

# Effects of Food and Drug Administration Warnings on Antidepressant Use in a National Sample

Mark Olfson, MD, MPH; Steven C. Marcus, PhD; Benjamin G. Druss, MD, MPH

**Context:** In June 2003, the Food and Drug Administration (FDA) recommended that paroxetine hydrochloride not be used to treat young people because of potential increased risk of suicidal behavior, and in October 2004, the FDA issued a black box warning concerning all antidepressants for youth.

**Objective:** To characterize associations between these warnings and antidepressant use.

**Design:** Interrupted time series analyses of trends in antidepressant use were performed with Medco pharmacy and enrollment data stratified by patient age, sex, antidepressant type, and specialty of the prescribing physician across 3 study periods: prewarning (May 1, 2002 to June 19, 2003), paroxetine warning (June 20, 2003 to October 15, 2004), and black box warning (October 16, 2004 to December 31, 2005).

**Main Outcome Measures:** The rate of antidepressant use, annualized percentage change in rate of antidepressant use, and difference in trend of antidepressant use between consecutive study periods.

**Results:** During the prewarning study period, there was a 36.0% per year ( $P < .001$ ) increase in total youth (aged

6-17 years) antidepressant use, which was followed by decreases of  $-0.8\%$  per year ( $P = .85$ ) and  $-9.6\%$  per year ( $P = .21$ ) during the paroxetine and black box warning study periods, respectively. The difference in trends between the prewarning and paroxetine warning periods was significant ( $P < .001$ ). Youth paroxetine use also significantly increased during the prewarning study period ( $30.0\%$  per year;  $P < .001$ ) before significantly declining during the paroxetine warning study period ( $-44.2\%$  per year;  $P < .001$ ), which was also a significant between-period difference in trends ( $P < .001$ ). Changes in antidepressant use were less pronounced in adults than in youth. For adults 65 years and older, overall antidepressant use significantly increased ( $8.1\%$  per year;  $P < .001$ ) during the black box study period. Changes in the pattern of antidepressant use varied little by patient sex.

**Conclusions:** The paroxetine and black box warnings had modest and relatively targeted effects on the intended populations. These changes, which were greatest for youth, were broadly consistent with the FDA warnings and the scientific literature.

*Arch Gen Psychiatry.* 2008;65(1):94-101

**Author Affiliations:** New York State Psychiatric Institute/Columbia University College of Physicians and Surgeons, New York, New York (Dr Olfson); University of Pennsylvania School of Social Policy and Practice, Philadelphia (Dr Marcus); and Rollins School of Public Health, Emory University, Atlanta, Georgia (Dr Druss).

**I**N SEVERAL CONTEXTS, FOOD AND Drug Administration (FDA) warnings of serious adverse drug events have been followed by reductions in use of the targeted medications.<sup>1-3</sup> Over the past 4 years, the FDA and other regulatory agencies have issued various warnings concerning the risk of suicidal thoughts and actions associated with antidepressant medications, especially in the treatment of children and adolescents. Although these warnings have been widely reported by the public and professional press, their effects on the prescription of antidepressant medications remain a subject of debate.<sup>4,5</sup> A recent analysis of Verispan data reported that the number of youth anti-

depressant prescriptions per month significantly increased from April 2002 to February 2004, then tended to decline until July 2004, before stabilizing over the next 8 months.<sup>5</sup> These trends suggest that media attention to antidepressant safety may have influenced antidepressant prescribing in youth. However, no information was provided in this study regarding the effects of individual FDA advisories on specific antidepressant medication use over time or on their effects on the rate of antidepressant use in specific demographic and clinical populations.

The possibility that antidepressant medications, especially selective serotonin reuptake inhibitors (SSRIs), increase the risk of suicidal behavior was first raised in sev-

## SOURCES OF DATA

eral case reports of children and adults during the early 1990s.<sup>6-9</sup> Concern over the safety of antidepressant medications received renewed attention following pooled analyses of placebo-controlled trials that revealed a significant overall increase in suicidal behavior or ideation in children and adolescents treated with newer antidepressants.<sup>10,11</sup> No suicide deaths were reported in these trials.

There is less evidence supporting suicidality as an adverse effect of antidepressant medications for adults.<sup>12-14</sup> Although 1 meta-analysis of controlled trial data reported that treatment of adults with SSRIs was associated with a significantly greater risk of nonfatal suicide attempts than treatment with placebo,<sup>12</sup> a second review reported that SSRIs had a nonsignificant protective effect for suicidal thoughts.<sup>13</sup> In a recent pooled analysis of placebo-controlled antidepressant trials for psychiatric disorders conducted by the FDA, antidepressant treatment was associated with a significantly reduced risk of suicidality for adults aged 25 to 64 years and for adults 65 years and older.<sup>14</sup> In practice, physicians seek to balance safety concerns against the known efficacy of antidepressants in the treatment of adolescent<sup>15</sup> and adult<sup>16</sup> depression and the risk of doing nothing given that depression is an important modifiable risk factor for suicide in adults<sup>17,18</sup> and youth.<sup>19,20</sup>

As evidence has accumulated concerning a possible increased risk of suicidal thoughts and behaviors associated with antidepressant treatment, regulatory agencies have warned the public and health care professionals of this potential risk. In the United States, the first such indication occurred on June 19, 2003, when the FDA announced that it was reviewing "a possible increased rate" of suicidal behavior in youth treated with paroxetine hydrochloride.<sup>21</sup> The FDA recommended that paroxetine not be used in children and adolescents for the treatment of major depressive disorder. The FDA also advised caretakers of young patients currently receiving paroxetine to speak with their physician before discontinuing the medication. Additional warnings from the FDA and other international drug regulatory agencies followed over the next several months.<sup>11,22</sup> On October 15, 2004, the FDA issued a boxed warning or so-called black box warning that all antidepressants pose significant risks of suicidality in children and adolescents and that children and adults treated with antidepressants should be watched closely for increased suicidal thinking or behavior.<sup>23</sup> This warning received extensive media attention<sup>24,25</sup> and academic interest.<sup>26,27</sup> It is the strongest action that the FDA can take short of withdrawing drug approval.

