Persisting Decline in Depression Treatment After FDA Warnings

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Context: In October 2003 the Food and Drug Administration (FDA) issued a Public Health Advisory about the risk of suicidality for pediatric patients taking antidepressants; a boxed warning, package insert, and medication guide were implemented in February 2005. The warning was extended to young adults aged 18 to 24 years in May 2007. Immediately following the 2003 advisory, unintended declines in case finding and non–selective serotonin reuptake inhibitor substitute treatment were shown for pediatric patients, and spillover effects were seen in adult patients, who were not targeted by the warnings.

Objective: To determine whether the unintended declines in depression care persisted for pediatric, young adult, and adult patients.

Design: Time series analyses.

Setting: Ambulatory care settings nationally.

Patients: Pediatric, young adult, and adult cohorts of patients with new episodes of depression (n=91,748, 70,311, and 630,748 episodes, respectively).

Interventions: Post–FDA advisory trends were compared with expected trends based on preadvisory patterns using a national integrated managed care claims database from July 1999 through June 2007.

Main Outcome Measures: Depression diagnosis; antidepressant, antipsychotic, and anxiolytic prescriptions; and psychotherapy visits.

Results: Changes in pediatric depression care were similar to changes for adults. National diagnosis rates of depression returned to 1999 levels for pediatric patients and below 2004 levels for adults. Primary care providers continued significant reductions in new diagnoses of depression (44% lower for pediatric, 37% lower for young adults, 29% for adults); diagnoses by mental health providers who were not psychiatrists increased. Numbers of prescriptions of anxiolytic and atypical antipsychotic medications did not significantly change from preadvisory trends. Psychotherapy increased significantly for adult, though not pediatric, cases. Selective serotonin reuptake inhibitor use decreased in all cohorts; serotonin-norepinephrine reuptake inhibitor use increased for adults.

Conclusions: Diagnosing decreases persist. Substitute care did not compensate in pediatric and young adult groups, and spillover to adults continued, suggesting that unintended effects are nontransitory, substantial, and diffuse in a large national population. Policy actions are required to counter the unintended consequences of reduced depression treatment.

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tion, which was not the target of the initial warnings. Following investigations in 2005 and a hearing in 2006, in May 2007 the warnings were revised to include young adults, defined as those aged 18 to 24 years.

Concerns remain about the long-term effect of the FDA warnings on the use of antidepressants for depression treatment generally and specifically for downstream association with increased rates of teenage suicides. Although there have been reports of short-term effects of the FDA warnings and other similar regulatory actions internationally, there is a gap in estimating the long-term effects of these policy actions. Whether these reductions in treatment were transitory or persistent and whether they have increased or decreased since the early months is not known.

Owing to design limitations, recent domestic and international examinations have drawn attention to, but have not adequately assessed, the short-term effects. One study examined the target age groups of pediatric and young adult persons in Canada. That study's limitation was that it assessed prevalent, not incident (new), cases of antidepressant prescriptions for depression. Analyses suffered from survivor bias and adherence bias from risk varying with time such that people who continue to take drugs for longer duration tolerate them better and may have lower risk for suicidality. Another study examined the effect of regulatory warnings on the Medicaid system in Tennessee. That study used incident antidepressant use; however, the limitation was the study cohort, comprised of new users for any cause, rather than the depressed subjects at heightened risk for suicidality to whom the warnings were targeted. Confounding bias would likely be large, given that antidepressant indications range from major depression to smoking cessation and weight loss, with varied suicidality risk.

A third study of the FDA warnings examined prescription records for youth, adults, and older adults. That study suffered from both prior limitations of prevalent use and antidepressant use for all causes. These study limitations have special importance because of interpretations placed on empirical findings for policy and clinical practice.

