Effect of Regulatory Warnings on Antidepressant Prescribing for Children and Adolescents

Benji T. Kurian, MD, MPH; Wayne A. Ray, PhD; Patrick G. Arbogast, PhD; D. Catherine Fuchs, MD; Judith A. Dudley, BS; William O. Cooper, MD, MPH

Objective: To evaluate the effect of UK and US warnings placed in response to reports of suicidal thinking in pediatric patients receiving selective serotonin reuptake inhibitor and selective norepinephrine reuptake inhibitor antidepressants on antidepressant prescribing for children and adolescents.

Design: Interrupted time-series analysis of antidepressant prescriptions.


Participants: A mean of 405,000 children and adolescents aged 2 to 17 years qualified each month.

Main Exposure: Piecewise linear regression models were used to estimate the cumulative effect of the warnings, which were considered the exposure of interest.

Main Outcome Measures: Monthly proportions of study children and adolescents who were new users of antidepressants, had discontinuity in antidepressant use, or were users of other psychotropic drugs.

Results: During the 2 years preceding the UK warning, there was no trend in the monthly proportions of new antidepressant users, with 23 new users per 10,000 persons per month. This proportion subsequently decreased 33% (95% confidence interval, 23% to 41%; \( P < .001 \)) by 21 months following the UK warning. The reduction was most pronounced for the nonfluoxetine selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors, where initiations decreased 54% (95% confidence interval, 46% to 62%; \( P < .001 \)). In contrast, new users of fluoxetine increased 60% (95% confidence interval, 9% to 135%; \( P = .02 \)). There was no increase in discontinuations of antidepressants, and there was no evidence of substitution of other psychotropic drugs.

Conclusion: The regulatory warnings led to decreased use of antidepressants in children and adolescents, but the clinical and public health consequences of this change are unknown.

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Effective disorders are common and potentially life-threatening illnesses of childhood and adolescence. The point prevalence of major depressive disorders in adolescence is estimated to be 2% to 5%, and the cumulative prevalence throughout adolescence is up to 20%. Suicidality is one of the most serious consequences of depression. Suicide attempts are frequent in adolescence and suicide is the third leading cause of death for ages 10 to 19 years in the United States. Thus, increasing priority has been given in recent years to better management of this potentially devastating and costly illness. In this context, one of the mainstays of treatment for pediatric depression has been the use of antidepressant medications.

In 2003, reports of self-harm and increased suicidality in pediatric patients receiving paroxetine hydrochloride raised serious concerns about the safety of the pediatric use of antidepressants. These data from unpublished pharmaceutical trials spurred independent reviews by regulatory agencies in both the United Kingdom (Committee on Safety of Medicines [CSM]) and the United States (Food and Drug Administration [FDA]), which led both agencies to issue strong warnings against the use of paroxetine in children and adolescents. This also led to reviews of other antidepressants. In December 2003, the CSM declared the risk-benefit profile of all selective serotonin reuptake inhibitor (SSRI) antidepressants (as well as venlafaxine hydrochloride and mirtazapine), with the exception of fluox-
etine, to be unfavorable for the treatment of major depressive disorders in children and adolescents.\textsuperscript{22} Shortly thereafter in 2004, the FDA convened a Psychopharmacology Advisory Committee meeting in February, issued a public health advisory in March, and in October required black box warning labels for all antidepressants (including fluoxetine) highlighting the potential increase in suicidal thinking and behavior in children and adolescents.\textsuperscript{23} The warning recommended more intense therapeutic monitoring to mitigate these risks but did not suggest avoiding the pediatric use of antidepressants.

Little is known about the effects of these regulatory warnings and the accompanying publicity on the prescribing of antidepressants for pediatric populations. We thus sought to assess subsequent changes in both initiation and overall use of antidepressant medications for children and adolescents in TennCare, Tennessee’s expanded Medicaid program. Our objectives were to quantify changes for all antidepressants as well as to determine whether the effects of the regulatory warnings differed for fluoxetine, specifically exempted from the CSM warning, and other SSRI and related antidepressants.

### METHODS

#### DESIGN

We assessed the effect of the regulatory actions with an interrupted time-series design,\textsuperscript{24} the standard for evaluation of policy changes.\textsuperscript{25} The unit of analysis was the study month. For each month, we calculated the proportions of study children (aged 2-11 years) and adolescents (aged 12-17 years) with use of antidepressant and other psychotropic medications and used piecewise linear regression models to estimate whether these were affected by the regulatory warnings.

