

National Trends in the Antipsychotic Treatment of Psychiatric Outpatients With Anxiety Disorders

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Objective: The purpose of the present study was to examine patterns and recent trends in the antipsychotic medication treatment of anxiety disorders among visits to office-based psychiatrists in the United States.

Method: Annual data from the 1996–2007 National Ambulatory Medical Care Survey were analyzed to examine the patterns and trends in antipsychotic medication treatment within a nationally representative sample of 4,166 visits to office-based psychiatrists in which an anxiety disorder was diagnosed.

Results: Across the 12-year period, antipsychotic prescriptions in visits for anxiety disorders increased from 10.6% (1996–1999) to 21.3% (2004–2007). Over the study period, the largest increase in antipsychotic prescribing occurred among

new patient visits. Antipsychotic prescribing also significantly increased among privately insured visits and visits in which neither antidepressants nor sedative/hypnotics were prescribed. Among the common anxiety disorder diagnoses, the largest increase in antipsychotic medication treatment was observed in visits for panic disorder. Antipsychotic prescribing rose from 6.9% (1996–1999) to 14.5% (2004–2007) among visits for anxiety disorders in which there were no co-occurring diagnoses with an indication approved by the Food and Drug Administration for antipsychotic medications.

Conclusions: Although little is known about their effectiveness for anxiety disorders, antipsychotic medications are becoming increasingly prescribed to psychiatric outpatients with these disorders.

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Since the introduction of second-generation antipsychotic agents over two decades ago, antipsychotic medications have become increasingly common in the management of diverse clinical populations (1–5). In 2009, U.S. spending for antipsychotic medications was estimated at \$14.6 billion, making them the most costly class of prescription drugs on the market (6). Part of this increase is explained by growth in the number of conditions for which the U.S. Food and Drug Administration (FDA) has approved antipsychotic medications. These conditions currently include schizophrenia, schizoaffective disorder, bipolar disorder, irritability associated with autistic disorder, and treatment-resistant depression when the antipsychotic is coadministered with an antidepressant.

Community practice patterns suggest that antipsychotic medications are often used for diagnoses outside of the FDA-approved indications (1–3, 5). For some, this practice raises questions regarding trade-offs between clinical benefit and risks. Potential adverse effects of antipsychotics, including metabolic, endocrine, and cerebrovascular risks, have been well documented (7–9).

Sedative properties associated with antipsychotic medications (10) may help to explain their broadened use in nonpsychotic patients. Some have suggested that from a pharmaco-epidemiological perspective, these drugs

should be considered “antineurotic” or “hypnotic” medications rather than antipsychotics (11). In this context, patients presenting with anxiety disorders represent a large potential population for antipsychotic treatment. Clinical guidelines recommend serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors as first-line pharmacologic treatments for anxiety disorders (12), although a significant number of patients do not respond to an adequate trial of these medications. Given risks of cognitive side effects, withdrawal syndrome, and the potential for abuse associated with benzodiazepines, antipsychotic medications have been viewed as playing a role in treatment-resistant anxiety disorders (12).

Patterns of antipsychotic medication treatment for anxiety disorders in psychiatric practice remain poorly defined. Evaluations have focused exclusively on either specific age groups (2–4), geographically restricted regions (13, 14), or selected insured populations (15). Large-scale population-based evaluations of broadening antipsychotic prescribing have not specifically addressed patterns and trends in the treatment of anxiety disorders.

The present report examines recent national trends and patterns in the antipsychotic medication treatment of anxiety disorders by office-based psychiatrists. Among office visits in which an anxiety disorder was mentioned

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across a 12-year period (1996–2007), antipsychotic treatment patterns and time trends were examined by patient sociodemographic and clinical characteristics. We predicted a broad-based national increase in the rate of antipsychotic prescribing in office visits for anxiety disorders, with particularly pronounced increases among anxiety disorder visits that did not include co-occurring diagnoses and those in which the diagnoses lacked FDA-approved antipsychotic indication. We further predicted that these increases would be largely attributable to expanded prescribing of second-generation antipsychotics.

Method

Sample

Encompassing a 12-year period (1996–2007), data were drawn from the National Ambulatory Medical Care Survey, a multistage probability survey of visits to office-based physicians of all medical specialties engaged in direct patient care. Survey response rates varied from 62.9% to 77.1% (median=67.7%). A systematic random sample of visits to each physician was drawn during a randomly selected 1-week period. We limited the sample to 4,166 outpatient visits to psychiatrists in which an anxiety disorder was diagnosed. The following six anxiety disorder classes were included: traumatic stress disorders, panic disorder/agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder (OCD), phobias, and other anxiety disorders.

Assessments

For each visit, the psychiatrist or member of the psychiatrist's staff provided information about patient sociodemographic and clinical characteristics and psychotropic medications prescribed or supplied to the patient. In the present article, the term "prescribed" is used to refer to prescribed or supplied medications.