Clinicians and scholars have continued to reflect on the importance of these warnings for community practice; they call for evidence of the magnitude and persistence of the effects of the warnings and for a policy remedy to correct negative unintended consequences. This article fills these gaps in several ways by (1) using an incident antidepressant user design, starting from a cohort of patients with incident episodes of depression, to reduce confounding and measurement error; (2) evaluating the effect of the FDA advisory on patterns of care for both targeted groups, pediatric and young adult, and on the comparison group of nontargeted adults; and (3) examining the time span from 1999 to 2007, providing recent national data on community treatment, which allowed us to examine the magnitude and persistence of the effects. As in our prior studies of the effects of the FDA advisories, this study uses a national integrated file with comprehensive accounting for health care visits and prescriptions, with large samples of patients allowing the creation of analytic cohorts of significant size.

Data for this study come from the PHARMetrics Patient Centric Database, the largest national database of longitudinal integrated health care claims data commercially available from PHARMetrics, a Unit of IMS, Inc (Hagerstown, Maryland), under unrestricted license. Data came from integrated medical, specialty, facility, and pharmacy-paid claims from more than 95 managed care plans nationally, representing more than 55 million covered patients from January 1999 to December 2007. Patients were unidentified and anonymous; therefore, an expedited review was obtained from the Colorado Multiple Institutional Review Board.

Identifying a cohort of new episodes of depression was the first step in building the analytic file. The definition of a new episode of depression was based on specifications of the National Committee for Quality Assurance Health plan and Employer Data and Information Set. The resulting time horizon that accounted for episode creation, follow-up, and seasonality spanned from July 1999 to June 2007. The total cohort of 643,313 individual patients was separated into 3 depression cohorts comprising 792,807 episodes of diagnosis and possible treatment. There were 91,748 pediatric cases (aged 5-18 years at time of diagnosis), 70,311 young adult cases (aged 19-24 years at diagnosis), and 630,748 adult cases (aged 25-89 years at diagnosis). Average ages for each cohort were 13 years for pediatric, 21 years for young adults, and 44 years for adults. Female patients accounted for roughly 60% of pediatric cases and 70% of adult cases; 4% of cases were receiving managed Medicaid benefits at the start of the episode.

The second step was to create time series based on aggregated measures of the cohorts. Continuous enrollment for 3 months before and 6 months after diagnosis was required for observation periods. As patients with new episodes of depression entered a cohort over time, measures were aggregated into successive monthly values. Thus, each observation is an aggregate measure of health care services used by new depression episodes for each cohort that were diagnosed nationally in that month.

MEASURES

FDA Advisory

The policy action of interest was the FDA advisory released in October 2003. It was empirically supported in earlier analyses, is still supportive with the acquisition of substantial new data, and was consistent with early reports of market-level changes. It also permits direct comparison with our earlier studies of the effects of the advisories on the targeted and nontargeted populations. For historical accuracy, we note that the October 2003 advisory was the first in a series of risk communications; a second Public Health Advisory followed in October 2004 and a Black Box warning and language for a Patient Medication Guide were implemented in February 2005. The target population was expanded to include young adults in December 2006, and the warning was amended in May 2007. When the FDA extended the original pediatric suicidality warning, they defined young adults as persons aged 18 to 24 years; we retained 18-year-olds in the pediatric cohort, however, to facilitate comparison with our earlier work. Sensitivity analyses were conducted to the timing of the shock (eg, examining a second shock for the February 2005 implementation of the warning and medication guide). Because overall patterns across all outcomes and all 3 cohorts showed no changes at these points,
we report only 2 periods: before and after the 2003 FDA advisory. Process-of-care measures were calculated based on the 3 age-based cohorts (pediatric, young adult, and adult).

Rates of Depression Diagnosis in the General (Managed Care) Population

The annual rate of depression diagnosis among managed care enrollees during calendar years 1999 through 2007 is expressed as the number of diagnosed cases of depression per 1000 enrollees per year.

The following national aggregate measures were calculated for each month:

Type of Depression Episode Diagnosed. The percentage of diagnosed depression episodes that were classified as new episodes (International Classification of Diseases, Ninth Revision [ICD-9] code 296.2, 300.4, or 311, with no previous episodes recorded) or recurrent episodes (ICD-9 code 296.3 or International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 296.2, 300.4, or 311, with 1 or more previous unique depression episodes recorded).

