National Trends in Second-Generation Antipsychotic Augmentation for Nonpsychotic Depression

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ABSTRACT

Objective: This study estimates national trends and patterns in use of second-generation antipsychotics (SGAs) for adjunctive treatment of nonpsychotic adult depression in office-based practice.

Method: Twelve consecutive years (1999–2010) of the National Ambulatory Medical Care Survey were analyzed to estimate trends and patterns of adjunctive SGA treatment for adult (≥ 18 years) nonpsychotic depression in office-based visits. Adjunctive SGA use was examined among all office visits in which depression was diagnosed (N = 7,767), excluding visits with diagnoses for alternative SGA indications (schizophrenia, bipolar disorder, pervasive development disorder, psychotic depression, dementia) and those without an active antidepressant prescription.

Results: From 1999 to 2010, 8.6% of adult depression visits included an SGA. SGA use rates increased from 4.6% in 1999–2000 to 12.5% in 2009–2010, with an adjusted odds ratio (AOR) for time trend of 2.78 (95% CI, 1.84–4.20). The increase in SGA augmentation was broad-based, with no significant differences in time trends between demographic and clinical subgroups. For the most recent survey years (2005–2010), SGA use rates were higher in visits to psychiatrists than to other physicians (AOR = 5.08; 95% CI, 2.96–8.73), visits covered by public than private insurance (AOR = 3.20; 95% CI, 2.25–4.54), visits with diagnosed major depressive disorder than other depressive disorders (AOR = 1.49; 95% CI, 1.08–2.06), and visits with diabetes, hyperlipidemia, or cardiovascular disease (AOR = 2.13; 95% CI, 1.12–4.03) and lower in visits by patients > 65 years than 18–44 years (AOR = 0.51; 95% CI, 0.32–0.82) and visits that included psychotherapy (AOR = 0.68; 95% CI, 0.47–0.96).

Conclusions: Between 1999 and 2010, SGAs were increasingly accepted in the outpatient treatment of adult nonpsychotic depression.

J Clin Psychiatry 2014;75(5):490–497

Submitted: *July 8, 2013; accepted October 2, 2013.*
Online ahead of print: *January 7, 2014 (doi:10.4088/JCP.13m08675).*
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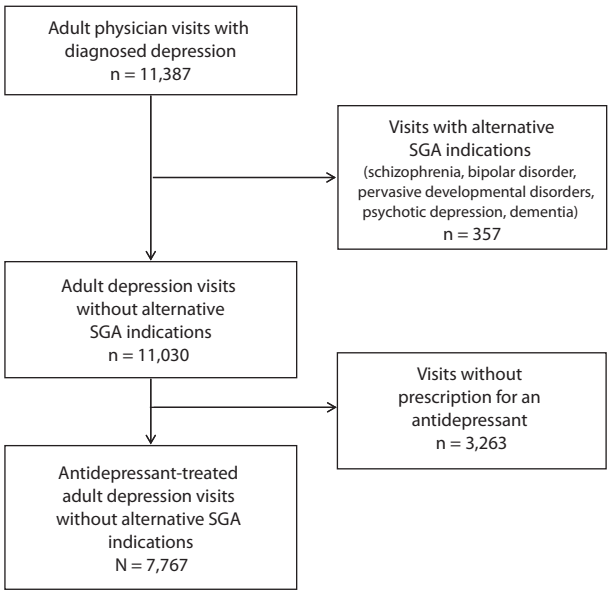
Antidepressant medications, particularly the newer selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, are the recommended first-line treatment for major depressive disorder (MDD).[1] However, only about half of patients suffering from depression are likely to respond to an initial antidepressant trial, and only about 30%–40% of patients achieve full remission.[2,3] Pharmacologic strategies for patients with incomplete response to a trial of antidepressant monotherapy include switching to another antidepressant (within or between antidepressant drug classes),[4] augmentation with a second antidepressant agent,[5] and augmentation with nonantidepressant agents, including lithium, triiodothyronine, and, more recently, second-generation antipsychotics (SGAs).[1,6] Several nonpharmacologic approaches, including various psychotherapies, electroconvulsive treatment, phototherapy, sleep deprivation, repetitive transcranial magnetic stimulation, and acupuncture, have also been used to treat depression following incomplete response to antidepressant monotherapy.[7]