In the current study, we describe the effects of the initial FDA announcement concerning paroxetine in June 2003 ("paroxetine warning") and the black box warning in October 2004 on the pattern of antidepressant prescriptions adjudicated by a large national pharmacy benefit manager representing more than 60 million Americans. We describe associations between the timing of these regulatory actions and population rates of antidepressant treatment over time by youth, adults 18 to 64 years of age, and older adults. With this analysis, we hope to provide a broader and more nuanced understanding of how FDA policy recommendations affect national prescribing practices.

Data were extracted from the Medco data warehouse. Medco is one of the largest pharmacy benefit management services in the United States. It administers prescription drug benefits for insurance carriers, employers, government agencies, managed care organizations, and union-sponsored benefit plans. Three 2% simple random samples without oversampling or stratification were drawn from the membership rolls for overlapping 2-year cohorts of members with continuous 24-month enrollment during calendar years 2002-2003, 2003-2004, and 2004-2005, respectively. Demographic information was extracted for all selected members while the prescription history was also extracted for those selected members who used an antidepressant medication.

We defined 3 cohorts during consecutive periods: (1) a paroxetine warning study period (May 1, 2002 to June 19, 2003), (2) a paroxetine warning study period (June 20, 2003 to October 15, 2004), and (3) a black box warning study period (October 16, 2004-December 31, 2005). Each study period included more than 2 million Medco members who were continuously eligible for antidepressant prescriptions during the study period whether or not they filled an antidepressant prescription.

Information concerning the medical specialty of the physicians who prescribed the antidepressant medications was derived from the American Medical Association (AMA) Masterfile.<sup>28</sup> The AMA Masterfile is the most comprehensive listing of physicians in the United States. It includes all allopathic (doctor of medicine degree) and most osteopathic (doctor of osteopathy degree) physicians whether or not they are members of the AMA. Physician medical license numbers from the pharmacy benefit manager database were used to link prescriptions to the prescribing physician's specialty variable in the AMA Masterfile. All study procedures were approved by the institutional review board of the New York State Psychiatric Institute.

## PATIENT CHARACTERISTICS

Patients were classified as male or female and as youth (ages 6-17 years), adults (ages 18-64 years), or older adults (65 years and older). The age range selected for the youth sample was based on the age criteria used in the FDA registration trials of antidepressant medications for pediatric major depressive disorder. Prescribing physicians were classified as psychiatrists (including all psychiatric subspecialties), primary care physicians (pediatrics, adolescent medicine, general practice, family practice, internal medicine, and geriatrics), and all other specialties and subspecialties.

## ANALYTIC STRATEGY

Patients were dichotomously classified as either having or not having received 1 or more antidepressant prescriptions (antidepressant use) during each month of each study period. Antidepressant medications were further subclassified as paroxetine, other SSRIs (citalopram hydrobromide, escitalopram oxalate, fluoxetine, fluvoxamine, and sertraline hydrochloride), tricyclic and heterocyclic antidepressants (amitriptyline hydrochloride, amoxapine, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, imipramine, maprotiline, nortriptyline hydrochloride, protriptyline hydrochloride, and trimipramine), and other antidepressants (bupropion hydrochloride, duloxetine, isocarboxazid, mirtazapine, nefazodone hydrochloride, phenelzine sulfate, tranylcypromine sulfate, and venlafaxine hydrochloride). New use of antidepressants was de-

defined as antidepressant prescriptions to patients who had not received any antidepressant prescriptions in the preceding 120 days given that patients were eligible during this period.

Antidepressant use rates during each month are expressed as the number of patients treated (numerator) divided by the number of patients eligible for antidepressant treatment during that period (denominator). The monthly rate of antidepressant use per 1000 persons was assessed for any antidepressant medication and for each of the 4 antidepressant subgroups (paroxetine, other SSRIs, tricyclics, and other). Similar rates of antidepressant use were assessed separately for the 3 age groups, males and females, and physician specialty group. Separate analyses were performed for new use of antidepressants.

The analyses examined changes in the rate of antidepressant use during each study period and the difference in those changes between contiguous study periods.<sup>29</sup> First, PROC GENMOD in SAS version 9.13 (SAS Institute Inc, Cary, North Carolina) was used to conduct a series of Poisson regression models with an autoregressive correlation structure to estimate the change in the monthly rate of antidepressant use during each of the 3 study periods and an associated *P* value testing the null hypothesis of no change over time. The results are expressed as annualized percentage change in the rate of antidepressant use. Next, interrupted time series techniques were used with the Poisson models<sup>29</sup> to generate coefficients that estimate the difference in the trend in antidepressant use from the prewarning to the paroxetine study period and from the paroxetine to the black box study period, controlling for seasonal variation. Finally, we used these coefficients and their standard errors to test with *z* statistics whether there were significant differences in the change of paroxetine use from the prewarning to the paroxetine warning periods and differences in the change of all antidepressant use from the paroxetine warning to the black box warning periods across age, sex, and physician specialty strata. We set  $\alpha$  at .01 (2-tailed).

## RESULTS

### ANTIDEPRESSANT TREATMENT OF YOUTH

During the prewarning study period, all antidepressant use by youth significantly increased at a rate of 36.0% per year (**Table 1**). Specific significant increases were evident for paroxetine, other SSRIs, and “other antidepressants” but not tricyclic antidepressants. During the paroxetine warning study period, the rate of paroxetine use by youth significantly declined, though the rate of use of the other 3 antidepressant groups did not significantly change. Nevertheless, there was a significant deceleration in the rate of change for each antidepressant group from the prewarning to the paroxetine study periods. During the black box warning study period, there was a nonsignificant decline in the rate of use of each antidepressant. For SSRIs other than paroxetine, this trend represented a significant difference from the trend during the paroxetine warning study period (Table 1).

