Notice of Correction: The text on page 255 (right column, lines 32–35) regarding mean changes in fasting glucose and triglycerides in adolescents versus adults has been corrected.

The Safety of Olanzapine in Adolescents With Schizophrenia or Bipolar I Disorder: A Pooled Analysis of 4 Clinical Trials

Ludmila A. Kryzhanovskaya, M.D., Ph.D.; Carol K. Robertson-Plouch, D.V.M.; Wen Xu, Ph.D.; Janice L. Carlson, Ph.D.; Karen M. Merida, B.S.; and Ralf W. Dittmann, M.D., Ph.D.

Objective: To describe the safety of olanzapine treatment in adolescents (aged 13–17 years) with schizophrenia or bipolar I disorder, and to compare these data with those of olanzapine-treated adults.

Data Sources and Study Selection: Placebo-controlled database, adolescents: acute phase of 2 double-blind, placebo-controlled trials (3–6 weeks; olanzapine, N = 179, mean age = 15.5 years; placebo, N = 89, mean age = 15.7 years); overall adolescent olanzapine exposure database, adolescents: 4 trials (e.g., the 2 aforementioned studies, each with a 26-week open-label extension phase, and 2 open-label, 4.5- and 24-week trials; N = 454, mean age = 15.9 years); and adult database: 84 clinical trials of up to 32 weeks.

Data Synthesis: The mean daily dosage of olanzapine was 10.6 mg/day (exposure = 48,946 patient days). In the overall adolescent olanzapine exposure database, the most common adverse events included increased weight (31.7%), somnolence (19.8%), and increased appetite (17.4%). In up to 32 weeks of treatment, when compared with adults, adolescents from the overall adolescent olanzapine exposure database gained statistically significantly more weight (7.4 kg vs. 3.2 kg, $p < .001$); statistically significantly more adolescents gained ≥ 7% of their baseline weight (65.1% vs. 35.6%, $p < .001$). Adolescents experienced statistically significant within-group baseline-to-endpoint changes in fasting glucose ($p < .001$), total cholesterol ($p = .002$), triglycerides ($p = .007$), and alanine aminotransferase ($p < .001$). Two patients from the overall adolescent olanzapine exposure database (0.4%) attempted suicide; 13 (2.9%) had suicidal ideation. In the placebo-controlled database, adolescents had statistically significant baseline-to-endpoint increases in prolactin (11.4 μg/L, $p < .001$); 47.4% had high prolactin levels.

Conclusions: The types of adverse events in olanzapine-treated adolescents appear to be similar to those of adults. The magnitude and incidence of weight and prolactin changes were greater in adolescents.

Trial Registration: clinicaltrials.gov Identifiers: NCT00051298, NCT00050206, and NCT00113594

J Clin Psychiatry 2009;70(2):247–258

Received June 26, 2007; accepted June 10, 2008. From Lilly Research Laboratories, Eli Lilly and Co., Lilly Corporate Center, Indianapolis, Ind (Drs. Kryzhanovskaya, Robertson-Plouch, Xu, and Carlson and Ms. Merida) and Lilly Deutschland GmbH, Bad Homborg, Germany (Dr. Dittmann).

The reported studies were supported with funding from Eli Lilly and Co.

The authors thank Evelyn Lobo, Ph.D., (Eli Lilly) for her assistance with the study design of HGMF; Gopalan Sethuraman, Ph.D., and Fangyi Zhao, M.S., (Eli Lilly) for their assistance with data analysis; Svetlana Dominguez, B.A., (Eli Lilly) for her editorial assistance with the manuscript; Robert Hauk, B.S., (Eli Lilly) for his assistance with the manuscript submission; and Lori Heath, M.S., and Jeffrey W. Florczak, B.S., (Eli Lilly) for their assistance with the figures.

Drs. Kryzhanovskaya, Robertson-Plouch, Xu, Carlson, and Dittmann and Ms. Merida are employees and stock shareholders of Eli Lilly.

Corresponding author and reprints: Ludmila A. Kryzhanovskaya, M.D., Ph.D., Lilly Research Laboratories, Indianapolis, IN 46285-6156 (e-mail: kryzhanovskayalu@lilly.com).

Estimates of psychotic disorder prevalence in patients < 18 years of age range from 0.4% to 17.0%.[1] Atypical antipsychotics, including olanzapine, are efficacious at treating schizophrenia and bipolar I disorder in adults,[2,3] but few have been approved for the treatment of schizophrenia in adolescents. Despite this fact, atypical antipsychotics are often prescribed for adolescents: the rate of prescriptions has increased in the United States by approximately 140% from 1997 to 2000.[4] Studies in this population are important, as there may be differences in the tolerability of these agents between adolescents and adults. For example, the weight gain that occurs in adults during treatment with antipsychotics[5] may be more pronounced in adolescents.[6–10] However, there is still a lack of large, controlled trials in this population, which would provide essential efficacy and safety data.

Recently, data from 2 double-blind, placebo-controlled trials of olanzapine treatment in adolescents with

Reprinted with correction to page 255.

Table 1. Summary of the 4 Eli Lilly Clinical Trials of Flexible Doses of Olanzapine Treatment[a] in Adolescents With Schizophrenia or Bipolar I Disorder

Study ID	Patient Population[b]	N	Age Range, y	Country	Phase	Duration, wk
HGIN[c,d]	Schizophrenia	107	13–17	United States, Russia	Acute, open-label	6, 26
HGIU[c,e]	Bipolar I disorder	161	13–17	United States, Puerto Rico	Acute, open-label	3, 26
HGMF[f]	Schizophrenia, bipolar I disorder	107	13–17	United States, Puerto Rico, Russia	Open-label	4.5
LOAY[g,h]	Schizophrenia, schizophreniform disorder, schizoaffective disorder	89	13–17	Germany	Open-label	24

[a]2.5–20.0 mg/day in studies HGIN, HGIU, and HGMF; 5.0–20.0 mg/day in study LOAY.
[b]Diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision.
[c]Studies HGIN and HGIU were combined to create the placebo-controlled database (olanzapine, N = 179; placebo, N = 89).
[d]Data from Kryzhanovskaya et al.[12]
[e]Data from Tohen et al.[11]
[f]Data from E. Lobo, Ph.D., written communication, Jan. 2007.
[g]Data from Dittmann et al.[13]
[h]Study LOAY enrolled patients from 12–21 years of age (total N = 96); only those patients aged 13 to 17 years were included in this analysis.

schizophrenia or bipolar I disorder suggested that although the types of adverse events that occur in adolescents treated with olanzapine are similar to those of adults, the magnitude and incidence of weight gain and hyperprolactinemia may be greater in adolescents.[11–13] However, without direct comparisons with adult data, it is difficult to ascertain the extent of these differences. The safety of olanzapine has been extensively studied in trials in adults,[2,3] but very few systematic studies in adolescents have been conducted. Of those, the available data come from studies of relatively small sample sizes[14–16] or case study reports.[7,17] While this information is helpful, data from a larger sample might assist to identify and better define tolerability issues of olanzapine treatment for adolescents.

In this analysis, we present data pooled from 4 clinical trials of olanzapine in adolescents with schizophrenia or bipolar I disorder treated for up to 32 weeks. The adolescent data were compared with the data pooled from up to 84 clinical trials of adults with schizophrenia or bipolar I disorder treated with olanzapine. To our knowledge, this is the first pooled clinical trial data article on the safety of olanzapine treatment in patients < 18 years.

