ARTICLE

# New Users of Antipsychotic Medications Among Children Enrolled in TennCare

*William O. Cooper, MD, MPH; Gerald B. Hickson, MD; Catherine Fuchs, MD; Patrick G. Arbogast, PhD; Wayne A. Ray, PhD*

**Background:** The use of antipsychotic medications in children and adolescents for indications other than psychosis or Tourette syndrome is controversial. Newer atypical antipsychotics with profiles of adverse effects that differ from those of traditional antipsychotics may lead providers to prescribe antipsychotics more frequently than in the past for behavioral indications not strongly supported by clinical study.

**Objective:** To identify population-based new use of antipsychotics among patients aged 2 to 18 years.

**Design:** Retrospective cohort study, January 1, 1996, through December 31, 2001.

**Setting:** Tennessee's managed care program for Medicaid enrollees and the uninsured (TennCare).

**Main Outcome Measures:** New use of antipsychotic medications and indications for use by the child's diagnosis, adjusted for age, sex, race, county of residence, enrollment category, and income.

**Results:** The proportion of TennCare children who were new users of antipsychotics, adjusted for demographic characteristics, nearly doubled from 23/10 000 in 1996 to 45/10 000 in 2001 (adjusted incidence rate ratio, 1.98; 95% confidence interval, 1.82-2.16). In 1996, 6.8% of new users received an atypical antipsychotic; by 2001, this had increased to 95.9%. New use for attention-deficit/hyperactivity disorder and affective disorders increased 2.5-fold. New use of antipsychotics for schizophrenia, acute psychotic reaction, Tourette syndrome, and mental retardation or autism remained relatively constant. Secular trends of increasing use were most pronounced for those aged 6 to 12 years (93% increase) and 13 to 18 years (116% increase), although use among preschool children increased 61% during the study period.

**Conclusion:** The proportion of TennCare children who became new users of antipsychotics nearly doubled from 1996 to 2001, with a substantial increase in use of antipsychotics for attention-deficit/hyperactivity disorder, conduct disorder, and affective disorders.

*Arch Pediatr Adolesc Med. 2004;158:753-759*

*From the Division of General Pediatrics, Department of Pediatrics (Drs Cooper and Hickson), the Division of Child and Adolescent Psychiatry, Department of Psychiatry (Dr Fuchs), and the Divisions of Biostatistics (Dr Arbogast) and Pharmacoepidemiology (Dr Ray), Department of Preventive Medicine, Vanderbilt University, Nashville, Tenn.*

THE USE OF ANTIPSYCHOTIC medications in children and adolescents for indications other than psychosis or Tourette syndrome is controversial.[1-4] Modest evidence from controlled clinical studies supports the use of antipsychotics to treat severe disruptive behaviors associated with autism and mental retardation.[5-10] Antipsychotics have been used clinically to treat behavioral symptoms associated with attention-deficit/hyperactivity disorder (ADHD) and conduct disorders, although no evidence from controlled studies supports such practices in community-dwelling children.[2,3,11] Historically, use of antipsychotics for behavioral symptoms has been limited by the very high risk of movement disorders conferred by the available agents.[2,12] However, the introduction of the atypical antipsychotics, which at least in adults confer markedly lower risk of extrapyramidal symptoms,[12] has led to the possibility of more frequent antipsychotic use in children for behavioral indications.

Although the use of atypical agents avoids some of the well-described dangerous adverse effects of the traditional drugs, they nevertheless are associated with different serious adverse effects, including weight gain,[13] diabetes,[14,15] galactorrhea,[16,17] and adverse cardiovascular effects.[18] If the use of these drugs for behavioral indications were increasing among children, this would raise the concern as to whether this practice was beneficial and clinically justified.[2]

We therefore conducted a population-based study of secular trends of new use of antipsychotics among children and adolescents from January 1, 1996, through December 31, 2001. The study period be-

gan after the introduction of risperidone (1993) and olanzapine (1995), two of the most widely used atypical antipsychotics. The study population, the expanded Tennessee Medicaid (TennCare) population, included large numbers of children and data from which medication use and diagnoses could be identified.

## METHODS

### STUDY DESIGN, POPULATION, AND SOURCES OF DATA

The study was conducted as a retrospective cohort study among children aged 2 through 18 years in the TennCare population. TennCare is Tennessee's program for Medicaid enrollees and uninsured individuals, which operates under a 1994 federal waiver that permitted broadened eligibility to include persons of low-to-moderate income who were uninsured but would not qualify for Medicaid under federal guidelines.[19] The study analysis was restricted to the uninsured and those whose enrollment was through the largest Medicaid component of the program, Aid to Families with Dependent Children. This excluded children who qualified for TennCare because of severe disability (the Aid to the Disabled program accounted for approximately 6% of the potential study population), because many of these children would have been enrolled as the result of severe mental illness and thus were likely to have had antipsychotic use before TennCare enrollment, which would be undocumented in our database.

