Rates of 5 Common Antidepressant Side Effects Among New Adult and Adolescent Cases of Depression: A Retrospective US Claims Study

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ABSTRACT

Background: Antidepressants are the first-line treatment for depression, yet medication-related side effects may be associated with antidepressant discontinuation before reaching a period of exposure believed to result in effectiveness. There is a gap in knowledge of the prevalence of side effects across commonly prescribed antidepressants and the effect of the type of antidepressant on the likelihood of side effects in real-world clinical practice.

Objective: The aim of this study was to estimate and compare the prevalence of headaches, nausea or vomiting, agitation, sedation, and sexual dysfunction among patients diagnosed with depression who initiated monotherapy across different classes of antidepressants and to estimate the effect of the type of antidepressant on the likelihood of each of the 5 side effects.

Methods: A retrospective cohort of patients aged ≥13 who were newly diagnosed with depression and began antidepressant monotherapy was created using LifeLink managed care claims from 1998 to 2008. Antidepressant groups included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), bupropion, phenylpiperazine, and tetracyclic antidepressants. Prevalence of headache, nausea or vomiting, agitation, sedation, and sexual dysfunction were compared across antidepressant groups. Propensity-adjusted Cox proportional hazards regression was used to estimate the likelihood of each of the 5 side effects for each antidepressant group compared with SSRIs, adjusted for demographic, clinical, and treatment characteristics.

Results: The study cohort included 40,017 patients (3617 adolescents, aged 13–18 years, and 36,400 adults, aged ≥19 years; mean age = 45 years; 67% female) with a new episode of depression who were initiated on antidepressant monotherapy within 30 days of diagnosis (SSRI [66%], bupropion [14%], SNRI [12%], other [8%]). The most common side effects were headache (up to 17/1000 person-months of therapy in adults and adolescents) and nausea (up to 7.2/1000 in adults, 9.3/1000 in adolescents). Relative to adults receiving SSRIs, adults receiving SNRIs had a higher risk of nausea (hazard ratio [HR] = 1.26; 95%CI,1.05–1.51). Adults (HR = 0.78; 95% CI, 0.62–0.96) and adolescents (HR = 0.43; 95% CI, 0.21–0.87) taking bupropion were less likely to experience headaches compared with adults and adolescents, respectively, taking an SSRI. Adolescents receiving a tetracyclic were more likely to experience headaches than adolescents receiving an SSRI (HR = 3.16; 95%CI, 1.13–8.84).

Conclusions: Prevalence and risk of the 5 side effects varied across types of antidepressants for both adults and adolescents. Results from this study were consistent with prior clinical trials, suggesting that variation in side effect profiles exists in a more generalized managed care population. (*Clin Ther*. 2012;34:113–123)

Key words: antidepressants, depression, side effects, tolerability.

INTRODUCTION

Major depressive disorder (MDD) is common in the United States, with lifetime prevalence estimated at 16% for adults and 14% for adolescents, and 1-year

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prevalence estimated at 7% for adults and 13% for adolescents.[1,2] The disease is burdensome, evidenced by its ranking as one of the leading causes of disability worldwide.[3] The most common treatment for MDD is a second-generation antidepressant medication, such as selective serotonin reuptake inhibitors (SSRIs).[4–6] A recent study of depression diagnoses and treatment patterns reported that 86% to 90% of adult patients diagnosed with a new or recurrent episode of depression filled a prescription for an antidepressant within 30 days of their diagnoses; SSRIs were the most commonly filled antidepressant (54%–66%).[7]

Antidepressant therapy is considered first-line treatment in the acute phase of depression in both adolescents and adults, yet up to 68% of patients stop taking antidepressants within 3 months of their initiation and 54% do not reach remission.[8–11] Side effects are an important reason for discontinuing antidepressants.[12–15] One study conducted telephone surveys among 672 patients at 3 and 6 months after starting an SSRI for new or recurrent depression and reported that 43% discontinued their SSRI within 3 months because of an adverse effect; 27% discontinued using the SSRI by 6 months. Other studies have estimated that 15% to 30% of patients discontinue using their SSRI because of side effects.[12,13]

There is evidence that various antidepressants have differential tolerability profiles.[16–20] One systematic review reported that users of the SSRI fluvoxamine experienced more gastrointestinal side effects than users of tricyclic antidepressants (TCAs).[20] The same systematic review, however, reported no differences across antidepressants with respect to trial dropout due to side effects. Another meta-analysis of randomized, controlled trials reported fewer side effects among patients treated with fluoxetine compared with TCAs but not compared with other SSRIs.[17] The majority of these studies comparing the tolerability of different agents are based on efficacy trials or small clinical studies, neither of which is generalizable to broader, nonspecific populations of depressed people.