METHOD

Overview of Studies

Data were pooled from 4 clinical trials of olanzapine in adolescents (F1D-MC-HGIN [HGIN],[12] F1D-MC-HGIU [HGIU],[11] F1D-MC-HGMF [HGMF] [E. Lobo, Ph.D., written communication, Jan. 2007], and F1D-SB-LOAY, [LOAY][13]) conducted by Eli Lilly and Company in Germany, Puerto Rico, Russia, and the United States (from March 1999 to March 2006; Table 1). Consent forms were signed by the patients and/or guardians in each study, and review board approval was granted for each study.

Study HGIN was designed to examine the safety and efficacy of olanzapine in adolescents (aged 13–17 years) with schizophrenia. It consisted of 3 periods: (1) a 2- to 14-day screening and washout period; (2) a 6-week, double-blind, acute period of olanzapine or placebo treatment; and (3) an optional 26-week, open-label period of olanzapine treatment. For the placebo-controlled phase, patients were randomly assigned in a 2:1 ratio to either olanzapine (2.5–20.0 mg/day) or placebo.

Study HGIU was designed to examine the efficacy and safety of olanzapine in adolescents (aged 13–17 years) with bipolar I disorder. It consisted of 3 periods: (1) a 2- to 14-day screening and washout period; (2) a 3-week, double-blind, acute period of olanzapine or placebo treatment; and (3) an optional 26-week, open-label period of olanzapine treatment. For the placebo-controlled phase, patients were randomly assigned in a 2:1 ratio to either olanzapine (2.5–20.0 mg/day) or placebo.

Study HGMF was an open-label study designed to examine the population pharmacokinetics of olanzapine in adolescents (aged 13–17 years) with schizophrenia or bipolar I disorder. It consisted of 2 periods: (1) a 2- to 14-day screening and washout period and (2) a 4.5-week, open-label period of olanzapine treatment (2.5–20.0 mg/day).

Study LOAY was an open-label study to evaluate the efficacy and tolerability of olanzapine (5.0–20.0 mg/day) in adolescents and young adults (aged 12–21 years) with schizophrenia, schizophreniform disorder, or schizoaffective disorder. It consisted of 3 periods: (1) a 2- to 14-day screening and washout period; (2) a 6-week, open-label period of olanzapine treatment; and (3) an 18-week, open-label period of olanzapine treatment for responders at the end of study period II only (defined as a ≥ 30% decrease from baseline on the Brief Psychiatric Rating Scale-Anchored Version for Children[18]). Only patients aged 13 to < 18 years were included in this analysis.

In all 4 studies' washout periods, all previous antipsychotic drugs were tapered so that patients were free of psychotropic medications for at least 2 days before randomization. Diagnoses were made using the *Diagnostic*

Reprinted with correction to page 255.

and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. In studies HGIN, HGIU, and HGMF, diagnoses were confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version.[19]

Databases

Two adolescent databases were created from the pooled adolescent data. The placebo-controlled database included data from olanzapine-treated and placebo-treated adolescents from the double-blind placebo-controlled phases of studies HGIN and HGIU. The overall adolescent olanzapine exposure database included data from olanzapine-treated patients from all 4 studies. Safety data (weight, metabolic parameters, prolactin, etc.) from the overall adolescent olanzapine exposure database were compared with a third database of adult data, created by pooling data from up to 84 olanzapine clinical trials of adults with schizophrenia or bipolar I disorder (data on file, Eli Lilly and Co., Indianapolis, Ind., 2007). The maximum length of the adolescent trials was 32 weeks; for the adult trials, the data cutoff was 32 weeks to allow for comparison with the adolescent database. Four adult studies collected fasting glucose and lipids and were pooled for comparison with adolescents; 30 adult studies collected prolactin and were pooled for the comparison.

Treatments

In studies HGIN, HGIU, and HGMF, the starting dosage of olanzapine was 2.5 or 5.0 mg/day and could be increased (to a maximum dose of 20.0 mg/day) or decreased by 2.5- or 5.0-mg/day increments at the investigator's discretion. The dosage was titrated to at least 10.0 mg/day by the third week, provided there were no tolerability issues. Doses would continue to be increased to the highest tolerated dose, if there were no tolerability concerns. Dose adjustments were allowed at any time in any number of increments/decrements. Patients unable to tolerate the minimum dose (2.5 mg/day) were discontinued from the study. The starting dose in study LOAY was 10.0 mg/day. The mean daily dosage of olanzapine for all studies was 10.6 mg/day (exposure = 48,946 patient days).

Safety Measures in the 4 Adolescent Studies

Treatment-emergent adverse events, laboratory test results, vital signs, weight, electrocardiograms (from studies HGIN, HGIU, and HGMF only), and extrapyramidal symptoms (EPS; from studies HGIN, HGIU, and HGMF only) were monitored. Laboratory tests included clinical chemistry, electrolyte levels, lipid levels, prolactin levels, and hematology panels. These tests were performed at protocol-specified time points, when clinically indicated, and any time a patient completed the study period or discontinued from the study. Fasting (≥ 8 hours) glucose and lipid data were collected at baseline, acute endpoint or discontinuation, and open-label endpoint or discontinuation in studies HGIN, HGIU, and HGMF. In study LOAY, nonfasting samples were taken at baseline, week 8 of treatment, and study endpoint or discontinuation.

Treatment-emergent adverse events, including suicidality and hostility-related events, were defined using the Medical Dictionary for Regulatory Activities (MedDRA; Northrop Grumman MedDRA, Chantilly, Virginia; available at http://www.meddramsso.com/MSSOWeb/index.htm) preferred terms. Treatment-emergent high and low laboratory values were defined as a change from low or normal at any time before olanzapine treatment to high or low, respectively, at any time after baseline. Treatment-emergent high prolactin levels were defined using the following sex- and age-specific reference ranges: male patients aged 12 to < 14 years, ≥ 24 μg/L; male patients ≥ 14 years, ≥ 16.1 μg/L; female patients 12 to < 14 years, ≥ 16.9 μg/L; and female patients ≥ 14 years, ≥ 39 μg/L.[20] Lipid and glucose categories were defined using National Cholesterol Education Program (NCEP)[21] and American Diabetes Association[22] criteria, respectively. Elevations in alanine aminotransferase (ALT) were examined in the following ranges: less than 1, 3, and 5 times the upper limit of the laboratory reference range at baseline to greater than 1, 3, and 5 times the upper limit of the laboratory reference range, respectively. Potentially clinically significant weight gain was defined as weight gain ≥ 7% of baseline weight.

Vital signs were monitored at each visit; height was measured at baseline, at various visits throughout the studies, and at the discontinuation visit. Weight was measured at each visit. An electrocardiogram was recorded at enrollment and endpoint or study discontinuation visit. QT intervals were corrected for heart rate using Bazett's and Fridericia's formulae. In studies HGIN, HGIU, and HGMF, EPS were assessed by observation and administration of the Barnes Akathisia Scale (BAS),[23] the Simpson-Angus Scale,[24] and the Abnormal Involuntary Movement Scale (AIMS)[25]; in study LOAY, EPS were assessed using the Simpson-Angus Scale only. Baseline was defined as the beginning of olanzapine treatment.

Statistical Analyses

Placebo-controlled database. All data were analyzed on an intent-to-treat basis. Baseline characteristics and mean changes in weight, lipids, prolactin, and EPS were compared between the treatment groups using a type III sum of squares analysis of variance, with country, therapy, and protocol as independent factors. Frequencies of baseline characteristics, discontinuation, serious adverse events, and categories of abnormal lipids, hepatic enzymes, and prolactin were analyzed using Fisher exact test. The relative risk of suicidal behaviors was compared using Mantel-Haenszel risk difference stratified by study.[26]

Reprinted with correction to page 255.