Psychotropic Medications

Up to six medications were recorded in each visit from 1996 to 2002. Starting in 2003, up to eight medications were recorded. To make years comparable in the present study, we limited the maximum number of medications to the first six listed in all years. Antipsychotic medications, including first- and second-generation agents, as well as antidepressants, sedative/hypnotics, and mood stabilizers were included. Psychotropic agents included in each medication class are presented in the Appendix in the data supplement accompanying the online version of this article. Visits were classified as either antipsychotic visits, in which the patient was prescribed at least one antipsychotic, or nonantipsychotic visits, in which the patient was not prescribed an antipsychotic medication.

Antipsychotic indication status was based on FDA-approved indications for antipsychotic treatment as of May 20, 2010. One or more antipsychotics have been approved for the following illnesses: schizophrenia or schizoaffective disorder, bipolar disorder, pervasive developmental disorder, and major depressive disorder when coprescribed with an antidepressant. Although no antipsychotic medications are currently approved for the treatment of schizophreniform disorder, since most patients with this disorder transition to schizophrenia within 1 year, we deemed schizophreniform disorder an approved antipsychotic indication. We considered all visits in which any of these clinical diagnoses was assigned as visits for which FDA indication for antipsychotic treatment was established, regardless of whether the visit occurred before or after the first FDA-approved antipsychotic use for that diagnosis. To cast a broad net in capturing FDA-approved antipsychotic indications, we considered a visit as establishing an

approved indication if any antipsychotic was FDA-approved for the diagnosis assigned, regardless of the specific antipsychotic drug prescribed. We also disregarded age when considering approved antipsychotic indications.

Up to three diagnoses were recorded for each visit. Anxiety disorder diagnoses were classified into the following six broad categories: 1) traumatic stress disorders (ICD-9-CM: 309.81, 308.3), which included posttraumatic and acute stress disorders; 2) panic disorder/agoraphobia (ICD-9-CM: 300.01, 300.21, 300.22); 3) generalized anxiety disorder (ICD-9-CM: 300.02), characterized by excessive/uncontrollable worry with associated somatic symptoms; 4) OCD (ICD-9-CM: 300.3); 5) phobias (ICD-9-CM: 300.2, 300.23, 300.29), characterized by marked, persistent, and interfering fear of specific objects or situations, including specific and social phobias; and 6) other anxiety disorders (ICD-9-CM: 293.84, 300.0, 300.09, 309.21, 313.0), which included anxiety state (unspecified), other anxiety states, anxiety disorder as a result of a general medical condition, substance-induced anxiety disorder, separation anxiety disorder, and overanxious disorder. Primary source of payment was classified as private insurance, public insurance, self-pay, or other.

Other variables were patients' sex, age range (≤ 17 years, 18–34 years, 35–54 years, ≥ 55 years), race/ethnicity (non-Hispanic Caucasian, non-Hispanic African American, Hispanic, other), visit sequence (returning patient versus new patient), and comorbidity (single or multiple anxiety disorders only, anxiety diagnoses and other classes of comorbid axis I disorders). Visits for anxiety disorders in which other classes of comorbid mental disorders were also determined were further broken down into the following three overlapping groups: comorbid mood disorders (ICD-9-CM: 296.0–296.9, 298.09, 300.4, 301.13, and 311), comorbid psychotic disorders (ICD-9-CM: 295 and 297–299), and other comorbid disorders.

Analysis

First, we charted the change in the number of visits for anxiety disorders in which an antipsychotic medication was prescribed and considered this change relative to trends in visits in which antidepressants or sedative/hypnotics were prescribed across the same period. We next examined sociodemographic and clinical correlates of antipsychotic prescribing in visits for anxiety disorders. Third, we assessed time trends in antipsychotic medication treatment in visits for anxiety disorders across strata based on clinical and sociodemographic characteristics, adjusting for the effects of other demographic and clinical characteristics.

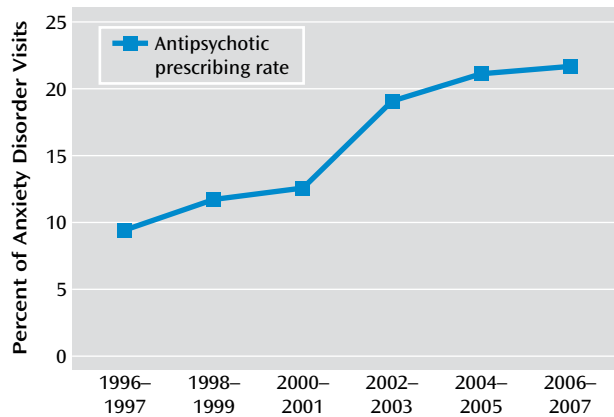
Analyses were adjusted for visit weights, clustering, and stratification of data using design elements provided by the National Center for Health Statistics. When adjusted for these elements, survey data represent annual visits to U.S. office-based physicians (16). We examined time trends in visits in which antipsychotic medication was prescribed using multivariate binary logistic models. The survey year was transformed by subtracting 1996 from the year and dividing the results by 11. Thus, the transformed value was 0 for the year 1996 and 1 for the year 2007. The odds ratios associated with this transformed variable represent change in the odds of visits in which antipsychotic medication was prescribed across the entire study period. Analyses were conducted using STATA, version 11 (StataCorp., College Station, Tex.).