Study data were obtained from a research database derived from files maintained by the TennCare program.[20,21] The enrollment file included the dates of each child's periods of enrollment and demographic characteristics. This file has been linked with 1990 US census data to provide information on neighborhood income and death certificates to identify children lost to follow-up.[22-25] The pharmacy file includes records of prescriptions for outpatients filled at the pharmacy, which specify the drug, dose, and days of supply dispensed. Computerized pharmacy records have been shown to be an excellent source of medication data because pharmacy records are not subject to information bias and have high concordance with patient self-reports of medication use.[20,26-29] The outpatient, emergency department, and inpatient files include records of office visit encounters or hospital admission. These files include up to 9 diagnoses, which during the study period were coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).[30]

### NEW USERS OF ANTIPSYCHOTICS

Antipsychotic medication use was identified from the pharmacy files. The typical antipsychotics included chlorpromazine hydrochloride, fluphenazine hydrochloride, mesoridazine besylate, perphenazine, thioridazine hydrochloride, trifluoroperazine hydrochloride, haloperidol decanoate, droperidol, thiothixene hydrochloride, loxapine succinate, molindone hydrochloride, and pimozide. The atypical antipsychotics included the mixed serotonin/dopamine antagonists clozapine, risperidone, olanzapine, quetiapine fumarate, and ziprasidone hydrochloride.

The study focused on new use of antipsychotics because this analysis was unaffected by long-term users of these drugs and therefore provided a better assessment of the impact of the introduction of the atypical antipsychotics on clinical practice. We examined the first antipsychotic prescription for each child during the study period. New users were those who were alive and continuously enrolled in TennCare for the 365 days before and the 90 days after the date of the first antipsychotic prescription, defined as the qualifying date. Children and adolescents had to be 2 to 18 years of age on the qualifying date and could not have used antipsychotics in the preceding 365 days. Each child could contribute only 1 period of new use to the study. Children with missing sociodemographic variables were excluded (0.7% of new users).

The indication or diagnosis associated with beginning the use of the antipsychotic was identified from medical care encounters in the 90 days before and including the qualifying date. We first reviewed outpatient or emergency department visits or hospital admissions. The diagnostic categories were identified from 1 of up to 9 diagnosis fields in each claim. Schizophrenia (*ICD-9-CM* code 295) or other psychosis (292.1, 293, 294.1, 294.8, 297.9, 298, 299.1, 299.8, 299.9, and 780.1) was defined if these codes were present and there was at least 1 additional prescription for an antipsychotic in the 90 days after the first prescription. If there was only a single antipsychotic prescription and a diagnosis of schizophrenia or psychosis, the indication was classified as an acute psychotic reaction. Other diagnostic categories included Tourette syndrome (*ICD-9-CM* code 307.23), autism (299.0), mental retardation or severe neurological conditions associated with mental retardation (315, 317, 318.0, 318.1, 318.2, 319, 330.1, 331.4, 345, 348.3, 780.3, and V79.2), ADHD (314) or conduct disorder (312 and 313.81), affective disorders (296, 300.4, 301.13, 309.0, 309.1, 309.28, and 311), and other psychiatric disorders (290-319 not listed above, V40, V66.3, V67.3, and V71.0). If there was a diagnosis for more than 1 of these categories, diagnoses were assigned in the order just provided, which generally corresponded to the strength of evidence during the period of the study for the use of antipsychotics in each condition. This approach allowed for consideration of a clinician's decision making when treating a child with multiple psychiatric diagnoses.

Among children for whom this procedure failed to identify a diagnosis, we then reviewed prescriptions filled for these children in the 90 days preceding the qualifying date and assigned diagnoses according to the most frequent indications for these drugs. These included ADHD for stimulants (methylphenidate hydrochloride, pemoline, and amphetamines), affective disorders for lithium and other mood stabilizers (carbamazepine or valproic acid in the absence of a seizure diagnosis) or antidepressants (amitriptyline hydrochloride, desipramine hydrochloride, doxepin hydrochloride, nortriptyline hydrochloride, protriptyline, clomipramine hydrochloride, bupropion hydrochloride, mirtazapine, phenelzine sulfate, tranylcypromine sulfate, and nefazodone hydrochloride but not imipramine hydrochloride, which is used for other pediatric conditions), and other psychiatric disorders for benzodiazepines (in children who did not have a seizure diagnosis). This procedure ultimately identified a diagnosis for 88.5% of new users, of whom 95.2% were identified from physician encounters. An alternative analysis that did not include the diagnoses assigned through medication use gave essentially identical results to those from the primary analysis.

Because the proportion of children for whom no diagnosis was identified decreased steadily during the study period (21.1% in 1996, 13.2% in 1997, 15.0% in 1998, 10.4% in 1999, 8.4% in 2000, and 8.8% in 2001), we performed sensitivity analyses to assess the effect of this decrease on study estimates. First, we assumed that a consistent proportion of children with no linked diagnosis would all be classified as receiving antipsychotics for behavioral indications. Study estimates were not materially affected. Second, we assessed the effect of including data from 1997 onward because of the differences between 1996 and other years in the proportion of children for whom no diagnosis was linked. Again, we found no material difference in study results. Thus, we included all

children who met the study requirements, including those for whom no diagnosis was linked.