Provider Types Diagnosing Depression. The percentage of new depression episodes that were diagnosed by each of the following types of providers: pediatrician, nonpediatrician primary care physician (PCP) (primary care, internal medicine, obstetrician, or gynecologist), psychiatrist, and other mental health provider (psychologist, social worker, therapist). Other provider type (not already specified) and unknown provider type were analyzed, but not reported.

Antidepressant Drug Prescribing for Depression. The percentage of depression episodes for which the following were filled within 30 days of the depression diagnosis date: selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressant, other antidepressant, multiple antidepressants (of any class, concurrently or consecutively), or no antidepressants prescribed.

Provider Types Prescribing Antidepressants for Depression. For depression episodes in which there was an antidepressant prescription filled within 30 days of the depression diagnosis date, the percentage of those prescriptions that were written by the following provider types: pediatrician, PCP, psychiatrist, and other mental health care provider. Other provider type (not already specified) and unknown provider type were not reported.

Use of Psychotherapy After Depression Diagnosis. The percentage of the depression episodes that received any visit coded as psychotherapy within 180 days of the depression diagnosis date.

Use of Antidepressant Alternatives After Depression Diagnosis. The percentage of depression episodes for which a prescription was filled for the following within 30 days of their depression diagnosis: atypical antipsychotic drugs (general product identifier [GPI] 590700, 591520, 591530, 591540, 591570, 592500, 594000) or anxiolytic drugs (GPI 601000-609980).

STATISTICAL ANALYSIS

The first analysis was conducted to determine changes in rates of depression diagnosis in the general managed care population for each cohort from 1999 to 2007. Total numbers of unique depression diagnoses were determined from the physician visit file. Population sizes were provided by PHARMetrics as single annual counts by age and sex bands for the 8 calendar years (1999-2007). Owing to the small number of data time points (9), the binomial distribution of the numerator and denominator data, and to account for curvature of the fitted line, a linear regression line was fit on a logit scale. This regression line was fit to the years 1999 through 2004 and used to estimate a predicted rate for 2007. This predicted rate was compared with the observed rate for 2007 using a t test.

The second set of analyses focused on the process-of-care measures among monthly cohorts of subjects diagnosed with depression. Segmented regression analysis of time series was used for spans of 90 to 96 months (depending on follow-up restrictions), with 51 months before and up to 45 months after the FDA advisory. Linear regression models included variables to test for a change in level (mean) and rate (slope) after the FDA advisory compared with preadvisory estimations. A test of differences in the before and after mean level estimates was also calculated. Model specification details are reported elsewhere.¹

Figure 1 presents the annual rates of depression per 1000 enrollees in the pediatric, young adult, and adult general managed care populations from 1999 to 2007. The rate of diagnosed episodes of depression increased steadily, with some fluctuations, across each group from 1999 to 2004. After 2004 the observed national rate of pediatric case-finding fell significantly, with the postadvisory decline persisting such that the rate per 1000 enrollees in 2007 (3.5) approached the 1999 level (3.2). Based on the historical trend established in the 5 years prior to the advisory, the 2007 rate per 1000 enrollees would have been 15.6 for young adults and 20.3 for adults; the actual observed rate was 9.6 for young adults and 12.4 for adults. Changes for female patients were similar to male patients, shifted up to higher overall rates. Two notable patterns emerged in these national population-based rates of depression diagnoses in managed care. First, ob-

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Figure 1. PHARMetrics Patient Centric Database population rates of major depressive disorder (actual and predicted) by age group (male and female individuals combined).

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served diagnosis rates were significantly lower than history predicted based on the preadvisory trend using the newest available data; that is, depression rates have continued to decline. Second, even after accounting for changes to the targeted young adult population, the spillovers to adults in the general medical and specialty managed care enrollee population have persisted.

