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Impact of FDA Black Box Advisory on Antipsychotic Medication Use

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Abstract

Background—In April 2005, the US Food and Drug Administration (FDA) issued an advisory and subsequent black box warning regarding the risks of atypical anti-psychotic use among elderly patients with dementia. The impact of these warnings on atypical drug use is unknown.

Methods—We used quasi-experimental, interrupted time-series analyses to examine nationally representative data from IMS Health's National Disease and Therapeutic Index from January 2003 through December 2008. The primary measurement from this audit of office-based physicians was the use of an atypical antipsychotic agent. We quantified the impact of the advisory on atypical anti-psychotic use among all individuals and those 65 years or older with dementia.

Results—From January 2003 to March 2005, mentions of total atypical antipsychotic drugs increased at an annual rate of 34%, and among patients with dementia, 16%. In the year prior to the FDA advisory, there were approximately 13.6 million atypical drug mentions, including 0.8 million among those with dementia. In the year following the advisory, atypical drug mentions fell 2% overall and 19% among those with dementia. In 2004, 19% (0.8 of 4.1 million) of drug mentions for dementia were for an atypical agent. By 2008, this proportion decreased to 9% (0.4

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of 4.3 million). Atypical drug use slowed for both FDA-approved and off-label indications and declined through 2008 for all populations examined.

Conclusion—The FDA advisory was associated with decreases in the use of atypical antipsychotics, especially among elderly patients with dementia.

THE FIRST ATYPICAL ANTIPSYCHOTIC, clozapine, was introduced in the United States in 1989, followed by risperidone, olanzapine, and most recently, paliperidone (2006). Many agents that were initially approved to treat schizophrenia have been subsequently approved by the Food and Drug Administration (FDA) to treat mania associated with bipolar affective disorder and irritability associated with autism.¹ Although they are less likely to cause extrapyramidal adverse effects (eg, parkinsonism) than conventional or typical antipsychotics,² several safety concerns have arisen regarding atypical agents, including a 2003 Medwatch warning³ about increased risk of stroke with risperidone use and a 2004 warning about an association between atypical drug use and hyperglycemia and diabetes.⁴

In April 2005, further concerns were manifest in an FDA public health advisory that asked manufacturers of atypical antipsychotic medications to include a boxed warning (“black box”) in their label. Based on a review of clinical trial data, the FDA

determined that the treatment of behavioral disorders in elderly patients with dementia with atypical ... antipsychotic medications is associated with increased mortality.⁵

On the basis of further research,^{6,7} the FDA extended this warning to conventional, or “typical,” antipsychotic medications in June 2008.⁸

Several studies have examined the impact of FDA warnings on the use of medicines such as acetaminophen,⁹ droperidol,¹⁰ cisapride,¹¹ and most recently, selective serotonin reuptake inhibitors (SSRIs).^{12–16} In the case of SSRIs, it appears that physicians were aware of safety concerns and decreased their prescribing for adolescents prior to the advisory; after the warning, use further de-creased.^{14,15} Assessing whether regulatory warnings improve the public’s health is a more complex task because decreases in use may occur in nontargeted populations¹⁵ and other health effects may ensue.¹⁷ Moreover, other factors such as coincident widespread media coverage or changes in marketing and promotion, may exert a strong independent effect on prescribing.¹⁸

Although, to our knowledge, antipsychotic prescribing in the United States in response to the 2005 FDA warning has not been examined, Valiyeva and colleagues¹⁹ used prescription claims from Canada and found that among patients with dementia, Health Canada warnings slowed the growth of typical and atypical drug therapies, though absolute rates of use continued to climb. In the present analyses, we sought to determine the impact of the April 2005 FDA advisory and subsequent black box warning on the clinical use of antipsychotics among a nationally representative sample of office-based physicians in the United States. Although we focus on atypical drug use, which accounted for approximately 90% of all antipsychotic use during the period examined, we also examined whether the April 2005 FDA advisory was associated with changes in typical drug therapies.

METHODS

DATA ON DRUG THERAPY

We used the proprietary IMS National Drug and Therapeutic Index (NDTI) to derive monthly data regarding atypical and typical antipsychotic use from January 2003 to December 2008. The data were obtained under a license from IMS Health Incorporated (Norwalk, Connecticut). Atypical drugs included clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone. We excluded the fixed-dose combination medication consisting of olanzapine and fluoxetine because it accounted for less than 1% of antipsychotic use.