Over the last decade, there has been an accumulation of evidence describing the effectiveness of SGAs as an adjunctive treatment for depression, particularly when patients fail to respond to first-line treatment.[8–22] Currently, augmentation with SGAs is the only US Food and Drug Administration (FDA)–approved pharmacologic treatment alternative for patients with incomplete response to antidepressant monotherapy.[6,23] A meta-analysis[6] based on 16 trials comparing adjunctive SGAs to placebo in patients with treatment-resistant or inadequately responsive MDD (N = 3,580) has generated estimates of efficacy of an odds ratio (OR) = 1.69; 95% confidence interval (CI), 1.46–1.95; and number needed to treat (NNT) = 9 for response and OR = 2.00; 95% CI, 1.58–2.72; NNT = 9 for remission. Since 2007, the FDA has approved aripiprazole (2007), olanzapine (in fixed combination with fluoxetine; 2009), and quetiapine (2009) as adjunctive therapy to antidepressants for the treatment of MDD in adults who have an inadequate response to antidepressant treatment alone.

Despite having the strongest evidence base for adjunctive use in MDD patients with inadequate response to standard antidepressant therapy, SGAs are associated with increased risks for extrapyramidal side effects, tardive dyskinesia, weight gain, diabetes, and dyslipidemia.[24–29] The metabolic risks may be increased in antipsychotic-naive patients,[28,30] a patient group that is most likely overrepresented in individuals with nonpsychotic depressive disorders. Although the risk for cardiometabolic adverse effects associated with SGA treatment can be mitigated by adequate monitoring and management,[31] metabolic monitoring in SGA-treated patients remains suboptimal in clinical practice.[32,33] Moreover, SGAs have also been associated with rare, but serious, adverse events in other clinical populations, including death, acute myocardial infarction, and stroke.[34–37]

Figure 1. Study Sample and Details of Exclusions[a]



[a]Data from National Ambulatory Medical Care Survey (NAMCS). Ns reflect NAMCS sample visits.
Abbreviation: SGA = second-generation antipsychotic.

Surprisingly little is currently known about the prevalence and patterns of antipsychotic use in outpatients treated for depression. One study[38] estimated a 1-year prevalence of SGAs of 20.6% in veterans with MDD uncomplicated by schizophrenia, schizoaffective disorder, or bipolar disorder. In another study,[39] approximately one-third (32.9%) of adult Medicaid patients in 1 state who were diagnosed with MDD but not psychotic disorders received antipsychotics. To date, however, no national estimates are available.

The aim of the present study was to determine nationally representative estimates of prevalence, patterns, and trends in the office-based use of SGAs for adjunctive treatment of adult, nonpsychotic depression. A greater understanding of this emerging clinical practice may help to identify patient populations with high and low likelihoods of receiving SGA adjunctive treatment and put into perspective concerns over the safety profiles of SGAs for treatment-resistant depression.

METHOD

Data Source and Sample

We analyzed 12 years (1999–2010) of data from the National Ambulatory Medical Care Survey (NAMCS). NAMCS is an annual survey conducted by the National Center for Health Statistics that yields nationally representative estimates of visits to US physicians in office-based practice. Each year, the survey samples approximately 3,000 non–federally employed office-based physicians who are primarily engaged in direct patient care. The treating physician or a member of the physician's staff provides information about patient demographics, current diagnoses, and prescriptions. The unit of observation is the physician-patient encounter or visit. Further details on survey and sampling design are available from the National Center for Health Statistics.[40]

Clinical Points

- Second-generation antipsychotics (SGAs) are increasingly used in the outpatient treatment of adult nonpsychotic depression.
- Although approval for SGAs for the treatment of depression is limited to adjunctive use in combination with antidepressants, SGAs were also increasingly prescribed without concurrent antidepressant treatment.
- Given the significant metabolic adverse effects associated with SGAs, careful examination of the long-term benefit-risk balance of adjunctive SGA treatment of depression is vital to guide clinical decision-making.

For the present study, we examined visits with a diagnosis for depression (*ICD-9-CM* 296.2, 296.3, 300.4, 311). Because the scope of the present study is limited to adults, visits of patients younger than 18 years were excluded. To restrict the study population to those most likely to receive antipsychotics for treatment-resistant depression rather than for another indication, we excluded all visits with a diagnoses for schizophrenia (*ICD-9-CM* 295), bipolar disorder (*ICD-9-CM* 296.00–296.16, 296.4–296.81, 296.89), pervasive development disorder (*ICD-9-CM* 299), major depression with psychotic features (*ICD-9-CM* 296.24, 296.34), or dementia (*ICD-9-CM* 290, 294.1, 331.0–2, 331.82, 331.9). Because the FDA has approved antipsychotics in combination with antidepressant treatment and to ensure that patients were actively treated for depression at the time of the visit, visits without a prescription for an antidepressant were also excluded from the primary analysis sample (Figure 1).

