ORIGINAL ARTICLE

Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States

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Context: IMS Health Inc data presented by the Food and Drug Administration (FDA) on September 13 and 14, 2004, at a joint meeting of the Center for Drug Evaluation and Research's Psychopharmacologic Drugs Advisory Committee and the FDA's Pediatric Advisory Committee suggested that the number of children and teenagers who were prescribed antidepressants continued to increase in 2004, despite widespread publicity surrounding 2 FDA advisories regarding the potential for pediatric suicidality with selective serotonin reuptake inhibitor use. These results are contradictory to findings from the Medco Health Solutions, Inc, March 2004 analysis of pharmacy benefit claims and a separate subsequent analysis conducted by NDC Health using dispensing data from March 31, 2004, through June 30, 2005.

Objectives: To investigate the contradictory findings and provide additional analyses on the prescribing trends of antidepressants across age groups and physician specialties in the United States.

Design: Retail pharmacy prescription data and physician audit data were obtained from Verispan, a joint venture between Quintiles Transnational and McKesson. In addition to examining prescribing trends, a joinpoint regression analysis was conducted to identify the timing for significant changes in prescription use.

Results: The analyses suggest that the number of children and teenagers who were prescribed antidepressants has decreased significantly ($P = .02$) in the wake of widespread publicity surrounding the FDA public health advisories. Another impact of the advisories seems to be a shift in care from "generalists" to psychiatric specialists when it comes to prescribing antidepressants to patients younger than 18 years. Finally, the analyses highlight a slight shift in prescribing toward the non–selective serotonin reuptake inhibitor bupropion hydrochloride, even though it carries the same FDA "black box" warning as the selective serotonin reuptake inhibitors.

Conclusions: The effect on antidepressant prescribing volume observed in our analysis of the Verispan data parallels earlier findings reported by Medco Health Solutions, Inc, and NDC Health that the FDA actions have had a significant effect on the prescribing of antidepressants to children and adolescents. Together, these findings underline the importance of presenting a fair balance within the media due to the significant reach of this channel among prescribing physicians.

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In response to a US Food and Drug Administration (FDA) request for clarification of findings from a review of 3 pediatric studies of paroxetine hydrochloride, GlaxoSmithKline, Research Triangle Park, NC, submitted a report in May 2003 to the FDA and the Medicines and Healthcare Products Regulatory Agency of Great Britain describing the relationship between paroxetine use and pediatric suicidality, defined as suicidal thoughts and/or behavior among pediatric patients.[1] Specifically, the report suggested an increase in risk of events termed *possibly suicide related* and *suicide attempts* for paroxetine-treated patients compared with placebo-treated patients. At the same time, a pooled analysis from all 3 studies failed to demonstrate significantly greater efficacy vs placebo, attributed at least in part to unusually high placebo response rates.[2]

Following the data analysis, the FDA requested pediatric suicidality data from all clinical trials from all antidepressant manufacturers, including paroxetine hydrochloride (Paxil; GlaxoSmithKline), citalopram hydrobromide (Celexa; Forest Laboratories, Inc, New York), fluvoxamine maleate (Luvox; Solvay Pharmaceuticals, Marietta, Ga), mirtazapine (Remeron; Organon, Roseland, NJ), nefazodone (Serzone; Bristol-Myers Squibb, New York, NY), sertraline hydro-

chloride (Zoloft; Pfizer Inc, New York), fluoxetine (Prozac; Eli Lilly and Co, Indianapolis, Ind), venlafaxine (Effexor; Wyeth, Madison, NJ), and bupropion hydrochloride (Wellbutrin; GlaxoSmithKline). Based on the FDA's preliminary analysis, the agency issued a public health advisory on October 27, 2003, to call attention to the health care professional reports of the occurrence of suicidality in clinical trials for antidepressants in pediatric and adolescent patients with depression. In addition, the agency scheduled a hearing in February 2004 to review data analyzed to date. At this hearing, which received a great deal of media attention, the committee discussed plans for a more comprehensive analysis and advised the FDA to issue a more substantial warning related to the potential adverse effects of the selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants (before the completion of the more comprehensive analysis). On March 22, 2004, the FDA issued another public health advisory asking manufacturers of SSRIs and newer antidepressants to include a warning statement in product labeling that recommends monitoring in adult and pediatric patients for the emergence of suicidality.