The pattern of new use of antidepressants by youth generally resembled the pattern of all antidepressant use by youth (data not shown). The trend in new use of all antidepressants during the paroxetine warning study period (+5.5% per year; *P* = .66) was significantly different from the trend during the prewarning study period (+32.6% per year; *P* = .01) (*P* < .001). There was a nonsignificant decrease in new use of all antidepressants by youth during the black box study period (−17.1% per year; *P* = .30).

The rate of new use of paroxetine by youth remained little changed during the prewarning study period (−0.6% per year; *P* = .96), declined significantly during the paroxetine warning study period (−32.3% per year; *P* < .001), and was nearly constant during the black box warning period (+0.2% per year; *P* = .99).

### ANTIDEPRESSANT TREATMENT OF ADULTS AGED 18 TO 64 YEARS

There was a significant increase in use of all antidepressants by adults aged 18 to 64 years during the prewarning study period (Table 1). During the paroxetine warning study period, the rate of all antidepressant use in this age group remained nearly constant, though use of paroxetine significantly declined and use of “other antidepressants” significantly increased (Table 1). Trends in use of all antidepressants, paroxetine, and other SSRIs during this period were significantly different from the prewarning study period. During the black box study period, paroxetine and tricyclic antidepressant use significantly decreased and use of “other antidepressants” significantly increased (Table 1).

New use of all antidepressants by adults aged 18 to 64 years did not significantly change during any of the study periods (data not shown). However, during the prewarning (−20.5% per year; *P* < .001) and paroxetine warning (−22.8% per year; *P* < .001) study periods, there were significant declines in new use of paroxetine by adults in this age range. During the black box study period, there was a significant decline in new use of tricyclic antidepressants (−14.0% per year; *P* < .004), but not other antidepressant groups (data not shown).

### ANTIDEPRESSANT TREATMENT OF ADULTS 65 YEARS AND OLDER

Use of all antidepressants by older adults significantly increased during the prewarning and black box warning study periods (Table 1). During the paroxetine warning study period, all antidepressant use by older adults remained almost constant, though use of paroxetine significantly declined while use of other SSRIs and “other antidepressants” significantly increased (Table 1). Trends in use of all antidepressants, paroxetine, other SSRIs, and “other antidepressants” during the paroxetine period were significantly different from their trends in the prewarning study period (Table 1).

The rate of new use of all antidepressants by older adults also did not significantly change during the 3 study periods (data not shown). However, new use of paroxetine significantly declined during the paroxetine warning (−16.0% per year; *P* < .001) and black box warning (−15.7% per year; *P* = .004) study periods. New use of tricyclic antidepressants by older adults also significantly decreased during the black box study period (−11.9% per year; *P* = .002).

### ANTIDEPRESSANT TREATMENT OF MALES AND FEMALES

For males and females, use of all antidepressants significantly increased during the prewarning study period. There

**Table 1. Rates and Trends of Antidepressant Use per 1000 Persons by Patient Age Group and Sex During the Prewarning, Paroxetine Warning, and Black Box Warning Study Periods<sup>a</sup>**

Group	Period 1: Prewarning Study Period (May 1, 2002-Jun 19, 2003)		Period 2: Paroxetine Warning Study Period (Jun 20, 2003-Oct 15, 2004)		P Value Difference in Trend of Antidepressant Use From Period 1 to 2	Period 3: Black Box Warning Study Period (Oct 16, 2004-Dec 31, 2005)		P Value Difference in Trend of Antidepressant Use From Period 2 to 3
	Antidepressant Use per 1000 First Month of Period	Annualized Change In Antidepressant Use During Period, % (P Value)	Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (P Value)		Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (P Value)	
<b>Age 6-17 y</b>								
All antidepressants	8.91	36.0 (<.001)	10.69	-0.8 (.85)	<.001	11.65	-9.6 (.21)	.19
Paroxetine	1.45	30.0 (<.001)	1.62	-44.2 (<.001)	<.001	0.85	-22.2 (.16)	.04
Other SSRIs	4.47	49.3 (<.001)	6.01	10.9 (.03)	<.001	7.42	-7.7 (.33)	.009
Tricyclics	1.06	9.5 (.06)	1.03	-3.4 (.31)	.001	1.07	-8.2 (.05)	.26
Others	2.40	26.9 (<.001)	2.60	-5.4 (.37)	<.001	2.87	-11.5 (.10)	.55
<b>Age 18-64 y</b>								
All antidepressants	54.84	10.9 (<.001)	61.27	1.5 (.11)	<.001	63.50	0.8 (.74)	.42
Paroxetine	9.01	3.0 (.21)	9.33	-13.6 (<.001)	<.001	7.80	-11.0 (.002)	.58
Other SSRIs	26.78	15.5 (<.001)	30.96	2.1 (.04)	<.001	32.4	0.6 (.80)	.37
Tricyclics	7.04	-0.2 (.88)	6.97	2.7 (.02)	.23	6.74	-9.3 (.003)	<.001
Others	16.26	12.4 (<.001)	18.85	10.2 (<.001)	.34	21.8	7.1 (.001)	.06
<b>Age ≥ 65 y</b>								
All antidepressants	57.56	9.9 (<.001)	66.29	2.8 (.05)	<.001	67.96	8.1 (<.001)	.03
Paroxetine	9.98	3.6 (.15)	10.86	-8.1 (<.001)	<.001	9.52	-2.7 (.001)	.04
Other SSRIs	23.98	19.2 (<.001)	30.03	6.7 (<.001)	<.001	32.20	12.0 (<.001)	.07
Tricyclics	13.66	-4.3 (.02)	13.32	-2.1 (.10)	.70	12.72	-3.6 (<.001)	.24
Others	13.64	13.4 (<.001)	16.63	7.7 (<.001)	<.001	18.31	14.5 (<.001)	.01
<b>Males</b>								
All antidepressants	29.72	11.7 (<.001)	33.5	0.7 (.52)	<.001	34.31	-0.3 (.92)	.42
Paroxetine	5.24	5.3 (.03)	5.5	-11.7 (<.001)	<.001	4.76	-11.5 (.006)	.72
Other SSRIs	12.87	19.3 (<.001)	15.5	4.8 (<.001)	<.001	16.67	1.4 (.70)	.23
Tricyclics	4.33	-1.7 (.31)	4.3	-4.3 (.001)	.18	4.01	-11.4 (<.001)	<.001
Others	9.28	10.7 (<.001)	10.5	3.4 (.006)	.001	11.31	4.7 (.04)	.99
<b>Females</b>								
All antidepressants	64.81	11.3 (<.001)	73.14	2.2 (.03)	<.001	76.14	2.5 (.21)	.68
Paroxetine	10.50	3.5 (.12)	11.02	-14.0 (<.001)	<.001	9.06	-8.7 (.001)	.07
Other SSRIs	31.69	16.7 (<.001)	37.14	3.1 (.006)	<.001	39.18	2.5 (.21)	.53
Tricyclics	10.17	-1.3 (.32)	10.03	-3.4 (.007)	.10	9.61	-6.5 (<.001)	.01
Others	17.39	14.1 (<.001)	20.67	12.8 (<.001)	.40	24.44	9.0 (<.001)	.03