Psychotropic Medications

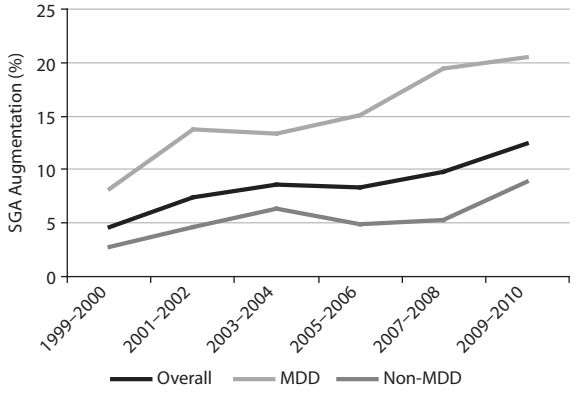
We created a binary variable indicating whether an SGA was prescribed during the visit. In addition, we recorded individual SGAs, specifically aripiprazole, olanzapine, quetiapine, risperidone, and a residual group of all other SGAs. NAMCS recorded up to 6 medications for each visit from 1999 to 2002. Starting in 2003, up to 8 medications were recorded. To make years comparable for our study, we limited the maximum number of medications to the first 6 listed in all years (all 8 medications were included in a sensitivity analysis to empirically assess the impact of the aforementioned restriction). First-generation antipsychotics (FGAs) were included in a secondary analysis to examine the extent to which increase in SGA utilization may reflect a substitution of FGAs in the study population.

Demographic and Clinical Characteristics

Demographic characteristics assessed included patient sex, age, ethnicity/race, and expected source of payment. The survey year was transformed by subtracting 1999 from the year and dividing the results by 11. Thus, the transformed value was 0 for the year 1999 and 1 for the year 2010.[41]

We also included several clinical variables associated with each visit, such as visit sequence (new or repeat visit); physician

Figure 2. Trends in Percentage of Antidepressant-Treated Nonpsychotic Depression Visits With Antipsychotic Augmentation, United States, 1999–2010[a]



[a]Data from National Ambulatory Medical Care Survey.
Abbreviations: MDD = major depressive disorder, SGA = second-generation antipsychotic.

specialty (psychiatry vs not); comorbid anxiety disorder (*ICD-9-CM*: 309.81, 308.3, 300.01, 300.21, 300.22, 300.02, 300.3, 300.2, 300.23, 300.29, 293.84, 300.0, 300.09, 309.21, 313.0); type of depression diagnosis (MDD [296.2, 296.3] vs non-MDD [300.4, 311]); presence of other mental disorders (*ICD-9-CM* 290–319 not listed above); comorbid diabetes, hyperlipidemia, or cardiovascular disease (*ICD-9-CM* 250, 401–404, 410–416, 425–437, 440–447, 272.0–272.4, 272.7, 272.9); and whether psychotherapy was ordered or provided during the visit. All diagnoses were assigned on the basis of any of the 3 diagnosis fields in the survey instrument.

Analysis

Initially, we estimated the proportion of visits with SGA augmentation among all qualifying depression visits with active antidepressant treatment over the 12-year study period (1999–2010). To examine time trends in SGA use, we built multivariate logistic regression models to estimate the association between the transformed survey year variable and SGA augmentation, controlling for all demographic and clinical characteristics described above. Estimated coefficients are presented as odds ratios for ease of interpretation. These models were fit for the study population overall and separately for each subpopulation to estimate overall and subgroup specific trends. Following the analyses of trends in SGA augmentation on the class level, we also examined trends in the use of individual SGAs. In secondary analyses, we also examined trends in use of 2 concurrent antidepressants, use of any antipsychotic (FGA or SGA), and use of an SGA in nonpsychotic depression visits without active antidepressant use.

We then compared demographic and clinical characteristics of patients receiving and not receiving SGA augmentation and modeled the likelihood of receiving an antipsychotic prescription using similar multivariate logistic regression models. These analyses were limited to the 6 most recent survey years to assure that the estimates reflect recent practice patterns.

