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## Emergency Department Visits by Children and Adolescents for Antipsychotic Drug Adverse Events

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The per capita number of outpatient visits in which an antipsychotic drug was supplied or prescribed increased approximately 660% among children and 380% among adolescents between the mid-1990s and the mid-2000s in the United States,<sup>1</sup> prompting concerns about possible inappropriate prescribing. The most recent revisions to the *DSM-5* were intended in part to decrease inappropriate child and adolescent antipsychotic drug use,<sup>2</sup> and the American Psychiatric Association has warned against using antipsychotics as first-line therapy in children and adolescents for conditions other than psychotic disorders.<sup>3</sup> To quantify acute harms from child and adolescent antipsychotic drug use, we estimated the numbers and rates of US emergency department (ED) visits and hospitalizations for adverse drug events (ADEs) from therapeutic use of antipsychotics and comparator psychotropic medications among children 10 years or younger and adolescents 11 to 18 years.

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**Author Contributions:** Dr Hampton had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Hampton, Alexander, Budnitz.

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## Methods

We used the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) system to estimate child and adolescent US ADE ED visits from antipsychotics, antidepressants, and stimulants available only by prescription (2009–2011) and estimated child and adolescent outpatient prescription visits using the National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Surveys (2009–2010).<sup>4–6</sup> We excluded ADE ED visits resulting from therapeutic failures, nonadherence, drug withdrawal, and nontherapeutically intentioned use (intentional self-harm, drug abuse, or unsupervised ingestions) or involving ADEs that led to a patient's death in or before arrival at the ED. We also calculated the annual number of ADE ED visits per 10 000 outpatient visits at which each medication was prescribed. We classified medications as antipsychotics, antidepressants, or stimulants; categorized adverse effects; and calculated 95% CIs as described by Hampton et al.<sup>4</sup>

The human participant oversight bodies of the Centers for Disease Control and Prevention and Food and Drug Administration determined the methods and analyses in this study to be public health surveillance activities and did not require institutional review board approval or patient consent.

## Results

From 2009 through 2011, there were an estimated 1350 antipsychotic ADE ED visits (95% CI, 821–1879) involving children 10 years and younger and 2674 visits (95% CI, 1779–3569) involving adolescents 11 to 18 years old annually in the United States (**Table 1**). Patients were admitted, held for observation, or transferred to another acute care facility after 18.6% of child and adolescent antipsychotic ADE ED visits (95% CI, 12.3%–24.9%), a hospitalization rate higher than the 7.3% rate (95% CI, 4.0%–10.5%) for nonantipsychotic ADE ED visits. Atypical antipsychotics were implicated in 97.6% of child antipsychotic ADE ED visits (95% CI, 94.0%–100.0%) and 83.4% of adolescent visits (95% CI, 77.2%–89.7%). Among children, antipsychotics were implicated in ADE ED visits at a 3.9-fold higher rate than stimulants (17.6 vs 4.5 ADE ED visits per 10 000 out-patient prescription visits) (**Table 2**). Among adolescents, antipsychotics were implicated in ADE ED visits at a 3.8-fold higher rate than stimulants (14.6 vs 3.8 ADE ED visits per 10 000 outpatient prescription visits) and a 2.7-fold higher rate than antidepressants (14.6 vs 5.5 ADE ED visits per 10 000 outpatient prescription visits). Movement disorders, including dystonia, extrapyramidal disorders, and muscle spasticity, were the most common antipsychotic drug adverse effects, occurring in 47.7% of child and adolescent antipsychotic ADE ED visits (95% CI, 37.8%–57.6%).

## Discussion

Adverse events from therapeutically intentioned use of antipsychotics cause thousands of child and adolescent ED visits annually in the United States and significantly more ED visits relative to their outpatient use than either stimulants or antidepressants. These national estimates are probably conservative because the NEISS-CADES may be biased toward the

detection of drug adverse effects that are acute, known, testable in an ED, or readily distinguished from problems caused by patients' comorbidities.<sup>4</sup> Chronic problems from medication use, such as metabolic disorders associated with antipsychotics,<sup>3</sup> are unlikely to be identified by the NEISS-CADES. In addition, the NEISS-CADES does not collect information on the specific indication for each medication implicated in an ADE or on whether a medication was used on label or off label. National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data are commonly used to estimate outpatient medication use<sup>1,4</sup>; however, they do not provide direct estimates of person-year exposure to medications and may overestimate or underestimate the use of psychiatric medications.

The higher rates of antipsychotic ADE ED visits should remind clinicians of antipsychotics' risks and of the importance of heeding the American Psychiatric Association's warning that antipsychotics should be used cautiously.<sup>3</sup> Nationally representative public health surveillance data may be useful in assessing the impact of efforts to reduce inappropriate antipsychotic drug use on ADEs.