Because the majority of what is known about antidepressant side effect profiles comes from randomized trials,[6,17,18] little is known about how different antidepressants compare with respect to side effect rates in real-world clinical practice. The objective of the current study was to measure and compare the prevalence of 5 specific side effects (headache, nausea or vomiting, agitation, sedation, and sexual dysfunction) among patients newly diagnosed with depression who were new users of antidepressants. Data were drawn from a large national database of integrated medical and pharmacy claims. Prevalence estimates and adjusted effects of antidepressant group on each of the 5 side effects were stratified by adults and adolescents.

PATIENTS AND METHODS

Data Source and Study Population

A new-user, open cohort design was implemented by searching 11 years of data (1998–2008) from a large, commercially available national data source (IMS LifeLink Health Plan Claims Database) to identify a retrospective cohort of patients receiving an antidepressant to treat a new episode of MDD. The LifeLink data source includes medical, specialty, facility, and pharmacy paid claims for >68 million covered lives from >102 managed care plans nationally. Patients in LifeLink are representative of the US commercially insured population with regard to age and gender; the distributions of age and gender among patients in the LifeLink database are not significantly different from distributions in the 2000 US census.[21] Using claims from the LifeLink database, adolescent (aged 13–18 years) and adult (age ≥19 years) patients with new episodes of MDD were identified according to the following criteria: (1) a claim indicating a primary or secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic code of 296.2 or 296.3; (2) at least 90 days without taking antidepressants before the MDD claim date; (3) at least 120 days without an MDD diagnosis(es) or receipt of psychotherapy services (2 or more visits) before the MDD claim date; and (4) at least 180 days of continuous health plan eligibility before and 210 days after the MDD claim date. These criteria are based on the Healthplan Employer Data Information System (HEDIS) criteria for defining and measuring new episodes of depression, employed by the National Committee for Quality Assurance (NCQA),[22,23] and have been used by the authors in prior published work.[24–26]

For patients with >1 MDD episode during the study period, only the earliest episode was selected. Patients who did not receive an antidepressant within 30 days of their episode diagnosis date were excluded from the study cohort. This resulted in a cohort of 40,017 patients (36,400 adults, 3617 adolescents). The study was approved by the Colorado Multiple Institutional

Review Board and granted a waiver of consent owing to the unidentified and anonymous data.

Antidepressant Treatment Groups

The 6 antidepressant groups of interest for this study were based on the Agency for Healthcare Research and Quality (AHRQ) *Comparative Effectiveness Report on Second-Generation Antidepressant Treatment of Adult Depression*[8]*:* SSRI, serotonin-norepinephrine reuptake inhibitor (SNRI), TCA, bupropion, monoamine oxidase inhibitor (MAOI), phenylpiperazine (PP), and tetracyclic antidepressant. Patients were classified into one of these 6 monotherapy treatment groups based on the first class of antidepressant they received within 30 days of their episode diagnosis date. Patients who received an antidepressant within 30 days of their MDD diagnosis but were initiated on more than 1 class that day, or were initiated on an antidepressant >30 days after their diagnosis, were excluded from the study cohort.

The patients were followed for side effect occurrence during their periods of exposure to the class of antidepressant with which their treatment was initiated. Follow-up began the day after the antidepressant was filled and ended at the earliest of the following: (1) discontinuation of the antidepressant (identified by a gap of ≥45 days between last fill date plus last days supplied and the next claim for the same class of antidepressant); (2) start date of an antidepressant from one of the other antidepressant classes—1 day; (3) start date of the next MDD episode—1 day; or (4) the end of continuous eligibility.

Measures

The primary outcome was *treatment-emergent side effects*. The side effects of interest included 5 specific side effects most commonly associated with antidepressant discontinuation in clinical trials: headache, nausea or vomiting, agitation, sedation, and sexual dysfunction.[16,27] These side effects were identified in the claims data using primary and secondary ICD-9-CM diagnostic codes during the antidepressant exposure period. A treatment-emergent side effect was defined as 1 of the 5 specific side effects detected in a patient's claims after the antidepressant was started but not during the 6 months before antidepressant initiation. Side effects detected during the 6 months before antidepressant initiation and during antidepressant exposure were assumed to be preexisting and therefore not treatment-emergent. For each patient with a treatment-emergent side effect reported during the follow-up period, the first occurrence was identified and days to event were calculated. A composite variable indicating the occurrence of ≥1 of the 5 side effects was also created.