Results

Trends in Visits for Anxiety Disorders and Antipsychotic Treatment in Office-Based Psychiatric Practice

Across the study period, there was a significant increase in the percentage of office-based visits to psychiatrists in which an anxiety disorder was diagnosed, from 21.2%

FIGURE 1. Patterns in Antipsychotic Prescribing in U.S. Office-Based Visits to Psychiatrists for Anxiety Disorders (1996–2007)

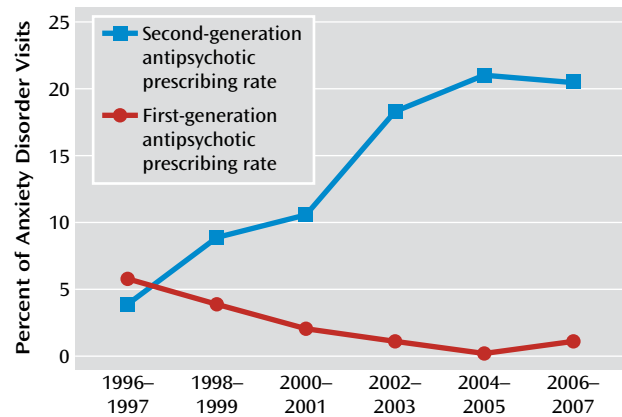


(1996–1999) to 25.7% (2004–2007). There was also an increase in the percentage of psychiatry visits in which antipsychotic medications were prescribed, from 17.8% (1996–1999) to 26.5% (2004–2007) (adjusted odds ratio=2.03, 95% confidence interval [CI]=1.46–2.82, $p<0.001$). However, the increase in prescriptions for antipsychotic medication in visits for anxiety disorders could not be fully attributed to increased use of antipsychotics overall. Over time, visits for anxiety disorders accounted for an increasing proportion of the visits in which antipsychotic medication was prescribed, from 12.6% (1996–1999) to 20.7% (2004–2007) (adjusted odds ratio=2.18, 95% CI=1.24–3.84, $p=0.007$).

The percentage of U.S. office-based psychiatrist visits for anxiety disorders that included antipsychotic medication prescriptions roughly doubled across the 12-year period, increasing from 10.6% (1996–1999) to 21.3% (2004–2007) (odds ratio=3.34, 95% CI=2.0–5.5, $p<0.001$). For perspective, similar but less impressive increases were also observed in the odds ratios for prescriptions for antidepressants (odds ratio=2.03, 95% CI=1.3–3.1, $p=0.001$) and sedative/hypnotics (odds ratio=1.52, 95% CI=1.0–2.3, $p<0.05$) in these visits, and no statistically significant finding was observed in odds ratios for mood stabilizer prescriptions. The increase in the percentage of visits for anxiety disorders in which antipsychotics were prescribed was monotonic (Figure 1). The percentage of visits for anxiety disorders in which only anxiety diagnoses were mentioned and antipsychotic medication was prescribed significantly increased.

During the study period, there was a marked transition in the class of antipsychotic medications prescribed in visits for anxiety disorders. The percentage of these visits in which second-generation antipsychotics were prescribed increased from 3.8% (1996–1997) to 20.5% (2006–2007) (odds ratio=5.82, 95% CI=3.4–9.8, $p<0.001$), whereas the percentage in which first-generation antipsychotics were prescribed decreased from 5.8% (1996–1997) to 1.0% (2006–2007) (odds ratio=0.07, 95% CI=0.02–0.2, $p<0.001$) (Figure 2). These findings parallel the overall course in the

FIGURE 2. Patterns in First- and Second-Generation Antipsychotic Prescribing in U.S. Office-Based Visits to Psychiatrists for Anxiety Disorders (1996–2007)



increased use of second-generation antipsychotics (odds ratio=4.36, 95% CI=3.2–6.0, $p<0.001$) and decreased use of first-generation antipsychotics (odds ratio=0.12, 95% CI=0.1–0.2, $p<0.001$) in office-based psychiatric care during this period.

