Adverse Effects of Second-Generation Antipsychotics in Children and Adolescents

A Bayesian Meta-Analysis

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Abstract: In adults, second-generation antipsychotics (SGAs) have a low frequency of extrapyramidal syndrome (EPS) and a moderate frequency of metabolic adverse effects. Here we aimed to assess short-term adverse effects of SGAs in children and adolescents. We searched for relevant studies in MEDLINE and EMBASE (1996–2010), Food and Drug Administration and European Medicines Agency clinical trial registries, and reference lists of review articles. We found 41 were short-term (3–12 weeks) controlled studies that evaluated SGA adverse effects in youths. Using Bayesian meta-analysis, we analyzed odds ratios (ORs) or mean average effects. Numbers of arms (subjects) in the 41 trials were aripiprazole, 10 (n = 671); olanzapine, 14 (n = 413); quetiapine, 10 (n = 446); risperidone, 25 (n = 1040); ziprasidone, 4 (n = 228); clozapine, 5 (n = 79); and placebo/untreated, 23 (n = 1138), totaling 93 arms (4015 patients). Clozapine was assessed only for weight gain and somnolence. Compared with placebo, significant treatment-related increases were observed for weight gain with olanzapine (mean ± SD = 3.99 ± 0.42 kg; 95% credible interval, 3.17–4.84 kg), clozapine (2.38 ± 1.13 kg; 95% credible interval, 0.19–4.62 kg), risperidone (2.02 ± 0.32 kg; 95% credible interval, 1.39–2.66 kg), quetiapine (1.74 ± 0.38 kg; 95% credible interval, 0.99–2.5 kg), and aripiprazole (0.89 ± 0.32 kg; 95% credible interval, 0.26–1.51 kg); glucose levels with risperidone (3.7 ± 1.36 mg/dL; 95% credible interval, 1.08–6.42 mg/dL) and olanzapine (2.09 ± 1.08 mg/dL; 95% credible interval, 0.13–4.32 mg/dL); cholesterol levels with quetiapine (10.77 ± 2.14 mg/dL; 95% credible interval, 6.6–14.95 mg/dL) and olanzapine (4.46 ± 1.65 mg/dL; 95% credible interval, 1.24–7.73 mg/dL); triglyceride levels with olanzapine (20.18 ± 5.26 mg/dL; 95% credible interval, 9.85–30.53 mg/dL) and quetiapine (19.5 ± 3.92 mg/dL; 95% credible interval, 11.84–27.17 mg/dL); hyperprolactinemia with risperidone (OR, 38.63; 95% credible interval, 8.62–125.6), olanzapine (OR, 15.6; 95% credible interval, 4.39–41.1), and ziprasidone (OR, 9.35; 95% credible interval, 1.24–37.03); and EPS with ziprasidone (OR, 20.56; 95% credible interval, 3.53–68.94), olanzapine (OR, 6.36; 95% credible interval, 2.43–13.84), aripiprazole (OR, 3.79; 95% credible interval, 2.17–6.17), and risperidone (OR, 3.71; 95% credible interval, 2.18–6.02). All SGAs increased the risk of somnolence/sedation. We conclude that short-term metabolic effects and EPS are frequent in children treated with SGAs. Second-generation antipsychotics have distinct profiles of secondary effects, which should be considered in making treatment decisions.

Key Words: second-generation antipsychotics, childhood, adolescence, adverse effects, meta-analysis

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Atypical or second-generation antipsychotics (SGAs) have been proven to be effective for treating several conditions in children and adolescents. As of March 2010, aripiprazole, olanzapine, quetiapine, and risperidone are Food and Drug Administration (FDA)–approved medications for bipolar mania in children and adolescents (aged 10–17 years; except olanzapine, aged 13–17 years) and for adolescent schizophrenia (aged 13–17 years). In addition, aripiprazole and risperidone are also FDA-approved medications for behavioral disturbances (irritability and aggression) associated with autism and/or intellectual disabilities in children and adolescents (aged 6–17 years). Second-generation antipsychotics were developed to limit the frequency of extrapyramidal syndrome (EPS). Six SGAs are now commonly prescribed to children and adolescents both in the United States[1] and in Europe.[2] The risk of adverse effects (weight gain, somnolence, and EPS) with olanzapine was reported to be significantly increased in young patients compared with adults,[3] leading to concerns about the use of SGAs in children.[4] Emerging findings indicate that children and adolescents are more vulnerable to weight gain, cardiometabolic effects (increase in glucose, triglyceride, and cholesterol levels), and hyperprolactinemia.[5,6] Nevertheless, SGA use in children has increased by 22% from 2004 to 2008 in the United States, with an average of 250,000 prescriptions per year for children younger than 6 years and numerous prescriptions for nonpsychotic disorders and off-label indications.[7]