The time series regressions used monthly aggregates of new episodes of care comprising the cohort that accrues in each month, so each monthly observation was a national measure characterized by new cases of depression in that period (eTables 1, 2, and 3; http://www.archgenpsychiatry.com). The table shows preadvisory mean level and trend (slope), postadvisory mean level and slope, and the preadvisory to postadvisory slope change that indicates the policy change. Mean level changes were described as tests of differences between preperiod and postperiod averages. The baseline linear trend from the preadvisory period was used to forecast to June 2007 and a $t$ test was used to compare this forecasted estimate with the observed rate. The last column presents the percentage of the projected value accounted for by the observed value. These same columns are reported across the table for each age-related cohort.

Case finding was measured by the percentage of new episodes of depression diagnosed by each provider type during the month. Before the 2003 FDA advisory, the percentage of episodes of depression diagnosed by pediatricians or PCPs increased steadily and accounted for most diagnoses. After the advisory and through June 2007, both provider types significantly decreased case finding. The rate predicted for PCPs was 44% lower than history would have predicted, and was echoed by significant declines of PCP diagnoses for the young adult (37%) and adult cohorts (29%) (Figure 2). The only provider type that increased in case finding was nonpsychiatrist other mental health providers. Still accounting for a small share of total new cases, this group increased in the post period for all ages.

A subset of new episodes had a record of whether the case was new or recurrent (Figure 3). For all cohorts, the percentage of newly diagnosed cases fell significantly after the advisory, and the observed rate in 2007 was significantly lower than the trend would have predicted. The change was larger for adult populations (18% decrease) than for pediatric (11% decrease).

From the postadvisory period through June 2007, SSRI prescriptions within 30 days of the new depression episode fell significantly, by 10% for pediatric and 15% for adult cases. This rate is lower than previously reported, and is likely owing to the nature of the final 3 months of the data set. Pharmacy data are particularly sensitive to follow-up because of multimonth prescriptions (such as 3-month fills that do not post a claim for 90 days), which retroactively add information to a prior period. For this study, a more conservative 6-month follow-up period from the end of observations was used to guard against this retroactive posting problem with pharmacy claims. Primary care physicians decreased their prescriptions of SSRIs in the largest magnitude (40% lower than history would have predicted for pediatric; 30% lower for young

Figure 2. Percentage of cases in each cohort diagnosed with depression by a primary care physician before and after the 2003 Food and Drug Administration (FDA) advisory.
adult; 25% lower for adults). Thus, the intended effect of the FDA policy actions was a decrease in SSRI prescriptions that has proved substantial and persistent. The unintended effect of this change was that the same decline persists in the adult cohort, which was never a target of the advisory or warnings.

Substitution of other forms of treatment might have been an expected outcome of a decrease in the first-line treatment for the acute phase of depression. Because the patterns are almost identical across cohorts, trends are presented for all ages (Figure 4). There was a small but significant increase in the proportion of new depression cases that received at least 1 visit for psychotherapy within 180 days of diagnosis for adults only. Antidepressant alternatives—atyypical antipsychotics and anxiolytics—did not increase statistically or in clinically meaningful ways from their very low base rates in the preadvisory period.

**COMMENT**

This study examined the persistence of unintended effects of the FDA advisories about suicidality risk with SSRI antidepressants. Time series through June 2007 showed that the major trends in unintended effects—decreased case finding in primary care with no compensatory increase in substitute psychosocial or pharmacological treatment—persisted. In addition, the effects on depression treatment were substantial and significant for all ages. The largest practice changes that have persisted are in the general medical sector, which has special importance because it sees the largest proportion of people seeking mental health care in the United States.18

The latest study on costs of depression used the National Comorbidity Study-Replication, which collected employment and functioning data and produced estimates of social costs associated with depression. Kessler and colleagues19 estimated $193 billion decrement in earnings associated with mental illness in the United States. In fact, this economic loss outpaced the $152 billion economic stimulus package passed in early 2008.20 These figures reinforced depression’s standing as one of the most burdensome diseases worldwide, in part owing to productivity loss and sick leave days.21-23 This is one tangible, unintended, and costly consequence associated with the FDA policy actions around suicidality and antidepressants.