Patterns and Clinical Correlates of Antipsychotic Medication Treatment in Visits for Anxiety Disorders

During the study period, 16.7% (N=596) of visits to office-based psychiatrists for anxiety disorders included an antipsychotic medication prescription. In adjusted analyses, visits in which antipsychotic medication was prescribed were significantly associated with younger patient age, African American race/ethnicity, public insurance, and comorbidity (Table 1). Relative to visits in which there was no diagnosis with an FDA-approved indication, those in which a codiagnosed FDA indication was present had a significantly greater likelihood of including a prescription for an antipsychotic medication. Prescribing of antipsychotics in visits for anxiety disorders was not associated with antidepressant or sedative/hypnotic prescription after accounting for potentially confounding patient characteristics.

Stratified Time Trends in Antipsychotic Medication Treatment

Across the 12-year period, a significant increase occurred in the percentage of visits for anxiety disorders in which an antipsychotic medication was prescribed, among both sexes as well as among several mental disorder diagnosis groups (Table 2). After controlling for several patient characteristics, including comorbidity, the largest proportionate increase in antipsychotic prescriptions was among new patient visits. Antipsychotic prescribing also substantially increased among privately insured visits, visits in which neither antidepressants nor sedative/hypnotics were prescribed, and visits in which there were no comorbid nonanxiety diagnoses. Among office visits for anxiety disorder diagnoses, those for panic disorder as well as the residual other anxiety disorders group showed the largest

TABLE 1. Patterns in Antipsychotic Prescribing for Anxiety Disorders Among 4,166 Visits to Office-Based Psychiatrists in the United States (1996–2007)^a

Characteristic	Total N	Antipsychotic Treatment Visits		Statistical Analysis					
		N	%	Odds Ratio ^b	95% CI	p	Adjusted Odds Ratio ^c	95% CI	p
Sex									
Female	2,564	389	17.9	1.00			1.00		
Male	1,602	207	14.7	0.79	0.6–1.0	0.05	0.99	0.8–1.3	0.92
Age (years)									
≤17	484	100	23.0	1.00			1.00		
18–34	846	87	12.2	0.47	0.3–0.7	<0.001	0.51	0.3–0.8	<0.01
35–54	2,009	287	17.0	0.69	0.5–1.0	0.02	0.76	0.5–1.1	0.15
≥55	827	122	17.0	0.69	0.5–1.0	0.03	0.58	0.4–0.9	0.01
Race/ethnicity									
Caucasian	3,679	495	15.6	1.00			1.00		
African American	181	48	30.4	2.37	1.6–3.4	<0.001	1.97	1.2–3.1	<0.01
Hispanic	201	31	17.9	1.18	0.7–1.9	0.49	1.13	0.7–1.9	0.62
Other	86	18 ^d	23.7	1.68	1.0–2.8	0.05	1.70	1.0–2.9	0.06
Payment source									
Private insurance	1,847	236	15.3	1.00			1.00		
Public insurance	776	204	29.0	2.25	1.7–2.9	<0.001	2.02	1.5–2.7	<0.001
Self-pay or other	1,405	133	11.1	0.69	0.5–1.0	0.04	0.86	0.6–1.2	0.38
Visit sequence									
Returning patient	3,889	561	16.8	1.00			1.00		
New patient	245	34	16.9	1.00	0.6–1.6	0.99	1.00	0.6–1.7	0.99
Anxiety disorder diagnosis^e									
Traumatic stress disorders	737	182	26.2	2.08	1.6–2.7	<0.001	1.66	1.1–2.4	0.01
Panic disorder/agoraphobia	969	115	14.4	0.79	0.6–1.0	0.08	0.81	0.5–1.2	0.34
Generalized anxiety disorder	858	104	14.8	0.83	0.6–1.2	0.36	0.82	0.5–1.3	0.43
Obsessive-compulsive disorder	655	99	16.6	0.99	0.7–1.4	0.95	1.20	0.8–1.8	0.40
Phobias	144	10 ^d	10.7	0.59	0.3–1.2	0.15	0.60	0.3–1.3	0.18
Other anxiety disorder	1,103	135	15.6	0.90	0.7–1.2	0.51	0.98	0.6–1.5	0.94
Comorbidity status									
Single or multiple anxiety disorders only	1,704	101	7.2	0.26	0.2–0.4	<0.001	0.25	0.1–0.6	<0.01
Other classes of axis I disorders	2,462	495	22.8	1.00			1.00		
Specific classes of other axis I comorbid disorders^f									
Mood disorder	1,805	356	23.2	2.40	2.0–3.0	<0.001	1.30	1.0–1.7	0.05
Psychotic disorder	82	61	76.5	17.90	10.2–31.3	<0.001	14.80	8.0–27.3	<0.001
Other disorder	1,154	199	19.0	1.20	1.0–1.6	0.06	0.68	0.5–0.9	<0.01
FDA-approved antipsychotic indication status^g									
Approved	1,200	308	28.5	3.14	2.5–3.9	<0.001	2.07	1.6–2.7	<0.001
No approval	2,966	288	11.2	1.00			1.00		
Nonantipsychotic medication category^h									
Antidepressant (no), sedative/hypnotic (no)	1,052	106	12.8	1.00			1.00		
Antidepressant (yes), sedative/hypnotic (no)	1,408	216	16.8	1.38	1.0–1.9	0.06	1.00	0.7–1.5	0.99
Sedative/hypnotic (yes), antidepressant (no)	459	60	13.9	1.10	0.7–1.7	0.64	1.10	0.7–1.7	0.70
Antidepressant (yes), sedative/hypnotic (yes)	1,247	214	20.1	1.72	1.2–2.4	<0.01	1.15	0.7–1.8	0.52
Survey year				3.34	2.0–5.5	<0.001	2.54	1.6–4.0	<0.001