On September 13 and 14, 2004, the Center for Drug Evaluation and Research's Psychopharmacologic Drugs Advisory Committee and the FDA's Pediatric Advisory Committee met again to discuss the analysis of the pediatric suicidality data based on the reclassification of events performed by Columbia University, New York. Key conclusions resulting from this meeting included the following:

1. The data from these studies suggest that antidepressants increase the risk of suicidality in pediatric patients.
2. Although there was some variability in findings, the panel was unable to conclude that any single agent was free of risk.
3. The committee supports a "black box" warning for all antidepressants for pediatric use.

Shortly after the September meetings, Medco Health Solutions, Inc, Franklin Lakes, NJ, at the request of the *New York Times*, conducted an analysis of its pharmacy benefit claims and found that the number of teenagers and children prescribed antidepressants had decreased by 18% during the past year.[3] This finding contradicts information presented by the FDA based on data from IMS Health Inc, Fairfield, Conn. The FDA officials told the committee that prescriptions continued to increase in 2004, despite the confusion regarding antidepressant safety. An analysis of prescription-dispensing data provided by NDC Health, Atlanta, from March 31, 2004, through June 30, 2005, supports the Medco Health Solutions, Inc, finding and demonstrates that prescriptions for antidepressants in patients 18 years and younger have decreased by approximately 20% in the aftermath of the FDA public health advisory.[4]

Given that the data released by Medco Health Solutions, Inc, and now NDC Health are in stark contrast to the information released by the FDA in 2004, there is a clear need for a more comprehensive analysis of the impact of the publicity of the pediatric suicidality data on physician practice patterns. Herein, we use a combination of prescription data (based on approximately 55% of all US retail pharmacy claims—private payers, Medicaid, and cash) and physician survey data to provide additional insight on the impact of the pediatric suicidality findings.

METHODS

We obtained retail pharmacy prescription data from Verispan, Yardley, Pa, a joint venture between Quintiles Transnational and McKesson, San Francisco, Calif. The Verispan data capture more than 1.4 billion patient-centric prescriptions per year, nearly half of all prescription activity in the United States. This data set includes prescriptions from a variety of retail channels (eg, national retail chains and mass merchandisers) from a near census of US pharmacies. The Verispan retail pharmacy database also captures information from all payer types, including cash. The average payer mix for antidepressants from January 2002 through December 2005 was as follows: 77.6% third-party private payers, 12.7% Medicaid, and 9.7% cash. In addition to payer type, because the data are patient-centric, information on patient age is available for every prescription from mid-2002 to the present (obtaining age data before that time frame is complex because of changes in the Verispan data).

To highlight the impact of the suicidality data on antidepressant use, we did the following: (1) focused our analysis on the June 2000 to March 2005 time frame to clearly depict the prescribing effect; (2) analyzed total antidepressant prescriptions as a moving quarterly total, a time series aggregate over 3 months, to "smooth out" some of the monthly variation observed in the data; and (3) created a "suicide index" to normalize for the differences in prescription volume between the younger than 18, 18 to 25, and 26 years and older age categories. Specifically, the suicide index assigns a baseline value of 100 to the initial time point in each of the age series. Subsequent data points are presented relative to this baseline value: numbers greater than 100 signify an increase in market volume compared with baseline, while values less than 100 are indicative of market contraction.