### STUDY VARIABLES AND ANALYSIS

Because of the large size of the study population (>300 000 per year), the number of children in the denominator population at risk of becoming new users of antipsychotics was estimated from midyear enrollment in TennCare. The enrollment file was examined to identify children who were enrolled on July 1 of each year and met the study inclusion criteria of 365 days of continuous enrollment before and 90 days after this date.

The new antipsychotic users and denominator population estimates were classified according to study variables. Race was classified as white, African American, Latino (persons descended from Spanish-speaking ancestors), other, or unknown. Residence county was classified according to location in a standard metropolitan statistical area.[31] TennCare enrollment was classified as Aid to Families with Dependent Children or uninsured. Neighborhood (block group or census tract) mean per capita income was obtained from 1990 census data for the address of the child during the period of enrollment closest to the qualifying date. Incomes thus obtained were classified into quintiles according to the entire TennCare population.

Unadjusted rates of new use of antipsychotics were calculated by dividing the number of new users in a particular stratum by the estimated number of children in the denominator population. Adjusted rate ratios for each year were calculated from Poisson regression using as the reference calendar year 1996. The model included age, sex, race, category of enrollment, standard metropolitan statistical area residence, and neighborhood income. Adjusted rates of new use of antipsychotics were then calculated using the method of marginal prediction.[32] In the analysis of rates by indication, because the proportion of new users for whom no diagnosis was identified varied by year, the denominator for each year was reduced according to this proportion.

The study was reviewed and approved by the institutional review board at Vanderbilt University, Nashville, Tenn; the State of Tennessee; and the TennCare Bureau.

**Table 1. Characteristics of New Users of Antipsychotics Among Children Enrolled in TennCare, 1996-2001***

| Characteristic | New Users (n = 6803) |
|---|---|
| Sociodemographic characteristics | |
| Age, y, mean ± SD | 11.5 ± 4.2 |
| Male | 4380 (64.4) |
| African American | 1564 (23.0) |
| Urban county of residence | 4405 (64.8) |
| Enrolled in the AFDC program | 5079 (74.7) |
| Neighborhood annual income <$7154 | 991 (14.6) |
| Diagnoses in the 90 d before the first antipsychotic prescription† | |
| ADHD | 1565 (23.0) |
| Conduct disorder | 1368 (20.1) |
| Bipolar disorder | 965 (14.2) |
| Schizophrenia or psychosis | 592 (8.7) |
| Depression | 491 (7.2) |
| Mental retardation | 421 (6.2) |
| Other psychiatric conditions | 308 (4.5) |
| Acute psychotic reaction | 153 (2.2) |
| Tourette syndrome | 143 (2.1) |
| Autism | 16 (0.2) |
| Other psychotropic drugs used in the 90 d before the first antipsychotic prescription | |
| SSRIs | 1404 (20.6) |
| Stimulants (methylphenidate hydrochloride, pemoline, amphetamines) | 1388 (20.4) |
| Mood stabilizers (carbamazepine, valproic acid without seizure diagnoses) | 714 (10.5) |
| Other antidepressants | 607 (8.9) |
| Lithium | 215 (3.2) |
| Benzodiazepines (without seizure diagnoses) | 137 (2.0) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AFDC, Aid to Families with Dependent Children; SSRI, selective serotonin reuptake inhibitor.

*TennCare is Tennessee's expanded program for Medicaid enrollees and uninsured individuals who do not qualify for Medicaid. Unless otherwise indicated, data are expressed as number (percentage) of new users.

†Psychiatric diagnoses were linked for 6022 new users (88.5%).

## RESULTS

During the 6 study years, the annual number of study children increased from 313 454 in 1996 to 432 101 in 2001. This reflected a trend of increasing enrollment for uninsured children. In 1996, uninsured children constituted 21% of the study population; by 2001, this proportion had increased to 42%. Otherwise, the demographic characteristics of the study population varied little with calendar time.

There were 6803 children who became new users of antipsychotic medications during the study (**Table 1**). The mean age of these children was 11.5 years (SD, 4.2 years); 64.4% were male; 23.0% were African American; 64.8% lived in standard metropolitan statistical areas; 74.7% had TennCare enrollment through the Aid to Families with Dependent Children program; and 14.6% had income in the lowest quintile for the entire TennCare population.

Just before receiving the antipsychotic, children who were new users had substantial prevalence of diagnosed mental illness. There were 43.1% diagnosed as having ADHD or conduct disorder; 14.2%, bipolar disorder; 8.7%, schizophrenia or other psychosis; 7.2%, another affective disorder; 6.2%, mental retardation; 4.5%, other psychiatric disorders (primarily adjustment reactions); and 2.2%, an acute psychotic reaction. Only a small proportion of new users had diagnoses of Tourette syndrome (2.1%) or autism (0.2%). The new users had substantial previous use of other psychotropic drugs, primarily stimulants (20.4%), selective serotonin reuptake inhibitors or other antidepressants (29.6%), and lithium or other mood stabilizers (13.7%).