Table 2. Baseline Characteristics of Adolescents With Schizophrenia or Bipolar I Disorder in the Placebo-Controlled and Overall Adolescent Olanzapine Exposure Databases

Characteristic	Placebo-Controlled Database			Overall Adolescent Olanzapine Exposure Database (2.5–20.0 mg/d), N = 454
	Olanzapine (2.5–20.0 mg/d), N = 179	Placebo, N = 89	p Value[a]	
Male, N (%)	112 (62.6)	48 (53.9)	.188	286 (63.0)
Age, mean (SD), y[b]	15.5 (1.4)	15.7 (1.4)	.200	15.9 (1.4)
Schizophrenia, N (%)	119 (66.5)	35 (39.3)	…	227 (50.0)
Ethnic origin, N (%)[c]			.359	
White	123 (68.7)	66 (74.2)	…	355 (78.2)
African descent	30 (16.8)	9 (10.1)	…	50 (11.0)
Asian[d]	0 (0.0)	1 (1.1)	…	1 (0.2)
Hispanic	20 (11.2)	9 (10.1)	…	37 (8.2)
Other	6 (3.4)	4 (4.5)	…	11 (2.4)
Country, N (%)[c]			1.00	
United States	133 (74.3)	67 (75.3)	…	263 (57.9)
Germany	0 (0.0)	0 (0.0)	…	89 (19.6)
Russia	34 (19.0)	16 (18.0)	…	80 (17.6)
Puerto Rico	12 (6.7)	6 (6.7)	…	22 (4.9)

[a]Frequencies analyzed using Fisher exact test.
[b]Means analyzed using a type III sum of squares analysis of variance, with country, therapy, and protocol as independent factors.
[c]Percentages may not equal 100, due to rounding.
[d]Includes East and Southeast Asian.
Symbol: … = not applicable.

Overall adolescent olanzapine exposure database. Mean changes in laboratory values, vital signs, and metabolic parameters were analyzed using a 1-sample t test. Mean changes in weight, metabolic parameters, and prolactin in adolescents were compared with those in the adult database with an analysis of covariance, with baseline and population as independent factors. Incidence of weight gain and abnormal levels of lipids, glucose, and prolactin in adolescents were compared with those of adults using Fisher exact test. Changes in weight, height, and body mass index (BMI) in olanzapine-treated adolescents were compared with standardized growth curves from the United States[27] using z scores.

All analyses were tested using a 2-sided α level of .05. SAS software version 8.2 (SAS Institute Inc., Cary, N.C.) was used to perform all statistical analyses.

RESULTS

Patient Characteristics

The placebo-controlled database included 268 patients (olanzapine, N = 179; placebo, N = 89), and the overall adolescent olanzapine exposure database included 454 patients. The mean (SD) age of patients in the placebo-controlled database was 15.5 (1.4) years in the olanzapine and 15.7 (1.4) years in the placebo treatment groups; mean (SD) age in the overall adolescent olanzapine exposure database was 15.9 (1.4) years. The majority of the adolescents in both databases were male, white, and from the United States; most patients in the placebo-controlled database had a diagnosis of bipolar I disorder (60.1% [161/268]). Adolescents with schizophrenia or bipolar I disorder were equally represented in the overall adolescent olanzapine exposure database (50.0%; 227/454 each). In the placebo-controlled database, there were no significant differences in baseline characteristics between the 2 treatment groups (Table 2).

The mean modal dosage of olanzapine in the placebo-controlled database was 11.5 mg/day (mean exposure = 26.7 days); in the overall adolescent olanzapine exposure database, it was 11.4 mg/day (mean exposure = 108 days). In the placebo-controlled database, 4.5% (8/179) of olanzapine-treated and 1.1% (1/89, p = .279) of placebo-treated patients discontinued treatment due to an adverse event; in the overall adolescent olanzapine exposure database, 11.2% (51/454) of olanzapine-treated patients discontinued due to an adverse event, with the most common being weight increased (4.0%) and pregnancy (1.2%).

Treatment-Emergent Adverse Events

In the placebo-controlled database, treatment-emergent adverse events occurring significantly more often in olanzapine-treated compared with placebo-treated patients were weight increased (29.6% [53/179] vs. 5.6% [5/89], p < .001), somnolence (24.6% [44/179] vs. 3.4% [3/89], p < .001), increased appetite (24.0% [43/179] vs. 5.6% [5/89], p < .001), and sedation (19.0% [34/179] vs. 5.6% [5/89], p = .003) (Table 3). The most common adverse events occurring in olanzapine-treated patients in the overall adolescent olanzapine exposure database included increased weight (31.7% [144/454]), somnolence (19.8% [90/454]), increased appetite (17.4% [79/454]), headache (16.7% [76/454]), and sedation (14.1% [64/454]). In the placebo-controlled database, 3.4% (6/179) of olanzapine-treated versus 1.1% (1/89) of placebo-treated patients experienced ≥ 1 serious adverse event (p = .431). The most common MedDRA serious

Reprinted with correction to page 255.

Table 3. Treatment-Emergent Adverse Events Occurring Significantly More Often in Olanzapine-Treated Compared With Placebo-Treated Adolescents With Schizophrenia or Bipolar I Disorder in the Placebo-Controlled Database and in ≥ 5% of Olanzapine-Treated Adolescents in the Overall Adolescent Olanzapine Exposure Database

	Placebo-Controlled Database			Overall Adolescent Olanzapine
Treatment-Emergent Adverse Event	Olanzapine (N = 179), N (%)	Placebo (N = 89), N (%)	p Value[a]	Exposure Database (N = 454), N (%)
Weight increased	53 (29.6)	5 (5.6)	< .001	144 (31.7)
Somnolence	44 (24.6)	3 (3.4)	< .001	90 (19.8)
Increased appetite	43 (24.0)	5 (5.6)	< .001	79 (17.4)
Sedation	34 (19.0)	5 (5.6)	.003	64 (14.1)
Dry mouth	11 (6.1)	0 (0.0)	.018	…
Headache	…	…	…	76 (16.7)
Fatigue	…	…	…	43 (9.5)
Dizziness	…	…	…	29 (6.4)
Nausea	…	…	…	29 (6.4)
Vomiting	…	…	…	27 (5.9)
Tremor	…	…	…	26 (5.7)
Upper abdominal pain	…	…	…	23 (5.1)
Nasopharyngitis	…	…	…	23 (5.1)
Upper respiratory tract infection	…	…	…	23 (5.1)

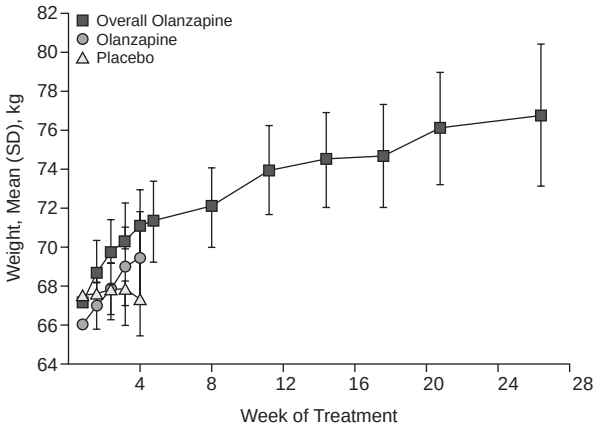
[a]Analyzed using Fisher exact test.
Symbol: … = not applicable.

adverse event terms reported in olanzapine-treated patients in this database included worsening of bipolar disorder (0.6% [1/179]) and worsening of bipolar I disorder (0.6% [1/179]). In the overall adolescent olanzapine exposure database, 7.7% (35/454) of olanzapine-treated adolescents experienced ≥ 1 serious adverse event, which included worsening of bipolar I disorder (1.8% [8/454]), worsening of schizophrenia (1.3% [6/454]), worsening of bipolar disorder (0.9% [4/454]), and aggression (0.7% [3/454]).

