

Trends in Off-Label Use of Second-Generation Antipsychotics in the Medicare Population From 2006 to 2012

Julia Driessen, Ph.D., Seo Hyon Baik, Ph.D., Yuting Zhang, Ph.D.

Objective: The study evaluated trends in the off-label use of second-generation antipsychotics in the Medicare population, a practice that has been identified as lacking adequate supporting evidence for many indications.

Methods: Medicare claims data from 2006 to 2012 were used to identify beneficiaries who filled at least one prescription for any second-generation antipsychotic. Any use that was not associated with a medical claim for an approved indication in a given year was classified as off-label use. Rates of off-label use and of diagnoses associated with off-label use were compared over time. Fill counts standardized for 30-day supply and costs were compared by type of use.

Results: On the basis of a sample of 490,314 patient-years, the rate of off-label use among beneficiaries prescribed a second-generation antipsychotic declined from 51% to 45%. Fill counts were 16% lower for off-label users compared with on-label

users. Off-label users had higher out-of-pocket costs but lower total costs for second-generation antipsychotics. Off-label users most commonly had claims related to dementia, minor depression, anxiety disorders, and other psychosis. The proportion of off-label users without any claims for the most common off-label uses of second-generation antipsychotics declined from 45% in 2006 to 30% in 2012.

Conclusions: Off-label use of second-generation antipsychotics has declined, especially among persons without any of the common off-label conditions. The diagnoses accompanying off-label use did not systematically reflect changes in the evidence base for the use of these drugs, suggesting a mismatch between evidence supporting the use of off-label second-generation antipsychotics and prescribing practices.

Psychiatric Services 2016; 67:898–903; doi: 10.1176/appi.ps.201500316

Once the Food and Drug Administration (FDA) approves a medication to enter the U.S. market, providers can prescribe the medication for an unapproved indication, age group, dosage, or form of administration. This is referred to as off-label use. Although the FDA follows a set of rigorous criteria in approving new drugs, providers are not regulated for off-label prescribing. Off-label use is common—a 2006 study found that just over one-fifth of prescriptions for commonly used medications were for off-label use (1). In some cases, off-label use of a drug evolves to become a first-line treatment option, as in the case of trazodone for insomnia among elderly patients (2). Usually, however, a potential inconsistency exists between the evidence corroborating on-label and off-label use of a drug. Whereas the efficacy and safety of a drug for on-label conditions have typically been rigorously established, the evidence base for off-label uses of a drug is not subject to the same standards, leading to concerns about medication errors, adverse drug events, and inadequate monitoring (3).

Concerns abound about the off-label use of second-generation antipsychotics. Compared with their first-generation

counterparts, these medications are more expensive and are associated with a different set of side effects owing to their different chemical structure. There are also a number of recent studies challenging the touted superior efficacy of second-generation antipsychotics (4–6). A 2007 study found that 60.2% of prescriptions for second-generation antipsychotics by the U.S. Department of Veterans Affairs were not associated with approved conditions (7). A 2007 report by the U.S. Department of Health and Human Services found that 83% of claims for second-generation antipsychotics among elderly nursing home residents were for off-label uses, 88% of which were for a condition covered by a 2005 “black box” warning by the FDA (8). That warning cautioned against the use of second-generation antipsychotics for treating dementia-related psychosis or agitation among elderly persons. More broadly, there is concern that these expensive drugs are being used in ineffective ways, resulting in suboptimal and possibly even harmful treatment of patients at a much higher cost to payers (9,10).

In 2006, the Agency for Healthcare Research and Quality (AHRQ) conducted a comparative-effectiveness review of the off-label use of second-generation antipsychotics. It concluded that for most conditions there was not sufficiently strong evidence that off-label use was efficacious but that there was strong evidence of increased risk of adverse events associated with such use (11,12). An updated version of this review, published in 2011, found some evidence that second-generation antipsychotics were effective for specific off-label uses, such as anxiety disorder and obsessive-compulsive disorder, while maintaining that there was a lack of evidence to support other off-label uses, such as for eating disorders and substance abuse (11).

The objective of this study was to examine trends in off-label prescribing of second-generation antipsychotics among elderly Medicare beneficiaries since the FDA's 2005 black-box warning. We used Medicare claims data from 2006 to 2012 to identify users of second-generation antipsychotics and their associated conditions on an annual basis. This study contributes to the literature on the use of second-generation antipsychotics by examining trends in on-label and off-label use, rather than providing cross-sectional snapshots, allowing us to pinpoint how changes in prescribing patterns reflect changes in the evidence base around the use of this drug class.