NAMCS is a multistage probability sample. Analyses were adjusted for visit weights, clustering, and stratification and reflect national estimates.[42] Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

eTable 1 (at PSYCHIATRIST.COM) presents demographic and clinical characteristics of all qualifying depression visits with active antidepressant treatment during the 12-year study period (N = 7,767). Overall, 8.6% (95% CI, 7.7%–9.6%) of these visits included a prescription for an adjunctive SGA. Weighted to the US population, this represents approximately 17.85 million office-based visits with an SGA prescription or an average of 1.49 million visits per year.

Trends in Antipsychotic Augmentation

The percentage of visits that included an adjunctive SGA increased from 4.6% (95% CI, 2.9%–6.3%) in 1999–2000 to 12.5% (95% CI, 9.7%–15.3%) in 2009–2010, representing an annualized estimated 0.7 million visits in 1999–2000 and 2.2 million visits in 2009–2010. Adjusted for all covariates, this increase translates into a multivariate adjusted odds ratio (AOR) for time trend of 2.78 (95% CI, 1.84–4.20). Similar relative increases occurred in patients with and without MDD (Figure 2). Over the same period, treatment with 2 concurrent antidepressants increased from 15.4% in 1999–2000 to 21.4% in 2009–2010 (AOR = 1.82; 95% CI, 1.42–2.30; data not shown). Overall antipsychotic use (FGA or SGA) increased from 6.3% (95% CI, 4.4%–8.1%) in 1999–2000 to 13.0% (95% CI, 10.2%–15.9%) in 2009–2010 with an AOR for time trend of 2.39 (95% CI, 1.60–3.58). The restriction to 6 medication fields for the period from 2003 to 2010 had minimal impact on the results. Inclusion of all 8 medication fields over the 8-year period increased the number of survey visits with adjunctive SGA use by 1.6% from 568 to 577 (unweighted counts).

The increase in SGA augmentation of antidepressant-treated depression visits was broad based (Table 1). Significant increases occurred among visits by men and women, adult patients of all age groups, and patients treated by psychiatrists and nonpsychiatrists. The only visit group that did not experience a substantial numerical increase in antipsychotic augmentation was patients of nonwhite or Hispanic backgrounds, who already had extensive use of antipsychotic augmentation at the start of the study period. The largest increases in antipsychotic augmentation were apparent in visits by patients with cardiovascular diagnoses, patients ≥ 65 years of age, new patients, publicly insured patients, non-Hispanic white patients, and men. However, confidence intervals were wide, and none of the differences across visit strata in time trend for antipsychotic use reached statistical significance.

Marked changes in prescribing preferences for individual SGAs were observed over the study period (Figure 3). From 1999 to 2002, olanzapine (42%) was the most frequently used antipsychotic medication for augmentation, followed by risperidone (32%) and quetiapine (22%), with 0%

Table 1. Antipsychotic Prescribing Trends in Office-Based Medical Visits of Antidepressant-Treated Adult Nonpsychotic Depression, United States, 1999–2010[a]

Variable	SGA Prescription Rates 1999–2002 (n = 2,506)	2003–2006 (n = 2,686)	2007–2010 (n = 2,575)	AOR for Time Trend (95% CI)[b,c]
Overall	6.1	8.4	11.2	2.78 (1.84–4.20)
Demographic characteristics				
Sex				
Male	6.3	8.2	12.5	3.21 (1.78–5.83)
Female	6.0	8.6	10.6	2.60 (1.59–4.24)
Race/ethnicity				
White, non-Hispanic	5.4	8.0	11.1	3.22 (2.14–4.84)
Other	15.3[d]	13.4	12.3	1.12 (0.41–3.08)
Age				
18–44 y	5.9	7.3	10.1	3.06 (1.73–5.43)
45–64 y	7.0	10.5	10.5	2.17 (1.31–3.57)
≥ 65 y	4.6[d]	6.4[d]	12.2	4.60 (1.34–15.80)
Payment source				
Private insurance	4.9	5.7	7.1	2.63 (1.31–5.25)
Public insurance	8.6	14.7	18.4	3.44 (1.79–6.60)
Self-pay, other[e]	7.0	9.9	9.4	2.82 (1.56–5.08)
Clinical characteristics				
Physician-patient relationship				
New patient	6.1[d]	5.6[d]	12.3[d]	4.14 (0.88–19.38)
Established patient	6.1	8.6	11.1	2.71 (1.77–4.17)
Physician specialty				
Other	2.3[d]	4.6	4.7	2.85 (1.29–6.32)
Psychiatry	10.5	13.1	20.1	2.91 (1.87–4.55)
Major depressive disorder				
No	3.8	5.7	7.1	3.16 (1.75–5.71)
Yes	11.0	14.2	20.0	2.67 (1.62–4.39)
Anxiety disorder				
No	5.4	7.5	10.3	2.97 (1.85–4.78)
Yes	11.3	15.3	17.7	2.23 (1.19–4.20)
Other mental health condition				
No	4.1	5.8	7.6	3.19 (1.76–5.77)
Yes	9.7	12.6	14.2	2.41 (1.48–3.91)
Diabetes, hyperlipidemia, or cardiovascular disease				
No	7.1	8.7	11.2	2.57 (1.71–3.88)
Yes	1.7[d]	7.3[d]	7.2[d]	9.65 (1.76–53.07)
Psychotherapy provided				
No	5.1	7.4	8.8	3.07 (1.78–5.17)
Yes	9.6	11.0	15.5	2.52 (1.49–4.26)