The NDTI, which has been used previously to examine office-based prescribing,^{20,21} collects data 2 days per quarter from a sample of 4800 office-based physicians in the United States and applies sample weights to derive nationally representative estimates. The universe of the NDTI is derived from the American Medical Association Masterfile and American Osteopathic Association and includes physicians providing direct patient care in both community and academic settings. The NDTI is similar in coverage and scope to the National Ambulatory Care Medical Survey, a nationally representative survey of office-based physicians conducted by the National Center for Health Statistics.^{22,23} Our primary unit of analysis was a patient-physician interaction during which an antipsychotic was mentioned as a therapy, referred to as a drug mention or use. For a single patient encounter, drug mentions are duplicated by the number of diagnoses for which the drug is used.

Physicians in the NDTI record diagnoses, therapies, and patient characteristics for all clinical encounters over a consecutive 2-day period. Thus, the NDTI reflects an audit of physicians' practice, rather than data that are derived from pharmacy claims or some other administrative source. Each therapy record is linked to a specific 6-digit taxonomic code that is similar to the *International Classification of Diseases* system. We queried this code at a 4-digit level for diagnoses of dementia (290.0–290.4), after excluding patients younger than 65 years with dementia to increase clinical specificity and to more closely match the black box warning, which specifically refers to elderly patients.

STATISTICAL ANALYSIS

We used segmental interrupted time-series analysis to examine nationally representative estimates of the effect of the April 2005 FDA advisory on antipsychotic use. Because we examined monthly estimates for a 6-year retrospective period, our analyses included no fewer than 66 and as many as 72 observation points, depending on number of missing values for covariates and length of lags included in the analysis.

We first visually inspected the data, while superimposing the policy intervention of interest, to identify general trends and potentially influential outliers. Next, we modeled the data using time-dependent linear regression in which the outcome variable was defined as total monthly antipsychotic drug mentions measured in thousands. Because the monthly estimates reflected large sampling variance, we used smoothed data in the regressions reflecting 6-month moving averages for therapy volume. The regression included a linear trend, a dummy for the postadvisory period, and an interaction term involving these 2 terms.^{24,25}

Thus, we directly estimated and compared the preadvisory and postadvisory monthly trends (slope) using this regression. In our primary analyses, we examined the outcomes of interest from January 2003 through March 2005 (before period) and from May 2005 through December 2008 (after period).

We were interested in both the immediate and longer-term effects of the warnings. We determined the immediate impact by comparing the predicted monthly atypical drug use in March 2005 (based on trends from January 2003 to March 2005) with the predicted monthly use in May 2005 (based on trends from May 2005 to December 2008) using a linear model including the aforementioned time trends and interaction terms. Because absolute levels of use among some populations (eg, elderly patients with dementia) were an order of magnitude smaller than levels of use in other groups (eg, all patients), we used log-linear models to estimate preadvisory and postadvisory growth rates in these populations. When examining the longer-term impact, we tested annualized growth rates and their differences for the 2 periods using a generalized version of the *t* test because it involved nonlinear combinations of regression coefficients. Using the Durbin-Watson test in each model, we found evidence of first-order serial autocorrelation in the data. We corrected this using a General Least Squares (GLS) model with Prais-Winsten function for the error terms.²⁶ We examined the data for an underlying higher-order autocorrelation structure using correlogram and autocorrelation functions. In addition, because time-dependent outcomes such as those examined are prone to regular variation (eg, seasonality), we assessed the importance of such variation by re-estimating the models assuming a more sophisticated seasonally adjusted Autoregressive Integrated Moving Average method (ARIMA).²⁷ The results using ARIMA did not differ substantively and are not reported herein.

We conducted 2 exploratory analyses. First, we examined whether the warning's impact varied based on new vs continued therapies and on levels of evidence for the clinical uses of atypical antipsychotics. After linking physician-reported diagnoses from the NDTI with drug-specific indications for each antipsychotic provided by the FDA and the DrugDex compendium (Thomson Micromedex, Greenwood Village, Colorado), we stratified drug mentions by 3 levels of evidence: (1) FDA-approved indications, (2) nonapproved (off-label) indications with moderate or strong scientific support, and (3) off-label indications with uncertain scientific support.²⁸ Second, although the NDTI does not allow for a comprehensive analysis of the use of antipsychotics among elderly residents residing in institutions (eg, nursing homes), we quantified such use after restricting our sample to the 3% to 6% of patient encounters involving atypical drug mentions that occurred in nursing home facilities. This was possible because although the majority of patient encounters captured by the NDTI occur in office-based settings, a smaller proportion may occur in other settings such as nursing home facilities.

