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Observed Clinical and Health Services Outcomes in Pediatric Inpatients Treated with Atypical Antipsychotics: 1999–2003

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ABSTRACT

Objective: **The aim of this study was to compare clinical and health services outcomes in pediatric inpatients prescribed an atypical antipsychotic (AA) to those not prescribed an AA at discharge.**

Methods: **Descriptive statistics, analysis of variance (ANOVA), and, where necessary, analysis of covariance (ANCOVA) were used to compare differences between and within an inpatient group prescribed risperidone, olanzapine, or quetiapine (n = 1,131) with an inpatient group not prescribed an antipsychotic at discharge (n = 1,741).**

Results: **The AA treatment group showed greater psychiatric symptom difficulty at admission as measured by the Brief Psychiatric Rating Scale for Children (Mean BPRS-C) than the group not prescribed AAs (40.3 [n = 433] vs. 35.2 [n = 452], respectively, $p < 0.001$). AA-treated inpatients also had a higher number of mental health outpatient visits during the 6 months prior to admission. Patients receiving AAs (n = 1,050) had significantly longer adjusted length of stay (LOS) than those not receiving antipsychotics (n = 1,664): 26.4 days versus 22.4 days, respectively ($p < 0.04$).**

Conclusions: **The findings suggested pediatric inpatients presenting with greater psychiatric symptom difficulty at hospital admission were more likely to be prescribed an AA. Choice of AA may influence certain clinical and health services outcomes. Additional prospective controlled studies evaluating AA efficacy and safety, including head-to-head comparisons, in pediatric inpatients are warranted.**

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INTRODUCTION

Recent publications in the psychiatric literature indicate a significant increase in the use of psychotropic medications in children and adolescents over the past two decades (Zito et al. 2003). One large-scale analysis found that the prevalence of psychotropic medication use in patients under 20 years of age rose two- to three-fold from 1991 through 2000 (Zito et al. 2003). Similarly, a study of private insurance plans represented in a nationwide database indicated that the prevalence of psychotropic medication use among children and adolescents who filed at least one claim for mental health care was 62.3% in 2000 (Martin and Leslie 2003a).

Results of these population-based studies have been mirrored in analyses of psychotropic drug use at individual institutions. Najjar and colleagues (Najjar et al. 2004) found that even after controlling for a 2.3-fold increase in admissions from 1991 through 1998, there was a 73% increase in the rate of psychotropic drug use among children in a psychiatric hospital during the same period. Several possible reasons for the trend include: Increased acceptance of criterion-based diagnoses introduced with *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994); changing concepts of psychiatric disorders in children and adolescents; new indications for existing psychotropic agents; and the improved safety profile of newer agents (Najjar et al. 2004).

Over the past few years, there has been a sharp rise in prescriptions of atypical antipsychotic (AA) agents in children and adolescents, concurrent with a reduced use of older typical antipsychotic agents (Martin and Leslie 2003a; Najjar et al. 2004). A review of the Texas Medicaid program found that the overall utilization rates of antipsychotic medications rose from 7.63 to 19.88 per 1,000 enrollees during the period 1996–2000, an increase of 160%. However, this overall increase was derived from a 21% decrease in the use of typical antipsychotics and a 494% increase in the use of AAs (Patel et al. 2002). In part, the increase in AA utilization may be explained by concerns about adverse events related to typical antipsychotics, especially extrapyramidal symptoms (EPS). Lewis and colleagues (Lewis 1998) presented evidence that younger patients may be at higher risk than adults for EPS, including acute dystonia. Although pediatric safety and tolerability data are limited, in adult studies the reduced incidence of EPS demonstrated by AAs, compared with typical antipsychotics, has supported the notion that AAs may be prescribed judiciously to pediatric patients (Glick et al. 2001; Findling and McNamara 2004). Some researchers suggest that the increased prescribing of these medications is a result of an overall lack of time and resources as well as an increased pressure to shorten hospital stays (Scahill 2005).

The use of AAs has expanded largely in the absence of clearly defined, evidence-based guidelines for the use of psychotropic medications in the pediatric population (Cheng-Shannon et al. 2004). Pappadopulos and colleagues (Pappadopulos et al. 2002) studied factors that may affect inpatient AA prescribing practices. In a series of focus group discussions involving 140 mental health-care professionals from 12 child and adolescent inpatient facilities, investigators found that the lack of research and training with respect to management of severe psychiatric conditions has led to the development of ad hoc treatment strategies, possibly influenced by social and financial pressures.

The AAs have demonstrated efficacy in reducing problematic symptoms in children with disruptive behavior disorders, pervasive developmental disorder, psychotic disorders, and bipolar disorder (for review, see Jensen et al. 2006). However, the majority of available studies are anecdotal or short-term open-label trials (Cheng-Shannon et al. 2004). Risperidone is currently the only Food and Drug Administration (FDA)-approved antipsychotic for the treatment of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Risperdal® prescribing information, October, 2006). The efficacy of risperidone in children with autistic disorder was established in two 8-week, placebo-controlled trials in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for

autistic disorder (McCracken et al. 2002; Pandina et al. 2006). The benefit of maintaining patients (aged 5–17 years) with irritability, severe tantrums, aggression, or self-injurious behavior associated with autistic disorder on therapy with risperidone after achieving a responder status for an average duration of about 140 days was demonstrated in a placebo-controlled study (Research Units on Pediatric Psychopharmacology Autism Network [RUPP] 2002).

However, the lack of empirical evidence, as opposed to experience-based consensus, to guide the use of AAs is reflected in extensive variability in treatment patterns, including the broad use of AAs for nonpsychotic disorders. A study of 100 charts from three inpatient child and adolescent psychiatric facilities showed that typical antipsychotics were prescribed at discharge for 86% of patients, despite a prevalence of only 20% for psychotic disorders in this cohort (Pappadopulos et al. 2002). Another study of inpatients (aged 18 years or younger) at a state psychiatric hospital from 1997 to 2000 revealed that 23% received an AA, although a psychotic disorder was the primary diagnosis in only 17% of patients treated with an AA. The authors noted that neither particular diagnoses nor symptoms guided a rationale for the use of AAs in this population (Kelly et al. 2004).

Outcomes research seeks to provide a comprehensive evaluation of particular current health-care practices through documentation and measurement of effectiveness, economic, and health-care outcomes, including those related to quality of life. Outcomes research is generally conducted to identify factors that are associated with successful outcomes in patients and guide health-care decision making in clinical practice settings. Given the gap between the current level of outcomes research evidence regarding the use of AAs in child and adolescent populations and the rapidly expanding use of these agents as described above, it is important to understand current trends in prescribing practices and the clinical outcomes that result from these practices (Martin and Leslie 2003a; Kelly et al. 2004). For these reasons, we conducted a retrospective study using a large mental health outcomes database to evaluate prescribing patterns, effectiveness, and length of stay associated with the use of AAs in a large sample of pediatric psychiatric inpatients.