[a]Data from National Ambulatory Medical Care Survey (NAMCS). Visits with diagnoses for schizophrenia, bipolar disorder, pervasive development disorder, psychotic depression, or dementia were excluded.
[b]Based on pooled NAMCS data from 1999 to 2010.
[c]Estimates from the logistic regression models in which the dependent variable is antipsychotic prescription. We report the coefficients of the transformed survey year variable, converted to odds ratios. The models were calculated separately for each subpopulation and control for all remaining covariates.
[d]Cell size is less than 30.
[e]Includes self-pay, worker's compensation, no charge/charity, and others. Rates are based on weighted calculations and therefore reflect national estimates.
Abbreviations: AOR = adjusted odds ratio, SGA = second-generation antipsychotic.

representation of aripiprazole (which was first approved in the United States in November 2002, at that time for schizophrenia). By 2007 to 2010, quetiapine (34%) and aripiprazole (30%) had largely displaced olanzapine (11%) and risperidone (18%). Changes in prescribing preference over the course of the study period were significant for aripiprazole ($P < .001$), olanzapine ($P < .001$), quetiapine ($P < .001$), and risperidone ($P = .025$).

Of patients diagnosed with depression, but not receiving current treatment with antidepressants (3,263 observations representing approximately 88 million visits), 6.1% received SGAs, an increase from 3.6% in 1999–2002 to 6.8% in 2007–2010 (AOR = 3.36; 95% CI, 1.63–6.90; data not shown). Trends in prescribing preferences over the study period were similar to those observed in patients receiving SGAs as adjunctive treatment. From 1999 to 2002, olanzapine (44%) and risperidone (45%) were the dominant SGAs, with quetiapine (11%) a distant third. In contrast, by 2007 to 2010, quetiapine (45%) was the most widely used SGA, followed by aripiprazole (20%), risperidone (19%), and olanzapine (11%) (data not shown).

Antipsychotic Augmentation Patterns

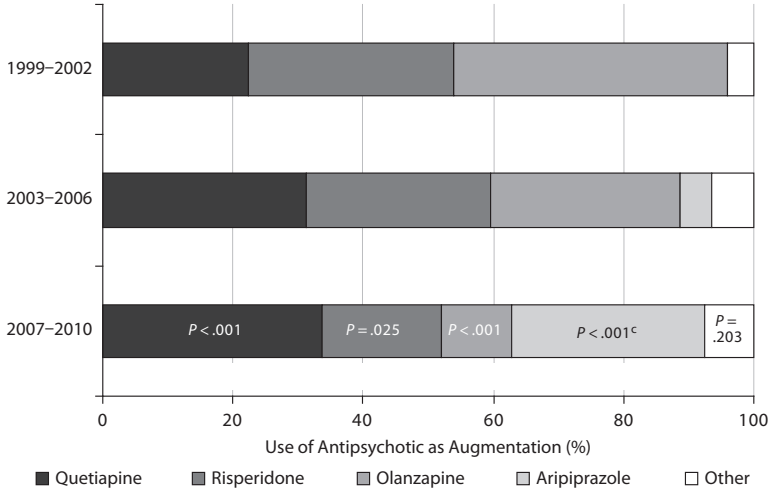
Among depression visits with active antidepressant treatment during 2006–2011 (n = 3,920), SGA use rates were higher in visits to psychiatrists than to other medical specialists, visits covered by public insurance or self-pay/other as compared with private insurance, and visits with a diagnosis of MDD, but lower in visits that provided or ordered psychotherapy and visits of patients ≥ 65 years (Table 2). Visits with comorbid cardiovascular diagnoses were more likely than those without these diagnoses to include an SGA. Visits with comorbid anxiety disorder or other comorbid mental disorder diagnoses were not significantly related to SGA use.