METHODS

Data Source and Study Sample

We used 2006–2012 Medicare medical and pharmacy claims data for a random sample of 5% of Medicare beneficiaries to identify second-generation antipsychotic use and associated medical conditions. The observation of interest was a person-year, so individuals were not tracked longitudinally. In each study year between 2006 and 2012, we identified beneficiaries who were continuously enrolled for 12 months in parts A, B, and D and filled at least one prescription for second-generation antipsychotics; our sample included a total of 490,314 patient-years. We included the following second-generation antipsychotics: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, olanzapine/fluoxetine, paliperidone, quetiapine, risperidone, and ziprasidone.

Measurement of Off-Label Use

We searched for the presence of any relevant diagnoses in the same calendar year as a prescription fill for a second-generation antipsychotic medication. This approach was adopted from the approach used elsewhere in the literature to distinguish on-label and off-label prescribing by using Medicare data (7,13). On-label users of second-generation antipsychotics were defined as persons with a claim associated with bipolar disorder, schizophrenia, or major depressive disorder

TABLE 1. Use of second-generation antipsychotics among Medicare beneficiaries, 2006–2012, by on-label and off-label use

Year	Beneficiaries	All users		Off-label users ^b		Mean fill count ^a			
		N	%	N	%	On-label users		Off-label users	
						M	SD	M	SD
2006	504,130	56,787	11	28,972	51	11.43	7.61	9.69	6.41
2007	818,886	68,778	8	35,599	52	11.36	7.81	9.56	6.56
2008	827,704	69,547	8	35,353	51	11.54	7.95	9.79	6.77
2009	831,323	71,217	9	35,298	50	11.51	7.86	9.78	6.78
2010	845,017	72,534	9	32,590	45	11.58	7.83	9.60	6.58
2011	879,987	75,082	9	33,403	44	11.53	7.82	9.64	6.62
2012	922,760	76,369	8	34,409	45	11.62	7.75	9.70	6.58

^aFills were adjusted to reflect a 30-day supply.

^bThe denominator is all users of second-generation antipsychotics in that year.

during the same calendar year as the fill. To be conservative in the determination of off-label use, we included all available diagnosis codes in the search. The remaining observations were classified as off-label users.

For off-label users, we also identified the off-label conditions for which they had claims during the same calendar year as a prescription fill for a second-generation antipsychotic medication. The conditions were identified on the basis of the literature as well as a series of systematic reviews on antipsychotic use conducted by the AHRQ (7,11,13), which included a synthesis of the evidence associated with the use of these drugs for each condition and a determination about whether there was solid evidence of a positive impact.

The carrier claim files of off-label users were searched for claims associated with the following conditions and ICD-9 codes: dementia, organic brain syndrome, and Alzheimer's disease (290*, 293*, 294*, 310*, and 331.0); obsessive-compulsive disorder (300.3); posttraumatic stress disorder (309.81); personality disorders (301*); Tourette's syndrome (307.23); eating disorders (307.1 and 307.5*); anxiety disorders (300.0*); hyperkinetic syndromes (314*); insomnia (780.51 and 780.52); drug abuse and dependence (292*, 304*, and 305.20–305.93); alcohol abuse and dependence (303* and 305.0*); adjustment reaction (309* excluding 309.81); minor depression (296.9*, 300.4*, and 311); other psychosis (297*–299*); and personality disorders (301*). Again, all available diagnosis codes were searched as part of this process.

Analysis

We compared mean second-generation antipsychotic fills, adjusted for 30-day supply, and costs of second-generation antipsychotics (total and out of pocket) for off-label and on-label users over time. The pharmacy claim variables gross drug cost and patient pay amount were used to define total and out-of-pocket costs, respectively. We also examined the demographic and health profiles of on-label and off-label users, after which we explored the various conditions associated with off-label use of second-generation antipsychotics. We examined trends in the conditions associated with off-label use over time and compared these patterns

TABLE 2. Ratio of annual total costs to out-of-pocket (OOP) costs per user for second-generation antipsychotics, by off-label and on-label use, 2006–2012