Demographic characteristics included age (in years, at time of start of MDD episode), gender, region (West, Midwest, East, and South), health plan type (HMO vs non-HMO), and Medicaid status (yes/no). *Baseline clinical characteristics* included the Chronic Disease Indicator (CDI), a score that indicates a person's total number of chronic diseases,[28] and the following characteristics that were identified during the 180 days before the start of the MDD episode: presence of other specific psychiatric comorbidities such as bipolar disorder, schizophrenia, and anxiety spectrum disorder; presence of clinical comorbidities such as terminal diagnoses, seizure disorder, fibromyalgia, and chronic pain; use of other medications such as antiepileptics, anxiolytics, and antipsychotics; receipt or use of other health services; prior suicide attempt history; severity of MDD episode assessed using the fifth digit of the ICD-9 diagnosis code, if available; and diagnosing and prescribing provider specialty.

Exposure covariates were defined during each patient's antidepressant exposure period: persistence of antidepressant use (number of days from first prescription fill to last prescription fill plus last days supplied); calculated daily dose (product of the quantity and strength of the medication divided by the days supplied); receipt of ≥2 psychotherapy visits; presence of other specific psychiatric comorbidities as described earlier; presence of clinical comorbidities as described previously; and use of concomitant medications as described earlier (measured as drug-months of exposure).

Statistical Analyses

Descriptive statistics were used to characterize patients at baseline with respect to demographic and clinical measures. Next, prevalence (%) and crude (unadjusted) rates of each side effect (per 1000 person-months of antidepressant exposure) were calculated separately for adults and adolescents within each antidepressant treatment group. The percentsage of patients with each specific side effect was compared across antidepressant groups using one-way analysis of variance and the Tukey post-hoc test for significant differences.[29] Crude relative risks were also calculated

for each antidepressant treatment group relative to the SSRI group for both adults and adolescents.

Because this was an observational study, our sample was not randomly assigned to an antidepressant group. Thus, the study faced a major threat of validity common to observational comparative effectiveness studies. To address this, we employed a 2-stage propensity analysis approach.[30] First, a multinomial logistic regression model estimated the likelihood of receiving each of the antidepressant monotherapies, resulting in 6 propensity scores for each patient (those in the MAOI group were excluded owing to small numbers). Baseline demographic and clinical characteristics described previously were included as covariates.

The second stage of the propensity analysis approach was to include the propensity scores in subsequent multivariate analyses of the side effect outcomes.[31] Propensity-adjusted Cox proportional hazards regression was used to model the relative likelihood of each side effect adjusted for measured demographic and clinical characteristics, specified comorbidity and concomitant drug use measures, and propensity for receiving each antidepressant monotherapy.[32] Each side effect was modeled individually; the composite measure of 1 or more side effects was also modeled. SAS Language version 9.1 (SAS Institute, Cary, North Carolina) was used for all data management and statistical analyses.

RESULTS

A total of 40,017 patients met HEDIS criteria for a new episode of MDD and were initiated on antidepressant monotherapy within 30 days of diagnosis. An additional 27,166 patients with a new episode of MDD were identified but excluded from the analysis because they did not receive an antidepressant within 30 days of their MDD diagnosis. The average antidepressant exposure period was 198 days (median = 104 days; range = 1–2993 days).

The most common antidepressant monotherapy was SSRI (66%), followed by bupropion (14%) and SNRI (12%). The following specific agents were represented within each antidepressant group: SSRI (fluvoxamine [0.5%], paroxetine [13%], citalopram [18%], fluoxetine [21%], escitalopram [22%], sertraline [25%]); SNRI (desvenlafaxine [0.5%], duloxetine [33%], venlafaxine [66%]); TCA (amoxapine [0.1%], trimipramine [0.4%], protriptyline [0.9%], desipramine [5%], clomipramine [5%], doxepin [8%], imipramine [10%], notriptyline [26%], amitriptyline [45%]); MAOI (isocarboxazid [2%], phenelzine sulfate [30%], selegiline [34%], tranylcypromine sulfate [34%]); PP (nefazodone [16%], trazodone [84%]); and tetracyclic (maprotiline [0.3%], mirtazapine [99%]). Very few patients received an MAOI (46 adults and 1 adolescent) and were therefore excluded from propensity-adjusted analyses.