We therefore need a better understanding of secondary effects of each compound. Fortunately, indeed, the Pediatric Research Equity Acts (2003 and 2007) and the Best Pharmaceuticals for Children Act (2002), enacted following the controversy about the use of serotonin reuptake inhibitors in children,[8] have increased the number of large double-blind, placebo-controlled studies of SGAs and other medications in children. To assess the most common short-term adverse effects for each SGA, we performed a meta-analysis of the relevant short-term, controlled studies published between 1980 and 2009, using Bayesian statistics, which permitted

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us to include both multiarm comparative studies and secondary-effect studies (eg, see Correll et al[5] and Sikich et al[9]). We hypothesized that compounds have distinct profiles of secondary effects that should be known and taken into account in treatment decision making.

METHODS

Search and Study Selection

We searched the MEDLINE and EMBASE databases for articles describing controlled trials of SGAs in children and adolescents. Searches included combinations of the following keywords: *aripiprazole*, *ziprasidone*, *risperidone*, *olanzapine*, *quetiapine*, *clozapine*, *children/adolescents*, and/or *controlled*. References from identified articles and reviews were also examined. We also searched FDA and European Medicines Agency databases for complementary information and synopses of unpublished trials, using the same keywords. We found and screened 128 potentially relevant publications between January 1980 and October 2010. Exclusion criteria included the following: (1) crossover, retrospective, combination, or discontinuation design; (2) no indication of adverse events in either the original report or the available reviews; (3) fewer than 9 individuals per arm; (4) lack of control medication or placebo arm in short-term studies (≤12 weeks); (5) unrelated research questions (eg, young adult, pharmacovigilance, or kinetics studies); (6) literature reviews; (7) data already reported; (8) study duration 13 weeks or greater; and (9) incomplete reporting of variables of interest (see below). A diagram of the flow is given in Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/JCP/A121). Excluded studies are listed in Supplemental Annex 1 (Supplemental Digital Content 2, http://links.lww.com/JCP/A122). In total, we found 41 short-term studies of the relevant drugs, all published in English.

Data Extraction and Pertinent Criteria

Two coauthors (D.C. and O.B.) independently extracted the relevant data from the original selected reports, whose main characteristics are summarized in Supplemental Table 1 (Supplemental Digital Content 3, http://links.lww.com/JCP/A123) for those treatment arms including SGAs or placebo/untreated control groups. Extracted data were compared to ensure accuracy. In case of disagreements, we checked original report for relevant data. The authors decided not to impute missing data with replacement values given the Bayesian statistics performed. To improve the accuracy of the meta-analysis, the study authors were contacted to obtain the missing data. To assess quality of adverse effect reporting in the studies, we constructed a score as follows: for each criterion, we attributed 1 point when detailed data were given (meaning for continuous variables mean and SD) and 0 when data were incomplete or absent; the adverse effect quality score (AEQS) was the sum. It could range from 1 to 13. Supplemental Table 2 (Supplemental Digital Content 4, http://links.lww.com/JCP/A124) shows how each study contributed to the different metacalculations presented in this report and how the AEQS was scored. We did not use a "classic" quality score (eg, criteria of Detsky et al[10]) that includes items related to randomization, blindness, inclusion/exclusion criteria, outcome measures, treatment description, and statistical analysis, because these criteria were intended to assess the quality of reporting of the efficacy rather than to assess the quality of reporting of adverse effects. The AEQS we constructed simply reflected how a study contributed to our meta-analysis in terms of the secondary-effect reporting, which was our main goal.

We analyzed mean changes during each trial for the variables that were reported by the largest numbers of studies, as follows: (1) weight (in kilograms) and the percentage of subjects with clinically significant weight gain as declared by the investigator or as defined in the trial (weight gain >7% or weight gain >5%), (2) glucose (in milligrams per deciliter), (3) cholesterol (in milligrams per deciliter), (4) triglycerides (in milligrams per deciliter), (5) prolactin (in nanograms per deciliter) and the percentage of subjects judged to have clinically significant hyperprolactinemia, (6) the percentage of subjects reporting somnolence/sedation, and (7) the percentage of subjects with clinically EPS and/or akathisia. Analyses for the percentage of subjects with clinically significant increase in cholesterol, triglyceride, and glucose and for change in body mass index were not conducted as these variables were poorly reported across studies.