To test for significance among observed prescription trends, we performed a joinpoint regression analysis to determine average monthly percentage change in antidepressant prescribing. The analysis was performed using computer software (Joinpoint Software, version 3; National Cancer Institute, Bethesda, Md). This software performs a series of Monte Carlo permutation-based tests to test for the significance of the number of joinpoints in the data (ie, points at which trends change), first testing for 0 joinpoints and then up to as many as 3 joinpoints.[5] The software program used (Joinpoint Regression Program) fits a joinpoint model to the trend data, and has been used to analyze antidepressant prescription data over time in England.[6] The models were based on linear regression, with the log monthly prescription volume as the dependent variable and the month as the independent variable.

Finally, to further explore the effect of the reported suicidality data on practice patterns, we also examined data from Verispan's Physician Drug and Diagnosis Audit. The Physician Drug and Diagnosis Audit provides a national-level disease and treatment database on a survey of approximately 3400 office-based physicians across 29 specialties. Information collected by the audit is projected by region and specialty to provide a representative view of physician practice in the United States. The Physician Drug and Diagnosis Audit data were analyzed to better understand changes in specialty physician treatment of patients younger than 18 years for depression and the antidepressants prescribed.

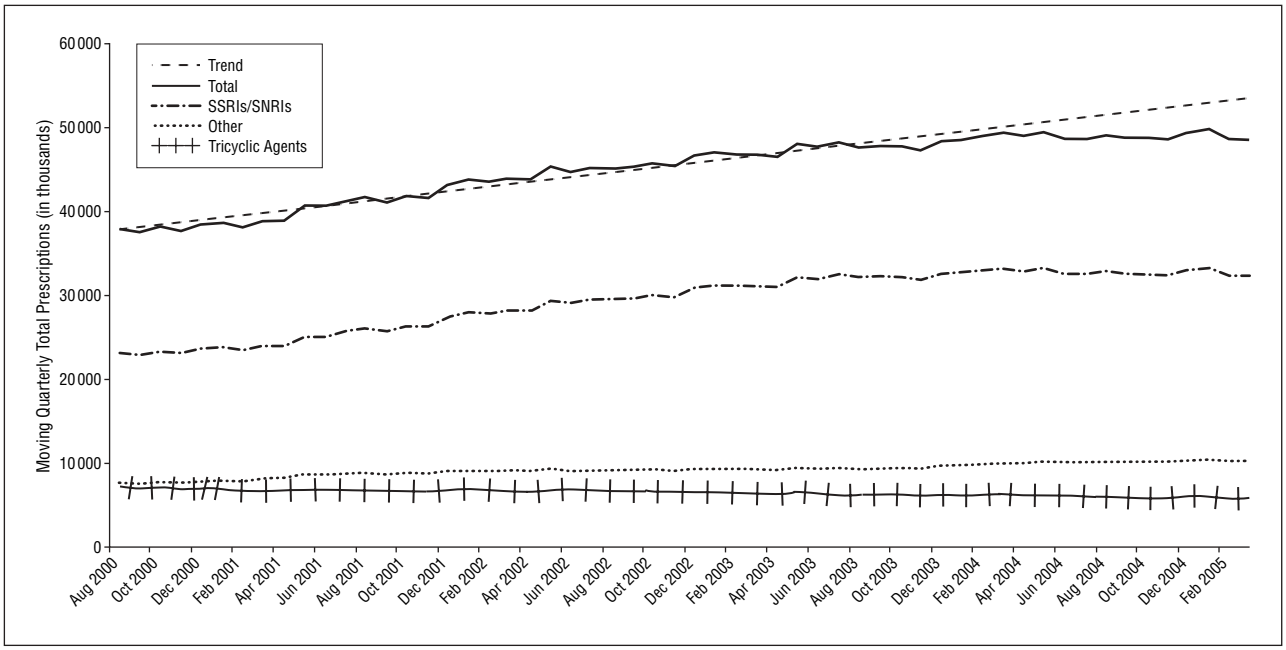

Figure 1. Antidepressant total prescriptions moving quarterly total for quarter August 2000 to quarter March 2005.[7] "Other" includes bupropion hydrochloride, trazodone hydrochloride, mirtazapine, benzodiazepines, and atypical antipsychotic agents. SSRIs/SNRIs indicates selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors.