Abbreviations: paroxetine, paroxetine hydrochloride; SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup>Data from Medco Health Solutions, Inc.

were no significant changes during either the paroxetine or black box study periods in the rate of all antidepressant use by males or females. Use of “other antidepressants” significantly increased among both sexes during the prewarning and paroxetine warning study periods. Nevertheless, the rate of increase in use of “other antidepressants” by males, but not females, significantly decelerated between these 2 periods. In addition, during the black box warning period, use of “other antidepressants” by females, but not males, significantly increased (Table 1). New use of antidepressants followed generally similar trends in males and females (data not shown).

#### ANTIDEPRESSANT TREATMENT OF YOUTH BY PHYSICIAN SPECIALTY

During the prewarning study period, there were significant increases in all antidepressant use by youth prescribed by psychiatrists, primary care physicians, and other

physicians (Table 2). For all 3 physician groups, the rate of all antidepressant use by youth did not significantly change during either the paroxetine or black box warning study periods. During the paroxetine warning study period, paroxetine use prescribed by all 3 physician groups significantly declined and continued to decline, although not significantly, during the black box warning period. During this period, use of other SSRIs prescribed by psychiatrists significantly increased, use of other SSRIs prescribed by primary care physicians tended to increase, and use of other SSRIs prescribed by other physicians was little changed. There was a significant decline during the black box warning study period in use of “other antidepressants” prescribed by physicians who were neither psychiatrists nor primary care physicians (Table 2).

During the prewarning study period, new use of all antidepressants by youth prescribed by psychiatrists (+32.7% per year;  $P < .001$ ), primary care physicians (+25.7% per year;  $P = .07$ ), and other physicians (+37.1% per year;

**Table 2. Rates and Trends of Antidepressant Use per 1000 Persons Aged 6 to 17 Years by Specialty Group of the Prescribing Physician During the Prewarning, Paroxetine Warning, and Black Box Warning Study Periods<sup>a</sup>**

Group	Period 1: Prewarning Study Period (May 1, 2002-Jun 19, 2003)		Period 2: Paroxetine Warning Study Period (Jun 20, 2003-Oct 15, 2004)		P Value Difference in Trend of Antidepressant Use From Period 1 to 2	Period 3: Black Box Warning Study Period (Oct 16, 2004-Dec 31, 2005)		P Value Difference in Trend of Antidepressant Use From Period 2 to 3
	Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (P Value)	Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (P Value)		Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (P Value)	
All antidepressants								
Psychiatrists	3.57	25.0 (<.001)	4.06	2.9 (.36)	<.001	4.70	0.6 (.88)	.80
Primary care	1.64	44.1 (<.001)	1.98	5.6 (.27)	<.001	2.29	-8.0 (.45)	.10
Other	1.35	46.0 (<.001)	1.75	-6.2 (.17)	<.001	1.70	-1.8 (.71)	.13
Paroxetine								
Psychiatrists	0.54	2.6 (.003)	0.58	-49.6 (<.001)	<.001	0.28	-12.4 (.20)	.006
Primary care	0.33	43.0 (<.001)	0.35	-31.9 (<.001)	<.001	0.20	-13.0 (.47)	.10
Other	0.54	48.6 (<.001)	0.58	-46.9 (<.001)	<.001	0.28	-18.5 (.38)	.38
Other SSRIs								
Psychiatrists	1.89	35.7 (<.001)	2.36	17.0 (.001)	.004	3.13	3.7 (.35)	.004
Primary care	0.77	71.1 (<.001)	1.13	17.6 (.02)	<.001	1.45	-6.8 (.58)	.03
Other	0.62	66.4 (<.001)	0.86	-1.5 (.85)	<.001	0.90	2.3 (.71)	.29
Tricyclics								
Psychiatrists	0.20	-16.3 (<.001)	0.13	-16.1 (.004)	.92	0.13	12.6 (.05)	<.001
Primary care	0.25	4.4 (.52)	0.24	-3.9 (.58)	.37	0.28	-23.0 (.03)	.01
Other	0.37	8.3 (.16)	0.39	4.2 (.24)	.84	0.40	8.6 (.28)	.46
Other								
Psychiatrists	1.18	22.1 (<.001)	1.27	-4.2 (.40)	<.001	1.43	-3.4 (.49)	.59
Primary care	0.33	9.1 (.41)	0.29	9.8 (.24)	.95	0.39	-3.4 (.65)	.34
Other	0.18	53.3 (.009)	0.26	0.3 (.97)	<.001	0.30	-18.8 (.001)	.08

Abbreviations: See Table 1.