The proportion of TennCare children who were new users of antipsychotics, adjusted for demographic characteristics, nearly doubled during the 6 study years, from 22.9 per 10 000 in 1996 to 45.4 per 10 000 in 2001 (**Table 2**; adjusted incidence rate ratio [IRR], 1.98; 95% confidence interval [CI], 1.82-2.16). In 1996, 6.8% of new users received an atypical antipsychotic; by 2001, this had increased to 95.9%.

There were marked trends in the use of antipsychotics according to indication for new use (Table 2). Use for ADHD or conduct disorder increased 2.5-fold, from 9.6 per 10 000 children in 1996 to 24.2 per 10 000 in 2001 (IRR, 2.52; 95% CI, 2.19-2.91). A similar increase in magnitude was identified for affective disorders, from 5.0 per 10 000 children in 1996 to 12.1 per 10 000 by 2001 (IRR,

**Table 2. Adjusted Rates of New Use of Antipsychotics by Indication per 10 000 TennCare Children, 1996-2001***

| | 1996 (n = 740) | 1997 (n = 715) | 1998 (n = 811) | 1999 (n = 1061) | 2000 (n = 1577) | 2001 (n = 1899) | IRR (95% CI)† |
|---|---|---|---|---|---|---|---|
| All | 22.9 | 22.1 | 22.6 | 28.3 | 40.5 | 45.4 | 1.98 (1.82-2.16) |
| Schizophrenia/other psychosis | 2.4 | 3.1 | 2.5 | 3.5 | 3.9 | 2.7 | 1.11 (0.81-1.53) |
| Acute psychotic reaction | 1.1 | 0.8 | 0.7 | 0.8 | 0.8 | 0.8 | 0.76 (0.46-1.27) |
| Tourette syndrome | 0.8 | 0.8 | 0.4 | 0.6 | 1.1 | 0.7 | 0.81 (0.45-1.45) |
| Mental retardation/autism | 2.5 | 1.8 | 1.5 | 2.6 | 2.5 | 2.6 | 1.01 (0.74-1.39) |
| ADHD/conduct disorder | 9.6 | 9.5 | 11.3 | 12.6 | 20.4 | 24.2 | 2.52 (2.19-2.91) |
| Affective disorders | 5.0 | 5.0 | 4.9 | 6.4 | 10.0 | 12.1 | 2.42 (1.99-2.95) |
| Other psychiatric disorders | 1.4 | 0.9 | 1.2 | 1.6 | 1.7 | 2.5 | 1.73 (1.18-2.53) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; IRR, incidence rate ratio.
*TennCare is Tennessee's expanded program for Medicaid enrollees and uninsured individuals who do not quality for Medicaid. Unless otherwise indicated, data are expressed as rates per 10 000 children, adjusted for age, sex, race, county, enrollment category, income, and study year using the method of marginal prediction. The number of new users does not permit direct calculation of rates from this table because the adjustment accounts for changes in the denominator population during the study years.
†Adjusted for age, sex, race, county, enrollment category, and income using Poisson regression.