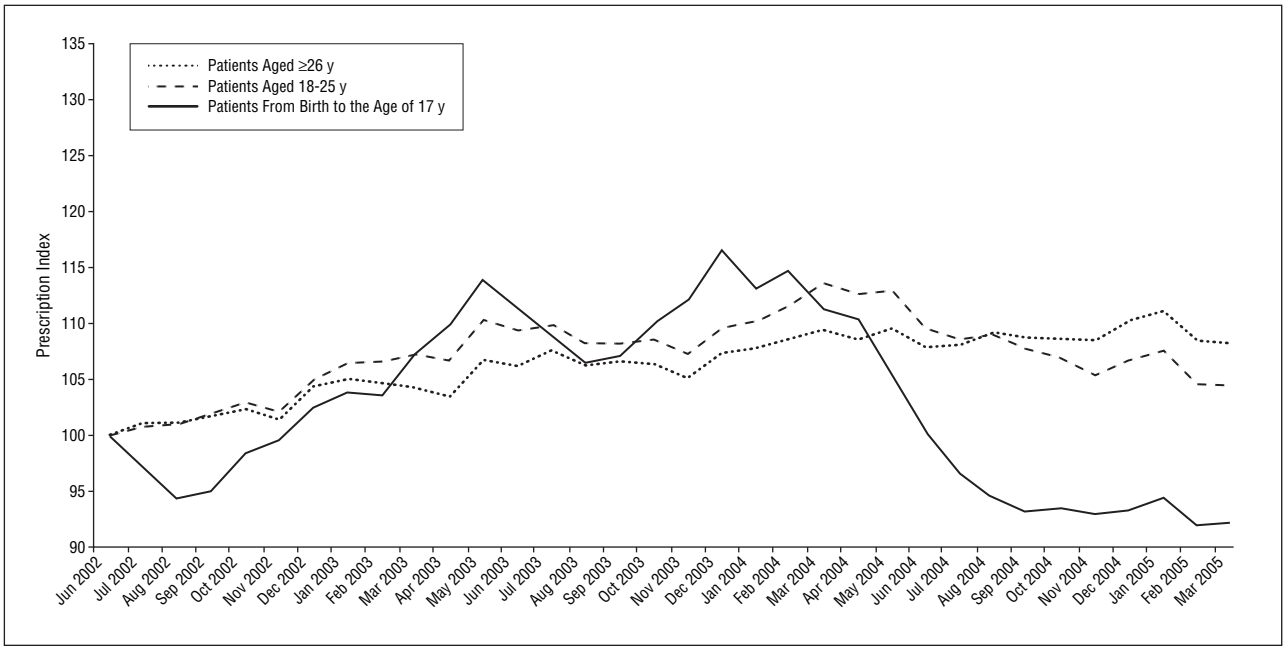

Figure 2. Prescription volume indexed to normalize the difference in prescription volume between the age groups. June 2002=100, and subsequent data points are relative to this baseline value. Antidepressant total prescriptions by age.[8] In May 2003, there was a Food and Drug Administration (FDA) data request; in October 2003 and March 2004, there were FDA public health advisories; and in September 2004, there was an FDA advisory panel meeting.

RESULTS

Figure 1 presents total antidepressant prescriptions as a moving quarterly total from quarter August 2000 to quarter March 2005. As seen in Figure 1, the growth in total antidepressant prescriptions seemed to begin to slow around the timing of the public health advisories in October 2003 and March 2004 about pediatric suicidality. However, by the time the FDA panel met to discuss the data findings in September 2004, the proceedings from the meeting had little effect on the market—behavior had already been altered.