Weight Gain

Olanzapine-treated patients in the placebo-controlled database gained statistically significantly more weight from baseline to endpoint compared with those treated with placebo (3.9 kg vs. 0.2 kg, $p < .001$). Mean weight gain by week in patients in both the placebo-controlled and overall adolescent olanzapine exposure databases is shown in Figure 1. When compared with olanzapine-treated patients from the adult database, olanzapine-treated adolescents in the overall adolescent olanzapine exposure database (treated for up to 32 weeks) gained statistically significantly more weight from baseline to endpoint (7.4 kg [N = 450] vs. 3.2 kg [N = 7847], $p < .001$). In addition, 4.0% of adolescents in the overall adolescent olanzapine exposure database compared with 0.3% of adults in the adult database discontinued treatment due to weight gain. When compared with U.S. standardized growth curves,[26] olanzapine-treated adolescents in the overall adolescent olanzapine exposure database had statistically significantly greater baseline-to-endpoint increases in mean weight, mean height, and mean BMI. The mean changes in the standardized percentiles and z scores were also statistically significant. Olanzapine-treated adolescents in the overall adolescent olanzapine exposure database experienced an 11.8 percentile point increase in weight ($p < .001$), a 1.5 percentile point increase in height ($p < .001$), and a 13.3 percentile point increase in BMI ($p < .001$).

Figure 1. Weight (by week) of Adolescent Patients With Schizophrenia or Bipolar I Disorder Treated With Olanzapine or Placebo[a,b,c]



[a]The placebo-controlled database: olanzapine, N = 179; placebo, N = 89, LOCF; the overall adolescent olanzapine exposure database: only those patients who remained in the study for ≥ 24 weeks.
[b]The error bars represent standard deviations.
[c]For the overall olanzapine database, week 1, N = 448; week 2, N = 440; week 3, N = 331; week 4, N = 400; week ≤ 5, N = 314; weeks > 5– ≤ 9, N = 287; weeks > 9– ≤ 13, N = 238; weeks > 13– ≤ 17, N = 217; weeks > 17– ≤ 21, N = 190; weeks > 21– ≤ 25, N = 174; weeks > 25– ≤ 32, N = 131.

Significantly more olanzapine-treated adolescents in the overall adolescent olanzapine exposure database gained ≥ 7% of their baseline body weight at any time during treatment compared with olanzapine-treated adults (65.1% [293/450] vs. 35.6% [2794/7847], $p < .001$). One

Reprinted with correction to page 255.

Table 4. Mean Changes From Baseline to Endpoint in Glucose, Lipid Parameters, Hepatic Parameters, and Prolactin at Any Time During Olanzapine (2.5–20.0 mg/day) or Placebo Treatment in Adolescents With Schizophrenia or Bipolar I Disorder

	Placebo-Controlled Database			Olanzapine Adolescents[a] vs Adults		
Parameter	Olanzapine, Mean Change (SD)	Placebo, Mean Change (SD)	p Value[b]	Adolescents, Mean Change (SD)	Adults, Mean Change (SD)	p Value[c]
Metabolic parameter, mmol/L						
Glucose, fasting	0.2 (0.6)	–0.2 (0.6)	< .001	0.1 (0.7)	0.3 (1.8)	.002
Cholesterol, total	0.3 (0.6)	0.0 (0.7)	.002	0.2 (0.7)	0.0 (0.9)	.305
LDL	0.2 (0.5)	0.0 (0.6)	.109	0.2 (0.6)	0.0 (0.8)	.917
HDL	0.0 (0.2)	0.0 (0.3)	.751	–0.1 (0.2)	–0.1 (0.3)	.519
Triglycerides	0.3 (0.9)	–0.1 (0.6)	.007	0.3 (0.9)	0.2 (1.4)	.007
Hepatic parameters						
ALT, U/L	20.0 (54.8)	–3.1 (11.7)	< .001	21.4 (82.7)	…	< .001[d]
AST, U/L	6.4 (26.4)	–2.5 (7.5)	.002	9.0 (54.6)	…	< .001[d]
GGT, U/L	7.5 (20.0)	–0.4 (6.0)	< .001	8.2 (32.4)	…	< .001[d]
Bilirubin, total, µmol/L	–1.7 (3.8)	0.8 (6.0)	< .001	–1.1 (4.6)	…	< .001[d]
Alkaline phosphatase, U/L	1.4 (25.6)	–4.0 (16.6)	.396	4.4 (18.2)	…	< .001[d]
Prolactin, µg/L	11.4 (14.5)	–0.2 (10.7)	< .001	23.0 (83.7)	–4.2 (125.6)	.004

[a]From the overall adolescent olanzapine exposure database.
[b]Analyzed using a type III sum of squares analysis of variance (ANOVA); model = protocol × country × therapy.
[c]Analyzed using a type III sum of squares ANOVA; model = population × baseline.
[d]Analyzed using a 1-sample t test.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltransferase, HDL = high-density lipoproteins, LDL = low-density lipoproteins.
Symbol: … = not applicable.

olanzapine-treated adolescent in the placebo-controlled database discontinued treatment due to increased weight, whereas none of the placebo-treated adolescents did (0.6% vs. 0.0%, p = 1.00); in the overall adolescent olanzapine exposure database, 18 (4.0%) of the 454 olanzapine-treated patients discontinued treatment due to increased weight.

Glucose and Lipids

In the placebo-controlled database, olanzapine-treated adolescents experienced statistically significantly greater baseline-to-endpoint mean increases in fasting glucose (p < .001), total cholesterol (p = .002), and fasting triglycerides (p = .007) compared with placebo-treated adolescents. No significant differences between the treatment groups were observed in baseline-to-endpoint mean changes in levels of low-density lipoproteins (LDL; p = .109) or high-density lipoproteins (p = .751; Table 4).

In the overall adolescent olanzapine exposure database, olanzapine-treated adolescents experienced statistically significant baseline-to-endpoint mean changes in all metabolic parameters (Table 4). When compared with olanzapine-treated adolescents in the overall adolescent olanzapine exposure database, olanzapine-treated adults had statistically significantly greater baseline-to-endpoint mean changes in fasting glucose (p = .002); mean changes from baseline to endpoint in fasting triglycerides were also statistically significantly different between olanzapine-treated adolescents and adults (p = .007), with the latter experiencing smaller increases. No other statistically significant differences were observed between adolescents and adults (Table 4).

In the placebo-controlled database, statistically significantly more olanzapine-treated compared with placebo-treated adolescents developed treatment-emergent changes from normal to borderline total cholesterol at any time during treatment (p = .039; Table 5). Significantly more olanzapine-treated adults compared with olanzapine-treated adolescents from the overall adolescent olanzapine exposure database had treatment-emergent changes from normal to high (p = .033) and normal/impaired to high (p < .001) glucose, normal to borderline (p < .001) and normal to high (p = .001) total cholesterol, normal to borderline (p < .001) and normal to high (p = .014) LDL cholesterol, and normal to borderline (p < .001) and normal to high (p = .030) triglycerides at any time during treatment (Table 5). The percentages of adolescents in the overall adolescent olanzapine exposure database (N = 454) who experienced lipid-related adverse events were as follows: blood cholesterol increased, 0.4%; blood triglycerides increased, 2.4%; hypercholesterolemia, 0.4%; and hypertriglyceridemia, 0.4%.