The MDD episodes included in this study are similar to typical depressed populations in managed care plans (**Table I**). Two thirds were female, and the average age ranged from 40 to 54 years (91% were adults aged ≥19 years). The patients in the MAOI group were significantly older than patients in the other antidepressant groups ($P < 0.05$), which is consistent with the fact that this medication has been on the market for a much longer period of time and the assumption that patients who have been successfully treated with this medication in the past are more likely to receive it again at older ages. About 3% were on Medicaid at the time the MDD episode started. The distribution of episodes across regions is consistent with the general population distribution, with the majority of patients being in the Midwest and East.

Clinical characteristics of the episodes are described in the bottom half of **Table I**. Episodes tended to last approximately 2 years. On average, the first antidepressant prescription was filled within 7 to 10 days of the start of the MDD episode. The severity of the MDD episode is coded in the ICD-9-CM codes for MDD using the fifth digit. Approximately 60% of the MDD episodes had severity coded; among those with severity coded, 21% to 32% were coded as moderate and 16% to 38% were coded as severe with or without psychosis. Approximately 30% of the patients received 2 or more psychotherapy visits during their follow-up.

Detectable rates of each of the 5 common side effects were observed in the claims data for most antidepressant monotherapy groups (**Table II**). In each age group, the most commonly observed side effects were headache (up to 16.8/1000 person-months of therapy in adults and 17.6/1000 person-months of therapy in adolescents) and nausea or vomiting (up to 7.2/1000 in adults and 9.3/1000 in adolescents). Adults receiving bupropion had significantly fewer episodes of headache and nausea or vomiting in the claims data than adults receiving an SSRI or SNRI ($P < 0.01$). Adolescents receiving bupropion had significantly less nausea or vomiting than adolescents receiving an SSRI ($P < 0.05$). At least 1 of these 5

Table 1. Demographic and clinical characteristics of depressed cohort (N = 40,017) by antidepressant group.

	SSRI n (%)	SNRI n (%)	TCA n (%)	Bupropion n (%)	MAOI n (%)	PP n (%)	Tetracyclic n (%)
Total N	26,284	4975	818	5636	47	1288	969
Demographic Characteristics							
Age at start of episode							
Mean, median	41.18, 41	43.21, 44	46.54, 47	39.89, 41	54.11, 56	43.85, 45	48.80, 48
Adolescent (13–18 y)	2664 (10.14%)	213 (4.28%)	42 (5.13%)	541 (9.60%)	1 (2.13%)	88 (6.83%)	68 (7.02%)
Adult (≥19 y)	23,620 (89.86%)	4762 (95.72%)	776 (94.87%)	5095 (90.40%)	46 (97.87%)	1200 (93.17%)	901 (92.98%)
Gender (female)	17,792 (67.69%)	3375 (67.84%)	557 (68.09%)	3605 (63.96%)	23 (48.94%)	826 (64.13%)	535 (55.21%)
Medicaid status	750 (2.85%)	83 (1.67%)	27 (3.30%)	138 (2.45%)	0 (0.00%)	49 (3.80%)	47 (4.85%)
Region							
East	5923 (22.53%)	1366 (27.46%)	182 (22.25%)	1217 (21.59%)	19 (40.43%)	253 (19.64%)	221 (22.81%)
Midwest	13,308 (50.63%)	2234 (44.90%)	390 (47.68%)	2769 (49.13%)	16 (34.04%)	705 (54.74%)	508 (52.43%)
South	4144 (15.77%)	962 (19.34%)	156 (19.07%)	930 (16.50%)	9 (19.15%)	190 (14.75%)	175 (18.06%)
West	2909 (11.07%)	413 (8.30%)	90 (11.00%)	720 (12.78%)	3 (6.38%)	140 (10.87%)	65 (6.71%)
Clinical Characteristics							
Length of episode (d)							
Mean, median	717.62, 568	692.20, 563	765.82, 619.5	721.62, 586	543.19, 381	741.69, 568.5	707.35, 554
Range (min, max)	(2–3862)	(20–3452)	(25–3247)	(14–3870)	(126–2087)	(20–3704)	(28–3397)
Days to first AD prescription							
Mean, median	7.52, 3	10.22, 8	8.16, 5	7.43, 4	10.02, 9	8.45, 6	7.03, 4
Episode severity							
Unspecified/missing	10,997 (41.84%)	1909 (38.37%)	337 (41.20%)	2192 (38.89%)	12 (25.53%)	494 (38.35%)	313 (32.30%)
Mild	2772 (10.55%)	375 (7.54%)	78 (9.54%)	596 (10.57%)	7 (14.89%)	101 (7.84%)	51 (5.26%)
Moderate	8291 (31.54%)	1628 (32.72%)	263 (32.15%)	1817 (32.24%)	10 (21.28%)	380 (29.50%)	290 (29.93%)
Severe without psychosis	3751 (14.27%)	960 (19.30%)	134 (16.38%)	950 (16.86%)	17 (36.17%)	280 (21.74%)	276 (28.48%)
Severe with psychosis	473 (1.80%)	103 (2.07%)	6 (0.73%)	81 (1.44%)	1 (2.13%)	33 (2.56%)	39 (4.02%)
Psychotherapy visits							
None	16,067 (61.13%)	2724 (54.75%)	460 (56.23%)	3250 (57.67%)	17 (36.17%)	703 (54.58%)	506 (52.22%)
1	2355 (8.96%)	580 (11.66%)	123 (15.04%)	664 (11.78%)	12 (25.53%)	234 (18.17%)	152 (15.69%)
2 or more	7862 (29.91%)	1671 (33.59%)	235 (28.73%)	1722 (30.55%)	18 (38.30%)	351 (27.25%)	311 (32.09%)
Count of visits (mean, median)	2.36, 0	2.44, 0	1.90, 0	2.14, 0	3.49, 1	1.63, 0	1.91, 0
Range (min, max)	(0–177)	(0–103)	(0–47)	(0–117)	(0–54)	(0–78)	(0–40)