**Table 3. Adjusted Rates of New Use of Antipsychotics by Indication per 10 000 TennCare Children by Age, 1996-2001***

| Age Group | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | IRR (95% CI)† |
|---|---|---|---|---|---|---|---|
| 2-5 Years | | | | | | | |
| All | 9.6 | 8.9 | 8.5 | 9.6 | 10.4 | 15.4 | 1.61 (1.25-2.06) |
| Schizophrenia/other psychosis | 0.3 | 0.8 | 0.1 | 0.7 | 0.5 | 0.5 | 1.91 (0.34-8.90) |
| Tourette syndrome | 0.1 | 0.3 | 0 | 0.2 | 0.5 | 0.2 | 1.53 (0.13-15.24) |
| Mental retardation/autism | 3.3 | 2.2 | 2.5 | 3.1 | 2.4 | 2.9 | 0.88 (0.51-1.53) |
| ADHD/conduct disorder | 4.9 | 4.7 | 4.5 | 4.1 | 6.0 | 9.8 | 1.98 (1.36-2.89) |
| Affective disorders | 0.6 | 0.4 | 0.8 | 0.2 | 0.4 | 1.0 | 1.58 (0.52-4.77) |
| Other psychiatric disorders | 0.4 | 0.6 | 0.5 | 1.2 | 0.6 | 1.0 | 2.73 (0.74-10.16) |
| 6-12 Years | | | | | | | |
| All | 23.6 | 20.6 | 24.0 | 28.9 | 44.4 | 45.5 | 1.93 (1.69-2.19) |
| Schizophrenia/other psychosis | 1.7 | 1.9 | 2.0 | 3.0 | 3.6 | 2.7 | 1.54 (0.91-2.62) |
| Acute psychotic reaction | 0.5 | 0.4 | 0.4 | 0.8 | 0.4 | 0.4 | 0.89 (0.30-2.67) |
| Tourette syndrome | 1.2 | 1.0 | 0.8 | 0.9 | 1.3 | 0.9 | 0.70 (0.33-1.48) |
| Mental retardation/autism | 2.6 | 2.0 | 1.5 | 2.9 | 2.6 | 2.7 | 1.06 (0.66-1.70) |
| ADHD/conduct disorder | 12.9 | 11.5 | 15.1 | 16.5 | 27.7 | 29.5 | 2.28 (1.90-2.75) |
| Affective disorders | 3.2 | 2.9 | 3.2 | 3.7 | 7.0 | 7.2 | 2.25 (1.55-3.27) |
| Other psychiatric disorders | 1.5 | 1.0 | 1.2 | 1.2 | 1.9 | 2.0 | 1.33 (0.75-2.37) |
| 13-18 Years | | | | | | | |
| All | 35.4 | 38.1 | 35.1 | 46.6 | 65.2 | 76.4 | 2.16 (1.90-2.45) |
| Schizophrenia/other psychosis | 5.9 | 7.6 | 5.8 | 7.4 | 8.0 | 5.1 | 0.86 (0.57-1.30) |
| Acute psychotic reaction | 3.0 | 2.2 | 1.7 | 1.6 | 1.5 | 2.2 | 0.74 (0.41-1.32) |
| Tourette syndrome | 0.9 | 1.0 | 0.3 | 0.6 | 1.5 | 0.9 | 0.96 (0.29-2.23) |
| Mental retardation/autism | 1.6 | 1.3 | 1.1 | 1.7 | 2.7 | 2.0 | 1.27 (0.62-2.64) |
| ADHD/conduct disorder | 8.8 | 11.2 | 12.4 | 15.6 | 24.1 | 30.6 | 3.49 (2.65-4.60) |
| Affective disorders | 12.4 | 13.4 | 11.8 | 17.0 | 24.6 | 30.9 | 2.50 (1.97-3.17) |
| Other psychiatric disorders | 2.5 | 1.2 | 1.9 | 2.6 | 2.6 | 4.8 | 1.95 (1.12-3.38) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; IRR, incidence rate ratio.
*TennCare is Tennessee's expanded program for Medicaid enrollees and uninsured individuals who do not qualify for Medicaid. Unless otherwise indicated, data are expressed as rates per 10 000 children, adjusted for sex, race, county, enrollment category, and income using Poisson regression.
†Adjusted for age, sex, race, county, enrollment category, and income using Poisson regression.

2.42; 95% CI, 1.99-2.95). In contrast, the proportions of children beginning antipsychotic use with diagnoses of psychoses, acute psychotic reaction, mental retardation or autism, or Tourette syndrome remained relatively constant during the study period. The proportion of children who received antipsychotics for other psychiatric diagnoses increased; however, this practice was relatively infrequent.

When study children were classified according to age, the secular trend of increasing antipsychotic use was most pronounced for adolescents aged 13 to 18 years and for children aged 6 to 12 years (**Table 3**). The proportion of TennCare enrollees aged 13 to 18 years who were new users of antipsychotics increased 116%, from 35 per 10 000 in 1996 to 76 per 10 000 in 2001 (IRR, 2.16; 95% CI, 1.90-2.45). The trend was driven by increases for ADHD/conduct disorder (from 8.8/10 000 to 30.6/10 000; IRR, 3.49; 95% CI, 2.65-4.60) and affective disorders (from 12.4 per 10 000 to 30.9 per 10 000; IRR, 2.50; 95% CI, 1.97-3.17). For children aged 6 to 12 years, the proportion of new users of antipsychotics increased 93%, from 24 per 10 000 in 1996 to 46 per 10 000 by 2001. As

**Table 4. Adjusted Rates of New Use of Antipsychotics by Indication per 10 000 TennCare Children Qualifying Because of Uninsurance, 1996-2001***

| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | IRR (95% CI)† |
|---|---|---|---|---|---|---|---|
| All | 15.6 | 17.4 | 16.3 | 20.5 | 28.4 | 34.8 | 2.23 (1.81-2.74) |
| Schizophrenia/other psychosis | 1.9 | 3.3 | 2.5 | 1.8 | 2.4 | 2.2 | 1.14 (0.56-2.30) |
| Acute psychotic reaction | 0.8 | 0.9 | 0.5 | 0.4 | 0.2 | 0.6 | 0.60 (0.18-1.98) |
| Tourette syndrome | 0.6 | 1.1 | 0.3 | 1.2 | 0.9 | 0.7 | 1.23 (0.35-4.35) |
| Mental retardation/autism | 2.4 | 0.8 | 1.8 | 2.1 | 2.3 | 2.2 | 0.91 (0.46-1.80) |
| ADHD/conduct disorder | 4.5 | 7.1 | 7.8 | 9.3 | 13.1 | 16.2 | 3.52 (2.30-5.40) |
| Affective disorders | 4.4 | 3.9 | 3.1 | 5.1 | 8.5 | 11.3 | 2.54 (1.66-3.89) |
| Other psychiatric disorders | 0.9 | 0.3 | 0.5 | 0.8 | 1.2 | 1.8 | 1.87 (0.72-4.86) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; IRR, incidence rate ratio.
*TennCare is Tennessee's expanded program for Medicaid enrollees and uninsured individuals who do not qualify for Medicaid. These analyses included only the uninsured population. Unless otherwise indicated, data are expressed as rates per 10 000 children, adjusted for age, sex, race, county, enrollment category, income, and study year using the method of marginal prediction.
†Adjusted for age, sex, race, county, enrollment category, and income using Poisson regression.