Risperdal, Zyprexa, Invega, Geodon, Seroquel, and others, by off-label and on-label use, 2006-2012							
	Costs (\$)						
	Off label			On label			Expiring patent
Year	OOP	Total	Ratio	OOP	Total	Ratio	
2006	72	2,305	.031	54	3,852	.014	Risperdal
2007	144	2,378	.060	106	4,017	.026	
2008	148	2,612	.056	110	4,364	.025	
2009	133	2,500	.053	106	4,279	.025	
2010	137	2,512	.054	104	4,525	.023	Zyprexa
2011	116	2,800	.042	8	4,981	.018	
2012	76	2,163	.035	72	3,962	.018	
Average growth rate (%)	7.81	-.34		10.12	1.06		Seroquel, Invega, Geodon

with changes in the AHRQ assessment of the evidence base during this period (11). To facilitate this comparison, we summarized AHRQ's findings for each condition as either evidence of efficacy, inefficacy, both, or neither; of note, this determination focused on efficacy and did not reflect safety. We also identified off-label users who had no claims in a given year for any of the common off-label conditions associated with second-generation antipsychotics.

RESULTS

As shown in Table 1, the annual number of beneficiaries using second-generation antipsychotics grew by approximately 20,000 from 2006 to 2012, with 76,369 beneficiaries filling at least one prescription for this drug class in 2012. Because of comparatively low enrollment in 2006 relative to later years, the proportion of beneficiaries using a second-generation antipsychotic was highest in 2006 (11%), then stabilized at 8% or 9% in ensuing years. Thus, focusing only on 2007–2012, the number of beneficiaries using second-generation antipsychotics increased by approximately 8,000.

The proportion of individuals per year engaged in off-label use of a second-generation antipsychotic stayed fairly constant from 2006 to 2009, representing approximately half of users; the last three years of observation saw a decline in this trend, with a statistically significant decrease to a steady 45% from 2010 to 2012. Standardized monthly fills of second-generation antipsychotic drug prescriptions were, on average, 16% lower for off-label users throughout the study period, averaging 9.68 for off-label users and 11.51 for on-label users.

Costs, shown in Table 2, also differed in a fairly consistent way during this period. Total annual costs for second-generation antipsychotics were, on average, 42% lower for off-label users compared with on-label users. Out-of-pocket costs, however, were higher for off-label versus on-label users from 2006–2011, with the gap shrinking in 2012. This final year of the analysis saw significant declines in both out-of-pocket and total costs of second-generation antipsychotics for both types of users, with declines for out-of-pocket costs anywhere from 17% for on-label users to 34% for

off-label users. This sharp decline aligned with the expiration of patents for four second-generation antipsychotics (Zyprexa in 2011 and Seroquel, Invega, and Geodon in 2012). Overall, the proportional decline in out-of-pocket costs outpaced that in total costs, as seen in the trend in the ratio of out-of-pocket to total costs.

Table 3 summarizes the characteristics of beneficia-

ries by use of second-generation antipsychotics, broken out by on-label and off-label use. This table summarizes person-year observations, the unit of analysis for this study, so individuals may be counted more than once. Overall, on-label and off-label users of second-generation antipsychotics had different demographic and health profiles. Compared with off-label users, on-label users tended to be younger, were more likely to be male, and were less likely to be white. With the exceptions of chronic obstructive pulmonary disease and depression, off-label users had higher rates of most chronic conditions, as identified by Chronic Conditions Data Warehouse flags, compared with on-label users. The rate of depression was almost 14% higher among on-label users compared with off-label users, likely owing to approval of second-generation antipsychotics for treatment of certain types of depression.

Table 4 displays trends in the diagnoses associated with individuals engaged in off-label use of second-generation antipsychotics. The condition identified most commonly among off-label users was dementia, with 36% of off-label users having claims for this condition in 2006. The percentage of off-label users with a claim for dementia peaked in 2010 at 44% and fell to 42% in 2012. Other conditions consistently identified in the claims of over 10% of off-label users on average were anxiety disorders (14%), minor depression (23%), and other psychosis (15%). The off-label conditions associated with the most significant growth in prevalence among off-label users from 2006 to 2012 were hyperkinetic disorder (136%), anxiety disorder (113%), and insomnia (102%). Of note, drug abuse and alcohol abuse were indicated for an average of 2% and 1%, respectively, of off-label users in 2006–2011, but in 2012 no off-label users had claims associated with these conditions.