^a Weighted data are taken from the National Ambulatory Medical Care Survey and indicate office visits in which an anxiety disorder is diagnosed.

^b Ratios presented are associated with the transformed survey year variable.

^c Analyses accounted for sex, age, race/ethnicity, source of payment, visit sequence, anxiety disorder diagnosis, and the number of overall mental disorders.

^d Estimates based on survey data with <30 observations, or with a relative standard error <0.3, are deemed imprecise and are not to be interpreted.

^e Anxiety disorder categories are not mutually exclusive; the reference group for each anxiety disorder category represents office visits in which the specified disorder was not present.

^f The reference group for each comorbidity category represents office visits in which the specified comorbidity pattern was not present.

^g See the Method section for a description of FDA-approved antipsychotic indication status (ICD-9-CM: 295.0–295.95, 296.00–296.16, 296.2–296.81, 296.89, 299.00–299.9).

^h The reference group for each nonantipsychotic medication category represents office visits without prescription of the nonantipsychotic medication combination indicated.

increase in antipsychotic medication prescribing. Antipsychotic treatment rose significantly in office visits for generalized anxiety or traumatic stress disorders. Antipsychotic prescribing significantly increased in office visits for anxiety disorders with comorbid mood, comorbid nonmood, and comorbid nonpsychotic disorders but not comorbid psychotic disorders. For visits in which an FDA-approved antipsychotic indication was not present, the proportion of antipsychotic prescribing roughly doubled.

Quetiapine (8.9%), risperidone (4.3%), and olanzapine (3.8%) were the most common antipsychotics prescribed in visits for anxiety disorders in 2004–2007. Quetiapine was more commonly prescribed in visits for traumatic stress disorder (17.2% of visits; 95% CI=11.5%–24.8%) than for any other anxiety disorder type. Similarly, risperidone was more commonly prescribed in visits for traumatic stress disorder (7.1% of visits; 95% CI=4.3%–11.5%) than for any other anxiety disorder type. Olanzapine was most commonly prescribed in visits for OCD (4.8% of visits; 95% CI=2.3%–9.6%).

Discussion

The findings of this study should be interpreted in the context of several limitations. First, despite adjustment for several visit and patient characteristics, including clinical diagnosis, comorbidity, and payment source, we cannot exclude the possibility that trends reflect residual confounding as a result of changes in unmeasured clinical differences across years. For example, although there were not increases across time in comorbid psychotic or mood disorders in office visits for anxiety disorders, there was an increase in overall comorbid disorders, which we consequently accounted for in adjusted time-trend analyses. Second, the survey does not record previous clinical response to psychotropic regimens, measure the effects of antipsychotic treatment on clinical outcomes, or assess the duration of antipsychotic trials with patients' current or previous physicians. These shortcomings constrain the clinical meaning of visit sequence. It is accordingly not possible to determine at the patient level whether observed antipsychotic prescribing is associated with increased or decreased use of other medication classes. However, cross-sectional analyses demonstrate similar but less impressive increases across time in visits for anxiety disorders in which antidepressant and sedative/hypnotic medications were prescribed and no trend in mood stabilizer prescribing. At a population level, these patterns suggest that antipsychotics are augmenting, rather than replacing, other medication classes in the management of anxiety disorders. Nevertheless, a proportionate increase was also noted in the use of antipsychotic medications in the absence of other medication classes (Table 1). Third, information was not available on dosing, which is likely considerably lower in anxiety disorders than in psychotic disorders. For clozapine and olanzapine, the balance of evidence suggests a

dose-response relationship with metabolic side effects (17). Fourth, the analysis may misclassify combinations of medications used by patients who receive psychiatric care from multiple physicians. Fifth, because our analysis is limited to office-based psychiatrists, the results do not generalize to other specialties and treatment settings where patients receive mental health services. Sixth, clinical diagnostic determinations may vary over time with changing practice patterns. Without structured diagnostic interviews, it is not possible to examine such variations. It is also not possible to determine the extent to which survey data undercount psychotic disorders or other conditions, fail to document diagnosed mental disorders, or do not capture nonpsychiatric targets of antipsychotic treatment. Seventh, the two most recently approved antipsychotics, asenapine and iloperidone, were not included in the present analysis. Finally, because the survey records visits rather than patients, some patient duplication may occur.