was the case for the older group, this primarily was due to increasing use for ADHD/conduct disorder and affective disorders. Although the proportions of preschool children (aged 2-5 years) who became new users of antipsychotics were substantially lower than for the other age groups, these youngest children had a 61% increase in use during the study period (from 10/10 000 in 1996 to 15 per 10 000 in 2001; IRR, 1.61; 95% CI, 1.25-2.06).

We conducted a separate analysis of trends among children with the supplemental TennCare coverage for the uninsured (**Table 4**). The population of children enrolled through the TennCare coverage for the uninsured is more representative of the general state population of children than is that of the children qualifying for TennCare through Medicaid, because the uninsured category excludes the lowest-income families. The analysis also provided a further check as to whether the increased rates of antipsychotic use observed among all children were a secondary effect of the concurrent trend of increased enrollment of the uninsured.

Although the rates of new antipsychotic use were lower in the uninsured than in the Medicaid population, the increase in new use was even more pronounced than that for the entire population (Table 4). The new user rate increased 123%, from 15.6 per 10 000 in 1996 to 34.8 per 10 000 in 2001 (IRR, 2.23; 95% CI, 1.81-2.74). For ADHD/conduct disorder, the rate of new users increased more than 3-fold, from 4.5 per 10 000 in 1996 to 16.2 per 10 000 by 2001 (IRR, 3.52; 95% CI, 2.30-5.40).

## COMMENT

In the TennCare population studied, the proportion of patients aged 2 through 18 years who became new users of antipsychotics from 1996 to 2001 nearly doubled. The observed increase was driven by increases in the use of antipsychotics for ADHD/conduct disorder and affective disorders. The increase was most pronounced for adolescents, for whom the new user proportion more than doubled during the study period. Adolescents had a 3.5-fold increase in new use for ADHD/conduct disorder. During 2001, nearly 1 of every 100 adolescents in the TennCare study population became a new user of an antipsychotic.

Could the trend of increased antipsychotic use have been the result of concurrent secular trends in the composition of the study population or in the occurrence of mental illness? The only material trend identified in the study population was the increased number of children who received enrollment through the TennCare supplemental program providing coverage for moderate-income families without health insurance. However, all study results were adjusted by multivariate regression analysis for type of TennCare enrollment. Second, in a separate analysis of children in the supplemental program for the uninsured, the trend of increased antipsychotic use was even stronger than that for the entire population.

It is also highly unlikely that increased antipsychotic use reflected an increased incidence of serious mental disorders, particularly given the relatively short study period. Indeed, the new use of antipsychotics for schizophrenia and other psychosis was stable during the study period. The labeling of mental disorders, particularly by primary care providers, may have changed. For example, there may have been a trend toward better recognition of underlying affective disorders in patients who formerly received diagnoses of other mental disorders. However, strong evidence suggests that this phenomenon did not account for the study trends. First, changes in labeling would result in a shifting of new users from one diagnostic category to another; they could not explain a doubling of the overall rates of new use of antipsychotics that was identified. Second, the rates for the other diagnostic categories for which changes in labeling were most likely—psychoses and acute psychotic reactions—were stable during the study period.

Thus, the most probable interpretation of the study data is that there was a substantial expansion of the perceived indications for antipsychotic use during the study period. Although this trend coincided with the introduction of the atypical antipsychotics, it is also possible that it was influenced by changing attitudes and practices regarding the use of pharmacotherapy for mental disorders in children.

### What This Study Adds

Newer atypical antipsychotics with adverse effects that differ from those of traditional antipsychotics may lead providers to prescribe antipsychotics more frequently than in the past for behavioral indications not strongly supported by clinical study. Concomitant with the introduction of atypical antipsychotics between 1996 and 2001, this study identified a doubling in rates of new use among children in a state's managed care program for Medicaid enrollees and uninsured persons. Children with behavioral diagnoses substantially contributed to this increase.