MAOI = monoamine oxidase inhibitors; PP = phenylpiperazine; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

Table II. Crude rates (per person-month of antidepressant exposure) of 5 side effects and a composite measure of at least 1 side effect, adults (n = 36,400) and adolescents (n = 3617) by antidepressant group.

	No. Patients	Total Person-Months	Headaches		Nausea		Agitation		Sedation		Sexual Dysfunction		≥1 Side Effect	
			No. (%)	Rate*	No. (%)	Rate*	No. (%)	Rate*	No. (%)	Rate*	No. (%)	Rate*	No. (%)	Rate*
Adults (aged ≥19 y)														
SSRI	23,620	169,179	938 (4.0)	5.54	612 (2.6)	3.62	57 (0.2)	0.34	137 (0.6)	0.81	80 (0.3)	0.47	1643 (7.0)	9.71
SNRI	4762	34,986	240 (5.0)	6.86	175 (3.7)	5.00	16 (0.3)	0.46	39 (0.8)	1.11	13 (0.3)	0.37	437 (9.2)	12.49
TCA	776	4116	28 (3.6)	6.80	19 (2.4)	4.62	3 (0.4)	0.73	4 (0.5)	0.97	3 (0.4)	0.73	52 (6.7)	12.63
Bupropion	5095	29,541	158 (3.1)	5.35	95 (1.9)	3.22	11 (0.2)	0.37	7 (0.1)	0.24	12 (0.2)	0.41	263 (5.2)	8.90
MAOI	46	298	5 (10.9)	16.77	2 (4.3)	6.71	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	6 (13.0)	20.12
PP	1200	3750	28 (2.3)	7.47	27 (2.2)	7.20	1 (0.1)	0.27	4 (0.3)	1.07	5 (0.4)	1.33	57 (4.7)	15.20
Tetracyclic	901	3979	27 (3.0)	6.79	22 (2.4)	5.53	0 (0)	0.00	10 (1.1)	2.51	1 (0.1)	0.25	54 (6.0)	13.57
Adolescents (aged 13–18 y)														
SSRI	2664	15,071	124 (4.6)	8.23	94 (3.5)	6.24	7 (0.3)	0.46	19 (0.7)	1.26	0 (0)	0.00	221 (8.3)	14.66
SNRI	213	1072	9 (4.2)	8.39	5 (2.3)	4.66	1 (0.5)	0.93	4 (1.9)	3.73	0 (0)	0.00	17 (8.0)	15.85
TCA	42	108	0 (0)	0.00	1 (2.4)	9.29	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	1 (2.4)	9.29
Bupropion	541	2220	16 (3.0)	7.21	6 (1.1)	2.70	2 (0.4)	0.90	2 (0.4)	0.90	0 (0)	0.00	24 (4.4)	10.81
MAOI	1	4	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00
PP	88	196	2 (2.3)	10.20	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	2 (2.3)	10.20
Tetracyclic	68	227	4 (5.9)	17.62	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	0 (0)	0.00	4 (5.9)	17.62

MAOI = monoamine oxidase inhibitors; PP = phenylpiperazine; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.
*Per 1000 person-months.

common side effects was identified in 5% to 13% of adults and 2% to 8% of adolescents (adolescents in the MAOI group had none of the side effects reported).