Despite these limitations, the National Ambulatory Medical Care Survey offers a national statistical portrait of trends in antipsychotic treatment of anxiety disorders in office-based psychiatry. From 1996 to 2007, there was a roughly twofold increase in the rate of antipsychotic prescribing for anxiety disorders in this practice setting. The proportion of visits for anxiety disorders in which an antipsychotic medication was prescribed increased from roughly one in 10 visits to roughly one in five visits. This finding extends earlier reports of increasing overall psychotropic treatment for individuals with anxiety disorders (18) and increasing antipsychotic prescribing, particularly with second-generation antipsychotics, in the general population of outpatients (1, 19). Growth in antipsychotic treatment for anxiety disorders has been broad based, with the most pronounced increases among new patients, privately insured patients, and patients diagnosed with panic disorder (among other groups).

The reasons for these trends remain unclear. Thus, changes in patient characteristics, including increasing severity of illnesses encountered in outpatient practice and greater prevalence or recognition of comorbidities, offer possible explanations. We found an overall association between comorbid psychiatric diagnoses and prescription of an antipsychotic medication. However, across the study period, the antipsychotic prescribing rate roughly doubled among office visits in which only anxiety disorders were diagnosed. Changes in diagnosed psychiatric comorbidity cannot fully account for the observed trends in antipsychotic prescribing.

Greater patient or physician emphasis on symptom reduction, alongside increased acceptance of off-label antipsychotic prescribing, may have contributed to the observed trends (20). Some psychiatrists may generalize from their clinical experience, treating severely depressed patients with antipsychotic medications (21), to those patients with anxiety disorders. The availability of new antipsychotics, including olanzapine (1997), quetiapine (1997), zipras-

TABLE 2. Stratified Analyses of Trends in Antipsychotic Prescribing for Anxiety Disorders Among 4,166 Visits to Office-Based Psychiatrists in the United States (1996–2007)^a

Characteristic	Antipsychotic Treatment Visits								
	1996–1999			2000–2003			2004–2007		
	Total N	N	%	Total N	N	%	Total N	N	%
Sex									
Female	659	63	10.6	932	142	17.4	973	184	22.9
Male	389	29 ^d	10.5	584	70	13.1	629	108	18.7
Age (years)									
≤17	81	11 ^d	17.0	216	46	22.0	179	43	27.2
18–34	187	13 ^d	6.5	308	23 ^d	9.4	351	51	17.6
35–54	573	49	10.5	745	110	16.5	691	128	22.4
≥55	199	19 ^d	12.2	247	33	15.5	381	70	20.3
Race/ethnicity									
Caucasian	928	73	9.3	1,369	174	14.1	1,382	248	20.9
African American	39	7 ^d	19.7	72	24 ^d	36.7	79	17 ^d	28.1
Hispanic	47	6 ^d	16.2	52	9 ^d	16.2	102	16 ^d	19.8
Other	30	5 ^d	21.7	18	5 ^d	27.7	38	8 ^d	23.0
Source of payment									
Private insurance	381	29 ^d	8.5	684	80	13.7	782	127	19.8
Public insurance	142	24 ^d	21.2	306	68	23.2	328	112	36.7
Self-pay or other	516	39	9.2	454	54	14.8	435	40	9.8
Visit sequence									
Returning patient	975	87	10.8	1,404	200	16.0	1,510	274	21.3
New patient	70	5 ^d	8.0	83	11 ^d	17.5	92	18 ^d	22.2
Anxiety disorder diagnosis ^e									
Traumatic stress disorders	168	27 ^d	17.4	265	62	24.9	304	93	32.4
Panic disorder/agoraphobia	299	24 ^d	8.0	330	38	12.6	340	53	21.3
Generalized anxiety disorder	179	10 ^d	7.7	367	44	13.7	312	50	19.2
Obsessive-compulsive disorder	177	26 ^d	18.7	262	38	14.9	216	35	16.9
Phobias	38	3 ^d	13.4	67	4 ^d	7.2	39	3 ^d	12.9
Other anxiety disorder	254	10 ^d	4.9	347	41	15.0	502	84	20.8
Comorbidity status									
Single or multiple anxiety disorders only	495	14 ^d	3.7	611	43	8.7	598	44	8.5
Other classes of axis I disorders	553	78	15.9	905	169	20.5	1,004	248	28.3
Specific classes of other axis I comorbid disorders									
Mood disorder	423	54	15.4	688	122	21.5	714	180	28.7
Psychotic disorder	18	12 ^d	77.8	22	20 ^d	88.0	42	29 ^d	69.9
Other disorder	266	37	14.8	437	66	15.1	451	96	25.2
FDA-approved antipsychotic indication status ^f									
Approved	242	44	21.5	413	102	26.9	545	162	32.4
No approval	806	48	6.9	1,103	110	11.2	1,057	130	14.5
Nonantipsychotic medication category									
Antidepressant (no), sedative/hypnotic (no)	321	19 ^d	8.2	390	37	12.2	341	50	18.2
Antidepressant (yes), sedative/hypnotic (no)	306	32	11.3	538	77	15.6	564	107	20.8
Sedative/hypnotic (yes), antidepressant (no)	105	7 ^d	6.3	185	20 ^d	11.1	169	33	20.8
Antidepressant (yes), sedative/hypnotic (yes)	316	34	13.3	403	78	20.7	528	102	23.3
Total anxiety disorder visits	1,048	92	10.6	1,516	212	15.7	1,602	292	21.3