<sup>a</sup>Data from Medco Health Solutions, Inc.

$P=.04$ ) tended to increase. These trends were all significantly ( $P<.001$ ) different from trends in new use of all antidepressants during the paroxetine warning period (psychiatrists: +5.7% per year;  $P=.54$ ; primary care physicians: -1.7% per year;  $P=.88$ ; other physicians: -6.7% per year;  $P=.54$ ). New use of all antidepressants by youth did not significantly change during the black box warning period for any of the physician groups (psychiatrists: -11.6% per year;  $P=.21$ ; primary care physicians: +4.8% per year;  $P=.75$ ; other physicians: +2.4% per year;  $P=.88$ ).

During the prewarning study period, new use of paroxetine by youth prescribed by psychiatrists tended to decrease (-23.0% per year;  $P=.06$ ), while that prescribed by primary care physicians (+21.2% per year;  $P=.10$ ) and other physicians (+10.3% per year;  $P=.58$ ) tended to increase. These trends for primary care physicians ( $P=.006$ ), but not psychiatrists ( $P=.22$ ) or other physicians ( $P=.03$ ), were significantly different from trends in new use of paroxetine during the paroxetine warning period (psychiatrists: -49.4% per year;  $P<.001$ ; primary care physicians: -38.1% per year;  $P=.005$ ; other physicians: -32.2% per year;  $P=.007$ ).

#### DIFFERENCES IN TRENDS OF ANTIDEPRESSANT TREATMENT

The differential effects of the paroxetine warning on paroxetine use by patient age, sex, and physician prescrib-

ing group among youth were each assessed by comparing differences in trends of use from the prewarning to the paroxetine warning study period. As compared with the changes in trends of paroxetine use by adults (+3.0% per year to -13.6% per year) and older adults (+3.6% per year to -8.1% per year), youth experienced a significantly greater decrease (+30.0% per year to -44.2% per year) in the rate of paroxetine use over the 2 study periods ( $P<.001$  and  $P<.001$ , respectively). Changes in trends of paroxetine use were not significantly different for males as compared with females ( $P=.71$ ) nor were they significantly different in pairwise comparisons between each of the physician groups for youth paroxetine use (data not shown).

Similar methods were used to assess differential effects of the black box warning on all antidepressant use by patient age and sex and by physician specialty among youth. Changes in trends of all antidepressant use from the paroxetine to the black box study periods were not significantly different for any age, sex, or physician specialty pairwise comparisons (data not shown).

#### COMMENT

The FDA warnings concerning antidepressants and risk of suicidality appear to have had a modest and reasonably targeted effect on antidepressant treatment pat-

terns. After the FDA first recommended not treating youth with paroxetine, there was a significant absolute decline in paroxetine use by youth but not significant declines in use of other antidepressants by young people. Similar, though less pronounced, declines occurred in paroxetine treatment of older patients. Following the black box warning, there was a statistically nonsignificant decline in antidepressant treatment of youth, including a significant deceleration in the rate of treatment with SSRIs other than paroxetine. We found little evidence that the response to either FDA warning varied by patient sex. These patterns are generally consistent with what would be expected if the FDA warnings achieved their intended effects of increasing perceptions of risk of antidepressant treatment, especially in young people.

Concern has been expressed that the FDA advisories may have resulted in excessive declines in antidepressant prescribing, thereby putting depressed youth at increased risk.<sup>4,30,31</sup> Our report indicates that the absolute rate of overall antidepressant treatment of youth did not significantly decrease during the period of FDA regulatory activity. In accord with these findings, a study of Irish General Medical Services claims found little change in SSRI prescriptions to children between January 2001 and August 2004,<sup>32</sup> despite warnings from the Irish regulatory authorities.<sup>33</sup> In keeping with our finding of a marked decrease in youth paroxetine use following the paroxetine warning, paroxetine use by youth in Ontario, Canada, underwent a similar abrupt decrease following the first British paroxetine warning in June 2003.<sup>34</sup> The current results are also consistent with an analysis of monthly prescriptions from the Verispan database that revealed a nonsignificant decline in total antidepressant prescriptions to youth between January and June of 2004,<sup>5</sup> though the current results highlight the differential pattern of antidepressant use associated with the release of the paroxetine and black box advisories.

Given that the FDA warnings concentrated on risks associated with antidepressant treatment of youth, it is not surprising that they tended to be followed by larger changes in the rate of antidepressant treatment of youth than adults. At the same time, significant decelerations in the rate of growth of all antidepressant use were also evident for adults. These trends may reflect spreading concern over the safety of antidepressants in general.<sup>35</sup> Although some evidence suggests a possible link between antidepressant treatment and suicidal thoughts and behavior for adults,<sup>12,13</sup> the evidence of antidepressant-associated risk is less consistent for adults than youth.<sup>10</sup> There is also stronger empirical support for the efficacy of antidepressants in the treatment of adult<sup>14,36</sup> than child mood and anxiety disorders.<sup>37,38</sup>

The FDA advisories appear to have had similar effects on antidepressant use patterns of males and females. Although there are marked sex differences in the risks of suicide attempts and completed suicides,<sup>39,40</sup> these differences apparently did not have a substantial influence on broad patterns of antidepressant use following the advisories.

The black box warning was applied to all antidepressants in children and adolescents. Nevertheless, the effects of this warning on youth antidepressant treatment were most evident for SSRIs other than paroxetine. For

these SSRIs, but not other antidepressant classes, the black box warning was associated with a significant deceleration in the rate of youth antidepressant use. In the FDA analysis of pediatric controlled trials, venlafaxine, a non-SSRI, was the most strongly related to an increase in suicidal thoughts and behaviors.<sup>10</sup> In addition, the FDA issued an advisory in March 2004 that required manufacturers of 10 antidepressants, including several non-SSRIs (nefazodone, bupropion, venlafaxine, and mirtazapine), to include a warning of "possible worsening of depression or suicidality" for treated children and adults.