The study included the 45 months from January 1, 2002, through September 30, 2005. 12 months following the FDA black box warning. The study months were divided into 2 periods. The period before the regulatory warnings included the 24 months from January 1, 2002, through December 31, 2003, and that after the regulatory warnings included the 21 months from January 1, 2004, through September 30, 2005. In some analyses, the period after the regulatory warnings was further divided into 2 periods, that following the warning of the CSM (January 1, 2004, through October 31, 2004) and that following the FDA black box requirement (November 30, 2004, through September 30, 2005). We performed sensitivity analyses that excluded the months in which the warnings were issued; the results were essentially identical to those of the analyses presented here.

#### STUDY POPULATION

Data used to conduct this study were obtained from TennCare enrollment and pharmacy files.\textsuperscript{26} The enrollment file records each person’s periods of enrollment and demographic characteristics. The TennCare pharmacy claims file includes all outpatient prescriptions filled at the pharmacy. Prior studies have found high concordance between computerized pharmacy files and patient self-reports of medication use.\textsuperscript{27,28} There were no formulary restrictions affecting the availability of any of the medications of interest during the study period.

Children and adolescents who qualified for the study were TennCare enrollees who were aged 2 through 17 years and had at least 365 days of prior continuous enrollment. For each of the monthly measures of drug use, the theoretical denomin-
porary period of underascertainment of prescriptions for psychostimulants and mood stabilizers, the analyses for these drugs were restricted to the period following July 31, 2003.

**ANALYSIS**

For each of the study months, we calculated the proportion of study children and adolescents who were new or prevalent users of antidepressants, had discontinuations of antidepressant therapy, or were prevalent users of other psychotropic drugs. Because we hypothesized that the effect of the warnings would be proportional to the magnitude of baseline use (eg, a percentage reduction), the analysis used the logarithm of the monthly proportions. Alternative analyses using the untransformed proportions did not differ materially from the primary analysis.

The effect of the regulatory warnings was estimated from a piecewise linear regression model. The model included terms for a linear trend for the period prior to the regulatory warnings and a postwarning change in that trend (allowing for changes in both the intercept and slope). Because there was a strong seasonal effect in the use of antidepressants, with lower use in the summer months, the model also included terms for the calendar month. We also fitted more complex models that adjusted for potential confounding by age, sex, enrollment status, and residence county; however, the findings were essentially identical to those of the model described earlier. There was no evidence of serial autocorrelation, so all of the parameters were estimated assuming independence of the monthly proportions.

We used the predicted trends from the regression model to calculate the cumulative effect of the regulatory warnings by 21 months following the CSM warning. We expressed this change as a ratio of the predicted monthly proportions for month 21 following the warning. The denominator was the proportion predicted assuming no effect of the regulatory intervention, calculated by extrapolating the trend established prior to the warnings. The numerator was the proportion predicted using estimates of the change in the trend (changes in both the intercept and slope considered) that occurred following the warnings. We then subtracted 1 from this ratio to express the results as percentage change attributable to the regulatory warning.

![Table 1. Characteristics of the Study Children and Adolescents During the Periods Before and After the Regulatory Warnings of December 2003](image-url)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Period Before Regulatory Warnings</th>
<th>Period After Regulatory Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children and adolescents</td>
<td>410 572</td>
<td>398 959</td>
</tr>
<tr>
<td>per month, mean, No.</td>
<td>9.0 ± 4.6</td>
<td>9.0 ± 4.6</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>51.3</td>
<td>51.4</td>
</tr>
<tr>
<td>Male, %</td>
<td>56.4</td>
<td>54.6</td>
</tr>
<tr>
<td>White, %</td>
<td>6.9</td>
<td>7.1</td>
</tr>
<tr>
<td>Enrollment in TennCare via Aid to the Disabled, %</td>
<td>3.3</td>
<td>3.3</td>
</tr>
</tbody>
</table>

![Figure 1. Monthly proportions of new users of antidepressants for all antidepressants and for specific classes of antidepressants. Solid lines indicate the predicted values from the piecewise linear regression model (which allows changes in both the intercept and slope for the trend following the Committee on Safety of Medicines [CSM] warning); individual symbols, the observed monthly proportions. Both the predicted and observed values were adjusted for seasonality. SSRI indicates selective serotonin reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor; and FDA, Food and Drug Administration](image-url)
The study was reviewed and approved by the institutional review board at Vanderbilt University, Nashville, Tennessee; Tennessee Department of Health; and the TennCare Bureau.