Hepatic Parameters

In the placebo-controlled database, olanzapine-treated adolescents, compared with adolescents in the placebo group, had statistically significantly greater baseline-to-endpoint changes in ALT (p < .001), aspartate aminotransferase (AST; p = .002), γ-glutamyltransferase (GGT; p < .001), and total bilirubin (p < .001) levels. No significant difference between the groups was observed in baseline-to-endpoint mean changes in the alkaline phosphatase levels (p = .396; Table 4). Mean changes in ALT, AST, and GGT are presented in Figure 2.

Reprinted with correction to page 255.

Table 5. Incidence of Categorical Changes in Glucose, Lipid Parameters, Hepatic Parameters, and Prolactin at Any Time During Olanzapine (2.5–20.0 mg/day) or Placebo Treatment in Adolescents With Schizophrenia or Bipolar I Disorder

	Placebo-Controlled Database			Olanzapine Adolescents[a] vs Adults		
Parameter	Olanzapine, N/N (%)	Placebo, N/N (%)	p Value[b]	Adolescents, N/N (%)	Adults, N/N (%)	p Value[b]
Metabolic parameter[c]						
Glucose						
Normal to high (< 100 to ≥ 126 mg/dL)	0/122 (0.0)	1/51 (2.0)	.295	3/251 (1.2)	12/251 (4.8)	.033
Impaired to high (≥ 100 and < 126 to ≥ 126 mg/dL)	2/13 (15.4)	0/13 (0.0)	.480	6/47 (12.8)	32/121 (26.4)	.066
Normal/impaired to high (< 126 mg/dL to ≥ 126 mg/dL)	2/135 (1.5)	1/64 (1.6)	1.00	9/298 (3.0)	44/372 (11.8)	< .001
Total cholesterol						
Normal to borderline (< 200 to ≥ 200 and < 240 mg/dL)	19/121 (15.7)	2/55 (3.6)	.023	54/262 (20.6)	82/216 (38.0)	< .001
Normal to high (< 200 to ≥ 240 mg/dL)	2/121 (1.7)	0/55 (0.0)	1.00	3/262 (1.1)	15/216 (6.9)	.001
Low-density lipoproteins						
Normal to borderline (< 130 to ≥ 130 and < 160 mg/dL)	17/124 (13.7)	2/52 (3.8)	0.64	48/270 (17.8)	75/241 (31.1)	< .001
Normal to high (< 130 to ≥ 160 mg/dL)	2/124 (1.6)	0/52 (0.0)	1.00	4/270 (1.5)	14/241 (5.8)	.014
High-density lipoproteins, normal to low (≥ 50 to < 40 mg/dL)	2/45 (4.4)	2/21 (9.5)	.587	10/107 (9.3)	28/155 (18.1)	.052
Triglycerides						
Normal to borderline (< 150 to ≥ 150 and < 200 mg/dL)	21/113 (18.6)	4/53 (7.5)	.101	51/247 (20.6)	91/253 (36.0)	< .001
Normal to high (< 150 to ≥ 200 mg/dL)	14/113 (12.4)	1/53 (1.9)	.039	43/247 (17.4)	65/253 (25.7)	.030
Normal to extremely high (< 150 to ≥ 500 mg/dL)	0/113 (0.0)	0/53 (0.0)	…	1/247 (0.4)	1/253 (0.4)	1.00
Hepatic parameter (≥ 1 times the upper limit of normal)						
ALT	59/153 (38.6)	2/79 (2.5)	< .001	169/396 (42.7)	…	…
AST	45/163 (27.6)	3/79 (3.8)	< .001	127/418 (30.4)	…	…
GGT	17/169 (10.1)	1/83 (1.2)	.008	34/432 (7.9)	…	…
Bilirubin, total	0/170 (0.0)	6/45 (13.3)	.001	9/423 (2.1)	…	…
Alkaline phosphatase	11/159 (6.9)	2/77 (2.6)	.231	51/387 (13.2)	…	…
Prolactin	55/116 (47.4)	4/59 (6.8)	< .001	172/310 (55.5)	889/3062 (29.0)	< .001

[a]From the overall adolescent olanzapine exposure database.
[b]Analyzed using Fisher exact test.
[c]Categories defined by National Cholesterol Education Program[21] and American Diabetes Association[22] criteria.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltransferase.
Symbol: … = not applicable.

In the placebo-controlled database, the incidence of parameter elevation greater than 1 times the upper limit of normal for each parameter was statistically significantly greater in olanzapine-treated compared with placebo-treated adolescents for ALT ($p < .001$), AST ($p < .001$), and GGT ($p = .008$). Significantly fewer olanzapine-treated compared with placebo-treated adolescents had high bilirubin ($p = .001$); the incidence of high alkaline phosphatase did not differ between the treatment groups ($p = .231$; Table 5). Statistically significantly more olanzapine-treated compared with placebo-treated adolescents experienced ALT levels greater than 3 times the upper limit of normal (12.1% [21/174] vs. 2.3% [2/87], $p = .009$). In the overall adolescent olanzapine exposure database, the incidence of hepatic parameter elevation greater than 1 times the upper limit of normal for each parameter was 42.7% for ALT, 30.4% for AST, 7.9% for GGT, 2.1% for total bilirubin, and 13.2% for alkaline phosphatase. A total of 8 patients discontinued olanzapine treatment in the overall adolescent olanzapine exposure database due to the following hepatic-related adverse events: ALT increased (N = 2), AST increased (N = 1), hepatic enzymes increased (N = 2), abnormal liver function test (N = 2), and transaminase increased (N = 1).

Suicidality

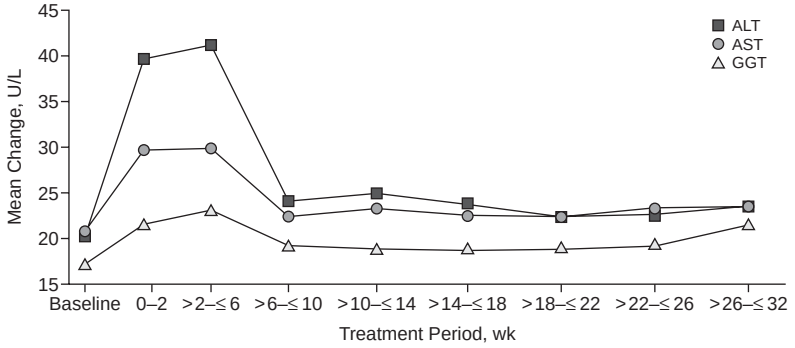
In the placebo-controlled database, 1 olanzapine-treated adolescent had suicidal ideation or behaviors (Mantel-Haenszel risk difference = 0.56, 95% confidence interval [CI] = –0.53 to 1.66, $p = .314$), and 2 olanzapine-treated adolescents and 1 placebo-treated adolescent had possible suicidal behavior or ideation (Mantel-Haenszel risk difference = 0.01, 95% CI = –2.66 to 2.68, $p = .994$). All suicidality-related events in the placebo-controlled database were reported in adolescents with bipolar I disorder. In the overall adolescent olanzapine exposure database, 0.4% (2/454) of the patients attempted suicide, 0.4% (2/454) made preparatory acts toward committing suicide, 2.9% (13/454) experienced suicidal ideation, and 1.3% (6/454) committed self-injurious behavior. Most of the suicidality-related adverse events (13/24) were reported in patients with bipolar I disorder.

Prolactin

In the placebo-controlled database, statistically significantly greater baseline-to-endpoint mean changes in prolactin were reported in olanzapine-treated compared with placebo-treated adolescents ($p < .001$). Adolescents in the overall exposure database had statistically significant baseline-to-endpoint increases in prolactin (23.0 μg/L),

Reprinted with correction to page 255.