DISCUSSION

Adjunctive SGA treatment for nonpsychotic depression in US office-based medical practice increased more than 2.5-fold since publication of the first major positive trial of SGA augmentation for treatment-resistant depression in the early 2000s.[20] Increase in use was broadly similar across a range of demographic and clinical subgroups, indicating a mainstreaming of SGA use for a large patient population that has historically had low rates of antipsychotic treatment. Treatment by a psychiatrist, public insurance, diagnosis of MDD, and comorbid diabetes, hyperlipidemia, or cardiovascular disease were among the strongest predictors of SGA augmentation. In more recent years (2007–2010), SGA augmentation rates approached or surpassed 20% in visits to psychiatrists, visits of patients diagnosed with MDD, and visits of those covered by public insurance. It is somewhat reassuring that the highest use rates are observed in patients likely to have more severe depression, that is, those with MDD and seen by a psychiatrist.

Elevated cardiovascular or metabolic risk was also associated with adjunctive SGA treatment. Given the well-established metabolic risks of SGAs,[26–30] and limited cardiometabolic

Figure 3. Trends in Antipsychotic Augmentation by Agent in Office-Based Medical Visits for Antidepressant-Treated Adult Nonpsychotic Depression, United States, 1999–2010[a,b]



[a]Data from National Ambulatory Medical Care Survey (NAMCS).
[b]*P* values reflect test of difference in proportions between the 3 time periods for each SGA.
[c]2003–2006 vs 2007–2010 only.
Abbreviation: SGA = second-generation antipsychotic.

monitoring in antipsychotic-treated patients,[31] this trend warrants closer scrutiny. It is possible that relatively high rates of SGA use in this population reflect a greater degree of depression severity and treatment resistance in patients with cardiovascular/metabolic conditions or associations between depression and insulin resistance, metabolic syndrome, and cardiovascular illness.[43–50]

A substantial increase in SGA use was also observed among visits by older depressed patients. Although older age was predictive of less antipsychotic augmentation compared to younger age, the substantial increase in SGA use in the older patient population should prompt a careful risk assessment, given the black-box warning for increased all-cause mortality of SGAs in the elderly with dementia.[51]

Another potentially concerning observation was the considerable and growing use of SGAs for nonpsychotic depression without concurrent antidepressant treatment, as approval for SGAs for this indication is limited to adjunctive treatment. We found no evidence that the increase in SGA augmentation was compensated by a corresponding decrease in antidepressant combination treatment, as antidepressant cotreatment also increased over time, although the evidence base for this combination treatment is weak.[5] Despite the inability to distinguish between antidepressant combination therapy and cross-titration between 2 antidepressants using cross-sectional survey data, it is unlikely that the observed increase in visits with 2 concurrent antidepressants is compatible with a reduction in intended antidepressant combination treatment. If confirmed in longitudinal datasets, this finding suggests an overall intensification of pharmacologic combination treatments in depression and may reflect greater clinical attention to incomplete treatment response. Our finding that inclusion of FGAs did not significantly alter the magnitude of the observed increase in antipsychotic use suggests that the increasing trend of SGA augmentation does not merely represent a substitution effect from first-generation agents.