RESULTS

During the 45-month study period, the mean number of children and adolescents eligible for the study was 405,000 per month. The mean age was 9 years, 51% were male, 56% were white, and 7% had enrollment through the Aid to the Disabled program. The study population characteristics were very similar for the periods before and after the regulatory warnings, although there was a slight decrease in the study population for the months after the regulatory warnings (Table 1).

NEW USERS OF ANTIDEPRESSANT MEDICATIONS

During the 24 months preceding the CSM warning, there was no evident trend in the monthly proportions of children and adolescents initiating antidepressant medications (Figure 1). During this period, there was a mean of 23 new antidepressant users per 10,000 persons per month. The nonfluoxetine SSRIs and SNRIs were the most frequently started antidepressants (12 new users per 10,000 persons per month, followed by the tricyclic and related antidepressants (5 new users per 10,000 persons per month, not shown in Figure 1), other antidepressants (5 new users per 10,000 persons per month), and fluoxetine (1 new user per 10,000 persons per month).

Following the CSM warning in December 2003, there were decreases in the numbers of children and adolescents who became new users of antidepressants (Figure 1). Twenty-one months after the warning, there were an estimated 15 new users per 10,000 persons per month (Table 2), a decrease of 33% (95% confidence interval [CI], 23% to 41%; P < .001) from the trend established prior to the warning. The reduction was present for the nonfluoxetine SSRIs and SNRIs, where initiations decreased 54% (95% CI, 46% to 62%; P < .001), and the other antidepressants, where initiations decreased 28% (95% CI, 13% to 40%; P = .001). There was no statistically significant change for the tricyclic and related antidepressants (P > .50). In contrast, there was a 60% (95% CI, 9% to 135%; P = .02) increase in new users of fluoxetine.

We assessed whether the FDA black box warning in October 2004 further affected the initiation of antidepressant therapy for children and adolescents by fitting regression models that included terms for subsequent changes in the intercept or slope. However, none of these were significant for new users of all antidepressants (P > .50) or for any of the specific types of antidepressants (P > .05).

Although the initiation of antidepressant use was less common for children (aged 2-11 years) than for adolescents (aged 12-17 years), each group had a similar decrease in new users of antidepressants following the CSM warning (Figure 2). For children and adolescents, there were respective means of 11 and 46 new antidepressant users per 10,000 persons per month prior to the warning. These subsequently decreased 34% (95% CI, 24% to 44%; P < .001) and 32% (95% CI, 20% to 42%; P < .001), respectively.

PREVALENCE OF ANTIDEPRESSANT AND OTHER PSYCHOTROPIC DRUG USE

The monthly proportions of study children and adolescents who were prevalent users of antidepressants also decreased following the CSM warning in December 2003 (Figure 3). Twenty-one months after the warning, there were an estimated 143 antidepressant users per 10,000 persons per month, a reduction of 31% (95% CI, 23% to 37%; P < .001) from the trend established prior to the warning. However, there was no evidence that discontinuation of antidepressant therapy increased (Figure 3). By 21 months after the warning, the estimated monthly discontinuation proportion was 30%, which did not differ significantly from the 29% predicted from the trend established prior to the regulatory warning (increase of 4%; 95% CI, −6% to 15%; P = .47).

There was no evidence that the decrease in antidepressant use in the study population was accompanied by a corresponding increase in the use of other psychotropic drugs (Figure 4). For psychostimulants, mood stabilizers, antipsychotics, and benzodiazepines, we compared the monthly proportion of prevalent users predicted from the trend established prior to the CSM warning with that estimated from the entire study period. In no case was there a statistically significant increase (P > .50).