Our data suggest that the increase in antipsychotic use was primarily driven by increased use among children with ADHD or conduct disorders and with affective disorders. The use of antipsychotics for ADHD and conduct disorders has been controversial.[2,33] Data from studies of hospitalized children suggest that atypical antipsychotics can successfully control disruptive behavioral symptoms.[6,34] On the other hand, before the introduction of the atypical antipsychotics, the severe and frequent adverse effects of antipsychotics led to the recommendation that these agents be used only in exceptional cases.[2] A recent systematic review of the evidence supporting use of atypical antipsychotics in children and adolescents for this indication concluded that there was insufficient evidence to support their efficacy.[35]

Zito et al[36] analyzed the prevalence of antipsychotic use in a cross-sectional study in 2 state Medicaid populations and 1 health maintenance organization population. In their study, neuroleptic use increased significantly from 1987 to 1996. Although their study included data before the introduction of most of the atypical antipsychotics and used slightly different methods, the increased rates of use paralleled those seen in the current study.

The increased use of antipsychotics for treatment of children and adolescents with affective disorders may be due in part to recent findings in adults. Data suggest that antipsychotics are effective among adults in the maniac phase of bipolar disorders.[37] Preliminary evidence now indicates that some of the atypical antipsychotics may be effective for treatment-resistant major depression.[38] However, whether comparable efficacy exists for children and adolescents is unknown.

Several limitations in the clinical data available for the study should be noted. In this very large population of children, identification of the underlying mental disorder among new antipsychotic users was based on diagnoses recorded in clinical practice rather than on standardized diagnostic assessments. Thus, diagnoses may best reflect a primary care physician's perception of the child's disorder. For children with multiple mental or neurological disorders, the study analysis retained only a single diagnosis, that for which there was best evidence that an antipsychotic was appropriate. The prioritization of diagnoses used in the current study is somewhat conservative in that it gives the provider the benefit of the doubt in identifying the possible indication for use. Additional research is needed for children with multiple mental disorders to further elucidate patterns of use in these children. We did not study factors that predicted which children would receive antipsychotics; further assessment of demographic and behavioral characteristics is important. In addition, further understanding of which providers are writing prescriptions for children would provide important information about provider practice and the mental health infrastructure. We did not attempt to study outcomes of antipsychotic use, including ultimate duration of therapy, behavioral, or somatic effects. Additional data are needed, particularly from well-controlled trials.

The study population consisted of children and adolescents in low- and moderate-income families who received medical care through TennCare, Tennessee's expanded Medicaid program. Thus, it is unknown whether or not similar trends are present for families not enrolled in TennCare. The finding that the doubling of new antipsychotic use persisted in the uninsured population suggests that a similar increase is occurring outside the Medicaid population. Furthermore, theTennCare population is in itself of substantial importance for children's health. By 2000, study children constituted 29.8% of all Tennessee children of comparable ages.[39] In 2001, 20% of children in the United States had Medicaid enrollment.[40] The prevalence of mental illness in this population is higher than that for other children.[41]

## CONCLUSIONS

New use of antipsychotics in study children and adolescents nearly doubled in the 6 years after the introduction of the atypical antipsychotics. The most probable explanation for this trend was substantially increased use for ADHD or conduct disorders and affective disorders. At present, no high-quality scientific evidence supports the use of atypical antipsychotics for these indications in pediatric populations. However, substantial evidence documents the adverse effects of these drugs. Thus, there is an urgent need to conduct well-controlled clinical studies to determine whether the benefits of this expanded use outweigh the risks.

*Accepted for publication March 29, 2004.*

*This study was supported by grant 036816 from the Generalist Physician Faculty Scholars Program of the Robert Wood Johnson Foundation, Princeton, NJ (Dr Cooper), and grant 1U18HS10384-01 from the Centers for Education and Research in Therapeutics program of the Agency for Healthcare Research and Quality, Rockville, Md (Drs Cooper, Arbogast, and Ray).*

*Correspondence: William O. Cooper, MD, MPH, Division of General Pediatrics, Department of Pediatrics, Vanderbilt University School of Medicine, Suite 5028 MCE, Nashville, TN 37232-8555 (william.cooper@vanderbilt.edu).*

## REFERENCES

1. McDougle CJ, Stigler KA, Posey DJ. Treatment of aggression in children and adolescents with autism and conduct disorder. *J Clin Psychiatry*. 2003;64(suppl 4):16-25.
2. Campbell M, Rapoport, JL, Simpson GM. Antipsychotics in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:537-545.