We assessed the robustness of our findings in several ways. First, we used a Joinpoint regression analysis to a priori identify the possible breaks in trends.²⁹ This analysis uses a permutation method to test for possible join points in the time series without defining interventions (eg, FDA advisory) that were possibly determined artificially by researchers.³⁰ Second, since marketing may confound the associations of interest, we included national monthly expenditures for atypical drug marketing in our model. This inclusion did not

substantively change our results and is not reported herein. Third, we assessed whether our findings would vary assuming different lag periods (eg, no lag, 3-month lag) between the timing of the black box warning and its impact. Finally, we performed analyses with equal numbers of observations before and after the black box warning (eg, 27 months before and following the warning) as well as modifying the overall number of months in the time series (eg, excluding 1 month prior to and following the April 2005 advisory). These findings yielded similar results and are not reported herein. All statistical analyses were done using STATA software, version 10.1 (StataCorp, College Station, Texas).

RESULTS

ATYPICAL ANTIPSYCHOTIC USE BEFORE THE FDA ADVISORY

Figure 1 illustrates that atypical antipsychotic drug mentions increased at an annual rate of 34% (95% confidence interval [CI], 2% to 65%) from January 2003 through March 2005, increasing from 1.0 million to 1.4 million monthly drug mentions (all monthly estimates hereafter reflect 6-month smoothed averages). For those 65 years or older with dementia, the annual growth rate was 16% (95% CI, 7% to 25%), and the number of monthly mentions increased from 49 000 (January 2003) to 65 000 (March 2005). Atypical drug mentions among individuals with dementia accounted for approximately 4% to 6% of all atypical drug mentions during this period (Table 1).

ATYPICAL ANTIPSYCHOTIC USE AFTER THE FDA ADVISORY

Figure 2 depicts the results of the Joinpoint regression analysis using atypical antipsychotic drug mentions by people 65 years or older with dementia. The analysis identified the inflection point at May 2005, which closely coincides with the FDA advisory that was issued in mid April.

Table 2 depicts the immediate effect of the FDA advisory derived from the segmented time series regressions; this estimated effect was based on comparisons of projected atypical and typical antipsychotic drug mentions from March 2005 with that of May 2005. The advisory did not appear to have any statistically significant immediate impact on aggregate atypical antipsychotic mentions. However, atypical antipsychotic use among elderly patients with dementia decreased by approximately 12 000 mentions from 1 month before to 1 month after the FDA advisory, amounting to a decline of 18% (95% CI, 8% to 28%).

There were longer-term decreases in mentions of atypical antipsychotic agents. For example, the number of atypical monthly drug mentions decreased from 1.4 million (May 2005) to 1.3 million (December 2008), representing an annual, nonstatistically significant, decline of -2.4% (95% CI, -11.0% to 6.2%). By contrast, among those 65 years or older with dementia, the number of drug mentions decreased from 56 000 (May 2005) to 28 000 (December 2008), an annual decline of 18.5% (95% CI, -22.5% to -14.5%). This decrease was similar to the decreased drug mentions among elderly patients with dementia residing in nursing homes (annual decrease of 18%; 95% CI, -30% to -5%). By December 2008, atypical drug mentions among those with dementia represented approximately 3% of all atypical drug mentions (Table 1).

TYPICAL USE BEFORE AND AFTER THE FDA ADVISORY

Between 2003 and 2008, approximately 10% of all anti-psychotic drug mentions were for typical (or “conventional”) agents. Prior to the advisory, mentions of typical antipsychotics were generally flat, with an annual growth rate of -0.9% (95% CI, -24.1% to 22.4%) from January 2003 through March 2005. Shortly after the advisory, the number of mentions of typical antipsychotics increased by 24 000, but this increase was not statistically significant (95% CI, -2000 to $50\ 000$). After May 2005, the annual rate of typical mentions decreased by -17.8% (95% CI, -27.2% to -8.3%) through December 2008 (Table 3).