COMMENT

In this large pediatric population, there was no evident trend in the initiation of antidepressant medications in the 24 months preceding the suicidality warning issued by the

Table 2. Estimated Overall Effect of the Regulatory Warnings on New Users of Antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>New Users/10 000 Persons, No.</th>
<th>Trend Estimated Prior to Regulatory Warnings</th>
<th>Estimate From the Full Model</th>
<th>Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antidepressants</td>
<td>22.60</td>
<td>15.14</td>
<td>-32.97</td>
<td>(-41.37 to -23.37)</td>
</tr>
<tr>
<td>Nonfluoxetine</td>
<td>12.67</td>
<td>5.78</td>
<td>-54.34</td>
<td>(-61.49 to -45.87)</td>
</tr>
<tr>
<td>SSRIs/SNRIs</td>
<td>4.49</td>
<td>4.19</td>
<td>-6.61</td>
<td>(-28.42 to 21.84)</td>
</tr>
<tr>
<td>Tricyclic and related antidepressants</td>
<td>4.89</td>
<td>3.54</td>
<td>-27.54</td>
<td>(-39.67 to -12.96)</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>1.29</td>
<td>2.07</td>
<td>60.13 (9.15 to 134.92)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

a The mean new user proportion for the last study month (September 2005) predicted by the trend that was established prior to the regulatory warnings is compared with that for the same month predicted by the full model that includes terms for the regulatory warning.

b Adjusted for calendar month.
CSM for paroxetine and other SSRIs and SNRIs. In the subsequent 21 months, there was a decrease in therapy initiation, resulting in an estimated 33% reduction in new users of antidepressants by the end of the study. Decreases of similar magnitude were present for children and adolescents. For the total population, the decrease was most pronounced for the nonfluoxetine SSRIs and SNRIs, where there was a reduction of 54%. In contrast, new users of fluoxetine increased by 60%. However, there was no evidence of an increase in discontinuations of therapy with antidepressant or other psychotropic drugs, which suggests that the primary effect of the warnings was to alter the decision to treat a newly presenting patient.

The study population comprised children and adolescents in low- and moderate-income families who received medical care through TennCare, Tennessee’s expanded Medicaid program. This raises the question as to whether a similar decrease occurred in other populations, particularly for children and adolescents outside of the Medicaid program. However, previous studies have...
shown that trends in the pediatric use of antipsychotics in TennCare are very similar to those in the entire United States. Furthermore, an analysis of antidepressant prescriptions dispensed to persons aged 18 years or older in the United States reported a 20% reduction between March 2004 and June 2005. Finally, the Medicaid population is in itself of substantial importance for children's health. During the study period, TennCare enrollees constituted 29.8% of all Tennessee children aged 2 to 17 years. In 2005, 26.7% of children in the United States had Medicaid enrollment.

We cannot determine whether the change following the regulatory warnings was owing to the warnings per se or to the accompanying media coverage. The debate leading up to the warnings was widely reported, and in the United States, there were Senate hearings on this topic that received extensive media coverage. While databases such as that provided by TennCare are excellent for studying medication use in large populations, they lack the detailed diagnostic evaluation that would be necessary to address this question. In addition, our ability to assess the change in the use of psychostimulants and mood stabilizers was limited by the incomplete data for these drugs for the period before the regulatory warnings.

The uncertainty over the clinical consequences of the regulatory warnings mirrors the current uncertainty regarding the pediatric use of antidepressants. The efficacies of many of the drugs most commonly used to treat childhood depression are unknown. It is unknown whether the SSRI- and SNRI-related increase in suicidality and self-harmful behavior also confers an increased risk of more serious outcomes, such as attempted or completed suicide, and whether this risk varies by drug. It is unknown whether more intensive therapeutic monitoring can alter these risks. Thus, while it is now evident that regulatory interventions can alter patterns of practice, whether this
is desirable is uncertain. There is an urgent need for better data on the efficacy and safety of antidepressants to guide pediatric practice.

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Correspondence: William O. Cooper, MD, MPH, Department of Pediatrics, Vanderbilt University Medical Center, AA-0216 MCN, Nashville, TN 37232 (william.cooper@vanderbilt.edu).

Author Contributions: Dr Ray had full access to all of the data in the study and takes responsibility for the integrity and accuracy of the data analysis. Study concept and design: Kurian, Ray, Fuchs, Dudley, and Cooper. Acquisition of data: Dudley and Cooper. Analysis and interpretation of data: Kurian, Ray, Arboagast, Fuchs, and Cooper. Drafting of the manuscript: Kurian. Critical revision of the manuscript for important intellectual content: Kurian, Ray, Arboagast, Fuchs, Dudley, and Cooper. Statistical analysis: Kurian, Ray, and Arboagast. Administrative, technical, and material support: Dudley. Study supervision: Ray, Fuchs, and Cooper.

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Additional Contributions: Data to conduct the study were obtained from the Tennessee Department of Health and the TennCare Bureau.

REFERENCES


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