Given the observed differences in the unadjusted rates of the tolerability outcomes across the antidepressant treatment groups, multivariable Cox proportional hazards models were created to estimate the effect of each antidepressant treatment group (relative to SSRIs as the referent group) on the risk of each of the 5 side effects, adjusting for antidepressant persistence, calculated daily dose, demographic and clinical measures, comorbidities, concomitant medications, and propensity for receiving each antidepressant therapy. Adjusted hazard ratios (HRs) for the effect of antidepressant group are reported in **Table III** and depicted graphically in the **Figure** (parameter estimates for all other covariates in the models are available by request from the authors).

Relative to adults receiving SSRIs, adults receiving SNRIs had a significantly higher risk of nausea or vomiting (HR = 1.26; 95% CI, 1.05–1.51) and of having 1 or more side effects of any type (HR = 1.19; 95% CI, 1.06–1.33). Adults receiving bupropion were significantly less likely to have headaches (HR = 0.78; 95% CI, 0.62–0.96) than adults receiving an SSRI. Adults receiving TCAs, PPs, or tetracyclics had neither increased nor decreased risk of any side effect types relative to adults receiving SSRIs.

As seen among adults, adolescents receiving bupropion were significantly less likely to have headaches than adolescents receiving an SSRI (HR = 0.43; 95% CI, 0.21–0.87). Adolescents receiving a tetracyclic, however, were more likely to have headaches than adolescents receiving an SSRI (HR = 3.16; 95% CI, 1.13–8.84). Although trends were seen for effects of antidepressant group on other side effects, no other significant effects were seen in adolescents.

DISCUSSION

Data from the current study suggest that after adjusting for demographic and clinical characteristics and propensity to receive each antidepressant group, adults taking an SNRI were significantly more likely to have a claim for nausea or vomiting and those taking bupropion were significantly less likely to have a claim for sedation compared with adults taking an SSRI. A recent multiple-treatments meta-analysis of randomized, controlled trials including depressed adults concluded that bupropion had a lower dropout rate owing to side effects than reboxetine and that duloxetine (an SNRI) had a higher dropout rate than escitalopram (an SSRI).[33] Although not specific to types of side effects, these results are consistent with the current study's findings. Results from the current study suggest no significant differences in side effects between SSRIs and TCAs. This is not consistent, however, with a recent meta-analysis that reported higher rates of gastrointestinal side effects among patients taking fluvoxamine compared with those taking a TCA.[20] It is possible that analyses comparing TCA users to other antidepressant users were underpowered in the current study because of the smaller size of the TCA group.

The current study suggests that headache and sedation were more likely among adolescents on a tetracyclic or an SNRI, respectively, than among adolescents on an SSRI. With respect to side effects, no studies comparing adolescents receiving different types of antidepressants are known to have been completed. This study was underpowered for some antidepressant treatment groups, however, owing to low prevalence of the side effects among adolescents.

Of the 5 specific side effects considered in the current study, the most commonly detected were headache (up to 11%) and nausea or vomiting (up to 4%) in both adults and adolescents; other side effects were detected less frequently, with rates often <1%. These rates are comparable to those reported in a study of 337 depressed adults on an SSRI from a managed care organization in Texas: headache in 3% of patients, gastrointestinal disturbances in 9%, sedation in 5%, agitation in 4%, and sexual dysfunction in 3%.[34] Another study conducted using a telephone survey of 672 depressed patients taking an SSRI reported comparable rates of the most commonly reported side effects among those who discontinued early (within 3 months): drowsiness or fatigue (10%), anxiety (6%), headache (6%), and nausea (5%).[15]

The prevalence estimates resulting from the current study's use of claims data are also comparable to rates in the clinical trials literature. For example, an open-label efficacy trial of almost 600 patients on an SSRI reported that 4% to 8% discontinued the medication owing to gastrointestinal side effects, 2% to 7% because of sleep problems, 2% to 5% because of agitation, 1% to 3% because of headache, and 0% to 2% because of sexual side effects.[16] However, data from medical claims are subject to a considerable degree of underdetection because fewer patients may actually go to a doctor for these particular symptoms. More gen-

Table III. Crude and adjusted risk of 5 side effects and a composite measure of at least 1 side effect, adults (n = 36,400) and adolescents (n = 3617).