^a Weighted data are taken from the National Ambulatory Medical Care Survey and indicate office visits in which an anxiety disorder is diagnosed.

^b Ratios presented are associated with the transformed survey year variable.

^c Analyses accounted for sex, age, race/ethnicity, source of payment, visit sequence, anxiety disorder diagnosis, and the number of overall mental disorders.

^d Estimates based on survey data with <30 observations, or with a relative standard error <0.3, are deemed imprecise and are not to be interpreted.

^e Anxiety disorder categories are not mutually exclusive.

^f See the Method section for a description of FDA-approved antipsychotic indication status (ICD-9-CM: 295.0–295.95, 296.00–296.16, 296.2–296.81, 296.89, 299.00–299.9).

Statistical Analysis					
Odds Ratio ^b	95% CI	p	Adjusted Odds Ratio ^c	95% CI	p
3.31	1.8–6.0	<0.001	2.99	1.7–5.2	<0.001
3.37	1.6–7.1	0.001	3.68	1.9–7.2	<0.001
3.24	1.1–9.5	0.03	3.69	1.4–9.7	<0.01
5.65	1.8–18.0	<0.01	3.49	1.2–10.4	0.03
3.59	2.1–6.2	<0.001	3.29	2.0–5.5	<0.001
2.19	0.9–5.1	0.07	2.05	0.3–1.3	0.21
4.03	2.5–6.5	<0.001	3.69	2.4–5.8	<0.001
1.12	0.2–5.2	0.88	1.23	0.3–5.2	0.78
2.41	0.5–12.3	0.29	1.77	0.3–10.0	0.52
0.76	0.1–5.0	0.78	22.10	1.5–317.1	0.02
4.36	1.9–9.9	<0.001	4.45	2.2–8.9	<0.001
3.07	1.5–6.3	<0.01	2.76	1.3–5.8	<0.01
1.40	0.8–2.6	0.22	1.43	0.8–2.6	0.23
3.14	1.9–5.2	<0.001	2.95	1.9–4.7	<0.001
5.50	1.3–22.2	0.02	8.40	1.9–38.0	0.006
2.62	1.4–5.1	<0.01	2.66	1.5–4.9	<0.01
5.20	2.2–12.1	<0.001	4.98	2.1–11.7	<0.001
3.61	1.1–12.1	0.04	3.89	1.1–14.0	0.04
1.32	0.4–4.2	0.64	1.61	0.5–5.5	0.45
1.66	0.1–26.1	0.72	0.36	0.02–4.6	0.43
5.80	2.6–12.8	<0.001	5.48	2.6–11.5	<0.001
3.58	1.7–7.5	<0.01	4.34	2.1–9.0	<0.001
2.89	1.7–4.9	<0.001	2.89	1.7–4.8	<0.001
3.03	1.7–5.4	<0.001	3.11	1.8–5.4	<0.001
0.48	0.1–4.9	0.53	1.52	0.1–18.7	0.75
3.33	1.5–7.5	<0.01	2.78	1.3–5.9	0.01
2.38	1.3–4.5	<0.01	2.61	1.3–5.0	<0.01
3.36	1.8–6.3	<0.001	3.08	1.7–5.5	<0.001
5.02	1.7–15.0	<0.01	4.50	1.3–15.1	0.02
3.06	1.6–5.9	<0.01	2.88	1.5–5.4	<0.01
4.63	1.4–15.6	0.01	4.13	0.8–20.1	0.08
2.39	1.2–4.6	0.01	2.27	1.2–4.4	0.02
3.34	2.0–5.5	<0.001	2.54	1.6–4.0	<0.001

done (2001), aripiprazole (2002), and paliperidone (2006), may have further contributed to the overall increased use of antipsychotic treatment. The observed trends in antipsychotic prescribing in visits for anxiety disorders was attributable to the increased prescribing of second-generation antipsychotics, paralleling earlier reports in general psychiatric outpatient care (1). An increasing number of office-based psychiatrists are also specializing in pharmacotherapy to the exclusion of psychotherapy (22). Limitations in the availability of psychosocial interventions may place heavy

clinical demands on the pharmacological dimensions of mental health care for anxiety disorder patients. Moreover, the role of outpatient psychiatry may have changed across time, such that office-based psychiatrists have been seeing a growing number of complicated cases (23).