The conceptual framework of this study was based on previous outcomes research studies on the use of AA in the pediatric population (Martin et al. 2003; Martin and Leslie 2003b; Kelly et al. 2004). Most of the available studies evaluated medication utilization and costs. The present study aimed to provide an evaluation of documented clinical end points in combination with observed health services outcomes. Specifically, this retrospective database study explored differences between AA-treated patients and patients who were not treated with antipsychotics in terms of their history, diagnosis at admission, severity of symptoms, mental health co-morbidities, and use of concomitant psychotropic medications. Differences among AA-treated inpatient groups were also explored. Clinical outcomes at admission and discharge were also evaluated, based on scores from the Global Assessment of Functioning (GAF) and the Brief Psychiatric Rating Scale for Children (BPRS-C). Published data have shown the BPRS-C score to be a useful outcomes measure for assessing treatment response in children with psychiatric disorders (Hughes 2001). Health services outcomes in this study included hospital length of stay (LOS) and changes in recorded weight associated with the use of risperidone, olanzapine, and quetiapine in this group of pediatric inpatients.

METHODS

Subjects and facilities

Patients in this study were children and adolescents aged 4–17 years who required psychiatric hospitalization and were admitted to 48 inpatient psychiatric treatment facilities located across the United States between July 1, 1999, and June 30, 2003. These inpatient psychiatric facilities were part of a nationwide program for outcomes measurement, quality improvement, and accreditation support, managed by Mental Health Outcomes, Inc. (Lewisville, TX). Participation in this program allowed behavioral health-care providers to measure outcomes against clinical pathways, treatment modalities, functional health status,

and patient satisfaction, and to understand how sociodemographic factors may impact clinical outcomes. Retrospective data on the patients and their inpatient treatment regimens were obtained retrospectively using the proprietary CQI+ Outcomes Measurement System developed by Mental Health Outcomes, Inc. The CQI+ System measures a wide range of behavioral health variables using valid and reliable patient survey instruments (http://www.mho-inc.net/mho/product.htm). CQI+ data were collected at three points in time during a patient's episode of care: Within 72 hours of admission, within 48 hours of discharge, and at 6 months postdischarge (followup). Nationally, this behavioral health database contains clinical data for more than 100,000 patients. Data for this study were based only on clinical information gathered at hospital admission and discharge.

Clinical outcome assessments used to collect inpatient data included a general admission questionnaire (referral source, patient demographics, psychiatric history, physical health, substance abuse, and legal history), the BPRS-C, a medication usage questionnaire (all psychotropic and nonpsychotropic medications prescribed), a medical record information form (level and duration of treatment, diagnosis, and payor information), the GAF, and a patient satisfaction form (completed at discharge). Participating facilities and staff members assessed a random sample of patients ($\geq$20 patients) admitted each month to complete these standardized questionnaires. Each hospital was required to sample patients in a method or manner that was consistent throughout the study period. The most common sampling approach was to assess patients in consecutive order until a predetermined recruitment goal was reached for that month; however, some hospitals chose to assess every other newly diagnosed patient admitted to the hospital until their target recruitment goal was met for the month. Sampling methods were not evaluated or recorded for the hospitals in this study. In addition, the hospitals chose the number of instruments to be used in the tracking system, which may have affected the availability of data for one of the psychiatric assessment instruments utilized in this study. Of the 48 hospitals participating in the survey, four did not submit data for the present analyses.

Consent to participate in the database was collected by the patient's parent or guardian upon admission, and permission was given to distribute and use anonymized data, as well as to be contacted for follow-up information. As this analysis was completed with deidentified, retrospective data, it was not necessary to obtain Institutional Review Board approval.

Diagnoses and medical record information

For each pediatric or adolescent inpatient, a primary or principal psychiatric diagnosis was assigned and recorded by the treating clinician at admission. In addition, the clinician was also required to assess and provide primary and secondary Axis I and Axis II disorders (DSM-IV) of patients at admission and discharge from the inpatient facility. Also collected as part of this multiaxial diagnostic assessment were data on the number of falls, incidents of seclusion, and number of times the patient was restrained during their stay. In addition, height and weight data at both admission and discharge were collected and used to calculate change in body weight (in kilograms) during hospitalization.

Psychiatric assessment instruments

The following validated measures were used as the primary clinical outcome measures in the study.

GAF: The GAF is a 100-point clinician-rated tool used to assess overall psychological, social, and occupational functioning. Higher scores indicate better functioning. The GAF is included in the DSM-IV-Text Revision (American Psychiatric Association 2000) in the section on multiaxial assessments as Axis V.

BPRS-C: The BPRS-C is a clinician-based rating scale designed to evaluate the presence and severity of 21 symptoms across a range of psychiatric disorders; it was completed at admission and at discharge to assess symptom severity. The BPRS-C rates each of the 21 items on a 7-point scale, ranging from "not present" (score 0) to "extremely severe" (score 6). The overall

score ranges from 0 to 126, with lower scores indicating better health. The BPRS-C also generates seven composite subscale scores (behavioral problems, depression, thinking disturbances, psychomotor excitation, withdrawal retardation, anxiety, and organicity), with three items per subscale (Overall and Pfefferbaum 1982).

Length of stay

The length of hospital stay in days (date of admission to date of discharge) was collected for each patient. Because LOS longer than 365 days suggested residential placement rather than acute management of psychiatric issues, any inpatient facility with a mean LOS greater than 365 days was excluded from the calculations. An examination of the 48 inpatient facilities found four units (contributing 80 patients to the study) with mean length of stays of greater than 30 days, representing 1.09% of the entire pediatric inpatient population in these 48 psychiatric facilities. These facilities were retained in the analyses.

Statistical analysis

All statistical analyses and comparisons were based on the following mutually exclusive patient categories.

Antipsychotic class treatment groups: Patients treated with an AA at discharge (AA group) versus patients not treated with an antipsychotic of any kind at discharge. We inferred that the medication at discharge was mostly likely the medication that the patient responded to and was stabilized during inpatient treatment. This inference was required because Mental Health Outcomes, Inc. collected data at three points in time during a patient's episode of care (admission, discharge, and follow up), and there was practically no information on the medication use during hospitalization.

Antipsychotic agent groups: This group was composed of patients treated with risperidone, olanzapine, or quetiapine at discharge. Use of other adjunctive psychotropic medications was allowed.