BROADER CHANGES IN PRESCRIBING FOR ELDERLY PATIENTS WITH DEMENTIA

We also examined the fraction of all drug mentions (for any prescription medication) among patients with dementia that were accounted for by an atypical agent (Figure 3). This proportion decreased from a peak of 19% of the 4.1 million drug mentions for dementia among individuals 65 years or older in 2004 to 9% of the 4.3 million drug mentions in 2008. Among drug mentions for dementia by those residing in nursing homes, the proportion that were accounted for by atypical antipsychotics decreased from 26% in 2003 to 15% in 2008. Despite these decreases, atypical antipsychotics continued to be a common therapeutic class used for dementia among elderly patients, ranking second only to acetylcholinesterase inhibitors in each year from 2003 through 2008 (data not shown).

EXPLORATORY ANALYSES BASED ON LEVELS OF EVIDENCE AND NEW vs CONTINUED USE

Following the advisory, atypical antipsychotic drug mentions decreased significantly for on-label indications, off-label indications with moderate or strong evidence, and off-label indications with uncertain evidence (Table 4). The fraction of atypical drug mentions stratified by levels of evidence shifted modestly. One year prior to the advisory, 35% of mentions were on-label, 8% were off-label with moderate or strong evidence, and 56% were off-label with uncertain evidence. By the last quarter of 2008, the corresponding values were 40%, 5%, and 54%, respectively.

The impact of the advisory was less for new than for continued antipsychotic mentions (eg, renewals) (Table 5). For example, among those with dementia, new antipsychotic drug mentions were declining at rate of -22.6% (95% CI, -38.7% to -6.4%) prior to the advisory and -13.5% (95% CI, -27.8% to 0.0%) following the advisory. By contrast, the annual growth rate of continued mentions among this population was 37.3% (95% CI, 16.1% to 58.4%) prior to the advisory and -21.5% (95% CI, -28.5% to -14.5%) following the advisory.

COMMENT

The April 2005 FDA advisory concerning the increased risk of mortality associated with the use of atypical antipsychotics in elderly patients with dementia was associated with a decrease in the use of the medications. The decline began within 1 month after the advisory and continued at least through the end of 2008. These findings are important because

atypical antipsychotics are a widely used drug class accompanied by noteworthy safety concerns and the impact of the FDA advisory has not been clear.

The decrease in atypical antipsychotic therapies that we identify was especially pronounced among elderly patients with dementia. Monthly drug uses dropped by more than 50% from the time the advisory was released to December 2008. While the potential benefit of decreased atypical drug use among this population may be large based on epidemiological studies,¹⁻³ considerable atypical drug use for dementia continues. Nearly 10% of prescription drug uses for dementia among elderly patients are for atypical antipsychotics; as of December 2008, there were 8000 new atypical drug uses each month among patients with dementia, despite the increased risk of death³¹ and limited evidence of their efficacy.^{32,33}

The appropriate impact of a safety is not clear, and the ultimate objective (eg, more informed and safe use of a given therapy) is difficult to assess. The safety advisory for atypical antipsychotics differs from other drug warnings in several ways that likely influenced the decline observed. First, the advisory exclusively applied to an unapproved “off-label” use of the drugs. Second, because of the unclear benefits of the medications for behavioral disorders in elderly patients with dementia, the risks cannot readily be weighed or quantified against the benefits as they can for other drugs.³⁴ Third, potential treatment substitutes (eg, typical antipsychotics) may also carry safety risks and were eventually the subject of their own safety alert.⁸ Our analysis suggested that the immediate effect of the atypical drug advisory may have been a modest increase in typical drug use, although their absolute numbers relative to atypical agents were small and longer-term trends suggest their use declined as well.

The April 2005 FDA advisory was also associated with statistically significant declines in atypical antipsychotic drug use among nonelderly individuals without dementia. In addition, we found that the use of atypical agents decreased for FDA-approved indications. Given the decline in use for populations outside the advisory’s target and for FDA-approved indications, for which effectiveness has been demonstrated, the observed “spillover” effect is likely unintended and may be detrimental to the public’s health. Such effects have previously been observed with antidepressants when use in adults declined after a black box warning indicating increased risk of suicide in the pediatric population was issued.^{15,16,35,36}

The continued use of atypical antipsychotics among those with dementia and the spillover effect into populations to whom the warning does not apply highlights the complex task faced by the FDA and also raises the question of whether the specificity and impact of FDA advisories could be increased. One element that may improve the effectiveness of such warnings is to focus the communication on the patient populations and physicians who are most likely to be affected. Such tailoring of the message to the appropriate patient and physician “segment” would parallel the efforts of pharmaceutical firms to market their products to different patients (eg, direct-to-consumer advertising) and physicians (eg, detailing by sales representatives) based on their attributes (eg, specialty, patient population). In addition to being used to disseminate safety information, market segmentation strategies could also be used to evaluate the impact of FDA advisories on physicians’ prescribing.