3. Vitiello B. Pyschopharmacology for young children: clinical needs and research opportunities. *Pediatrics.* 2001;108:983-989.
4. Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F. Trends in the prescribing of psychotropic medications in preschoolers. *JAMA.* 2000;283:1025-1030.
5. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavioral disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry.* 2002;41:1026-1036.
6. Van Bellinghen M, De Trooch C. Risperidone in the treatment of behavioral disturbances in children and adolescents with borderline intellectual functioning: a double-blind placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol.* 2001; 11:5-13.
7. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med.* 2002;347:314-321.
8. Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA. Olanzapine vs haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry.* 2001;40:887-894.
9. Masi G, Cosenza A, Mucci M, Brovedani P. Open trial of risperidone in 24 young children with pervasive developmental disorders. *J Am Acad Child Adolesc Psychiatry.* 2001;40:1206-1214.
10. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Arch Gen Psychiatry.* 1998;55:633-641.
11. Safer DJ, Zito JM, dosReis S. Concomitant psychotropic medication for youths. *Am J Psychiatry.* 2003;160:438-449.
12. Cortese L, Pourcher-Bouchard E, Williams R. Assessment and management of antipsychotic-induced adverse events. *Can J Psychiatry.* 1998;43(suppl):15S-20S.
13. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry.* 2002;41:337-343.
14. Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol.* 2003;56:164-170.
15. Gianfrancesco F, Grogg A, Mahmoud R, Wang RH, Meletiche D. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Ther.* 2003;25:1150-1171.
16. Wieck A, Haddad PM. Antipsychotic-induced hyperprolactinaemia in women: pathophysiology, severity and consequences: selective literature review. *Br J Psychiatry.* 2003;182:199-204.
17. Jordan MP. Ziprasidone-associated galactorrhea in a female teenager. *J Am Acad Child Adolesc Psychiatry.* 2003;42:4-5.
18. Stimmel GL, Gutierrez MA, Lee V. Ziprasidone: an atypical antipsychotic drug for the treatment of schizophrenia. *Clin Ther.* 2002;24:21-37.
19. Chang CF, Kiser LJ, Bailey JE, et al. Tennessee's failed managed care program for mental health and substance abuse services. *JAMA.* 1998;279:864-869.
20. Ray WA, Griffin MR. The use of Medicaid data for pharmacoepidemiology. *Am J Epidemiol.* 1989;129:837-849.
21. Cooper WO, Hickson GB, Gray CL, Ray WA. Changes in continuity of enrollment among high-risk children following implementation of TennCare. *Arch Pediatr Adolesc Med.* 1999;153:1145-1149.
22. Bureau of the Census. *Census of Population and Housing, 1990: Summary Tape File 3 on CD-ROM Tennessee* [abstract]. Memphis, Tenn: Bureau of the Census; 1992.
23. Bureau of the Census. *Census of Population and Housing, Summary: Summary Tape File 3 on CD-ROM Technical Documentation* [abstract]. Memphis, Tenn; Bureau of the Census; 1992.
24. Bureau of the Census. *TIGER/Line Files™, 1992* [abstract]. Memphis, Tenn: Bureau of the Census; 1993.
25. Bureau of the Census. *TIGER/Line Files™, 1992 Technical Documentation* [abstract]. Memphis, Tenn: Bureau of the Census; 1993.
26. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. In: Armenian HK, Gordis L, Levine MM, Thacker SB, eds. *Epidemiologic Reviews.* 12th ed. Baltimore, Md: Johns Hopkins University School of Hygiene and Public Health; 1990:87-107.
27. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol.* 1995;142:1103-1110.
28. Leister KA, Edwards WA, Christensen DB, Clark H. A comparison of patient drug regimens as viewed by the physician, pharmacist and patient. *Med Care.* 1981; 19:658-664.
29. Johnson RE, Vollmer WM. Comparing sources of drug data about the elderly. *J Am Geriatr Soc.* 1991;39:1079-1084.
30. *International Classification of Diseases, Ninth Revision, Clinical Modification.* Washington, DC: Public Health Service, US Dept of Health and Human Services; 1988.
31. Center for Business and Economic Research, University of Tennessee. *Tennessee Statistical Abstracts.* Knoxville: University of Tennessee; 1991.
32. Lane PW, Nelder JA. Analysis of covariance and standardization as instances of prediction. *Biometrics.* 1982;38:613-621.
33. Dulcan MK, Benson RS. AACAP Official Action: summary of the practice parameters for the assessment and treatment of children, adolescents and adults with ADHD. *J Am Acad Child Adolesc Psychiatry.* 1997;36:1311-1317.
34. Connor DF, Ozbayrak KR, Harrison RJ, Melloni RH Jr. Prevalence and patterns of psychotropic and anticonvulsant medication use in children and adolescents referred to residential treatment. *J Child Adolesc Psychopharmacol.* 1998;8:27-38.
35. Einarson TR, Iskedjian M. *Novel Antipsychotics for Patients With Attention-Deficit Hyperactivity Disorder: A Systematic Review.* Ottawa, Ontario: Canadian Coordinating Office for Health Techonlogy Assessment; 2001. Technology report 17.
36. Zito JM, Safer DJ, dosReis S, et al. Psychotropic practice patterns for youth: a 10-year perspective. *Arch Pediatr Adolesc Med.* 2003;157:17-25.
37. Keck PE Jr, Verisani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry.* 2003;160:741-748.
38. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry.* 2001;158:131-134.
39. US Census Bureau. 2000 Census data. Available at: http://factfinder.census.gov. Accessed April 2, 2003.
40. Mills RJ. Health insurance coverage: 2000. US Census Bureau Current Population Reports. September 2001. Available at: http://www.census.gov/prod/2001pubs/p60-215.pdf. Accessed April 2, 2003.
41. Frank RG, Goldman HH, Hogan M. Medicaid and mental health: be careful what you ask for. *Health Aff (Millwood).* 2003;22:101-113.