Comparisons between groups and variability within treatment groups were characterized using descriptive statistics and analysis of variance (ANOVA). Since groups could differ with respect to sociodemographic characteristics, diagnosis, severity of disease, length of time in treatment, and other comorbidities, analysis of covariance (ANCOVA) was used to adjust for potential heterogeneity in the sample where appropriate. Potential confounders included in the model are presented in Table 1. Only variables with an association ($p < 0.20$) in univariate regression with the outcome of interest were treated as covariates in subsequent analyses. Results with a two-tailed p value less than 0.05 were considered significant. All change

Table 1. List of Potential Covariates Tested in Univariate Regression Analysis for Association with the Variables of Interest

Primary diagnosis of
Depressive Disorder
Bipolar Disorder
Adjustment Disorder
Substance-Related Disorder
Impulse-Control Disorder
Schizophrenia Disorder
Psychotic Disorder
Attention-Deficit Disorder
Pervasive Developmental Disorder
Secondary diagnosis of
Anxiety Disorder
Substance-Related Disorder
Impulse-Control Disorder
Schizophrenia Disorder
Eating Disorder
Psychotic Disorder
Attention-Deficit Disorder
Pervasive Developmental Disorder
Other Childhood Disorder
Axis II Diagnosis of
Personality Disorder
Mental Retardation Disorder
Number of Secondary Axis I Diagnoses
Number of Axis II Diagnoses
BPRS-C overall score at admission
Substance abuse
GAF score at admission
Inpatient hospitalizations for mental health prior to admission*
Outpatient treatment visits prior to admission*
Suicide attempts prior to admission*
Age
Gender
Race
Payor source
Relationship with family at admission
Relationship with friends at admission
Quality of life at admission
Duration of illness

scores were calculated so that a higher (positive) value indicated greater improvement. No adjustments were made for multiple comparisons.

RESULTS

Using records from the total observed psychiatric inpatient population of 7,300 pediatric patients (1999–2003), we identified a total of 2,872 patients who met the age and date range criteria and constituted the sample for this study: 1,131 patients were treated with an AA and 1,741 patients were not treated with any antipsychotic at discharge. Of the 1,131 patients treated with an AA at discharge, 548 received risperidone, 339 received olanzapine, and 242 received quetiapine. Two patients who received more than one AA at discharge were excluded from comparisons among antipsychotic agent treatment groups.

Because of missing data in the CQI+ Outcomes Measurement System, the number of patients included in each analysis is indicated by a lower case 'n' in parentheses, if this deviated from the total sample size.

Baseline demographic characteristics are listed in Table 2. In addition, approximately 75% of the total patient sample were from hospitals in the southern or southwestern United States and lived at home with family prior to the current admission. About 70–75% had been hospitalized for mental health reasons in the 6 months prior to admission. The mean duration of psychiatric illness was approximately 2.5 years.

Patients receiving AAs, compared with those not receiving antipsychotics, were significantly more likely to be younger, male, nonwhite, and paying for hospitalization with public rather than private funds. They were also significantly more likely to have had one or more mental health outpatient visits, and significantly less likely to have abused substances, in the 6 months prior to admission.

Prescribing patterns

The primary diagnoses at admission were analyzed by the antipsychotic class treatment groups. In the total sample, the most common diagnoses (>10%) were depressive disorder (39.9%), bipolar disorder (13.0%), and impulse-control disorder (11.9%). Patients receiving AAs were significantly more likely to be diagnosed with bipolar disorder, schizophrenia, psychotic disorder, and attention-deficit hyperactivity disorder (ADHD) ($p < 0.001$ for all diagnoses), as well as with pervasive develop-

Table 2. Selected Baseline Characteristics of Treatment Groups (at Discharge)

	Antipsychotic class treatment groups		*Antipsychotic agent treatment groups*		
	Atypical Antipsychotic (n = *1131*)	*No antipsychotic* (n = *1741*)	*Risperidone* (n = *548*)	*Quetiapine* (n = *242*)	*Olanzapine* (n = *339*)
Age, years, mean (SD)	12.3 (3.1)[a]	13.6 (2.9)	11.8 (3.1)[b]	13.1 (2.9)	12.6 (3.1)
Gender (%)					
Male	65[a]	54	71	52[b]	67
Female	35	46	29	48	33
Race/ethnicity (%)					
White	74	78	69	83	78
Nonwhite	26[c]	22	31[b]	17	22
Payor source (%)					
Public	52[c]	47	61[b]	30	49
Private	48	53	39	70	51

[a] $p < 0.001$ vs. No Antipsychotic group.
[b] $p < 0.001$ vs. other Antipsychotic Agent groups.
[c] $p < 0.05$ vs. No Antipsychotic group.
SD = standard deviation; ANOVA = analysis of variance.
p value in ANOVA model (continuous variables) or chi-square test (categorical variables).

mental disorder ($p < 0.05$), when compared to patients who received no antipsychotics (Fig. 1). Patients receiving AAs were significantly less likely to be diagnosed with depressive disorder ($p < 0.001$) than patients not receiving antipsychotics.

Within the AA group, patients with depressive disorder and bipolar disorder were less likely to receive risperidone than olanzapine and quetiapine ($p < 0.05$). Patients with impulse control disorder and adjustment disorder were more likely to receive risperidone ($p < 0.05$), as were those with ADHD ($p < 0.001$). Patients with substance-related disorders were more likely to receive quetiapine ($p < 0.05$).

Among all patients, the most common secondary diagnoses at admission were as follows: impulse-control (32%), ADHD (17.9%), substance-related (15.2%), and anxiety (9.1%). For patients with a primary diagnosis of ADHD, 49% had a secondary diagnosis of impulse-control and 24% had a secondary diagnosis of depression.

To understand prescribing patterns further, data on the mean dosages of AAs at discharge were collected and analyzed with respect to primary diagnoses (Table 3).The mean (± standard deviation) dosages at discharge for each AA treatment group were: Risperidone, 2.3 ± 2.4 mg, olanzapine, 9.6 ± 5.9 mg, and quetiapine, 156.3 mg ± 159.5 mg (Table 3).

