]*Adjusted for age; gender; medical costs incurred in the 180-day baseline period; comorbid anxiety disorder, bipolar disorder or obsessive-compulsive disorder diagnosis in the 180-day baseline and follow-up periods; psychiatric medical care in the 180-day baseline period; and specific drug.*

CI = confidence interval; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

that costs were lower among patients starting a generic SSRI/SNRI compared with patients starting a brand drug, even after adjustment for other factors that may affect those costs.

Recent proposed legislation in at least 1 state (Missouri) has called for a limitation on pharmacy utilization management programs—such as step therapy—which promote the use of generic medications as first-line therapy.[35] Although the explicit occurrence of a step-therapy edit at the point of service was not measured in the present study, most of the sample patients could have been prescribed generic antidepressants, even though some patients were prescribed brand-name drugs, as almost all of the SSRIs had generic alternatives during the study period.[36] One report estimated that in 2005, 80% of antidepressant pharmacy claims could have been filled with generic drugs; however, the generic dispensing ratio in that year was only 50%.[37] The present study provided an approximation of the conditions in which step-therapy programs are commonly applied to promote increased use of generic medications. The findings provide evidence that first-line use of generic SSRIs or SNRIs in the treatment of major depressive disorder is not associated with a greater likelihood of discontinuation and may contribute to lower total health care costs, most likely by lowering the cost of drug therapy. The initiation of antidepressant therapy with a generic SSRI or SNRI could reduce the pharmacy costs for health care payers by almost 50% in some cases, without leading to treatment failure or increased medical costs in the short term. The study findings, therefore, have specific implications for cost management strategies like step therapy, and are important for health care payers who have an investment in patient health.

Limitations

This study has several limitations. First, because of its observational design, the study demonstrates associations but does not establish causality. As in any observational research, the study analyses could control only for measured confounders, not for all factors potentially affecting the study outcomes. In particular, the study may have been confounded by the failure to adequately control for disease severity. Information about previous treatment or duration of disease outside of the 180 days prior to treatment initiation is not included in the MarketScan database, and no tests of mental health disease severity are captured in the database. Medical service utilization and the likelihood of discontinuing therapy may be related to disease severity or the presence of treatment-resistant disease. Adjustments in regression models for factors that may be related to disease severity, such as whether the patient received psychiatric medical care, and stratification by other factors that may be related to disease severity, such as therapeutic augmentation with other non-SSRI/SNRI antidepressants, were used to mitigate the potential impact of disease severity.

Second, drug-specific side-effect profiles were another potential confounder. Side effects are potentially influential in a patient's decision to discontinue therapy, and may differentially disadvantage some drugs. Adjustment in regression models for the specific SSRI or SNRI medication potentially controlled for the impact of differential side effects on the risk of discontinuation and health care costs.

Third, the study results may be limited in generalizability because MarketScan data are restricted to populations of commercially insured beneficiaries less than 65 years old. It has been previously shown that depression and anxiety disorders

commonly affect elderly patients,[38] and that prescription drugs may differentially affect these patients.[21] In addition, patient location or access to a provider of mental health care are not available in the MarketScan data. The population may be restricted to those who have adequate geographic access to a provider of mental health care, and may not be generalizable to patients in all geographic locations.

Fourth, it is also possible that some patients taking a generic drug who appeared to have discontinued therapy actually began using a deeply discounted or low-cost generic program offered at local grocery stores and supermarkets during the study period.[39] This problem potentially overestimated the discontinuation rate among patients who initiated therapy on a generic medication. In addition, patients who were receiving samples of brand medications or patients who had been treated for previous episodes of major depressive disorder prior to the initial pharmacy claim or baseline period may not have been new users at the time of their initial pharmacy claim. New users were defined as patients without a pharmacy claim for an SSRI/SNRI in the 180 days prior to the index medication. Both the use of samples of brand medications and recurrences of previously treated depression have the potential to (a) underestimate true discontinuation among patients who had already experienced intolerance or lack of effect and (b) prevent discontinuation among patients who had already found the medication to be tolerable or effective. However, information about brand samples or previous history of SSRI/SNRI use prior to the study period was not available in the administrative claims data used for this study.

Fifth, our definition of therapy discontinuation did not differentiate patients who discontinued medication from patients who switched therapies. As the study objective was to evaluate the impact of the generic or brand status of the initial pharmacy claim only, which would most closely simulate the practice of a cost control program such as step therapy, any switches between SSRIs or SNRIs were intentionally labeled as discontinuations. Patients who switched therapy rather than refilling prescriptions for the index medication may have appeared to be discontinuing therapy entirely. This definition may have included patients who switched between the brand and generic formulations of the same medication. This decision represents a limitation especially for patients who initiated therapy on the branded formulation of sertraline because a generic version was made available in June of 2006 and may have prompted many patients to switch from the brand to generic formulation of sertraline. Although patients may have switched from a brand to a generic, which would presumably be beneficial and cost saving, a patient may have been just as likely to switch from a generic medication to a brand-name formulation, which would minimize any impact of differentially misclassifying a switch as a discontinuation between the exposure groups.

Finally, we were not able to determine whether a patient was enrolled in a health plan with behavioral health carve-out. Such a benefit design may have affected the use of psychiatric medical care, and information about psychiatric medical care in health plans with a behavioral health carve-out may be incomplete if claims for such care were billed through another benefit. This information was not available in the administrative claims data used in the present study.

Conclusions

Initiation of therapy on a generic SSRI or SNRI does not appear to be associated with a greater likelihood of therapy discontinuation and may be associated with decreased total health care costs in the first 180 days of therapy. The study's results do not support the contention sometimes made by critics of pharmacy utilization management tools that generic antidepressants are less effective or safe than brand drugs.

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