Figure 2. Mean Changes (by week) in Hepatic Enzymes During Olanzapine Treatment (2.5–20.0 mg/day) in Adolescents With Schizophrenia or Bipolar I Disorder[a]

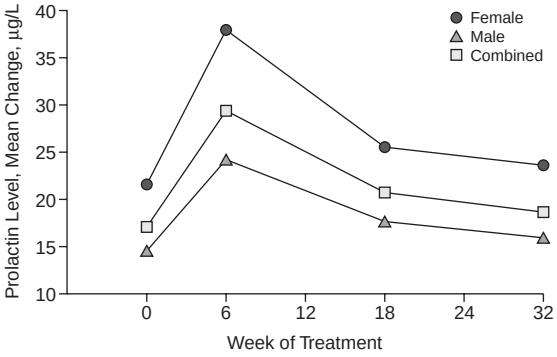


[a]The overall adolescent olanzapine exposure database, N = 454.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltransferase.

and 55.5% had high prolactin levels. Such changes in olanzapine-treated adolescents were statistically significantly greater compared with olanzapine-treated adults (–4.2 μg/L; p = .004). In adolescents from the overall adolescent olanzapine exposure database, prolactin levels peaked around week 6 of treatment, then continued to decrease for the remainder of treatment; however, prolactin levels at endpoint remained higher than at baseline (Figure 3).

In the placebo-controlled database, statistically significantly more olanzapine-treated compared with placebo-treated adolescents had high prolactin levels at anytime during treatment (p < .001). When analyzed by sex, statistically significantly more olanzapine-treated female (p = .006) and male (p < .001) patients had high prolactin levels at any time during treatment compared with those treated with placebo. In the olanzapine-treated adolescents in the placebo-controlled database, significantly fewer antipsychotic-naive patients compared with those previously treated with an antipsychotic medication had high prolactin levels (12.8% [21/164] vs. 52.9% [55/104], p < .001). When compared with adults, significantly more olanzapine-treated adolescents in the overall adolescent olanzapine exposure database had high prolactin levels at anytime during treatment (p < .001). In the overall adolescent olanzapine exposure database, significantly fewer olanzapine-treated female patients had high prolactin levels at any time during treatment compared with male patients (p < .001). Several prolactin-related adverse events were reported, including amenorrhea (1.2% [2/168]), dysmenorrhea (4.2% [7/168]), galactorrhea (0.7% [3/454]), gynecomastia (2.4% [7/286]), menorrhagia (0.6% [1/168]), metrorrhagia (0.6% [1/168]), and polycystic ovaries (0.6% [1/168]). One patient (0.6%; 1/168) in the overall adolescent olanzapine exposure database discontinued treatment due to galactorrhea.

Figure 3. Mean Changes (by week) in Prolactin Levels During Olanzapine Treatment (2.5–20.0 mg/day) in Adolescents With Schizophrenia or Bipolar I Disorder[a]



[a]The overall adolescent olanzapine exposure database, N = 454.

Sedation and Somnolence

In the placebo-controlled database, significantly more olanzapine-treated compared with placebo-treated adolescents experienced somnolence (24.6% vs. 3.4%, respectively, p < .001) and sedation (19.0% vs. 5.6%, respectively, p = .003). In the overall adolescent olanzapine exposure database, 19.8% and 14.1% of olanzapine-treated adolescents experienced somnolence and sedation, respectively. Three adolescents (0.7%) in the overall adolescent olanzapine exposure database discontinued treatment due to somnolence.

Extrapyramidal Symptoms

In the placebo-controlled database, no statistically significant differences were reported in the mean baseline-to-endpoint improvement in the AIMS total score (p = .540), BAS global clinical assessment of akathisia score (item 4; p = .628), or Simpson-Angus Scale total

Reprinted with correction to page 255.

Table 6. Mean Change From Baseline to Endpoint in Extrapyramidal Scales, and Incidence of Treatment-Emergent Extrapyramidal Symptoms at Any Time During Olanzapine Treatment (2.5–20.0 mg/day) in Adolescents With Schizophrenia or Bipolar I Disorder From the Overall Adolescent Olanzapine Exposure Database

Scale	Baseline Score, Mean (SD)	Endpoint Score, Mean (SD)	p Value[a]	Incidence, N/N (%)
AIMS, items 1–7 (dyskinesia)				
Bipolar I disorder (N = 219)	0.1 (0.7)	–0.1 (0.7)	.043	1/217 (0.5)
Schizophrenia (N = 137)	0.3 (0.8)	–0.1 (0.8)	.016	4/134 (3.0)
Overall (N = 356)	0.2 (0.7)	–0.1 (0.7)	.002	5/351 (1.4)
BAS, item 4 (akathisia)				
Bipolar I disorder (N = 219)	0.2 (0.5)	–0.1 (0.5)	.011	10/213 (4.7)
Schizophrenia (N = 137)	0.2 (0.5)	–0.1 (0.6)	.005	9/132 (6.8)
Overall (N = 356)	0.2 (0.5)	–0.1 (0.5)	< .001	19/345 (5.5)
SAS, items 1–10 (parkinsonism)				
Bipolar I disorder (N = 219)	0.2 (0.8)	0.0 (0.7)	.928	4/216 (1.9)
Schizophrenia (N = 136)	0.6 (1.7)	–0.3 (1.4)	.016	4/126 (3.2)
Overall (N = 355)	0.4 (1.3)	–0.1 (1.0)	.054	8/342 (2.3)

[a]Analyzed using a Type III sum of squares analysis of variance; Model = Country Therapy Protocol.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, SAS = Simpson-Angus Scale.

score (p = .271). In the overall adolescent olanzapine exposure database, olanzapine-treated adolescents continued to show significant improvement from baseline to endpoint in AIMS total score (p = .002) and BAS global clinical assessment of akathisia score (p < .001); the improvement in the Simpson-Angus Scale total score did not reach statistical significance (p = .054; Table 6). In the placebo-controlled database, no significant differences were observed between olanzapine-treated and placebo-treated adolescents in the incidence of treatment-emergent dyskinesia (p = 1.00), akathisia (p = .548), or parkinsonism (p = .304). In the overall olanzapine database, 1.4% of olanzapine-treated patients experienced treatment-emergent dyskinesia; 5.5%, akathisia; and 2.3%, parkinsonian symptoms. In the placebo-controlled database, no significant differences were observed between olanzapine-treated and placebo-treated adolescents in the incidence of anticholinergic medication use (4.5% vs. 2.2%, p = .504). In the overall adolescent olanzapine exposure database, 5.9% of olanzapine-treated adolescents were treated with anticholinergic medications. A breakdown of extrapyramidal symptoms and treatment-emergent incidence in the overall adolescent olanzapine exposure database is presented in Table 6.

DISCUSSION

Overall, the types of adverse events that were observed during olanzapine treatment in adolescents with schizophrenia and bipolar I disorder in our analyses are consistent with the data from other studies of olanzapine in children and adolescents,[7,14,16] as well as clinical trials in adults.[2,3] Treatment-emergent adverse events—such as somnolence,[2,3,28,29] increased appetite,[28] weight increase,[2,28,29] dry mouth,[3,28] and headache[2,28]—have been reported in adults in both acute and long-term studies.

However, the magnitude and incidence of changes in weight were significantly greater in adolescents compared to adults. Olanzapine-treated adolescents gained a mean of approximately 4 kg over a 3- to 6-week period during the double-blind, placebo-controlled period of the trials and gained approximately 7 kg over up to 32 weeks of treatment, the latter being statistically significantly greater compared with the U.S. standardized growth curves.[27] This rate of weight gain is similar to those found in other studies of olanzapine treatment in adolescents[7,14–16] but is greater than those found in studies of adults.[2,3] Weight change in these patients over the course of treatment continued to increase for up to 32 weeks. Given that adolescents are growing, BMI may be a better index of abnormal weight gain.