At discharge, the proportion of patients who were prescribed a concurrent psychotropic medication (including antidepressants, mood stabilizers, or anxiolytics) did not differ between those receiving AAs and those receiving no atypicals: 77.8% ($n = 880$) versus 79.6% ($n = 1{,}386$), respectively ($p = 0.247$). This proportion was not statistically significant even after adjustment for covariates. Covariates that were significant predictors of concurrent medication usage at discharge were: Primary diagnosis of depressive disorder, age, and the relationship with friends at admission ($B = 0.78$, $p < 0.004$; $B = 0.09$, $p < 0.01$; and $B = -0.35$, $p < 0.003$, respectively). Within the AA group, pediatric

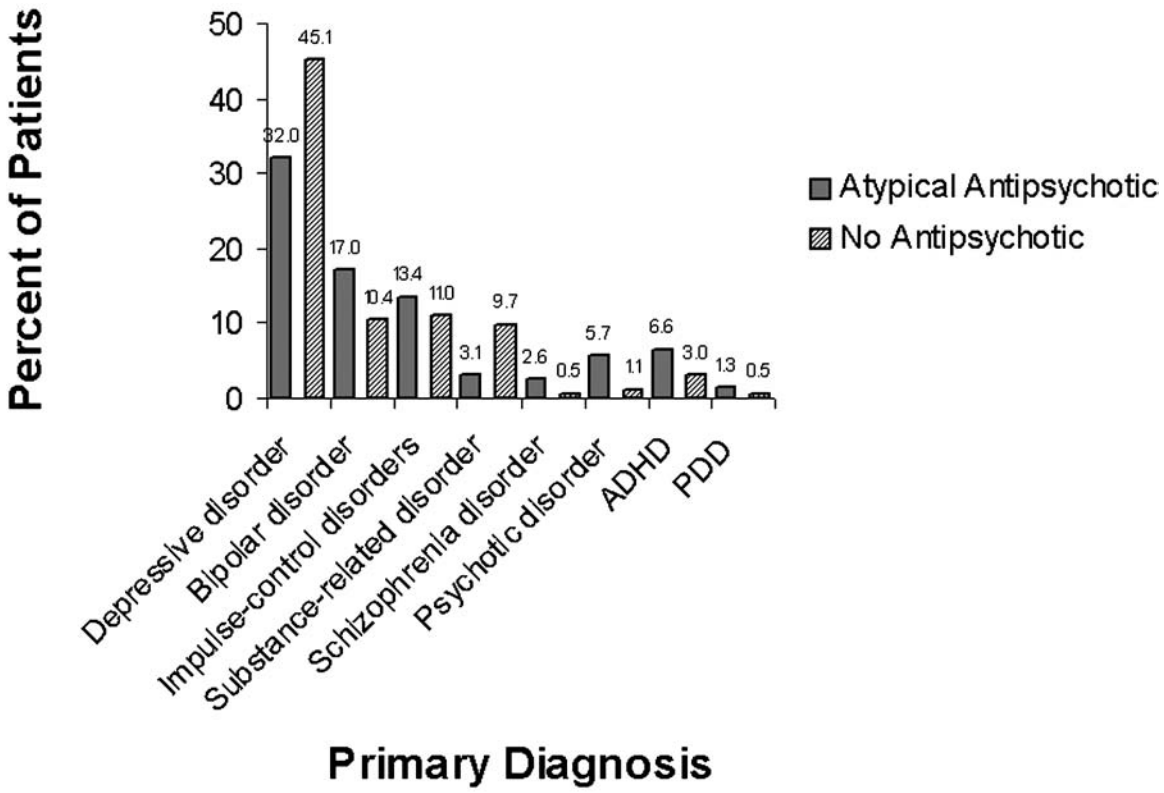

FIG. 1. Primary diagnoses by antipsychotic class group. p values for between-group differences in an ANOVA: $^{\ddagger}p < 0.001$; $^{\dagger}p < 0.05$. p value in chi-square test. ADHD = Attention Deficit-Hyperactivity Disorder; PDD = Pervasive Developmental Disorder; ANOVA = analysis of variance.

Table 3. Mean (±SD) Daily Dose at Discharge by Primary Diagnoses

	Depressive disorder	*Bipolar disorder*	*Impulse control disorder*	*Pervasive developmental disorder*	*All patients (all diagnoses)*
Olanzapine (*n*)	9.2 ± 5.6 (61)	11.8 ± 6.7 (37)	7.7 ± 3.84 (21)	7.6 ± 4.9 (5)	9.6 ± 5.9 (206)
Risperidone (*n*)	2.0 ± 1.9 (97)	3.3 ± 3.2 (46)	2.1 ± 3.0 (53)	3.8 ± 3.6 (4)	2.3 ± 2.4 (386)
Quetiapine (*n*)	129.0 ± 154.7 (65)	159.9 ± 143.2 (47)	210.9 ± 196.1 (15)	120.0 ± 0.0 (1)	156.3 ± 159.5 (216)

n = number of patients included in each analysis; SD = standard deviation.

Because of missing data in the CQI+ Outcomes Measurement System, the number of patients included in each analysis is indicated by a lowercase "*n*" in parentheses, if this deviated from the total sample size.

inpatients receiving risperidone were less likely to be prescribed concurrent psychotropic medications (71.2%) than were patients receiving either olanzapine (78.8%, $p < 0.02$) or quetiapine (89.3%, $p < 0.001$) before adjusting for covariates. After adjustment for covariates, patient groups receiving AA did not differ with respect to concurrent medication usage at discharge. The only covariate that was a significant predictor of concurrent psychiatric medication usage at discharge was primary diagnosis of an impulse-control disorder ($B = -1.45$, $p < 0.04$).

Prescribing patterns were also analyzed with respect to hospitalization variables. Patients receiving AAs were significantly more likely to be secluded during hospitalization (11.9% vs. 5.0%, $p < 0.001$) than those not receiving antipsychotics. They were also more likely to be restrained during hospitalization (10.1% vs. 6.3%, $p < 0.003$).

Clinical outcomes

GAF scores: Patients receiving AAs ($n = 1{,}010$) demonstrated a significantly lower level of functioning at admission, measured by the GAF score, than those not receiving antipsychotics ($n = 1{,}524$; 27.8 ± 7.46 vs. 29.2 ± 8.76, respectively; $p < 0.001$). At discharge, patients receiving no antipsychotics had a slightly, but significantly, higher level of functioning (49.5 ± 12.0; $n = 1{,}460$) than patients receiving AAs (48.3 ± 12.2; $n = 963$) as measured by the GAF ($p < 0.027$), although both groups' GAF scores improved markedly from admission to discharge.

There were no significant differences between patients receiving AAs versus patients not receiving antipsychotics with respect to change in GAF scores from admission to discharge after adjustment for covariates. Significant predictors in this model were primary substance-abuse disorder ($B = 5.51$, $p < 0.001$), primary pervasive developmental disorder ($B = 12.00$, $p < 0.005$), secondary impulse-control disorder ($B = 3.23$, $p < 0.001$), Axis 2 mental retardation disorder ($B = 8.51$, $p < 0.03$), prior outpatient treatment ($B = -1.75$, $p < 0.02$), payor ($B = -1.55$, $p < 0.05$), GAF at admission ($B = -0.43$, $p < 0.001$), total number of secondary Axis I diagnoses ($B = -2.77$, $p < 0.001$), and relationship with friends ($B = -0.97$, $p < 0.05$).