There are several reasons that our analyses may suggest a greater impact of the FDA warning on atypical drug use than a prior analysis of the impact of Health Canada warnings.¹⁹ Our unit of analysis, based on a physician's audit, may be more sensitive than pharmacy claims to changes in therapies, since claims may capture refills that were not based on a recent visit. In addition, other contextual features, including the method whereby dementia diagnoses were ascertained, the nature of the advisory, media coverage, and regional practice patterns, may contribute to differences in the findings.

Like other analyses examining the impact of regulatory actions on prescription use,^{11,14,15,35,36} we used interrupted time-series analyses. Although this approach has strengths, it also has weaknesses inherent in its nonexperimental design. Other interventions could have occurred that coincided with the timing of the FDA advisories and caused the changes observed. For example, some atypical antipsychotics were receiving new indications (eg, in mood disorders), others (eg, paliperidone) received initial US approval, and yet others were maturing as products. There was also widespread media coverage of the events we examined.^{37,38} We adjusted for changes in marketing and promotion around the time of the advisory and found that the results did not change substantially. While these and other factors are potential confounders, the results of the Joinpoint regression analysis suggest that the use of these drugs decreased soon after the FDA advisory. Nevertheless, to the degree that other factors contributed to the changes we describe, our estimates reflect the best case in terms of the impact of the FDA warnings and suggest that effective media communication strategies may be critical to the successful dissemination of emerging safety information regarding prescription medicines.

Our study has additional limitations. Our exploratory data on nursing home residents is limited to physicians who practice primarily in an ambulatory setting and do not capture the full scope of prescription use among this population. Second, our unit of analysis was drug mentions, rather than individuals, and thus we are not able to discern how the clinical application of antipsychotics (eg, use for 2 distinct diagnoses) may have changed over time. Third, we do not have information on the number of years that each physician sampled was in the NDTI panel, and thus data for any given year reflect a combination of new and continuing audit participants. Finally, our data do not include detailed clinical information that could help evaluate clinical outcomes and the appropriateness of use, such as the magnitude of behavioral disturbance, history of treatments, or relative symptom severity of those stopping vs those beginning treatment. Differences in relative symptom severity, for example, could help explain the greater decrease among continued drug mentions compared with new drug mentions.

In conclusion, the April 2005 FDA advisory was associated with a statistically significant decrease in the use of atypical antipsychotics among elderly patients with dementia that occurred soon after the advisory was issued. Despite the decrease, atypical antipsychotics still comprised 9% of prescription drug uses for dementia among elderly patients at the end of 2008. Without clinical data, the appropriateness of this use is uncertain. The residual use in the population at risk and the decrease in the use of atypical antipsychotics in the general population, who were not targeted by the warning, raise the question as to whether the effect and specificity of FDA regulatory actions could be enhanced.³⁹ Targeting specific segments

of patients and physicians (eg, high prescribers) and further customizing and evaluating the impact of regulatory actions may improve their impact at minimizing the risks associated with select prescription medications.

