ORIGINAL ARTICLE

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

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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.

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In several contexts, Food and Drug Administration (FDA) warnings of serious adverse drug events have been followed by reductions in use of the targeted medications.[1-3] 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.[4,5] A recent analysis of Verispan data reported that the number of youth antidepressant 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.[5] 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-

eral case reports of children and adults during the early 1990s.[6-9] 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.[10,11] No suicide deaths were reported in these trials.

There is less evidence supporting suicidality as an adverse effect of antidepressant medications for adults.[12-14] 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,[12] a second review reported that SSRIs had a nonsignificant protective effect for suicidal thoughts.[13] 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.[14] In practice, physicians seek to balance safety concerns against the known efficacy of antidepressants in the treatment of adolescent[15] and adult[16] depression and the risk of doing nothing given that depression is an important modifiable risk factor for suicide in adults[17,18] and youth.[19,20]

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.[21] 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.[11,22] 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.[23] This warning received extensive media attention[24,25] and academic interest.[26,27] 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.

METHODS

SOURCES OF DATA

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 prewarning 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.[28] 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-

fined 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, tricylics, 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.[29] 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[29] 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 α 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[a]

	Period 1: Prewarning Study Period (May 1, 2002-Jun 19, 2003)		Period 2: Paroxetine Warning Study Period (Jun 20, 2003-Oct 15, 2004)			Period 3: Black Box Warning Study Period (Oct 16, 2004-Dec 31, 2005)		
Group	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)	*P* Value Difference in Trend of Antidepressant Use From Period 1 to 2	Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (*P* Value)	*P* Value Difference in Trend of Antidepressant Use From Period 2 to 3
Age 6-17 y								
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
Age 18-64 y								
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
Age ≥ 65 y								
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
Males								
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
Females								
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.
[a] 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[a]

	Period 1: Prewarning Study Period (May 1, 2002-Jun 19, 2003)		Period 2: Paroxetine Warning Study Period (Jun 20, 2003-Oct 15, 2004)			Period 3: Black Box Warning Study Period (Oct 16, 2004-Dec 31, 2005)		
Group	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)	*P* Value Difference in Trend of Antidepressant Use From Period 1 to 2	Antidepressant Use per 1000 First Month of Period	Annualized Change in Antidepressant Use During Period, % (*P* Value)	*P* Value Difference in Trend of Antidepressant Use From Period 2 to 3
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.
[a] 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 prescribing 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.[4,30,31] 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,[32] despite warnings from the Irish regulatory authorities.[33] 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.[34] 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,[5] 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.[35] Although some evidence suggests a possible link between antidepressant treatment and suicidal thoughts and behavior for adults,[12,13] the evidence of antidepressant-associated risk is less consistent for adults than youth.[10] There is also stronger empirical support for the efficacy of antidepressants in the treatment of adult[14,36] than child mood and anxiety disorders.[37,38]

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,[39,40] 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.[10] 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.[41] 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.[42] 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[43] and income[44] likely exert independent influences on whether patients receive antidepressant treatment.[45] 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.[46] 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.

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Correction

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