Within the AA treatment groups, certain patterns were observed. Patients receiving risperidone ($n = 464$) had a greater change in the GAF score than patients receiving either olanzapine ($n = 293$) or quetiapine ($n = 201$) (22.9, 95% confidence interval [CI] [21.8, 24.1] vs. 19.2, 95% CI [17.9, 20.4] vs. 16.6, 95% CI [15.1, 18.1], respectively; $p < 0.001$ for risperidone vs. olanzapine and risperidone vs. quetiapine). These findings were confirmed using multivariate regression analyses: risperidone (mean = 10.525, 95% CI [−4.224, 25.275]) showed significantly greater improvement than olanzapine (mean = 4.581, 95% CI [−10.345, 19.506]) and quetiapine (mean = 4.777, 95% CI [−10.040, 19.594]) ($p < 0.001$ vs. both). Significant predictors in this model were primary adjustment disorder ($B = -16.89$, $p < 0.05$), primary pervasive developmental disorder ($B = 9.75$, $p < 0.03$), payor ($B = -3.95$, $p < 0.001$), GAF score at admission ($B = -0.43$, $p < 0.001$), total number of secondary Axis I diagnoses ($B = -3.01$, $p < 0.001$), and relationship with family ($B = 1.01$, $p < 0.05$).

Patients receiving olanzapine showed greater improvement than patients receiving quetiapine ($p < 0.04$), though it is important to note that these findings may be related to differences in dosing. The dose range for quetiapine was much wider than the ranges for either olanzapine or risperidone.

BPRS-C scores: At admission, patients receiving AAs ($n = 433$) had significantly higher mean overall scores on the BPRS-C (reflecting more severe symptoms) than those not receiving antipsychotics ($n = 452$), as illustrated in Fig. 2 (40.3 ± 18.6 vs. 35.2 ± 17.2, respectively, $p < 0.001$). At discharge, there was no significant difference between groups (19.1 [$n = 354$] vs. 18.1 [$n = 377$], respectively).

Patients receiving AAs ($n = 433$) had significantly higher scores at admission on the BPRS-C subscales of Behavior Problems (9.7 ± 5.0 vs. 8.6 ± 5.2, $p < 0.002$), Thinking Disturbances (3.0 ± 4.1 vs. 1.4 ± 2.6, $p < 0.001$), Psychomotor Excitation (7.1 ± 4.9 vs. 5.3 ± 4.4, $p < 0.001$), and Organicity (1.7 ± 2.9 vs. 1.0 ± 2.2, $p < 0.001$) compared with patients who were not treated with antipsychotics ($n = 452$). Subsequently, patients treated with AAs ($n = 280$) demonstrated greater improvement from admission to discharge than patients not receiving antipsychotics ($n = 267$) in the BPRS-C subscales of Behavior Problems (mean change ± standard deviation [SD] from admission to discharge: 4.7 ± 4.0 vs. 3.9 ± 4.2, $p < 0.03$), Thinking Disturbances (1.8 ± 3.3 vs. 0.6 ± 1.8, $p <$

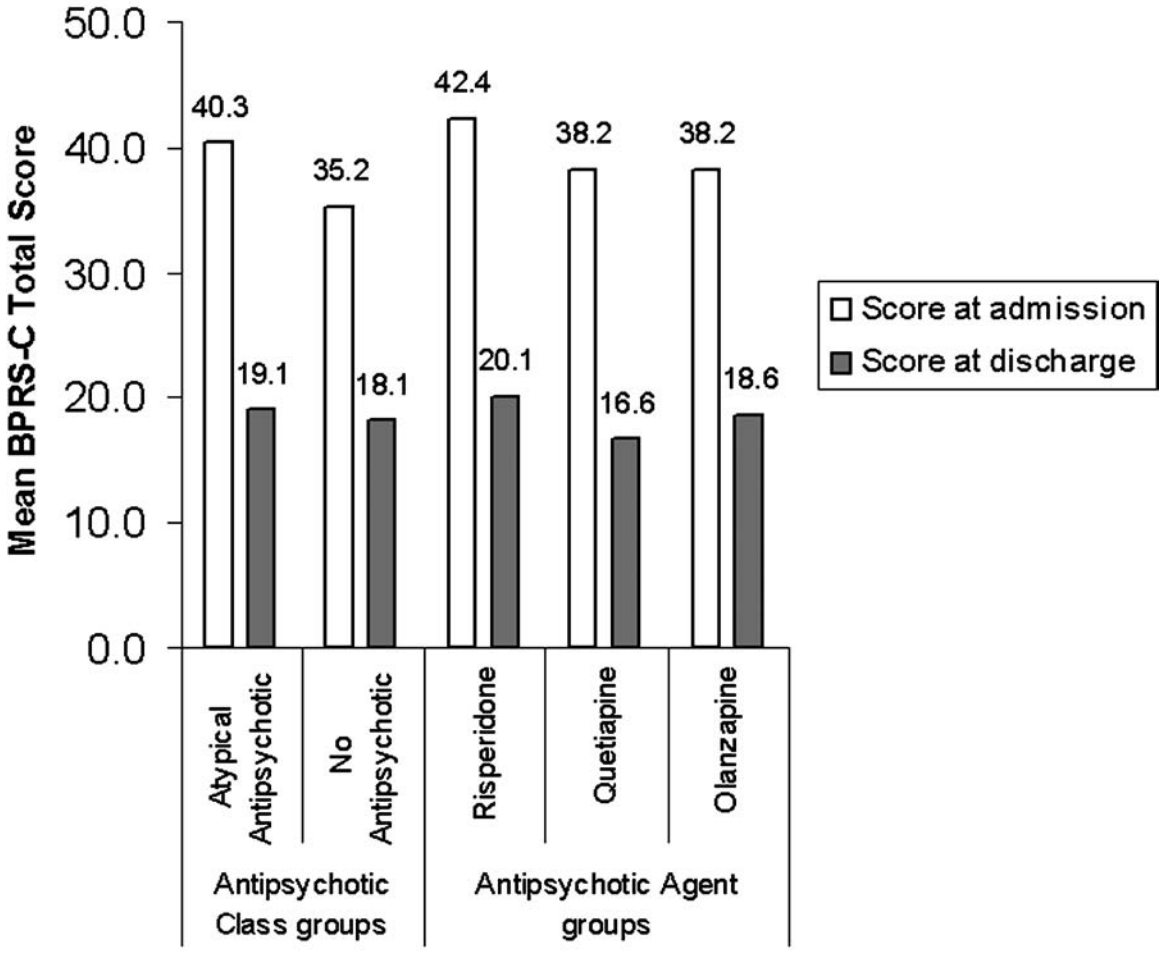

FIG. 2. Mean BPRS-C Scores at admission and discharge. Atypical antipsychotics: Admission, $n = 433$; discharge, $n = 354$. No atypical antipsychotics: Admission, $n = 452$; discharge, $n = 377$. Risperidone: Admission, $n = 209$; Discharge, $n = 129$. Quetiapine: Admission, $n = 116$; discharge, $n = 77$. Olanzapine: Admission, $n = 111$; discharge, $n = 75$. *Significant differences at admission between Antipsychotic Class groups in ANOVA ($p < 0.001$). BPRS-C = Brief Psychiatric Rating Scale for Children; ANOVA = analysis of variance.