A substantially larger proportion of publicly than privately financed depression visits included an SGA. While the surveys lack the necessary clinical detail to evaluate the causes of this treatment pattern, it is possible that public insurance serves as a proxy for greater depression severity or greater treatment resistance. Differences in SGA utilization may also reflect disparities in how physicians approach depression treatment in these 2 patient populations or a greater degree of formulary restrictions or cost-sharing in private insurance programs.[52,53]

The observation that SGA augmentation was approximately 30% less likely in visits that included or ordered psychotherapy is of potential importance, as it may indicate that psychotherapy can reduce the need for SGA augmentation[54,55] and may provide a safer initial treatment alternative for patients who do not achieve remission of depressive symptoms with antidepressant monotherapy. Adjunctive cognitive behavioral therapy has recently been shown to be a potentially effective treatment alternative for reducing depressive symptoms in this population.[56] However, because the NAMCS does not sample mental health professionals, other than psychiatrists, it is not possible to assess the full extent to which patients receive combined psychotherapy and pharmacologic treatments for depression. While an alternative explanation for this finding could be that visits with psychotherapy generally involve less severely ill patients or that physicians who provide psychotherapy are more reluctant to prescribe SGAs,[57] the fact that absolute SGA augmentation rates were higher in visits with psychotherapy militates against these explanations. Nonetheless, due to the aforementioned limitations, this finding should be viewed as strictly hypothesis generating.

In visits with SGA augmentation, we observed a clear trend toward treatment with aripiprazole and quetiapine and away from treatment with olanzapine and, to a lesser degree, risperidone. This observation parallels trends in the broader use of SGAs in other clinical populations during this time period, particularly the declining use of olanzapine in response to increased awareness of its metabolic risks.[58] Risperidone, despite not having FDA approval for augmentation in depression, still remains relatively commonly used for nonpsychotic depression.

Strengths and Limitations

Our study, the first to present nationally representative data on patterns and trends in SGA augmentation for nonpsychotic depression, is subject to several limitations. First,

Table 2. Patterns and Predictors of Antipsychotic Prescribing in Office-Based Medical Visits of Antidepressant-Treated Adult Nonpsychotic Depression, United States, 2005–2010[a]

Variable	SGA Augmentation (n = 435)	No SGA Augmentation (n = 3,485)	AOR for SGA Augmentation (95% CI)
Demographic characteristics			
Sex			
Female	66.0	68.9	0.95 (0.73–1.25)
Male	34.0	31.1	1.0
Race/ethnicity			
White, non-Hispanic	87.5	91.3	0.68 (0.43–1.08)
Other	12.5	8.7	1.0
Age			
18–44 y	40.6	38.6	1.0
45–64 y	45.9	45.3	0.87 (0.67–1.13)
≥ 65 y	13.6	16.8	0.51 (0.32–0.82)
Source of payment			
Private insurance	32.7	49.6	1.0
Public insurance	38.2	21.9	3.20 (2.25–4.54)
Self-pay, other[b]	29.1	28.5	1.57 (1.10–2.24)
Clinical characteristics			
Visit type			
New	5.8	6.2	1.0
Established	94.2	93.8	1.14 (0.61–2.12)
Physician specialty			
Other	25.3	60.3	1.0
Psychiatry	74.7	39.8	5.08 (2.96–8.73)
Major depressive disorder			
No	42.4	70.7	1.0
Yes	57.6	29.3	1.49 (1.08–2.06)
Anxiety disorder			
No	77.1	88.4	1.0
Yes	22.9	11.7	1.21 (0.89–1.64)
Other mental health condition			
No	52.8	62.6	1.0
Yes	47.2	37.4	1.03 (0.79–1.35)
Diabetes, hyperlipidemia, or cardiovascular disease			
No	88.7	84.6	1.0
Yes	11.3	15.4	2.13 (1.12–4.03)
Psychotherapy provided			
No	61.5	72.4	1.0
Yes	38.5	27.6	0.68 (0.47–0.96)

[a]Data from National Ambulatory Medical Care Survey. Visits with diagnoses for schizophrenia, bipolar disorder, pervasive development disorder, psychotic depression, or dementia were excluded.
[b]Includes self-pay, worker's compensation, no charge/charity and others.
Abbreviations: AOR = adjusted odds ratio, SGA = second-generation antipsychotic.

because of the cross-sectional design and limited clinical detail of the survey data, it is not possible to examine the history of a patient's depression treatment or follow patients over the course of their SGA trials. We thus cannot examine SGA augmentation rates in patients who meet criteria for treatment resistance, assess the appropriateness of SGA augmentation, characterize treatment dose or duration, or examine treatment outcomes. More detailed research is needed on dose and duration of SGA trials in usual practice to assess the potential metabolic risks at doses that are generally lower when given adjunctively for depression than when used in schizophrenia or bipolar mania.[38] Neither the randomized controlled trials for SGA augmentation in depression nor clinical practice guidelines give clinicians much guidance in terms of how long depressed patients should be maintained on SGAs if they respond to this adjuvant treatment.