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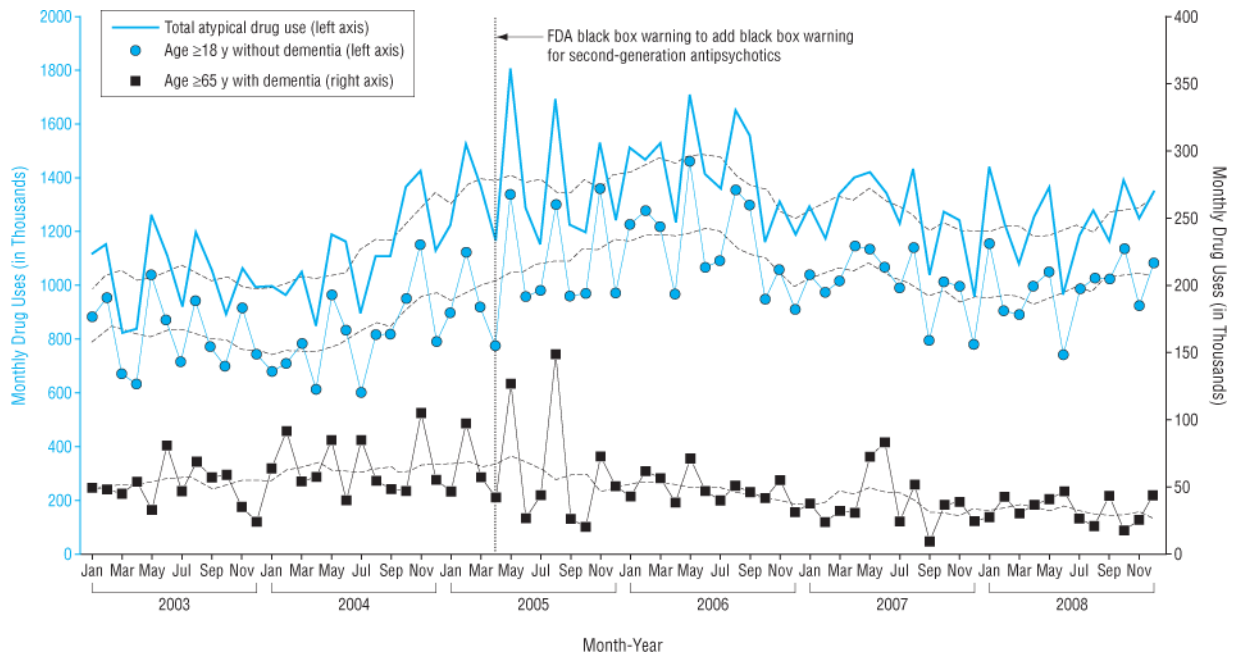


Figure 1. Trends in monthly atypical antipsychotic use, 2003–2008. The dashed line shows 6-month moving average; source: IMS Health National Disease and Therapeutic Index. FDA indicates Food and Drug Administration.