In **Figure 2**, we present the moving quarterly total antidepressant prescriptions for 3 different age groups: those younger than 18 years, those 18 to 25 years, and those 26 years and older. Data for each age group in Figure 2 are presented as an index relative to the baseline measure of total prescriptions to facilitate comparisons across groups. As seen in Figure 2, in contrast to

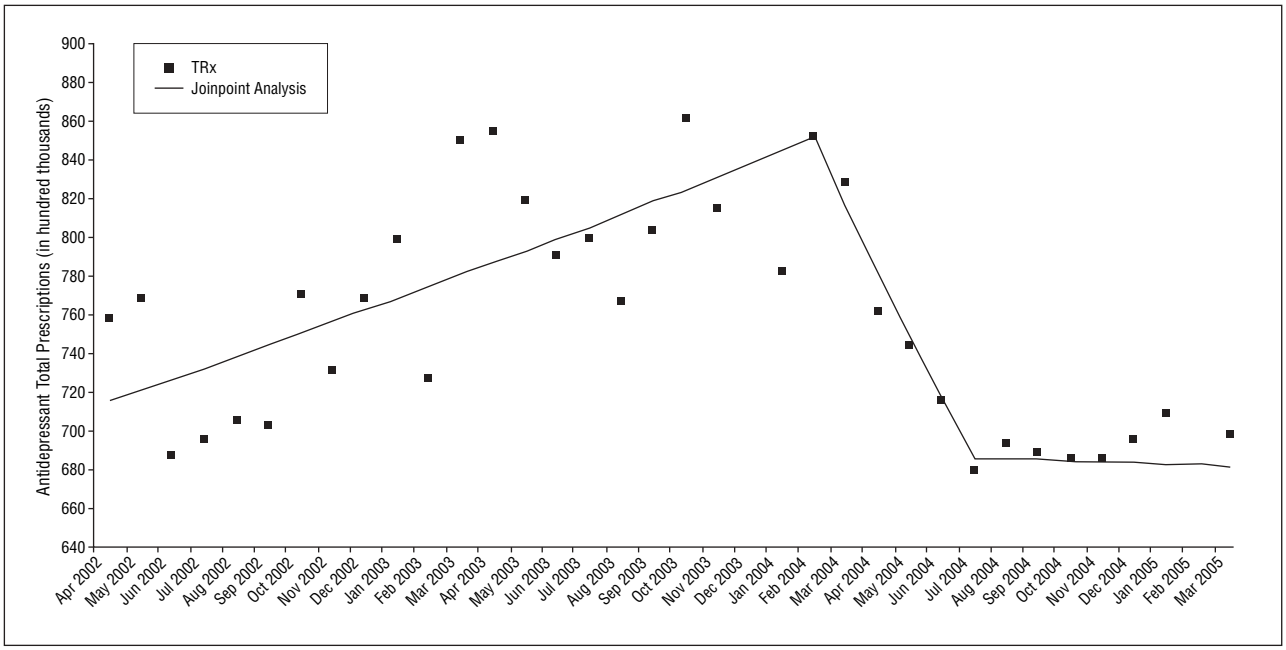

Figure 3. Antidepressant prescribing trend among those from birth to the age of 17 years.[6,8] In October 2003 and March 2004, there were Food and Drug Administration (FDA) public health advisories; and in September 2004, there was an FDA advisory panel meeting. TRx indicates total prescriptions.

the 18 to 25 and 26 years and older age groups, the younger than 18 years market seems to be seasonal, with a decrease in prescribing volume during the summer months. In addition to highlighting the seasonal nature of the younger than 18 years market, the data in Figure 2 also suggest that the 2 public health advisories issued in October 2003 and March 2004 likely caused significant deviation from the historical trend of antidepressant use in patients younger than 18 years. In comparison, the effect on patients 26 years and older was much more subtle: the market seemed to decelerate in growth, but did not actually contract. The effect on the population aged 18 to 25 years was in between these 2 findings: a contraction of the market occurred, but not to the extent observed in the younger than 18 years age group.