There were several similarities in the patterns of antidepressant treatment prescribed to youth by psychiatrists, primary care physicians, and other physicians during the study period. For all 3 physician groups, the rate of pediatric antidepressant use significantly increased during the prewarning study period and then leveled off following the paroxetine warning. Although psychiatrists tend to treat patients who have more severe mental illness than those treated by other physicians and presumably have greater knowledge of regulatory developments affecting antidepressants, differences in antidepressant prescribing patterns between the physician groups were modest.

During the period prior to the paroxetine warning, there was a decline in new use of paroxetine, especially by adults aged 18 to 64 years. It is possible that new prescriptions served as a leading indicator of building paroxetine safety concerns. Prior to the FDA paroxetine advisory, safety concerns may have developed following a widely publicized British Broadcasting Company report "The Secrets of Seroxat" (GlaxoSmithKline, Middlesex, England) (paroxetine) that first aired on October 13, 2002. This report chronicled serious symptoms, including suicide, of young patients treated with paroxetine. Related media attention may have contributed to a decline in new use of paroxetine before the FDA advisory.

The current study has several limitations. First, assessing the effects of individual regulatory developments on antidepressant use is complicated by the rapidity with which they occurred. In addition to the paroxetine warning in June 2003 and the black box warning in October 2004, the FDA issued relevant warnings in October 2003 and March 2004, held hearings in September 2004, and enacted label changes and a medication guide in April 2005.<sup>41</sup> In addition, less than 2 weeks before the FDA paroxetine warning, the UK Department of Health released a strongly worded warning to British physicians not to prescribe paroxetine to people younger than 18 years. Given the cascade of events and media reporting, it is difficult to discern the effects of each individual regulatory and media development on prescribing patterns. In addition, escitalopram (August 2002) and duloxetine (August 2004) were first approved by the FDA and patent protection of Paxil (GlaxoSmithKline) (paroxetine) expired (September 2003) during the study period. Second, we have no means of determining whether and to what extent the FDA advisories differentially influenced antidepressant treatment of specific disorders. We also have no means of assessing whether the advisories influenced use of psychotherapy, which serves as

an alternative to antidepressants for some psychiatric disorders.<sup>42</sup> Third, specialty of the prescribing physicians was not available for about 20% of the patients. For this reason, the results concerning the treatment patterns of psychiatrists should be viewed with particular caution. Fourth, the analyses are limited to members of 1 pharmacy benefit manager. Although the study samples were drawn from a random sample of roughly 60 million insured members, the members may differ from the general US population in socioeconomic status and treatment-seeking behavior. Insurance status<sup>43</sup> and income<sup>44</sup> likely exert independent influences on whether patients receive antidepressant treatment.<sup>45</sup> In addition, we were unable to model changes in pharmacy benefits over time that may influence rates of antidepressant use in this sample. Finally, because the analyses were limited to patients who were continuously enrolled in the pharmacy benefit plan throughout a given study cohort, we are not able to generalize to individuals with short-term enrollment.

The FDA warnings occurred following a long period of sustained national increase in the prescription of antidepressant medications to adults and children. From 1985 to 1999, there was a 4-fold national increase in per capita antidepressant prescriptions.<sup>46</sup> The FDA warnings appear to have slowed this longer-term growth of antidepressant treatment of children and adults. Despite fears that these advisories might result in a precipitous decline in antidepressant prescribing, it is reassuring that the pattern of changes in treatment, which were modest in size and greatest for treatment of youth, were broadly consistent with the FDA warnings and the scientific literature.

**Submitted for Publication:** October 3, 2006; final revision received May 25, 2007; accepted June 1, 2007.

**Correspondence:** Mark Olfson, MD, MPH, New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons, 1051 Riverside Dr, New York, NY 10032 (mo49@columbia.edu).

**Financial Disclosure:** Dr Olfson has received grant support from Eli Lilly, Bristol-Myers Squibb, and AstraZeneca and has been a consultant for Pfizer, McNeil, and Eli Lilly; on the advisory board for Eli Lilly and Bristol-Myers Squibb; and on the speakers' bureau for Janssen. Dr Marcus has received grant support from McNeil and has been a consultant for Eli Lilly, Bristol-Myers Squibb, AstraZeneca, and Pfizer.

**Funding/Support:** This research was supported by Agency for Healthcare Research and Quality grant HS016097 (Dr Olfson) and the Carmel Hill Fund (Dr Olfson) and the data were provided by Medco Health Solutions, Inc.