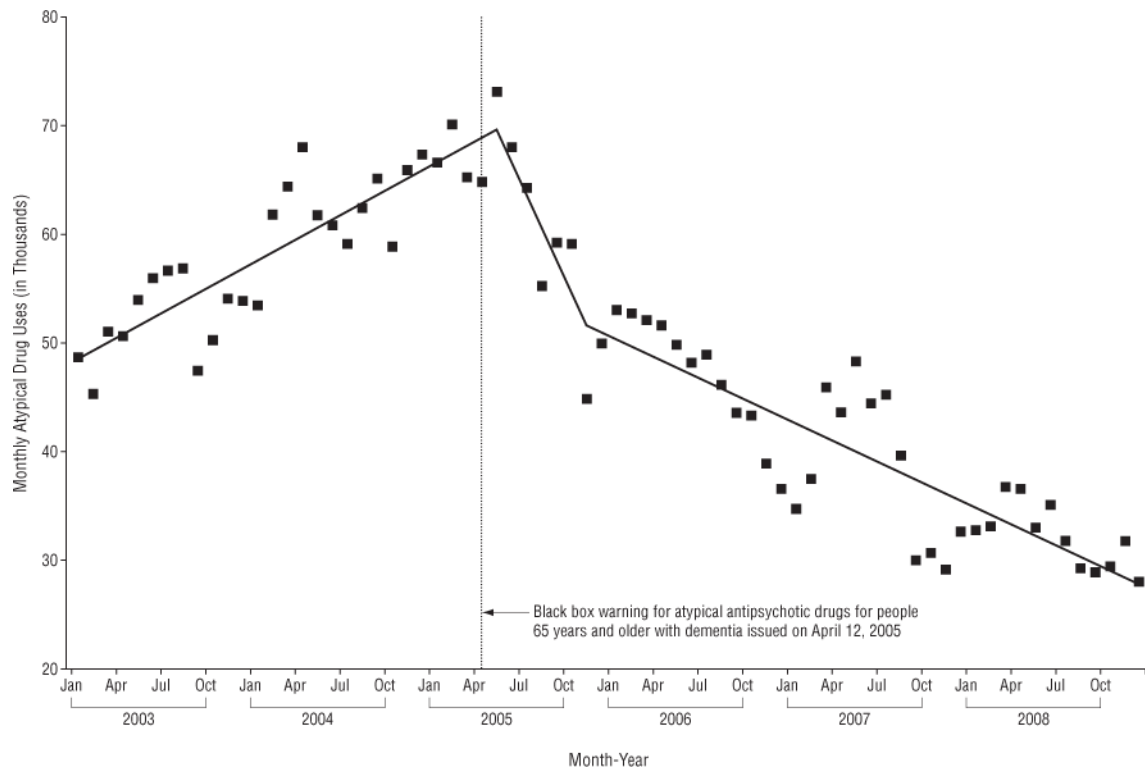


Figure 2. Joinpoint Regression Program analysis for atypical antipsychotics use among elderly patients with dementia. The data points represent patients 65 years and older with dementia (smoothed 6-month averages); the solid line, fitted joinpoint time series.

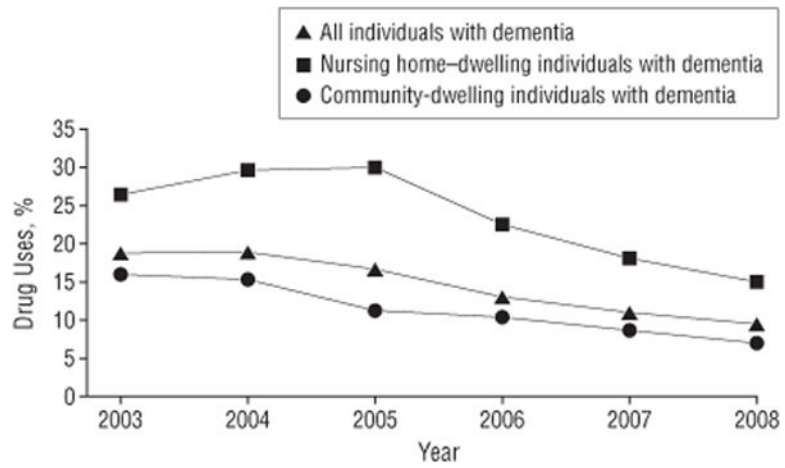


Figure 3. Proportion of drug uses that were atypical antipsychotics among individuals with dementia, stratified by visit location, 2003–2008.

Table 1
Drug Uses (in Thousands) in Which Atypical Antipsychotics Were Used Among Individuals With Dementia, 2003–2008^a

	Drug Uses, No. (%)					
	2003	2004	2005	2006	2007	2008
Community-dwelling individuals with dementia	370 (3)	480 (4)	360 (2)	370 (2)	280 (2)	230 (1)
Nursing home individuals with dementia	220 (2)	300 (3)	390 (3)	210 (1)	180 (1)	170 (1)
All individuals with dementia	590 (5)	780 (6)	750 (4)	570 (3)	460 (3)	400 (3)
All individuals	12 730 (100)	13 550 (100)	16 910 (100)	17 630 (100)	15 500 (100)	15 200 (100)

^aUse is measured in thousands. Values for those with dementia were restricted to individuals 65 years and older. Column percentages represent the fraction of all atypical use. Source data were derived from IMS Health National Disease and Therapeutic Index.

Table 2Impact of Food and Drug Administration Advisory on Trends in Atypical Antipsychotic Use^a

Trends in Atypical Antipsychotic Use	All Use	Use Among Elderly With Dementia
Predicted drug uses (in thousands)		
March 2005	1350.5 (1180.8 to 1520.2)	67.8 (62.6 to 72.9)
May 2005	1376.0 (993.9 to 1758.1)	55.5 (50.2 to 60.8)
Before-after change in level	25.5 (-393.9 to 444.9)	-12.2 (-19.8 to -4.6) ^b
Monthly change in number of drug uses (in thousands)		
January 2003–March 2005	31.9 (7.2 to 56.6) ^a	0.7 (0.4 to 1.1) ^c
May 2005–December 2008	-2.7 (-13.0 to 7.6)	-0.7 (-0.9 to -0.5) ^c
Before-after change in trend	-34.6 (-61.4 to -7.8) ^b	-1.4 (-1.8 to -1.0) ^c
Annual growth rate, %		
January 2003–March 2005	33.5 (2.0 to 64.9) ^b	16.0 (6.5 to 25.4) ^c
May 2005–December 2008	-2.4 (-11.0 to 6.2)	-18.5 (-22.5 to -14.5) ^c

^aUse is measured in thousands. Values for those with dementia were restricted to individuals 65 years and older; 95% confidence intervals are given in parentheses. Source data were derived from IMS Health National Disease and Therapeutic Index.