To test the significance of these observed market trends and to identify timing for market changes, we conducted a joinpoint analysis on each of the 3 age groups. As seen in **Figure 3**, the joinpoint analysis of prescription volume among patients younger than 18 years demonstrated that the number of prescriptions increased by a monthly average of 0.79% from April 2002 to February 2004 (95% confidence interval [CI], 0.45%-1.13%; $P<.001$ for test of the null hypothesis that monthly percentage change is 0). After February 2004, there was a decrease in the number of prescriptions by a monthly average of 4.23% (95% CI, –8.44% to 0.18%; $P=.06$), although the 95% CI for a joinpoint at February 2004 was wide (June 2002-April 2004). Although the CI is wide, we attribute the variation to the seasonality of the data and a natural decrease in antidepressant prescription volume in the summer months. By July 2004 (95% CI, August 2003-January 2005), the market began to stabilize such that there was no significant change in prescribing trends from July 2004 to March 2005 (95% CI, –1.16% to 1.48%; $P=.92$). In other words, the market effect may have potentially occurred before the FDA advisory panel in September 2004, when the results of the pediatric suicidality analysis were fully presented.

In the 18- to 25-year age group, prescription volume increased at a monthly average of 0.48% (95% CI, 0.27%-0.70%; $P<.001$) from April 2002 to March 2004 (95% CI, April 2003-June 2004). Following the public health advisory in March 2004, prescription trends changed significantly in this age group to reflect an average monthly decrease of 0.72% (95% CI, –1.29% to –0.14%; $P=.02$). With respect to the 26 years and older age group, although the market seemed to slow in growth following the October 2003 and March 2004 communications, the effect on prescribing trends was not statistically significant ($P=.98$).

To obtain a better understanding of the impact of the reported pediatric suicidality data on care patterns in depressed patients younger than 18 years, we compared physician specialty mix and antidepressant market share before and after March 2004. **Figure 4** includes a comparison of specialty mix, and the **Table** provides insight into the class of antidepressant prescribed.

As seen in Figure 4, there has been a shift in the providers of care of depressed patients younger than 18 years away from primary care and other providers to psychiatrists. In quarter February 2004, psychiatrists accounted for 44% of patient care for those younger than 18 years. In contrast, psychiatrists cared for 63% of pediatric/adolescent depressed patients in quarter February 2005.

Classes of antidepressants and other agents prescribed to treat depression in the younger than 18 years population have also changed after the black box warning (Table). Although fluoxetine is the only antidepressant indicated for use in pediatric patients, there has been

an increase in prescribing of non-SSRIs (eg, bupropion, tricyclic agents, and gabapentin) to patients younger than 18 years that is not observed in the 18 years and older population. While bupropion and tricyclic agents have demonstrated efficacy in treating depression in adults, neither of these products (nor gabapentin) is approved for use in depression in pediatric patients, and the tricyclic agents are associated with greater adverse effects than the SSRIs, and are lethal in overdose.

COMMENT

The level of effect on antidepressant prescribing volume observed in our analysis of the Verispan data supports the findings reported by Medco Health Solutions, Inc, and NDC Health, suggesting that the number of children and teenagers prescribed antidepressants has decreased dramatically since the October 2003 and March 2004 FDA-issued public health advisories that reported risks of suicidality with the use of antidepressants. According to Medco Health Solutions, Inc, the number of patients younger than 18 years prescribed antidepressants decreased sharply by 18% in the first quarter of 2004 and by an additional 5% in the second quarter of 2004.[3,11] The review by Medco Health Solutions, Inc, included the 10.1 million pediatric patients covered under its pharmacy benefit management program. Our analysis of the Verispan data, which capture approximately half of all prescriptions in the United States, including private insurance, Medicaid, and cash prescriptions, shows only a 5% decrease in the first quarter of 2004, with an additional 11% decrease in the second quarter of 2004. The difference in the magnitude of the effect on prescribing volume between the Medco Health Solutions, Inc, data (private payers only) and our analysis of the Verispan data (all payers) suggests that the prescribing behavior may have been slower to change for nonprivately insured individuals (eg, those with Medicaid insurance) than for the privately insured.