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**Table 1**

Numbers of Cases and National Estimates of Annual Pediatric ED Visits for Antipsychotic Drug Adverse Events by Patient and Case Characteristics in the United States, 2009-2011

| Characteristic                                      | ED Visits for Adverse Events <sup>a</sup> |               |                  |
|---|---|---------------|------------------|
|   | No. of Cases                              | No. of Visits | % (95% CI)       |
| Age, y  |   |               |                  |
| 0-10  | 86  | 1350          | 33.5 (25.1-42.0) |
| 11-18   | 178                                       | 2674          | 66.5 (58.0-74.9) |
| Sex   |   |               |                  |
| Male  | 173                                       | 2592          | 64.4 (58.1-70.8) |
| Female  | 91  | 1432          | 35.6 (29.2-41.9) |
| Mechanism of adverse event                          |   |               |                  |
| Adverse reaction                                    | 188                                       | 2807          | 69.8 (59.6-79.9) |
| Unintentional overdose or supratherapeutic effects  | 50  | 731           | 18.2 (11.3-25.0) |
| Allergic reaction                                   | 25  | 447           | 11.1 (5.0-17.2)  |
| Secondary effect                                    | 1   | SUE           | SUE              |
| Disposition   |   |               |                  |
| Admitted, observed, or transferred                  | 60  | 748           | 18.6 (12.3-24.9) |
| Treated and released or left against medical advice | 204                                       | 3276          | 81.4 (75.1-87.7) |
| No. of implicated medications                       |   |               |                  |
| 1   | 192                                       | 3036          | 75.4 (69.0-81.9) |
| 2   | 72  | 988           | 24.6 (18.1-31.0) |
| No. of concurrent medications                       |   |               |                  |
| None listed   | 82  | 1260          | 31.3 (20.6-42.0) |
| 1-2   | 108                                       | 1800          | 44.7 (32.4-57.1) |
| 3   | 74  | SUE           | 24.0 (11.5-36.4) |
| Total   | 264                                       | 4024          |                  |

Abbreviations: ED, emergency department; SUE, statistically unstable estimate.

<sup>a</sup>The number of cases and national estimates of ED visits from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance system. Emergency department visits for adverse drug events include visits in which the specified prescription medication was

either the only medication implicated or was implicated along with other medications. This excludes ED visits resulting from intentional self-harm, drug abuse, therapeutic failures, noncompliance, drug withdrawal, or unsupervised ingestions.

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**Table 2**

Numbers of Cases and National Estimates of Annual Pediatric ED Visits for Antipsychotic, Antidepressant, and Stimulant Medication Adverse Events by Patient Age and Medication Category in the United States, 2009-2011

| Medication                   | ED Visits for Adverse Events <sup>a</sup> |                                | Estimated Annual Prescription Visits, No. (1000s) <sup>b</sup> | Estimated Annual ED Visits/10 000 Outpatient Prescription Visits, No. (95% CI) |
|------------------------------|---|--------------------------------|--|--|
|                              | No. of Cases                              | Estimated Annual No. of Visits |  |  |
| <b>0-10 y</b>                |   |                                |  |  |
| Antipsychotics               | 86  | 1350                           | 1534   | 17.6 (13.1-22.1)   |
| Atypical antipsychotics      | 83  | 1318                           | 1504   | 17.5 (12.9-22.2)   |
| Stimulants <sup>c</sup>      | 134                                       | 1841                           | 8178   | 4.5 (3.4-5.6)  |
| Antidepressants              | 24  | SUE                            | 1498   | SUE  |
| <b>11-18 y</b>               |   |                                |  |  |
| Antipsychotics               | 178                                       | 2674                           | 3657   | 14.6 (11.2-18.0)   |
| Atypical antipsychotics      | 152                                       | 2231                           | 3603   | 12.4 (9.4-15.4)  |
| Antidepressants <sup>d</sup> | 136                                       | 2281                           | 8250   | 5.5 (4.3-6.7)  |
| Stimulants <sup>c</sup>      | 128                                       | 2057                           | 10884  | 3.8 (2.9-4.7)  |

Abbreviations: ED, emergency department; SUE, statistically unstable estimate.

<sup>a</sup> Number of cases and national estimates of ED visits from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance system. Emergency department visits for adverse drug events include visits in which the specified prescription medication was either the only medication implicated or was implicated along with other medications. This excludes ED visits resulting from intentional self-harm, drug abuse, therapeutic failures, noncompliance, drug withdrawal, or unsupervised ingestions.

<sup>b</sup> Estimated annual numbers of outpatient prescription visits for each medication are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2009 and 2010 and include outpatient prescription visits in which multiple psychiatric medications were prescribed at a single visit.

<sup>c</sup> Amphetamines were implicated in 93.8% (95% CI, 88.7%-98.9%) and 88.0% (95% CI, 81.4%-94.5%) of stimulant adverse drug event ED visits involving children 0 to 10 years old and adolescents 11 to 18 years old, respectively.

<sup>d</sup> Selective serotonin reuptake inhibitors were implicated in 59.7% (95% CI, 45.4%-74.0%) of antidepressant adverse drug event ED visits involving adolescents 11 to 18 years old.