Finally, a significant percentage of off-label users did not have claims for any of the common conditions associated with off-label use of second-generation antipsychotics, peaking at 45% in 2006 and declining to 30% in 2012. This decline in use of second-generation antipsychotics for conditions other than those commonly associated with off-label use was not steady; rather, it was spurred by a significant decline from 2009 to 2010, when the percentage of off-label users with such claims fell from 44% to 29%.

DISCUSSION

The analysis of trends in use of second-generation antipsychotics showed persistence in the off-label use of these drugs in the Medicare population from 2006 to 2012. During this period, off-label use decreased from 51% to 45% of beneficiaries using second-generation antipsychotics, a 12% decrease. This somewhat modest change belied the more dramatic shifts in the conditions associated with this off-label use: the percentage of off-label users with diagnoses of anxiety, hyperkinetic disorder, insomnia, and drug and alcohol abuse saw swings of more than 100% in magnitude during this time.

However, these changes in the indications associated with second-generation antipsychotics did not necessarily reflect changes in the evidence base around the efficacy and safety of these drugs for off-label indications. For example, the increase in the use of second-generation antipsychotics among beneficiaries diagnosed as having anxiety disorder is consistent with the emerging evidence during this time. However, the similar growth in the use of these drugs for insomnia was not supported by evidence (11). One of the more notable surges in off-label use of second-generation antipsychotics was the increasing prevalence in the use of these drugs among persons with dementia, despite a black-box warning from the FDA about increased mortality associated with use of second-generation antipsychotics among elderly patients with dementia-related psychosis. These findings are consistent with those from studies evaluating second-generation antipsychotic usage in other populations, which generally found a lack of evidence supporting a large proportion of their use (7,9).

The increase in off-label use of second-generation antipsychotics should be evaluated on the basis of its value to patients as well as its effect on broader utilization and cost outcomes. For example, an AHRQ review found evidence supporting the use of second-generation antipsychotics for hyperkinetic disorder, suggesting that this off-label use is somewhat “sanctioned” and is beneficial to patients. What is less clear, however, is the relative value of using second-generation antipsychotics for treating anxiety compared with other, potentially less expensive or more efficacious traditional treatments. Thus there is a need for further research as to the efficiency of this use.

On the other hand, the takeaway from the preponderance of second-generation antipsychotic users with insomnia is very different. AHRQ concluded that there is an absence of

evidence for the treatment of insomnia with second-generation antipsychotics; in this case, the findings speak to a need to understand what, if anything, is driving the continued and intensified use of these drugs for purposes that are not supported by evidence. These subthemes create ambiguity when interpreting the overall increase in off-label use during the time studied, and they raise further questions about whether the increase is substantial or surprising, given that the patents for many of these drugs expired during this time frame, perhaps giving the drugs broader appeal.

Although the conditions associated with off-label use of second-generation antipsychotics changed during 2006 to 2012, the usage and cost patterns of off-label versus on-label use were fairly consistent. It may not be surprising that on average, off-label users had two fewer monthly fills per year compared with on-label users, given that they may have less of a chronic need for a second-generation antipsychotic. Fewer fills, not surprisingly, translated to lower total costs for off-label users of second-generation antipsychotics, whereas the higher out-of-pocket costs among off-label users may reflect that the proportion of off-label users with dual eligibility was lower than for on-label users.

Another clear area for further study is off-label use of second-generation antipsychotics among persons without any of the common conditions associated with these drugs. This description characterized a significant proportion of off-label users in this sample; although this type of usage declined by about one-third during the study period, it still represented almost 30% of off-label use as of 2012. This unexplained usage is concerning from both financial and clinical perspectives. Second-generation antipsychotics are significantly more expensive than their first-generation counterparts, which has

TABLE 3. Characteristics of users (490,314 patient-years) of second-generation antipsychotics, by on-label and off-label use

Variable	On label (N=254,690)		Off label (N=235,624)		p
	N	%	N	%	
Age (M±SD)	52.2±16.2		66.1±19.6		<.001
Male	112,124	44.0	83,765	35.6	<.001
Race-ethnicity					<.001
White	190,704	74.9	186,589	79.2	
Black	40,048	15.7	30,444	12.9	
Hispanic	15,419	6.1	11,359	4.8	
Other	8,519	3.3	7,232	3.1	
CMS priority comorbidity ^a					
History of acute myocardial infarction	3,490	1.4	7,221	3.1	<.001
Alzheimer's disease	14,139	5.6	48,843	20.7	<.001
Other types of dementia	38,716	15.2	85,244	36.2	<.001
Chronic kidney disease	22,556	8.9	28,919	12.3	<.001
Congestive heart failure	41,440	16.3	62,450	26.5	<.001
Chronic obstructive pulmonary disease	56,976	22.4	50,511	21.4	<.001
Depression	162,556	63.8	119,212	50.6	<.001
Diabetes	67,940	26.7	67,148	28.5	<.001
History of stroke or transient ischemic attack	20,846	8.2	39,676	16.8	<.001