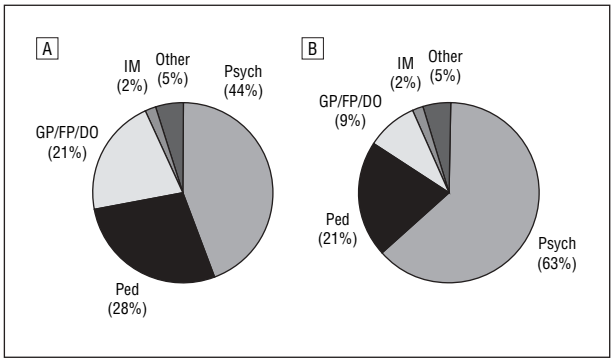

Figure 4. Specialty mix of antidepressant prescribers for patients younger than 18 years in quarter February 2004 (refers to December 2003 through February 2004) (A) and quarter February 2005 (refers to December 2004 through February 2005) (B).[9] DO indicates doctor of osteopathy; FP, family practitioner; GP, general practitioner; IM, internal medicine practitioner; Ped, pediatrician; and Psych, psychiatrist.

Although the Medco Health Solutions, Inc, NDC Health, and Verispan analyses suggest that the public health advisories regarding the safety of antidepressants have had a direct effect on physician practice patterns, the FDA reported that it did not observe a decline in pediatric antidepressant prescribing during the September 2004 hearings. Rather, FDA officials asserted that the use of antidepressants by children and teenagers was still increasing. Using data provided by IMS Health Inc, the FDA found that pediatric antidepressant prescriptions continued to increase by 7% in 2004.[3] Agency officials reported that the March 2004 advisory had no effect on prescription trends, with the number of prescriptions for antidepressants given to children and teenagers growing by almost 8% in the first half of 2004.[12] Whereas the Verispan, Medco Health Solutions, Inc, and NDC Health data are patient-centric, with age information readily available for each prescription captured, the IMS Health Inc data are primarily based on a survey of drug use by pharmacies, with no collection of patient-specific information; it remains unclear how the FDA distinguished between adult and pediatric prescriptions in its analysis.[3] Because of data limitations associated with the IMS Health Inc data, it is more likely that our analysis of Verispan data and the Medco Health Solutions, Inc, and NDC Health analyses more clearly depict reality—the FDA actions have had a significant effect on the prescribing of antidepressants to children and adolescents.

In addition to a decrease in prescribing of antidepressants to individuals younger than 18 years, the FDA ac-

Table. Classes of Therapeutic Agents Used to Treat Depression by Quarter*

	Subjects <18 y		Subjects ≥18 y	
Agent	Feb 2004	Feb 2005	Feb 2004	Feb 2005
Selective serotonin reuptake inhibitors	74.5	57.9	66.8	65.2
Serotonin-norepinephrine reuptake inhibitors†	2.5	5.8	1.9	5.3
Bupropion hydrochloride, trazodone hydrochloride, or mirtazapine	10.7	20.8‡	15.8	17.0
Tricyclic agents	2.8	6.1	2.7	1.7
Stimulants	2.1	2.3	NA	NA
Benzodiazepines	0	0	2.6	2.8
Atypical antipsychotic agents	7.4	3.0	10.0	9.1

Abbreviation: NA, data not available.

*Data are given as percentage of subjects in each age group and are taken from American College of Neuropsychopharmacology.[10] Quarter Feb 2004 refers to December 2003 through February 2004; and quarter Feb 2005 refers to December 2004 through February 2005.