^b $P < .05$.

^c $P < .01$

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Table 3Impact of Food and Drug Administration Advisory on Trends in Typical Antipsychotic Use^a

Trends in Atypical Antipsychotic Use	All Use
Predicted drug uses (in thousands)	
March 2005	63.0 (47.0 to 78.9)
May 2005	86.8 (67.7 to 106.0)
Before-after change in level	23.9 (-1.7 to 49.5)
Monthly change in number of drug uses (in thousands)	
January 2003–March 2005	-0.1 (-1.6 to 1.4)
May 2005–December 2008	-1.0 (-1.6 to -0.4) ^b
Before-after change in trend	-0.9 (-2.5 to 0.7)
Annual growth rate, %	
January 2003–March 2005	-0.9 (-24.1 to 22.4)
May 2005–December 2008	-17.8 (-27.2 to -8.3) ^b

^aUse is measured in thousands. Ninety-five percent confidence intervals are given in parentheses.

^b $P < .01$ (source data derived from IMS Health National Disease and Therapeutic Index)

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Table 4Trends in Atypical Drug Uses by Evidence of Clinical Effectiveness^a

Trends in Atypical Drug Use	Uncertain Evidence	Moderate or Strong Evidence	Food and Drug Administration-Approved Indications
Mean monthly change in number of drug uses (in thousands)			
January 2003–March 2005	68.7 (47.9 to 89.5) ^b	–8.3 (–14.5 to –2.1) ^c	32.7 (15.4 to 49.9) ^b
April 2005–December 2008	–36.7 (–60.9 to –12.8) ^b	–8.5 (–13.2 to –3.8) ^b	–0.8 (–16.4 to 14.8)
Before-after change in trend	–105.5 (–138.2 to –72.9) ^b	–0.2 (–7.8 to 7.4)	–33.4 (–56.7 to –10.1) ^b
Annual growth rate, %			
January 2003–March 2005	17.9 (11.9 to 24.0) ^b	–11.2 (–18.9 to –3.5) ^b	13.5 (4.2 to 22.8) ^b
May 2005–December 2008	–7.2 (–12.2 to –2.2) ^b	–14.7 (–22.7 to –6.68) ^b	0.3 (–4.7 to 5.2)

^aUse is measured in thousands and reflects the number of treatment visits for which atypical drugs were used as therapy. Values for those with dementia were restricted to individuals 65 years and older; 95% confidence intervals are given in parentheses. Source data derived from IMS Health National Disease and Therapeutic Index.

^b $P < .01$

^c $P < .05$.

Table 5Trends in New and Continued Atypical Antipsychotic Therapies^a

Trends in Atypical Drug Use	Therapy Among All Patients		Therapy Among Elderly Patients With Dementia	
	Continued	New	Continued	New
Mean monthly change in number of drug uses (thousands)				
January 2003–March 2005	17.9 (3.7 to 32.1) ^b	2.8 (0.5 to 5.2) ^b	0.4 (0.9 to 1.7)	-0.2 (-0.4 to 0.1)
May 2005–December 2008	-4.7 (-10.7 to 1.2)	0.8 (-0.4 to 2.1)	-1.0 (-1.4 to -0.6) ^c	-0.0 (-0.1 to 0.1)
Before-after change in trend	-22.6 (-38.1 to -7.2) ^c	-2.0 (-4.7 to 0.7)	-1.4 (-3.0 to 0.2) ^d	0.1 (-0.1 to 0.4)
Annual growth rate, %				
January 2003–March 2005	23.6 (3.7 to 43.4) ^b	13.9 (-0.4 to 28.3) ^d	37.3 (16.1 to 58.4) ^c	-22.6 (-38.7 to -6.4) ^c
May 2005–December 2008	-3.7 (-7.8 to 0.5) ^d	3.6 (-0.7 to 7.9) ^d	-21.5 (-28.5 to -14.5) ^c	-13.5 (-27.8 to 0.0) ^d

^aUse is measured in thousands. Values for those with dementia were restricted to individuals 65 years and older; 95% confidence intervals are given in parentheses. Source data derived from IMS Health National Disease and Therapeutic Index.

^b $P < .05$.

^c $P < .01$

^d $P < .10$.