^a CMS, Centers for Medicare and Medicaid Services. Identified by Chronic Conditions Data Warehouse flags

TABLE 4. Prevalence of common off-label conditions among off-label users of second-generation antipsychotics, 2006–2012

Condition	2006 (N=28,972)		2007 (N=35,599)		2008 (N=35,353)		2009 (N=35,298)		2010 (N=32,590)		2011 (N=33,403)		2012 (N=34,409)		Growth, 2006–2012 (%)		Evidence of efficacy ^a	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%			Yes	No
Dementia	10,360	35.8	12,708	35.7	12,464	35.3	12,206	34.6	14,381	44.1	14,634	43.8	14,414	41.9	17		✓	✓
Minor depression	5,068	17.5	6,424	18.1	6,905	19.5	7,238	20.5	8,784	27.0	9,650	28.9	9,967	29.0	66			
Other psychosis	3,977	13.7	4,786	13.4	4,838	13.7	4,747	13.5	5,640	17.3	6,091	18.2	6,177	18.0	31			
Anxiety disorder	2,673	9.2	3,639	10.2	3,960	11.2	4,273	12.1	5,304	16.3	5,952	17.8	6,760	19.7	113		✓	✓
Insomnia	1,090	3.8	1,456	4.1	1,595	4.5	1,809	5.1	2,142	6.6	2,422	7.3	2,610	7.6	102		✓	✓
Adjustment reaction	691	2.4	829	2.3	836	2.4	878	2.5	1,059	3.3	1,022	3.1	1,030	3.0	26			
Drug abuse	503	1.7	646	1.8	722	2.0	798	2.3	914	2.8	1,026	3.1	0	0	-100		✓	✓
Personality disorder	403	1.4	459	1.3	482	1.4	425	1.2	509	1.6	531	1.6	509	1.5	6		✓	✓
Alcohol abuse	378	1.3	464	1.3	435	1.2	486	1.4	553	1.7	581	1.7	0	0	-100		✓	✓
Obsessive-compulsive disorder	345	1.2	379	1.1	386	1.1	403	1.1	513	1.6	545	1.6	574	1.7	40		✓	✓
PTSD	253	.9	315	.9	316	.9	346	1.0	387	1.2	479	1.4	489	1.4	63		✓	✓
Hyperkinetic disorder	136	.5	180	.5	206	.6	226	.6	265	.8	347	1.0	382	1.1	136		✓	✓
Eating disorder	74	.3	89	.3	92	.3	94	.3	100	.3	105	.3	112	.3	27		✓	✓
Tourette's disorder		.1		.1		.1		.1		.2		.2		.2	47		✓	✓
None of the above		45.4		45.4		44.8		44.2		29.3		28.0		29.7	-35			

^a Results of a review by the Agency for Healthcare Research and Quality (11). Conditions not included in the review are left blank.

led to application of cost-saving measures, such as prior authorization, in Medicaid. In addition, second-generation antipsychotics are associated with significant safety risks, suggesting that they fall short of other therapeutic alternatives on the cost-effectiveness spectrum. This ongoing usage in the face of less expensive or more effective alternatives, again, speaks to the intransigence of prescribing behaviors in the face of emerging evidence.

The classification of drug use as “on label” or “off label” involved assumptions that serve as limitations of this study. We were unable to observe the true medical reason for prescribing of second-generation antipsychotics and instead identified conditions associated with claims occurring in the same calendar year as a prescription; this may have included medication claims issued before the associated diagnosis was made. This practice would mischaracterize second-generation antipsychotic use if, for example, a truly on-label user did not have any claims for bipolar disorder, schizophrenia, or major depressive disorder in a calendar year. Furthermore, the analysis of all claims within a one-year time frame also complicated assigning off-label use to a specific diagnosis; we were limited to merely identifying the conditions that also appeared during that calendar year but could not make any more concrete link between drug use and a specific diagnosis. Finally, our conclusions about trends in the off-label use of second-generation antipsychotics are specific to the Medicare population and may differ from patterns of use in the broader U.S. population.