†Venlafaxine hydrochloride (Effexor; Wyeth, Madison, NJ) or duloxetine hydrochloride (Cymbalta; Eli Lilly and Co, Indianapolis, Ind).

‡Primarily bupropion hydrochloride extended-release tablets (Wellbutrin XL) and bupropion hydrochloride sustained-release tablets (Wellbutrin SR), available from GlaxoSmithKline, Research Triangle Park, NC.

tions have also resulted in a shift of care from generalists to psychiatrists. Although the number of depressed individuals younger than 18 years is small relative to the broader population, anecdotal evidence suggests overdemand for specialist services and, as a result, longer than historically observed waiting times for appointments.

Finally, our analysis shows a slight shift in prescribing toward bupropion (a non-SSRI), which could stem in large part from physicians attributing the increased risk of suicidality primarily to SSRIs, even though bupropion is also labeled with a black box warning. Interestingly, we did not see any difference in trends within the SSRI class with respect to dosage or product selection, despite the fact that fluoxetine is the only SSRI formally approved by the FDA for the treatment of depression in children. This is perhaps a function of the fact that although some drugs demonstrated a weak association with suicidal signals, the FDA concluded that all drugs in the class carry the same black box warning.[13]

US psychiatrists, as represented by the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry, have expressed concern that "the FDA action may limit access to necessary, appropriate, and effective treatment for children and adolescents with depression, anxiety, and other psychiatric disorders."[14(p1)] This is especially interesting given that a previous preliminary study by the American College of Neuropsychopharmacology Task Force on SSRIs and Suicidal Behavior in Youth found no increase in suicidality among young patients taking SSRIs and other effective new-generation antidepressants,[10] and this has been confirmed and extended in their final report.[15] Although we are not able to comment on whether the observed decrease in prescription volume is appropriate, our analyses allow for the conclusion that the FDA's actions have had an effect on prescribing volume for patients younger than 18 years, the specialty mix of physicians treating patients younger than 18 years with antidepressants, and the types of medications used in treating depression.

In the current media environment in which safety concerns may be intensified because of several recent product recalls (eg, rofecoxib [Vioxx]; Merck & Co, Whitehouse Station, NJ, and natalizumab [Tysabri]; Biogen Idec, Cambridge, Mass), physician organizations (eg, the American Medical Association, the American Psychiatric Association, and the American Academy of Child and Adolescent Psychiatry) are concerned that the proved benefits of SSRI antidepressants may be underemphasized in discussions of potential risks and, as a result, there will be a decrease in access to appropriate treatment for children and adolescents.[14,16] The FDA recently released results from an analysis that evaluated adult suicide and ideation data. The findings were mostly positive, and suggested that antidepressant drugs do not exacerbate suicidal thoughts in patients 30 years and older, but that the suicide thoughts/ideation seen in the pediatric data extends in young adults up to age 25 years.[17] To date, these data results (both positive and negative) have received considerably less media attention in comparison with the release of the pediatric suicidality data. Recognizing that the results of the adult analysis were only public as of December 13, 2006, it remains to be seen if and how these findings will impact prescribing in both the 18 to 25 years population and the 26 years and older population. It is evident, however, that there is need for additional exploration into the relationship between FDA action, media reaction, and physician behavior change to ensure that dissemination of drug safety information does not interfere with appropriate access to care.

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Pharmaceutical, Inc, Quintiles Transnational, and Sepracore Inc; and has a confidentiality agreement with Forest Laboratories, Inc, and Novartis Pharmaceuticals Corp. Dr Schatzberg is a consultant to Eli Lilly and Co, Wyeth Pharmaceuticals, Corcept Therapeutics, Bristol-Myers Squibb, Novartis, Abbott Laboratories, Forest Laboratories Inc, Quintiles Transnational, and Lundbeck; is a cofounder of Corcept Therapeutics and has equity in Forest Laboratories, Pfizer Inc, and Merck and Co; and has received research funding from GlaxoSmithKline and Wyeth Pharmaceuticals.

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