Statistical Analysis

Given that data were available from double-blind, placebo-controlled trials and from naturalist controlled trials comparing 1 or more compounds, we used a Bayesian method to keep the maximum amount of information on adverse effects in the meta-analysis.[11,12] As stated previously, to limit bias, we decided not to impute missing data with replacement values as it is the case in many meta-analysis using more classic calculations, in particular regarding SDs, which are not systematically reported in studies. For binary outcome data, we used a logistic regression model. For continuous outcome data, however, a natural scale was used. Both log–odds ratio (OR) and mean difference in change were assumed to come from a random-effects model with homogeneous variance. The Bayesian model was implemented using WinBUGS version 1.4.[13] WinBUGS is a software used to analyze complex statistical models with Markov chain Monte Carlo methods,[14] using Gibbs sampling[15,16] and the Metropolis algorithm,[17] to generate a chain by sampling from full conditional distributions. Output and summary statistics of the data were saved and read into R version 2.11.0[18] using the R2WinBUGS package.[19]

For each variable, we estimated the mean effect of each compound compared with placebo/untreated patients and calculated 95% credible intervals. We used vague normal (mean, 0; variance, 10,000) and uniform (0–2) prior distributions for means and SDs. We then constructed posterior distributions of the treatment effects from 2 chains of simulations after an initial step of burn-in simulations. After thinning, the total number of simulations varied from 20,000 to 100,000, and the number of burn-in simulations varied from 250 to 1000. The number of simulations was chosen to ensure nonautocorrelation and the convergence of each chain. Those criteria were checked using the CODA package.[20] Convergence was assessed using Geweke convergence diagnostic (Z score), and the nonautocorrelation was assessed using Raftery and Lewis' dependence factor. Besides convergence and autocorrelation, a sensitivity analysis with different choices of low-information prior distributions showed the robustness of these choices. Finally, as we were aware that keeping nonrandomized and naturalistic studies to run calculation on the maximum of data regarding SGA adverse effects may be another source of bias, we performed the same meta-analysis on randomized studies to assess whether inclusion of naturalistic studies modified the results.

RESULTS

From 1972 to 2010, we found 41 short-term (3- to 12-week) controlled studies that assessed the secondary effects of SGAs in children and adolescents with schizophrenia, bipolar disorder, behavioral impairments comorbid to autism or intellectual disability, Tourette syndrome, and conduct disorder. In total, the

meta-analysis consisted of 93 arms, including 4015 children and adolescents who received aripiprazole (10 arms, n = 671), clozapine (5 arms, n = 79), olanzapine (14 arms, n = 413), quetiapine (10 arms, n = 446), risperidone (25 arms, n = 1040), or ziprasidone (4 arms, n = 228). Secondary effects occurring with SGAs were compared with those occurring in untreated children and adolescents or those treated with a placebo (23 arms, n = 1138). Supplemental Figure 2 (Supplemental Digital Content 5, http://links.lww.com/JCP/A125) shows the network of eligible comparisons for the multiple-treatments meta-analysis. Of the 21 possible pairwise comparisons between the 7 conditions (6 active SGAs and placebo), 14 have been studied directly in 1 or more trials for at least 1 secondary effect of interest.