The percentage of adolescents who had potentially clinically significant weight gain was greater than that of adults (65.1% vs. 35.6%), suggesting that adolescents may be more susceptible to weight gain during olanzapine treatment. Previous research with other antipsychotics in children and adolescents also suggests that this age group may be particularly vulnerable to weight gain during treatment.[6–9,30] Weight gain in this population may lead to difficulties with treatment compliance[31] in patients who are already at risk for nonadherence; in a 1-year open-label study of olanzapine in adolescents with schizophrenia, over 25% of patients discontinued olanzapine treatment because of weight gain.[16]

Adolescents treated with olanzapine experienced statistically significant mean baseline-to-endpoint increases in total cholesterol, as well as fasting glucose and triglycerides, when compared with adolescents treated with placebo. Unlike with weight gain, however, adolescents had significantly smaller mean changes in fasting glucose during olanzapine treatment compared with those of adults; adults had smaller mean changes in fasting triglycerides and a greater incidence of abnormal changes from normal to high glucose, total cholesterol, LDL cholesterol, and triglycerides at any time during treatment. This varies from a recently completed analysis that showed that the

Reprinted with correction to page 255.

mean changes in fasting glucose and lipid parameters were comparable between adolescents and adults, and more adolescents shifted to an abnormal glucose or lipid category at any time during treatment (data on file, Eli Lilly and Co., Indianapolis, Ind., 2007). However, even though the new analysis contained most of the same patients as in this presented analysis, the new analysis included patients aged 18 years who were pooled from other studies and had data from patients with borderline personality disorder, and the analysis was performed with adolescent-specific lipid criteria, instead of using NCEP criteria for adults. Significant changes in weight and metabolic parameters have been commonly reported in adults.[32,33] These parameters have not been extensively studied in adolescents. A double-blind study of olanzapine, risperidone, and haloperidol in adolescents with psychosis[33] suggested that the changes in nonfasting glucose seen in the olanzapine treatment group might be larger than in the other 2 treatment groups.

Concerning the data on hepatic parameters, olanzapine-treated adolescents had significant increases in the levels of ALT, AST, and GGT and significant decreases in total bilirubin compared with placebo-treated patients, and significantly more olanzapine-treated adolescents had high levels of these parameters, with the exception of bilirubin. The increases in ALT, AST, and GGT peaked by week 6 of treatment, then the levels proceeded to decrease; the levels of these parameters remained above baseline through up to 32 weeks of treatment. Approximately 40% of adolescents had ALT levels greater than the upper normal limit at any time during olanzapine treatment. There are few published studies of hepatic functioning during antipsychotic treatment in adolescents[34] or adults.[35]

No completed suicides occurred during these trials. Most adolescents who reported other suicidality-related events had bipolar I disorder. Both adolescents and adults with bipolar disorder are at a greater risk for suicidal ideation and attempts compared with persons with other psychiatric illnesses.[36–39] Suicidal behavior is of particular concern for this population, as first-episode patients are at a greater risk for suicide than those patients with multiple episodes.[37] Moreover, in the general population, adolescents have a greater risk for these behaviors compared with adults. Although it is difficult to assess the potential risk of suicidality in adolescents without the benefit of long-term placebo-controlled studies, the elevated risk for adolescents with schizophrenia and bipolar I disorder emphasizes the need for treatments that could minimize the risk of suicidality.[40]

Both male and female adolescents treated with olanzapine in these studies had significant elevations in prolactin concentrations, and a substantial number experienced high prolactin levels. Prolactin concentrations initially peaked at around 6 weeks of treatment, then decreased while remaining above baseline levels. Increases in prolactin have been reported during treatment with numerous other antipsychotics.[9,41,42] An open-label study switching adult patients previously treated with conventional antipsychotics or risperidone found that compared with patients who remained on their prestudy therapy, olanzapine-treated patients experienced improvement in hyperprolactinemia and the potential symptoms of hyperprolactinemia.[43] The rates of hyperprolactinemia seen in this analysis of olanzapine-treated adolescents (~56%) are lower than those previously reported in an open-label study in adolescents with psychoses (~70%).[41] However, the reference ranges used in this analysis were based on age and sex,[20] whereas the ranges used in the previous study[41] were not adjusted for age (1.6–18.8 ng/L for male adolescents, 1.4–24.2 ng/L for female adolescents). Modest elevation of prolactin levels can persist during chronic olanzapine administration in adults.[43,44] Adolescents in this analysis had greater mean increases in and greater occurrence of high prolactin levels when compared with adults. This suggests that adolescents may be more susceptible than adults to changes in prolactin during treatment with olanzapine. A potential issue may be that of timing; prolactin samples are most accurate in the 6 hours following dosing,[45] and the protocol for these studies suggested olanzapine be taken at night. The interval between treatment and sample collection would most likely be greater than 6 hours, which may have affected the results.[45] Prolactin-related adverse events are commonly the cause of treatment discontinuation in pediatric populations.[31] Long-term increases in prolactin may be related to breast enlargement, galactorrhea,[41] dysmenorrhea, and sexual dysfunction.[28] While in adults olanzapine may alleviate these symptoms,[31] patients ≤ 18 years may have a greater risk of hyperprolactinemia.[30]

Clinicians should be alert for any signs of hyperprolactinemia, including amenorrhea and galactorrhea, in their adolescent patients, as sustained elevated levels of prolactin may lead to difficulties with puberty and benign pituitary tumors.[30] However, these symptoms may not be the best signs of hyperprolactinemia; Fideleff and colleagues[46] reported that tumors can be seen in adolescent patients with prolactin levels below 100 ng/mL. The potential risks of sustained prolactin elevations in adolescents need to be examined further, as the effects of sustained, mildly elevated prolactin levels over an extended period of time in developing children are unclear.[47]

Both sedation and somnolence are commonly reported during olanzapine treatment in adults with schizophrenia[2] or bipolar I disorder.[3] These adverse events have also been reported in other studies of olanzapine treatment in adolescents.[15] Regarding EPS, olanzapine-treated adolescents experienced improvements similar to those of placebo-treated patients, and olanzapine-treated

Reprinted with correction to page 255.

adolescents in the overall adolescent olanzapine exposure database continued to show improvement. This is consistent with previous research in children, adolescents,[14] and adults[43] treated with olanzapine. Olanzapine is thought to have a good safety profile concerning EPS, although a few cases have been reported in olanzapine-treated youths.[7] Adolescents might be particularly vulnerable to developing EPS during antipsychotic treatment, as striatal D_2 concentrations are highest at this stage of development.[9] From this analysis, EPS occur rarely during olanzapine treatment, as evidenced by the EPS measures and low concomitant anticholinergic medications use.

The tolerability of antipsychotics in children is important; 1 study of adolescents with bipolar I disorder reported nonadherence rates as high as 65%.[48] In adults with schizophrenia, adverse events consistently lead to medication noncompliance, which can worsen the progression of the disease.[49] Adverse event tolerability is also a leading cause of discontinuation of treatment. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), approximately 15% of patients with schizophrenia discontinued treatment due to adverse events.[50] These results stress the importance of antipsychotic tolerability, especially in younger patients.

This analysis has several limitations. Although the studies from which the data were pooled are similar in design, there are some differences, particularly in the length of the placebo-controlled phases of studies HGIN and HGIU (6 weeks vs. 3 weeks). Additionally, the strict inclusion/exclusion criteria of the studies limit the applicability of the findings of this analysis, as the clinical trial samples may represent only a subset of adolescents with schizophrenia or bipolar I disorder. Furthermore, in this analysis, the last-observation-carried-forward method was used; this could affect the results as those adolescents who discontinued treatment may have had adverse events that differed from those patients who remained in the studies.