## REFERENCES

- Jacoby JL, Fulton J, Cesta M, Heller M. After the black box warning: dramatic changes in ED use of droperidol. *Am J Emerg Med.* 2005;23(2):196.
- Weatherby LB, Walker AM, Fife D, Vervaeke P, Klausner MA. Contraindicated medications dispensed with cispripide: temporal trends in relation to the sending of "dear doctor" letters. *Pharmacoepidemiol Drug Saf.* 2001;10(3):211-218.
- Soumerai SB, Avorn J, Gortmaker S, Hawley S. Effect of government and commercial warnings on reducing prescription misuse: the case of propoxyphene. *Am J Public Health.* 1987;77(12):1518-1523.
- Rosack J. New data show declines in antidepressant prescribing. *Psychiatr News.* 2005;40(17):1-3.
- Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, Stephenson H, Schatzberg F. Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. *Arch Gen Psychiatry.* 2007;64(4):466-472.
- Teicher MH, Gold C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry.* 1990;147(2):207-210.
- King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P, Scapellato L. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J Am Acad Child Adolesc Psychiatry.* 1991;30(2):179-186.
- Masand P, Gupta S, Deewan M. Suicide ideation related to fluoxetine treatment. *N Engl J Med.* 1991;324(6):420.
- Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry.* 1991;52(12):491-493.
- Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry.* 2006;63(3):332-339.
- Selective serotonin reuptake inhibitors (SSRIs): overview of regulatory status and CSM advice relating to major depressive disorder (MDD) in children and adolescents including a summary of available and efficacy data. Medicines and Healthcare Products Regulation Agency Web site. [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON019494&ssTargetNodeid=221](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON019494&ssTargetNodeid=221). Accessed June 20, 2006.
- Fergusson D, Doucette S, Glass K, Shapiro S, Healy D, Hebert P, Hutton B. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomized controlled trials. *BMJ.* 2005;330(7488):396-399.
- Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomized trials submitted to the MHRA's safety review. *BMJ.* 2005;330(7488):385-388.
- Laughren TP. Overview for December 13 Meeting of Psychopharmacology Drugs Advisory Committee. <http://www.fda.gov/OHRMS/DOCKETS/AC/06/briefing/2006-4272b1-01-FDA.pdf>. Accessed May 11, 2007.
- March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. Treatment for Adolescents With Depression Study (TADS) Team: fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression. Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA.* 2004;292(7):807-820.
- Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, Goodwin GM. Relapse prevention with antidepressant drug treatment in depressive disorders. *Lancet.* 2003;361(9358):653-661.
- Conwell Y, Duberstein PR, Cox C, Hermann JH, Forbes NT, Caine ED. Relationships of age and axis I diagnoses in victims of completed suicide: a psychological autopsy. *Am J Psychiatry.* 1996;153(8):1001-1008.
- Foster T, Gillespie K, McClelland R. Mental disorders and suicide in Northern Ireland. *Br J Psychiatry.* 1997;170:447-452.
- Shaffer D, Gould MS, Fisher P, Trautman P, Moreau D, Kleinman M, Flory M. Psychiatric diagnosis in child and adolescent suicide. *Arch Gen Psychiatry.* 1996;53(4):339-348.
- Brent DA, Perper J, Moritz G, Allman C, Friend A, Roth C, Schweers J, Balach L, Baugher M. Psychiatric risk factors for adolescent suicide: a case-control study. *J Am Acad Child Adolesc Psychiatry.* 1993;32(3):521-519.
- FDA talk paper: FDA statement regarding the anti-depressant Paxil for pediatric population. US Food and Drug Administration Web site. <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01230.html>. Published June 19, 2003. Accessed July 31, 2004.
- FDA public health advisory: worsening depression and suicidality in patients being treated with antidepressant. US Food and Drug Administration Web site. <http://www.fda.gov/cder/drug/antidepressants/AntidepressantPHA.htm>. Published March 22, 2004. Accessed March 17, 2005.
- FDA public health advisory: suicidality in children and adolescents being treated with antidepressant medications. US Food and Drug Administration Web site. <http://www.fda.gov/CDER/DRUG/antidepressants/SSRIIPA200410.htm>. Published October 15, 2004. Accessed December 20, 2004.
- Harris G. FDA toughens warning on antidepressant drugs. *New York Times.* October 16, 2004. <http://www.nytimes.com/2004/10/16/politics/16depress.html>. Accessed December 20, 2004.
- Vedantam S. Depression drugs to carry warning: FDA orders notice of risks for youths. *Washington Post.* October 16, 2004:A01.
- Brent DA. Antidepressants and pediatric depression—the risk of doing nothing. *N Engl J Med.* 2004;351(16):1598-1601.
- Newman TB. A black-box warning for antidepressants in children? *N Engl J Med.* 2004;351(16):1595-1598.
- Shea JA, Kletke PR, Wozniak GD, Polsky D, Escarce JJ. Self-reported physician specialties and the primary care content of medical practice: a study of the AMA physician masterfile. *Med Care.* 1999;37(4):333-338.
- Wagner AK, Soumerai SB, Zhang F, Ross-Degnan DR. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* 2002;27(4):299-309.
- Marshall RD, Posner K, Greenhill L. Risk perception research and the black box warning for SSRIs in children. *J Am Acad Child Adolesc Psychiatry.* 2006;45(7):765.
- Lineberry TW, Bostwick JM, Beebe TJ, Decker PA. Impact of the FDA black box warning on physician antidepressant prescribing and practice patterns: opening Pandora's suicide box. *Mayo Clin Proc.* 2007;82(4):518-520.
- Bennett K, Teeling M, Feely J. Overprescribing antidepressants to children: pharmacoepidemiological study in primary care. *BMJ.* 2005;331(7530):1451-1452.

33. Irish Medicines Board. *Statement on Behalf of the Irish Medicine Board on Selective Serotonin Reuptake Inhibitors*. Dublin, Ireland: Irish Medicines Board; 2003.
34. Kurdyak PA, Juurlink DN, Mamdani MM. The effect of antidepressant warnings on prescribing trends in Ontario, Canada. *Am J Public Health*. 2007;97(4):750-754.
35. Wild J. Adult suicides linked to popular antidepressant. *Nature*. 2005;436(7054):1073.
36. Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectr*. 2005;10(1):49-56.
37. Jureidini JN, Doecker CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. *BMJ*. 2004;328(7444):879-883.
38. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683-1695.
39. Brent DA, Baugher M, Bridge J, Chen T, Chiappetta L. Age- and sex-related risk factors for adolescent suicide. *J Am Acad Child Adolesc Psychiatry*. 1999;38(12):1497-1505.
40. Spicer RS, Miller TR. Suicide acts in 8 states: incidence and case fatality rates by demographics and method. *Am J Public Health*. 2000;90(12):1885-1891.
41. FDA medication guide about using antidepressants in children and teenagers. [http://www.fda.gov/cder/drug/antidepressants/mg\\_template.pdf](http://www.fda.gov/cder/drug/antidepressants/mg_template.pdf). Revised January 26, 2005. Accessed March 1, 2005.
42. Miller P, Chilvers C, Dewey M, Fielding K, Gretton V, Palmer B, Weller D, Churchill R, Williams I, Bedi N, Duggan C, Lee A, Harrison G. Counseling versus antidepressant therapy for the treatment of mild to moderate depression in primary care; economic analysis. *Int J Technol Assess Health Care*. 2003;19(1):80-90.
43. Melfi CA, Croghan TW, Hanna MP. Access to treatment for depression in a Medicaid population. *J Health Care Poor Underserved*. 1999;10(2):201-215.
44. Olsson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adult depression in the United States. *Am J Psychiatry*. 2006;163(1):101-108.
45. Harman JS, Edlund MJ, Fortney JC. Disparities in the adequacy of depression treatment in the United States. *Psychiatr Serv*. 2004;55(12):1379-1385.
46. Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ. Antidepressants and suicide risk in the United States. *J Clin Psychiatry*. 2004;65(11):1456-1462.