0.001), and Psychomotor Excitation (3.0 ± 3.2 vs. 2.2 ± 3.0, $p < 0.007$). However, adjusting for covariates, including BPRS overall and subscale scores at admission, and GAF score at admission if appropriate, eliminated these statistical significances. In addition, there were no significant between-group differences in BPRS-C overall or subscale scores with respect to AA treatment agents. No significant between-group differences among treatment classes or AA agents were found in mean change in BPRS-C overall score with respect to primary diagnoses (Fig. 3).

Length of stay

Patients receiving AAs ($n = 1{,}050$) had significantly longer adjusted LOS than those not receiving antipsychotics ($n = 1{,}664$): 26.4 days (95% CI [15.3, 37.2]) vs. 22.4 days (95% CI [11.1, 33.8]), respectively ($p < 0.04$). Primary diagnosis of substance-related disorder ($B = -21.44$, $p < 0.001$) and private payor status ($B = 3.99$, $p < 0.05$) were included as covariates in the model.

There were significant differences in LOS among the AA treatment groups after adjusting for selected covariates. Patients receiving risperidone ($n = 121$) had a significantly shorter mean adjusted LOS (8.9 days; 95% CI [−26.2, 43.9]) than those receiving olanzapine ($n = 160$; 16.2 days, 95% CI [−18.9, 51.4], $p < 0.002$) and quetiapine ($n = 111$; 19.4 days, 95% CI [15.2, 54.0], $p < 0.001$), as shown in Fig. 4. Significant predictors of LOS were primary diagnosis of substance-related disorder ($B = -13.53$, $p < 0.02$) and gender ($B = -4.13$, $p < 0.05$).

Safety

Safety data were limited to changes in body weight at admission and discharge. Patients receiving AAs gained more weight on average from admission to discharge than those not receiving antipsychotics (1.05 kg vs. 0.64 kg, respectively; $p < 0.01$). However, after adjusting for selected covariates, there was no difference in change in weight from admission to discharge between patients receiving AAs and

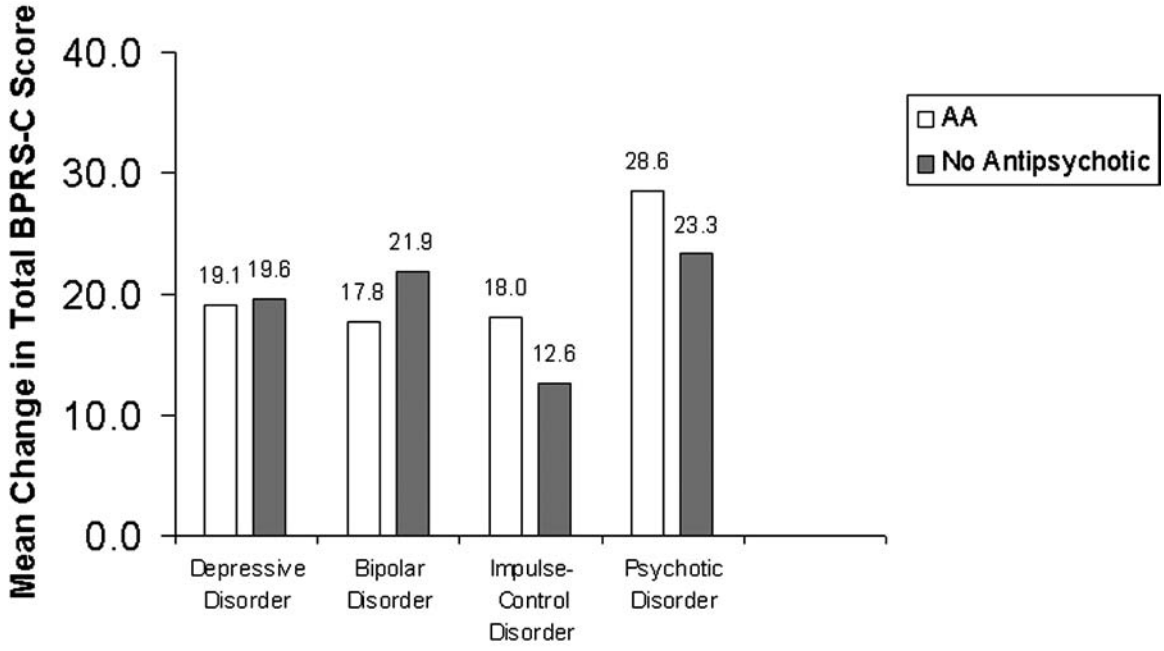

FIG. 3. Mean Change in BPRS-C total scores from admission to discharge by primary diagnoses. Depressive disorder: atypical antipsychotics, $n = 92$; no antipsychotics, $n = 114$. Bipolar disorder: Atypical antipsychotics, $n = 44$; no antipsychotics, $n = 15$. Impulse-control disorder: Atypical antipsychotics, $n = 27$; no antipsychotics, $n = 22$. Psychotic disorder: Atypical antipsychotics, $n = 12$; no antipsychotics, $n = 3$. BPRS-C = Brief Psychiatric Rating Scale for Children; AA = atypical antipsychotic.