Medications with anxiolytic properties, such as benzodiazepines, have historically played a prominent role in the treatment of anxiety disorders (18). The availability of second-generation antipsychotic agents with improved anxiolytic properties over first-generation agents (24),

while offering less sedation (25), has likely contributed to their clinical role in the treatment of anxiety disorders (11). The availability of antipsychotics with fewer short-term anticholinergic and extrapyramidal effects than first-generation antipsychotics (26) may have also contributed to the observed increases.

Antipsychotic prescribing grew especially rapidly among new patient visits. Psychiatrists may be becoming increasingly comfortable with treating anxiety disorders with antipsychotic medications before adjusting current medications or initiating trials of other medication classes. Alternatively, patients referred for psychiatric care may include a larger proportion that has received antipsychotic treatment prior to referral or patients with remaining symptoms despite trials of antidepressants or other medications.

Little is known about the efficacy and safety of antipsychotic regimens for the treatment of many of the common anxiety disorders. Controlled evaluations in this area have been largely confined to treatment-resistant OCD, traumatic stress disorders, and generalized anxiety disorder. Findings from these evaluations have been largely favorable with regard to adjunctive antipsychotic treatment for OCD (27, 28) and promising but somewhat inconclusive with regard to antipsychotic treatment for traumatic stress disorders (29, 30). Findings from the small set of controlled evaluations of antipsychotic treatment for generalized anxiety or social anxiety disorders either have found no clinical benefit (31, 32) or often yielded inconsistent findings across outcomes (33, 34). In one promising, large controlled trial of generalized anxiety disorder (35), quetiapine demonstrated significant anxiety reductions relative to placebo, although with higher discontinuation rates relative to paroxetine as a result of adverse events. Controlled evaluations of antipsychotic treatment for panic disorder have not been conducted.

Significant increases in antipsychotic prescribing for patients diagnosed with panic and generalized anxiety disorders suggest that high priority should be given to prospective clinical research on antipsychotics used to treat these disorders. In the meantime, current findings, alongside declining use of psychotherapy (22), support calls to improve access to established psychosocial treatments for panic and generalized anxiety disorders (36).

Increasing antipsychotic prescribing in visits in which no diagnosis with an FDA approval for antipsychotic treatment is present may raise concerns over the quality of care. Although off-label prescribing is highly prevalent, there is substantial variation in evidence supporting these practices. Across drug classes, antipsychotic medications rank near the top in off-label use with drug safety concerns and inadequate supporting evidence (37). However, in the absence of information on antipsychotic dosing and duration, a risk analysis cannot presently be determined. Off-label prescribing of antipsychotics for treating anxiety disorders raises difficult challenges for payers, who must balance the needs for treatment access, clinical flexibility,

and prescriber autonomy with concerns over safety, costs, and quality of care.

Prescription of medicines outside of FDA approval is not inherently cause for concern, particularly when there is reasonably consistent supporting evidence from controlled evaluations. Often, however, potentially important clinical differences exist between participants in controlled trials and individual patients in community practice (38). In these circumstances, physicians must grapple with the difficult task of leveraging the scientific literature against clinical experience. In the pharmacological treatment of complex anxiety disorders, consensus treatment algorithms have been developed to help inform clinical decisions (39). Some of these algorithms endorse antipsychotics as a third-line treatment. Responsible reliance on clinical guidelines should take into consideration panel expertise, methodological rigor of the consensus development process (40), sponsorship, and recency.

Although our analyses offer little insight into clinical decision making at the individual patient level, the observed antipsychotic prescribing trends appear to reflect a shift in the balancing of risks versus compelling clinical need in office-based psychiatry. Despite limited controlled data for several common anxiety disorders and emerging safety concerns, prescribing patterns suggest a growing acceptance of antipsychotics in the outpatient psychiatric treatment of common anxiety disorders. With increased antipsychotic use, there will be increased need for metabolic monitoring, especially in patient populations with known risk factors for diabetes and cardiovascular disease. Prudence further suggests that renewed clinical efforts should be made to limit use of these medications to clearly justifiable circumstances. At the same time, a new generation of research is needed to assess the efficacy and safety of antipsychotic regimens for anxiety disorders, especially in patients who have not responded to other treatments.

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