To our knowledge, this is the first pooled safety analysis of this size in adolescents treated with any antipsychotic medication. The larger sample size may have allowed us to detect safety signals that may have otherwise gone unnoticed in valuable studies of smaller sample sizes. The types of adverse events occurring in olanzapine-treated adolescents with schizophrenia or bipolar I disorder appear to be similar to those occurring in olanzapine-treated adults with the same diagnoses. However, it appears that the magnitude and incidence of weight gain and hyperprolactinemia may be greater in adolescents. For each patient, clinicians must weigh both the benefit and risk of available treatments for adolescents with schizophrenia or bipolar disorder.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

REFERENCES

1. Carlson GA, Naz B, Bromet EJ. The phenomenology of assessment of adolescent-onset psychosis. In: Findling RL, Schulz SC, eds. Juvenile-Onset Schizophrenia: Assessment, Neurobiology, and Treatment. Baltimore, Md: The Johns Hopkins University Press; 2005:1–38
2. Beasley CM Jr, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996;124:159–167
3. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. Am J Psychiatry 1999;156:702–709
4. Martin A, Leslie D. Trends in psychotropic medication costs for children and adolescents, 1997–2000. Arch Pediatr Adolesc Med 2003;157: 997–1004
5. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
6. Armenteros JL, Whitaker AH, Welikson M, et al. Risperidone in adolescents with schizophrenia: an open pilot study. J Am Acad Child Adolesc Psychiatry 1997;36:694–700
7. Ercan ES, Kutlu A, Varan A, et al. Olanzapine treatment of 8 adolescent patients with psychosis. Hum Psychopharmacol 2004;19:53–56
8. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. Arch Gen Psychiatry 1996;53:1090–1097
9. McConville BJ, Sorter MT. Treatment challenges and safety considerations for antipsychotic use in children and adolescents with psychoses. J Clin Psychiatry 2004;65(suppl 6):20–29
10. Zalsman G, Carmon E, Martin A, et al. Effectiveness, safety, and tolerability of risperidone in adolescents with schizophrenia: an open-label study. J Child Adolesc Psychopharmacol 2003;13:319–327
11. Tohen M, Dittmann R, Kryzhanovskaya L, et al. Olanzapine in the treatment of acute mania in adolescents with bipolar I disorder: a 3-week randomized, double-blind, placebo-controlled study. Presented at the 44th annual meeting of the American College of Neuropsychopharmacology; Dec 11–15, 2005; Waikoloa, Hawaii
12. Kryzhanovskaya L, Schulz C, McDougle CJ, et al. A double-blind, placebo-controlled study of olanzapine in adolescents with schizophrenia. Presented at the 44th annual meeting of the American College of Neuropsychopharmacology Dec 11–15, 2005; Waikoloa, Hawaii
13. Kryzhanovskaya L, Schulz SC, McDougle C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 2009;48:60–70
14. Mozes T, Greenberg Y, Spivak B, et al. Olanzapine treatment in chronic drug-resistant childhood-onset schizophrenia: an open-label study. J Child Adolesc Psychopharmacol 2003;13:311–317
15. Sholevar EH, Baron DA, Hardie TL. Treatment of childhood-onset schizophrenia with olanzapine. J Child Adolesc Psychopharmacol 2000;10:69–78
16. Ross RG, Novins D, Farley GK, et al. A 1-year open-label trial of olanzapine in school-age children with schizophrenia. J Child Adolesc Psychopharmacol 2003;13:301–309
17. Krishnamoorthy J, King BH. Open-label olanzapine treatment in 5 preadolescent children. J Child Adolesc Psychopharmacol 1998;8:107–113
18. Overall JE, Pfefferbaum B. The Brief Psychiatric Rating Scale for Children. Psychopharmacol Bull 1982;18:10–16
19. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980–988
20. Wiedemann G, Jonetz-Mentzel L. Establishment of reference ranges for prolactin in neonates, infants, children, and adolescents. Eur J Clin Chem Clin Biochem 1993;31:447–451
21. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
22. American Diabetes Association/American College of Cardiology. Diabetes and Cardiovascular Disease Review: Diabetic Dyslipidemia. 2002;3:1–8. Available at http://www.ihs.gov/NonMedicalPrograms/NC4/

Reprinted with correction to page 255.

Documents/ADACardioReview_3.pdf. Accessibility verified Oct 13, 2008
23. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
24. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
25. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 1982;39:486–487
26. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41:55–68
27. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45–60
28. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999; 156:79–87
29. Chrzanowski WK, Marcus RN, Torbeyns A, et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. Psychopharmacology 2006;189:259–266
30. Correll CU. Real-life switching strategies with second-generation antipsychotics. J Clin Psychiatry 2006;67:160–161
31. Patel NC, Crismon ML, Hoagwood K, et al. Unanswered questions regarding atypical antipsychotic use in aggressive children and adolescents. J Child Adolesc Psychopharmacol 2005;15:270–284
32. Koro CE, Fedder DO, L'Italien GJ, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59:1021–1026
33. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized 8-week trial. Neuropsychopharmacology 2004;29:133–145
34. Kumra S, Herion D, Jacobsen LK, et al. Case study: risperidone-induced hepatotoxicity in pediatric patients. J Am Acad Child Adolesc Psychiatry 1997;36:701–705
35. Ozcanli T, Erdogan A, Ozdemir S, et al. Severe liver enzyme elevations after 3 years of olanzapine treatment: a case report and review of olanzapine associated hepatotoxicity. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1163–1166
36. Brent DA, Johnson B, Bartle S, et al. Personality disorder, tendency to impulsive violence, and suicidal behavior in adolescents. J Am Acad Child Adolesc Psychiatry 1993;32:69–75
37. Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44:213–235
38. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 1995;34:454–463
39. Palmer CS, Revicki DA, Genduso LA, et al. A cost-effectiveness clinical decision analysis model for schizophrenia. Am J Manag Care 1998;4: 345–355
40. DelBello M, Grcevich S. Phenomenology and epidemiology of childhood psychiatric disorders that may necessitate treatment with atypical antipsychotics. J Clin Psychiatry 2004;65(suppl 6):12–19
41. Alfaro CL, Wudarsky M, Nicolson R, et al. Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. J Child Adolesc Psychopharmacol 2002;12:83–91
42. Saito E, Correll CU, Gallelli K, et al. A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. J Child Adolesc Psychopharmacol 2004;14:350–358
43. Kinon BJ, Ahl J, Liu-Seifert H, et al. Improvement in hyperprolactinemia and reproductive comorbidities in patients with schizophrenia switched from conventional antipsychotics or risperidone to olanzapine. Psychoneuroendocrinology 2006;31:577–588
44. Kinon BJ, Gilmore JA, Liu H, et al. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 2003;28(suppl 2):55–68
45. Goode DJ, Meltzer HY, Fang VS. Daytime variation in serum prolactin level in patients receiving oral and depot antipsychotic medication. Biol Psychiatry 1981;16:653–662
46. Fideleff HL, Azaretzky M, Boquete HR, et al. Tumoral versus nontumoral hyperprolactinemia in children and adolescents: possible usefulness of the domperidone test. J Pediatr Endocrinol Metab 2003; 16:163–167
47. Staller J. The effect of long-term antipsychotic treatment on prolactin. J Child Adolesc Psychopharmacol 2006;16:317–326
48. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. Am J Psychiatry 2007;164:582–590
49. Perkins DO, Gu H, Weiden PJ, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. J Clin Psychiatry 2008;69:106–113
50. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, M.D., Ph.D., at kwagner@psychiatrist.com.

Reprinted with correction to page 255.

   © COPYRIGHT 2009 PHYSICIANS POSTGRADUATE PRESS, INC.