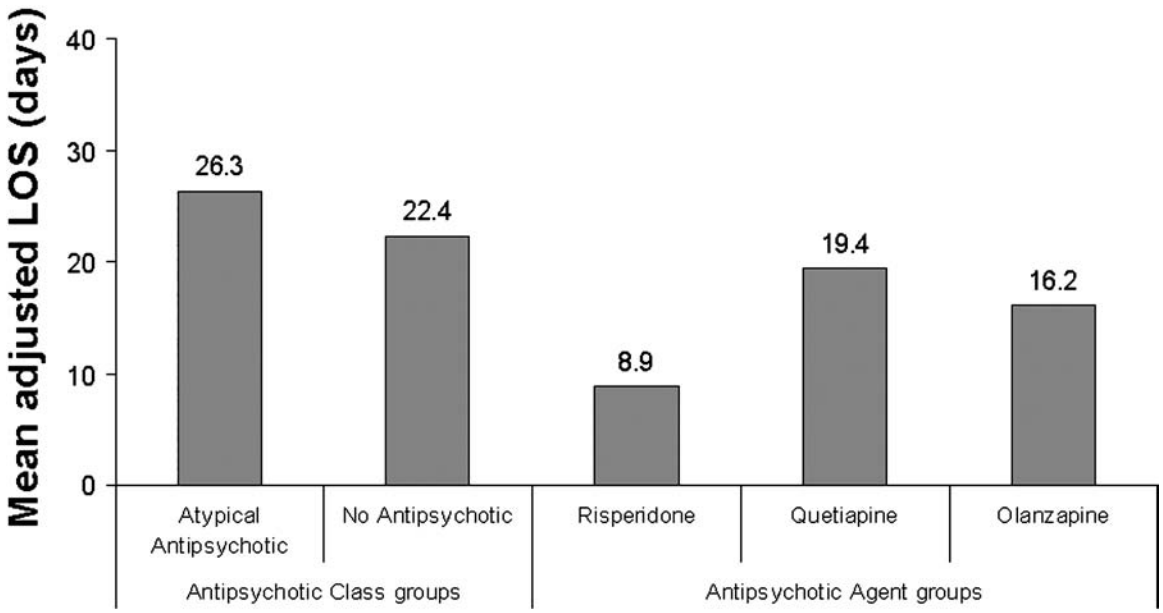

FIG. 4. Adjusted* length of inpatient stay. Patients with LOS > 365 days were excluded from analysis. *ANCOVA analysis. **Significant difference between antipsychotic class groups ($p < 0.04$). p values adjusted for substance-related disorder and payor type. ‡Significantly shorter than quetiapine ($p < 0.001$) and olanzapine ($p < 0.002$) groups. p values for antipsychotic treatment group differences in an ANCOVA model were adjusted for substance-related disorder and gender. LOS = length of stay; ANCOVA = analysis of covariance.

those not receiving antipsychotics. LOS was a significant predictor of change in weight ($B = 0.06$, $p < 0.001$). The mean weight changes by atypical antipsychotics were as follows: risperidone group, +0.91 kg, olanzapine group, +1.5 kg, and quetiapine group, +1.27 kg. A crude estimate of the weekly weight gain was calculated to account for differences in adjusted LOS: risperidone group, +0.72 kg/week, olanzapine group +0.65 kg/week, and quetiapine +0.49 kg/week. This estimate is highly conservative, given that the duration of therapy on the discharge medication is unknown.

DISCUSSION

In case reports and prospective studies, AAs have shown promise in the treatment of psychotic disorders as well as mood disorders, tic disorders, and disruptive behavior disorders, in addition to aggressive behavior across multiple diagnoses (Schur et al. 2003; Findling and McNamara 2004), and available data on the safety and efficacy of these agents continues to grow. In this retrospective analysis of child and adolescent inpatients, we found that patients discharged on an atypical antipsychotic demonstrated greater disease severity at admission than those not receiving antipsychotics, as shown by differences in GAF scores (level of functioning) and BPRS-C scores (symptom severity). AA-treated inpatients also had a history of mental health problems as measured by a higher number of mental health outpatient visits during the 6 months prior to admission. Our analysis also revealed that patients discharged on an AAs generally had a longer length of stays during their hospitalizations and were also more likely to be restrained or secluded during this period than those patients not receiving an atypical antipsychotic, suggesting that these behavioral symptoms required more intensive interventions, both behavioral and medication treatments, over a longer period of time.

These results are consistent with those from a study of medication practices (Kaplan and Busner 1997), in which adolescent inpatients who were treated with psychotropic drugs had significantly longer LOS ($p \leq 0.0001$) than non-

medicated patients. Overall, these results support the hypothesis that clinicians tend to prescribe AAs more frequently to patients with greater disease severity, and that these treatments are targeted toward specific debilitating symptoms for which clinicians are attempting to select the appropriate medication. The data also suggest that clinicians are prescribing an AA in patients whose diagnoses require longer duration of hospitalization. However, the rate of concurrent psychotropic medications prescribed at discharge was similar between groups, even when adjusting for covariates.

Similar to other publications regarding real-world AA utilization (Pappadopulos et al. 2002; Kelly et al. 2004), use of AAs in this study population was reflective of a wide variation in treatment patterns and diagnoses, including the broad use of AAs for psychotic (schizophrenia, psychotic disorder) and nonpsychotic disorders. It is possible that the underlying dimension of agitation rather than the diagnoses themselves were the basis of treatment, because AAs were prescribed for a broad range of potentially nonpsychotic disorders, including depressive disorder, bipolar disorder, impulse-control disorder, adjustment disorder, anxiety disorder, ADHD, substance-related disorders, pervasive developmental disorder, and tic disorders. It should be also recognized that admission diagnoses may not accurately reflect the child's true disorders, and preliminary admission diagnoses require confirmation with continued clinical observation. It is also true that assessments were not standardized, the relationship of admission/discharge diagnoses to structured assessments was questionable, and it is probable that admission diagnoses may have been influenced by reimbursement requirements. However, these data represent real-world findings and a clear need for evidence-based guidelines for the use of psychotropic medications in the pediatric population (Cheng-Shannon et al. 2004).

Patients receiving AAs were more likely to be male than those not receiving antipsychotics, a finding consistent with previous reports (Patel et al. 2002; Martin and Leslie 2003a; Martin et al. 2003; Lekhwani et al. 2004). Male patients may be more likely to exhibit aggression as a feature of disease, a behavior for which AAs have demonstrated efficacy in certain disorders. Alternately, certain disorders preferentially treated with AAs may be more prevalent in males (Costello et al. 1996).

Because of the lower risk of neurological side effects, the atypical antipsychotics have replaced the typical antipsychotics in the psychopharmacological treatment of adults and children alike. Although our study only evaluated clinical outcomes for risperidone, olanzapine, and quetiapine, the clinical trial literature supporting atypical antipsychotic use in children is limited. Most studies involve risperidone, which has been examined in both open-label and placebo-controlled trials in children with pervasive developmental disorders and disruptive behavior disorders. Risperidone has been recently approved for the treatment of irritability associated with autistic disorder in children and adolescents (McCracken et al. 2002; Pandina et al. 2006; Risperdal®, prescribing information, 2006). Data from a large-scale, multicenter trial showed that risperidone was effective in reducing serious behavioral problems such as tantrums, aggression, and self-injury in children with autism (Research Units on Pediatric Psychopharmacology Autism Network 2002). These gains were stable over 6 months of observation; symptoms returned when the medication was discontinued (Reseach Units on Pediatric Psychopharmacology Autism Network 2002). Secondary analyses also indicate that risperidone is associated with moderate reductions in repetitive behavior as well (McDougle et al. 2005).