### Correction

**Omissions in Acknowledgments.** In the Original Article by The TADS Team titled "The Treatment for Adolescents With Depression Study (TADS): Long-term Effectiveness and Safety Outcomes," published in the October issue of the *Archives* (2007; 64[10]:1132-1144), omissions occurred in the Financial Disclosure portion of the Acknowledgments on page 1142. The Financial Disclosure should have read as follows: "Dr Albano has received research support from Wyeth-Ayerst Pharmaceuticals, has been a consultant to Wyeth-Ayerst Pharmaceuticals and Pfizer Inc, has received an honorarium from Pfizer Inc, and has received royalties from Oxford University Press. Dr Casat has received research support from Eli Lilly and Company, GlaxoSmithKline, Shire, Bristol-Myers Squibb Company, AstraZeneca, Sanofi-Synthelabo, Pfizer Inc, and Ortho-McNeil Inc and has served on the advisory board and the speaker's bureau for Eli Lilly and Company and GlaxoSmithKline. Dr Emslie has received research funding from Eli Lilly and Company, Organon, RepliGen Corporation, Forest Laboratories Inc, Wyeth-Ayerst Pharmaceuticals, Novartis, and SmithKline Beecham; has been a consultant to Eli Lilly and Company, GlaxoSmithKline, Forest Laboratories Inc, Wyeth-Ayerst, and Pfizer Inc; and has served on the speaker's bureau for Ortho-McNeil Inc. Dr Fairbank has been a consultant to RTI International and Copernicus Group. Dr Findling has received research support from, has been a consultant to, and/or has served on the speaker's bureau for Abbott Laboratories, AstraZeneca, Best Practices, Bristol-Myers Squibb Company, Celltech-Medeva, Forest Laboratories Inc, GlaxoSmithKline, Johnson & Johnson, Layton BioSciences Inc, Eli Lilly and Company, Nature's Herbs, New River Pharmaceuticals Inc, Noven Pharmaceuticals Inc, Novartis, Organon, Otsuka America Inc, Pfizer Inc, Sanofi-Aventis, Shire, Solvay, Somerset Pharmaceuticals Inc, and Wyeth. Dr Ginsburg has received research support from Pfizer Inc. Dr Grimm has received research support from GlaxoSmithKline, Sepracor Inc, Shire, Ortho-McNeil Inc, AstraZeneca, Organon, Forest Laboratories Inc, Cephalon Inc, Jazz Pharmaceuticals Inc, Sanofi-Aventis, Merck & Co Inc, Eli Lilly and Company, ALZA Corporation, Johnson & Johnson, and New River Pharmaceuticals Inc. Dr Leventhal has been a consultant to Janssen, Eli

Lilly and Company, and the National Institutes of Health (NIH); has served on the speaker's bureau for Bristol-Myers Squibb Company and Cephalon Inc; and has received research funding from NIH, Eli Lilly and Company, Shire, Forest Laboratories Inc, Otsuka America Inc, and Novartis. Dr Kastelic has received an honorarium from Pfizer Inc. Dr Kratochvil has been a consultant or scientific advisor to Eli Lilly and Company, Shire, Cephalon Inc, Organon, AstraZeneca, Boehringer-Ingelheim, Abbott Laboratories, and Pfizer Inc; has received research support from Abbott Laboratories, Cephalon Inc, Eli Lilly and Company, Forest Laboratories Inc, GlaxoSmithKline, and Ortho-McNeil Inc; has served on the speaker's bureau for Eli Lilly and Company; and has received study drug for an NIMH-funded study from Eli Lilly and Company. Dr March has been a consultant or scientific advisor to Pfizer Inc, Eli Lilly and Company, Wyeth, GlaxoSmithKline, Jazz Pharmaceuticals Inc, and MedAvante; has held stock in MedAvante; has received research support from Eli Lilly and Company and study drug for an NIMH-funded study from Eli Lilly and Company and Pfizer Inc; and is the author of the Multidimensional Anxiety Scale for Children. Dr Pathak has received research support from Forest Laboratories Inc. Dr Posner has received research support from GlaxoSmithKline, Forest Laboratories Inc, Eisai Inc, AstraZeneca, Johnson & Johnson, Abbott Laboratories, Wyeth Research, Organon USA, Bristol-Myers Squibb Company, Sanofi-Aventis, Cephalon Inc, Novartis, Shire Pharmaceuticals, and UCB Pharma as part of an effort to help execute the US Food and Drug Administration adult suicidality classification mandates. Dr Silva has been a consultant to Pfizer Inc. Dr Walkup has received research support from Eli Lilly and Company, Pfizer Inc, and Abbott Laboratories; has been a consultant to Eli Lilly and Company, Pfizer Inc, Jazz Pharmaceuticals Inc, and Cephalon Inc; and has received honoraria from Eli Lilly and Company and Pfizer Inc. Dr Waslick has received research support from Eli Lilly and Company and Johnson & Johnson. Dr Weller has been a consultant to and/or received research support from Otsuka America Inc, AstraZeneca, Pharma Starr, Shire, Jazz Pharmaceuticals Inc, GlaxoSmithKline, Eli Lilly and Company, Johnson & Johnson, and Organon."