Second, because the NAMCS samples visits rather than patients, some duplication of patients is possible. However, because each sampled physician practice contributes visits during a single, randomly assigned week in the survey year, such duplication is likely to have limited impact on the reported estimates. Third, diagnoses in the NAMCS are based on the independent judgment of the treating physician, rather than research diagnostic interviews.[59] Fourth, we restricted the number of medications per visit to 6 to assure that trend analyses would not be biased by changes in the structure of the NAMCS medication assessment. While this could potentially result in an underascertainment of SGA use during the 2003–2010 period, the impact of the change in the assessment structure on the number of visits with adjunctive SGA treatment was minimal, as demonstrated in sensitivity analysis. Fifth, despite the relatively large sample sizes, the limited number of visits within certain patient groups resulted in wide confidence intervals for some estimates, particularly for subgroup-specific time trends. Sixth, several settings that provide ambulatory care for patients with depression, such as community mental health centers and hospital outpatient departments, are not within the scope of NAMCS.

SUMMARY AND CONCLUSION

Growing use of SGAs for nonpsychotic depression should be seen in the context of the evidence base of adjunctive SGA treatment. Despite being the best-supported intervention for treatment-resistant depression, SGA augmentation has a moderate effect size, with a number needed to treat of approximately 9 for both response and remission.[6] Given the significant metabolic adverse effects associated with SGAs, careful examination of the long-term benefit-risk balance of adjunctive treatment of depression with SGAs is vital to guide clinical decision-making for the treatment of patients who have inadequate response to antidepressant treatment. Education and a focus on medical comorbidities in depressed patients are particularly relevant, as our data point toward frequent use of SGAs in higher cardiovascular risk subgroups.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), lithium (Lithobid and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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Author contributions: Dr Gerhard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr Gerhard** has received an honorarium from Boehringer Ingelheim. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, Alexza; Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, Janssen/Johnson & Johnson, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva, and Vanda and has received grant support from Bristol-Myers Squibb, Janssen/Johnson & Johnson, and Otsuka. The other authors have no conflicts to report.

Funding/support: This work was supported by Agency for Healthcare Research & Quality—Centers for Education & Research on Therapeutics award U19 HS021112-02 for the Rutgers Center for Education and Research on Mental Health Therapeutics.

Role of the sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review or approval of the manuscript.

Previous presentation: An earlier version of this research was, in part, presented at the 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management; August 23–26, 2012; Barcelona, Spain.

Additional information: The National Ambulatory Medical Care Survey (NAMCS) is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The NAMCS public use data files may be obtained at http://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm.

Supplementary material: Available at PSYCHIATRIST.COM.

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THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: National Trends in Second-Generation Antipsychotic Augmentation for Nonpsychotic Depression

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DOI Number: 10.4088/JCP.13m08675

List of Supplementary Material for the article

1. eTable 1 Demographic and Clinical Characteristics of Office-Based Medical Visits of Antidepressant-Treated Adult Nonpsychotic Depression, United States, 1999 to 2010

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eTable 1.Demographic and Clinical Characteristics of Office-Based Medical Visits of Antidepressant Treated Adult Non-Psychotic Depression, United States, 1999 to 2010

Variable	Weighted Percentage n=7,767
Demographic Characteristics	
Sex	
Female	68.4
Male	31.6
Race/Ethnicity	
White, non-Hispanic	91.5
Other	8.5
Age (years)	
18 – 44	42.2
45 – 64	42.9
≥ 65	14.9
Source of Payment	
Private Insurance	52.8
Public Insurance	22.7
Self-Pay, Other[a]	24.5
Clinical Characteristics	
Visit Type	
New Patient	6.6
Established Patient	93.4
Physician Specialty	
Other	55.3
Psychiatry	44.7
Major Depressive Disorder	
No	67.9
Yes	32.1
Anxiety Disorder	
No	87.9
Yes	12.1
Other Mental Health Condition	
No	63.2
Yes	36.8
Diabetes, Hyperlipidemia or CVD	
No	86.3
Yes	13.7
Psychotherapy Provided	
No	70.4
Yes	29.6

Data from NAMCS. Visits with diagnoses for schizophrenia, bipolar disorder, pervasive development disorder, psychotic depression, or dementia were excluded.
[a]Includes self pay, worker's comp., no charge/charity and others. Rates are based on weighted calculations therefore reflect national estimates.