	Headaches		Nausea		Agitation		Sedation		Sexual Dysfunction		≥1 Side Effect	
	Crude RR*	Adjusted HR (95% CI)†	Crude RR*	Adjusted HR (95% CI)†	Crude RR*	Adjusted HR (95% CI)†	Crude RR*	Adjusted HR (95% CI)†	Crude RR*	Adjusted HR (95% CI)†	Crude RR*	Adjusted HR (95% CI)†
Adults (aged ≥19 y)												
SSRI	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
SNRI	1.24	1.11 (0.95, 1.29)	1.38	1.26 (1.05, 1.51)	1.36	1.78 (0.94, 3.37)	1.38	1.41 (0.92, 2.14)	0.79	0.89 (0.47, 1.67)	1.29	1.19 (1.06, 1.33)
TCA	1.23	1.03 (0.70, 1.50)	1.28	0.94 (0.59, 1.48)	2.16	2.15 (0.66, 6.99)	1.20	0.87 (0.32, 2.39)	1.54	1.53 (0.47, 4.93)	1.30	1.02 (0.77, 1.35)
Bupropion	0.96	0.78 (0.62, 0.96)	0.89	0.85 (0.63, 1.14)	1.11	3.18 (0.97, 10.47)	0.29	0.46 (0.17, 1.28)	0.86	0.72 (0.278, 1.88)	0.92	0.78 (0.66, 0.93)
PP	1.35	0.85 (0.58, 1.26)	1.99	1.16 (0.77, 1.75)	0.79	0.89 (0.12, 6.71)	1.32	0.82 (0.29, 2.35)	2.82	1.94 (0.71, 5.33)	1.57	0.96 (0.73, 1.26)
Tetracyclic	1.22	1.09 (0.74, 1.62)	1.53	1.08 (0.70, 1.68)	0.00	–	3.10	0.79 (0.39, 1.58)	0.53	0.47 (0.07, 3.43)	1.40	1.03 (0.78, 1.36)
Adolescents (aged 13–18 y)												
SSRI	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–	1.00	1.00
SNRI	1.02	0.81 (0.40, 1.64)	0.75	0.71 (0.25, 2.02)	2.01	0.92 (0.05, 18.28)	2.96	2.69 (0.74, 9.72)	0.00	–	1.08	0.85 (0.50, 1.45)
TCA	0.00	–	1.49	1.18 (0.14, 9.97)	0.00	–	0.00	–	0.00	–	0.63	0.44 (0.05, 3.57)
Bupropion	0.88	0.43 (0.21, 0.87)	0.43	0.98 (0.27, 3.56)	1.94	0.25 (0.01, 5.22)	0.71	0.29 (0.03, 2.87)	0.00	–	0.74	0.46 (0.25, 0.84)
PP	1.24	0.23 (0.04, 1.38)	0.00	–	0.00	–	0.00	–	0.00	–	0.70	0.15 (0.03, 0.80)
Tetracyclic	2.14	3.16 (1.13, 8.84)	0.00	–	0.00	–	0.00	–	0.00	–	1.20	1.55 (0.56, 4.28)

HR = hazard ratio; MAOI = monoamine oxidase inhibitors; PP = phenylpiperazine; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

– indicates antidepressant group left out of model because zero events (no model run for sexual dysfunction in adolescents because zero events).

*RR = relative risk (referent group = SSRI).

†HR from a Cox proportional hazards model adjusted for propensity to receive each class of antidepressant depression severity, antidepressant persistence, calculated daily dose, psychotherapy visits, age, gender, comorbid conditions and concomitant medications.