The spillover effect on adult depression care remained, even after removing the young adults from the analytic cohort. The young adults eventually became targets of the FDA warnings, but adults older than 25 years were not targets. This is important, in part, because the costs of depression from lost productivity are based on adult populations; therefore, the associated costs of untreated depression are likely to be high.
No greater cost can come than in human terms. Suggestive evidence has been described of a significant increase in pediatric suicide deaths for the first time in more than a decade. Much has been made of the temporal association of ecological data on antidepressant use and the inverse relation with suicide deaths. Clearly, there are limitations to drawing causal associations using population data. And clearly there is a compelling case for concern when a historical trend over a decade is reversed significantly and the change is temporally associated with a major change in a leading risk factor for death by suicide. Examining trends in Injury Mortality data from the Centers for Disease Control and Prevention, it appears that for youth aged 10 to 19 years, crude suicide rates either increased steadily since 2004 or have not declined to pre–2003 advisory levels and are significantly higher than history would have predicted based on levels from 1996 through 2003. Bridges and colleagues conclude that the marked increase in suicide rates in 2004 was not a single fluctuation. Of note is another population with steadily increasing rates of suicide; the crude suicide rate per 100,000 adults in their mid-40 and early 50 years of age (eg, aged 52 years) ranged from 12.52 in 1999 to 13.94 in 2002 to 16.88 in 2005 (the most recent data available were from 2005). There does not appear to be a large discontinuity around the time of the warnings, but given the spillover effects to depression treatment for adults, this could be an unexpected concern. There is a great need to use cohort data to examine patient records for which diagnosis, treatment, and suicide outcome are linked for the individual data.

Early reports of a significant increase in treatment of pediatric depression by psychiatrists provided some comfort. Two more years of observations showed that this upward trend turned back down and averaged out to a post-advisory decline for psychiatrists who accept managed care patients. The shortage of psychiatrists, especially child and adolescent psychiatrists in the community, is felt by every clinician who has ever been asked for help by desperate parents with a suicidal child. Policy actions may be called for in this regard. Training can be rewarded to improve physician supply. Another policy tool could be to bring parity to reimbursement with other medical specialties. True cost-based reimbursement will help ensure that inpatient psychiatry is an option in every community.

Limitations of this study largely derive from the nature of claims records. The reported rates of decline in SSRI prescriptions of around 10% to 15% were smaller than reported earlier. Pharmacy claims are subject to back coding in a way that single physician visits are not. Prior studies used data trimmed by 3 months from complete claims records; subsequent analyses showed those last 3 months of data to have been somewhat incomplete. This was remedied in the new data file by trimming off 6 full months. The variation in the trend lines leads us to believe that this is an accurate picture of the trend. Nevertheless, these measurement errors would not necessarily bias the hypothesis test in one direction. Increased nonpsychiatrist mental health provider diagnoses not being accompanied by increased psychotherapy visits might suggest that more treatment occurred outside of the health plan, which we could not observe in these data.
Regulating the safety of pharmacological agents is part of the FDA’s mission, and the boxed warning, medication guide, and package insert are all policy tools for communicating risk. All of these were used to communicate risk of suicidality in the absence of a single death in a randomized clinical trial for antidepressants; yet, the medication guide and package insert are considered the strongest form of warning short of pulling drugs off of the market. Initial concern about the safety of 2 specific antidepressants came under increased scrutiny in the United Kingdom; yet, the FDA warnings were class-level. Thus, the FDA advisories and policy actions were strong (the step before drug removal) and broad (all newer antidepressants). The intended effect was to reduce the use of antidepressants in young people. The unintended effects were substantial and diffuse effects on depression treatment at large. To their credit, the FDA and their advisors recognized early the potential unintended consequences of the suicidality warnings and modified the language in the May 2007 medication guide to state that depression was a serious illness and that the warning was not meant to dissuade people from seeking appropriate treatment. Nevertheless, the FDA has stated that if there was empirical evidence of unintended consequences—certainly if effects themselves may risk patient safety—that it would revisit its policy on antidepressants. We submit evidence of substantial, persistent, and diffuse unintended effects using a nationally representative database of 55 million managed care enrollees.

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