It is difficult to say whether this approach over- or underestimated the rate of off-label usage of second-generation antipsychotics in the Medicare population. Off-label usage will be overestimated if individuals with bipolar disorder, schizophrenia, or major depressive disorder commonly go one year or longer without an inpatient stay or outpatient visit related to these conditions. On the other hand, it will be underestimated if individuals with on-label conditions use these drugs for other indications or initiate their use for an off-label condition and are later diagnosed as having an on-label condition later in the calendar year.

CONCLUSIONS

The advent of second-generation antipsychotics was intended to offer a safer, albeit more expensive, alternative for the treatment of specific psychiatric disorders (14). Despite evidence and policy efforts to the contrary, these drugs have been used to treat a wide variety of conditions. From 2006 to 2012, the proportion of Medicare beneficiaries prescribed a second-generation antipsychotic for off-label use declined slightly, as did the proportion of off-label users without any of the conditions commonly associated with off-label uses. Nonetheless, given the significant proportion of users of second-generation antipsychotics without evidence of an approved condition, and the known higher cost of these drugs, further investigation and policy action are warranted concerning the

continued use of this expensive and at times risky therapeutic option despite a lack of supporting evidence.

AUTHOR AND ARTICLE INFORMATION

Dr. Driessen and Dr. Zhang are with the Department of Health Policy and Management, University of Pittsburgh, Pittsburgh, Pennsylvania (e-mail: driessen@pitt.edu). Dr. Baik is with the Lister Hill National Center for Biomedical Communications, National Library of Medicine, Bethesda, Maryland.

The authors acknowledge funding from the National Institute of Mental Health (R21 MH100721 and RC1 MH088510), the Commonwealth Fund, and the Institute of Medicine.

The authors report no financial relationships with commercial interests.

Received August 4, 2015; revision received November 17, 2015; accepted December 4, 2015; published online April 15, 2016.

REFERENCES

1. Radley DC, Finkelstein SN, Stafford RS: Off-label prescribing among office-based physicians. *Archives of Internal Medicine* 166:1021–1026, 2006
2. Wittich CM, Burkle CM, Lanier WL: Ten common questions (and their answers) about off-label drug use. *Mayo Clinic Proceedings* 87: 982–990, 2012
3. Maidment ID, Lelliott P, Paton C: Medication errors in mental health care: a systematic review. *Quality and Safety in Health Care* 15:409–413, 2006
4. Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine* 353:1209–1223, 2005
5. Jones PB, Barnes TR, Davies L, et al: Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry* 63:1079–1087, 2006
6. Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373:31–41, 2009
7. Leslie DL, Mohamed S, Rosenheck RA: Off-label use of antipsychotic medications in the Department of Veterans Affairs health care system. *Psychiatric Services* 60:1175–1181, 2009
8. Levinson DR, Pattison BT, Walden DK: Medicare Atypical Antipsychotic Drug Claims for Elderly Nursing Home Residents. Washington, DC, US Department of Health and Human Services, Office of Inspector General, 2011
9. Crystal S, Olfson M, Huang C, et al: Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. *Health Affairs* 28:w770–w781, 2009
10. Alexander GC, Gallagher SA, Mascola A, et al: Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiology and Drug Safety* 20:177–184, 2011
11. Maglione M, Maher AR, Hu J, et al: Off-Label Use of Atypical Antipsychotics: An Update. AHRQ pub no 11-EHC087-EFUS. Rockville, Md, Agency for Healthcare Research and Quality, 2011. Available at effectivehealthcare.ahrq.gov/ehc/products/150/778/CER43_Off-labelAntipsychotics_20110928.pdf
12. Shekelle P, Maglione M, Bagley S, et al: Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics. AHRQ pub no 07-EHC003-EF. Rockville, Md, Agency for Healthcare Research and Quality, 2007. Available at www.effectivehealthcare.ahrq.gov/reports/final.cfm
13. Chen H, Reeves JH, Fincham JE, et al: Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia Medicaid enrollees in 2001. *Journal of Clinical Psychiatry* 67:972–982, 2006
14. Seida JC, Schouten JR, Mousavi SS, et al: First- and second-generation antipsychotics for children and young adults. AHRQ pub no 11(12)-EHC077-EF. Rockville, Md, Agency for Healthcare Research and Quality, 2012. Available at www.ncbi.nlm.nih.gov/books/NBK84643/