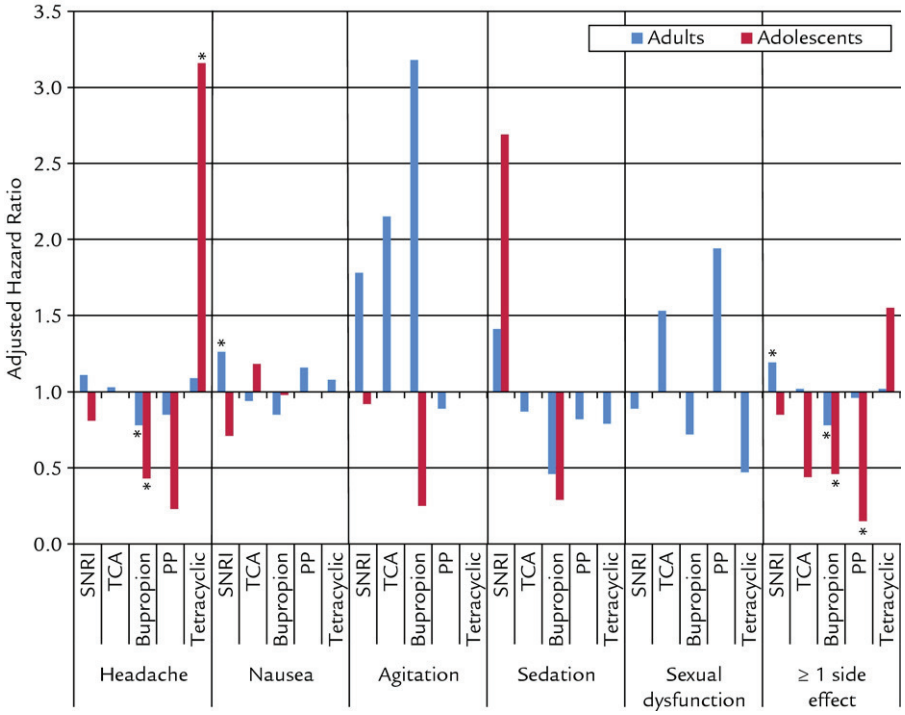

Figure. Adjusted hazard ratios representing the effect of each antidepressant class (referent group = SSRI) on the risk of each side effect and the composite measure (≥1 side effects) adjusted for propensity to receive each class of antidepressant, depression severity, antidepressant persistence, calculated daily dose, psychotherapy visits, age, gender, comorbid conditions, and concomitant medications, for adolescents and adults. PP = phenylpiperazine; SNRI = serotonin-norepinephrine reuptake inhibitors; TCA = tricyclic antidepressants. *$P < 0.05$.

eral estimates of the occurrence of side effects associated with SSRIs are higher: increased agitation in up to 20% of users, nausea in up to 20%, sedation in up to 20%, and sexual dysfunction in up to 20%.[35]

Although this study fills a gap in the comparative rates of 5 specific treatment-emergent side effects, there are limitations. The parent study that provided the retrospective cohort of new cases of depression focused only on MDD (ICD-9-CM codes 296.2 and 296.3) because of the ability to capture response and remission from the fifth digit of the diagnosis code in medical claims. Thus, the broader and more common depression diagnosis code of 311 was eliminated. Had this broader range of depression diagnoses been included, the cohort size would have been larger, thus affecting rates of antidepressant use and side effects. This is an obvious extension for future work. Another limitation was the grouping of individual antidepressant agents (eg, SSRI, SNRI, TCA). However, distributions of each of the 5 side effects of interest were compared across individual agents within each antidepressant group, and very few differences were found. Therefore, groups of antidepressants were compared rather than individual agents.

Two exclusion criteria may have affected the generalizability of these results. The exclusion of patients who received multiple types of antidepressants on the same day may have excluded more severely depressed patients. However, if they had been included, it would not have been possible to assign a patient to a single group of antidepressants, making interpretation of the results difficult. The exclusion of patients who received their first antidepressant >30 days after their depression diagnosis excluded patients who may or may not have experienced side effects once starting the antidepressant. However, it is difficult to know how this exclusion may have affected the generalizability of the results without further understanding of the associa-

tion among delayed antidepressant start, type of antidepressant, and side effects.

Another limitation was the reliance on medical and pharmacy claims data to detect clinical events such as drug-induced side effects. In recent years, interest in using observational databases for postapproval drug safety studies has increased.[36,37] A major benefit to using claims data is that it allows for more generalizable prevalence and effect estimates than those obtained from clinical trials, which have made up the majority of research in this area.[6,17,18] A trade-off, however, is relatively low sensitivity of medical claims data for detecting these side effects at their true rates in treatment settings.[38] This limitation of claims data highlights the need for other sources of data that are more generalizable than those from clinical trials but also allow for a more thorough collection of symptom data on patients. The promise of electronic health records and point-of-care data collection from patients and clinicians for this work is high.

Although it is difficult to know the amount of underdetection in claims data, it is assumed for the current study that the degree of underdetection is similar across groups of antidepressants. Even given the limitations of claims data, the rates of side effects reported in the current study are of clinical importance and lay the groundwork for future studies of the differential tolerability of antidepressants.

CONCLUSIONS

The results from this study of adolescent and adult patients being treated with an antidepressant for newly diagnosed depression suggest that side effects detected in claims were measureable. Prevalence and risk of headaches, nausea or vomiting, agitation, sedation, and sexual dysfunction varied across types of antidepressants for both adults and adolescents, suggesting that variation in side effect profiles exists in a more generalized managed care population.

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CONFLICTS OF INTEREST

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