An emerging concern with the atypical antipsychotics is weight gain and the potential for related health effects. For example, in the 2002 RUPP Autism Network trial with risperidone, children in the risperidone group gained 2.7 kg in the first 8 weeks compared with 0.8 kg in the placebo group (Research Units on Pediatric Psychopharmacology Autism Network 2002). Sixty three children were followed for 6 months of treatment and over this period of time, the children had an average weight gain of 5.6 kg (Martin 2004). In a 12-week, open-label study of 25 children receiving olanzapine, the average weight gain was 4.7 kg (Kemner et al. 2002). In another open-label trial of olanzapine, 22 children who were treated for 8 weeks gained

an average of 5.0 kg (Frazier et al. 2001). Shaw et al. (2001) found that 15 adolescents ages 13–17 who were treated with open-label quetiapine for 8 weeks experienced weight gain, an average of 3.4 kg, based on corrections for expected weight gain.

In our study, patients receiving AAs gained 1.05 kg on average compared with 0.64 kg in those not receiving antipsychotics. However, after adjustment for LOS, there was no difference in weight gain between the two groups. The lack of significant difference could be also explained by variability of the body weight data; parent report, rather than a direct assessment of admission weight by a caregiver, was used to collect some of the data. This finding cannot minimize the importance of continued clinical attention to weight and nutrition, especially during extended inpatient treatment. Based on the growing concerns about weight gain, baseline checks, and periodic monitoring of glucose and blood lipids are now recommended for adults with certain risk factors, it is prudent to consider employing these guidelines when treating children with similar risk factors

Comparisons between antipsychotic agents

There was evidence for a number of differences between the different AA treatments (olanzapine, quetiapine, and risperidone). However, these differences must be understood in the context of the real-world setting in which patients were treated. For example, it is possible that patients may have been switched between agents or may have been prescribed multiple treatments. Furthermore, patients had varying diagnoses.

Differences in this study were found with regard to the spectrum of disorders treated by the three AAs studied. Compared with olanzapine and quetiapine, risperidone was significantly more likely to be prescribed for impulse-control disorder, ADHD, and adjustment disorder, but significantly less likely to be used for depressive disorder or bipolar disorder. Quetiapine, relative to risperidone and olanzapine, was significantly more likely to be used in substance-related disorders. These real-world patterns of utilization need to be explored further.

Few studies have examined the pharmacoeconomic implications of pediatric AA use, despite documentation that prescription drugs represent the fastest-growing component of health-care costs across all ages (Martin and Leslie 2003b). A study of privately insured youth found that medication costs increased by 12.1% during the period 1997–2000, in the face of decreases in both outpatient and inpatient psychiatric costs (Martin and Leslie 2003a). In addition to direct medication costs, overall treatment costs may be profoundly affected by efficacy, which may influence the frequency and length of hospitalizations, the frequency of outpatient visits, and the need for adjunctive medication.

In this study, patients in the risperidone group had significantly shorter LOS, even after controlling for primary diagnosis of substance-related disorder and gender. Risperidone-treated patients were significantly less likely to also receive a psychotropic medication at discharge. Socioeconomic and other influences may impact these decisions and should be examined in future studies. These preliminary retrospective results need to be confirmed with data from prospective head-to-head studies comparing AA efficacy and safety. In addition, studies that provide information on the cost-effectiveness of the different atypical antipsychotics are warranted in pediatric inpatients.

Study limitations

Certain limitations of this study should be considered. In general, the retrospective design has inherent limitations owing to its observational nature, although the findings reflect real-world use of AAs. Our results may have been subjected to uncontrolled confounding because of the use of secondary data that were initially designed for quality improvement purposes. Although selected sampling techniques were used at the facility level, our sample is a sample of convenience based on the inclusion and exclusion criteria for this retrospective analysis. We attempted to control for differences using the multivariate analysis, however clustering by facility or providers within facilities was not assessed in this study. Another limitation

was the validity of assigned clinical diagnoses, especially at admission, as discussed previously in this paper. Individual patients were not tracked for readmission to inpatient units during the study period. As such, it is possible that some of these pediatric inpatients may have been admitted multiple times to these facilities over the 4 years of the study period. Furthermore, while all attempts were made to control for differences among the AA treatment groups, it is possible that other clinical or demographic factors may have influenced the relationship between atypical agents and LOS. Data were available only at admission and discharge, and therefore the inference was made that the medication at discharge was the medication that the patient responded to and received during hospitalization. There was no information on adjunctive psychosocial treatment during hospitalization. We were not able to determine which pediatric inpatients within the atypical agent samples had previously failed another atypical agent and were considered resistant to treatment with a particular medication. Use of an electronic medical record system or other longitudinal medical and pharmacy claims record may provide further clarification of the relationship between atypical agents and LOS.

Although this dataset provided information on primary and secondary diagnoses, we were unable to determine why these children were prescribed an atypical antipsychotic. Clinical practice suggests physicians first consider the identification of a target symptom and then follow up with a selection of medication for that symptom. However, in our study, the underlying reason for these prescriptions may have been different.

Our results are also restricted by limitations within the CQI+ System. In particular, the CQI+ System does not provide a comprehensive assessment of adverse events. Furthermore, a number of variables were not consistently represented in the CQI+ database, which required between-group comparisons to be made on the basis of partial patient sets. This was especially evident in the missing data for the BPRS-C scale. It is not known whether fully capturing the relevant variables for all patients would change the overall findings or their significance. In addition, these results are prone to geographical bias, because a considerable part of the total patient sample in the CQI+ database was from hospitals in the southern or southwestern United States. Therefore, findings cannot be generalized to the U.S. pediatric population.

CONCLUSIONS

This study provides additional information to illustrate the real-world use of AAs in a pediatric inpatient population across a wide spectrum of psychiatric disorders, including nonpsychotic disorders. The results suggest that patients who are severely ill are likely to be prescribed an AA, and that treatment of pediatric inpatients with AAs may be associated with improvement in behavioral symptoms. However, these retrospective results should be considered preliminary and need to be confirmed with data from prospective controlled trials evaluating AA efficacy and safety, including head-to-head comparisons. The present findings underscore the clear need for evidence-based guidelines for the use of psychotropic medications in the pediatric population.

DISCLOSURES

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