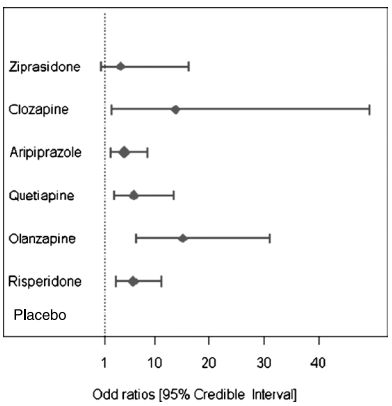
Weight Gain

For both weight gain parameters, all compounds except ziprasidone significantly differed from placebo/untreated patients (Fig. 1). First, we considered the percentage of patients who had meaningful weight gain during the trial and calculated the ORs –(95% credible interval) for each compound. This analysis included 25 studies, 62 arms, and 3401 patients. Odds ratios are represented in decreasing order as follows: olanzapine OR, 15.1 (6.56–31.1); clozapine OR, 13.83 (2.21–49.21); quetiapine OR, 6.2 (2.61–13.56); risperidone OR, 6.03 (3.02–11.4); aripiprazole OR, 4.44 (2.0–8.88); and ziprasidone OR, 3.77 (0.37–16.27). Second, we used the mean weight gain expressed in kilograms during trial and calculated the mean increase (SD) (95% credible interval) for each compound. This analysis included 30 studies, 66 arms, and 3221 patients. We found, in decreasing order, the following mean weight gains: olanzapine, 3.99 kg (0.42) (3.174.84); clozapine, 2.38 kg (1.13) kg (0.19–4.62 kg); risperidone, 2.02 (0.32) kg (1.39–2.66 kg); quetiapine, 1.74 (0.38) kg (0.99–2.5 kg); aripiprazole, 0.89 (0.32) kg (0.26–1.51 kg); and ziprasidone, −0.1 (0.7) kg (−1.48 to 1.1.29 kg). A mean increase in body mass index yielded similar results (data not shown), but fewer studies were available (14 studies, 35 arms, 1601 patients).

A

25 studies
62 arms - 3401 patients

Arm (N)	Patient (N)
3	212
3	57
9	653
6	381
9	242
16	794
16	962



B

30 studies
66 arms - 3221 patients

Arm (N)	Patient (N)
4	228
4	61
8	606
7	413
11	368
16	691
16	854

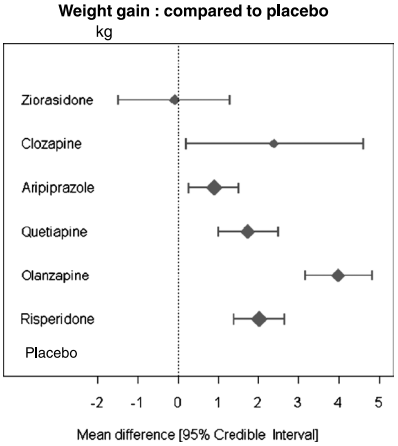


FIGURE 1. Odds ratios (95% credible interval) of patients with significant weight gain (A) and mean increase in kilograms per patient (95% credible interval) (B) in SGA trials for children and adolescents. In both metacalculations, all Geweke convergence diagnostic *Z* scores for each treatment variable were included between −1.96 and 1.96. All Raftery and Lewis' dependence factors were less than 5. A sensitivity analysis with different choices of low-information prior distributions showed the robustness of the model.

Metabolic Parameters

There were insufficient metabolic data on clozapine for this analysis (Fig. 2). For each other compound, for each trial, we calculated the mean increase and the SD and credible interval. For glucose (in milligrams per deciliter), the analysis included 10 studies, 27 arms, and 1784 patients. Risperidone and olanzapine significantly increased glucose levels compared with placebo. We found increases as follows: risperidone, 3.7 (1.36) mg/dL (1.08–6.42 mg/dL); aripiprazole, 2.21 (1.46) mg/dL (−0.63 to 5.09 mg/dL); olanzapine, 2.09 (1.08) mg/dL (0.13–4.32 mg/dL); quetiapine, 1.64 (1.03) mg/dL (−0.4 to 3.7 mg/dL); and ziprasidone, −1.24 (2.26) (−5.7 to 3.23 mg/dL).

The analysis of cholesterol (in milligrams per deciliter) included 10 studies, 27 arms, and 1784 patients. Quetiapine and olanzapine significantly increased cholesterol rates compared with placebo. We found increases as follows: quetiapine, 10.77 (2.14) mg/dL (6.6–14.95 mg/dL); olanzapine 4.46 (1.65) mg/dL (1.24–7.73 mg/dL); aripiprazole 2.65 (2.42) mg/dL (−2.11 to 7.34 mg/dL); risperidone 0.91 (2.11) mg/dL (−3.22 to 5.08 mg/dL); and ziprasidone 0.47 (3.1) mg/dL (−5.64 to 6.56 mg/dL).

The analysis of triglycerides (in milligrams per deciliter) included 10 studies, 27 arms, and 1655 patients. Olanzapine and quetiapine significantly increased triglyceride levels compared with placebo, with increases as follows: olanzapine, 20.18 (5.26) mg/dL (9.85–30.53 mg/dL); quetiapine, 19.5 (3.92) mg/dL (11.84–27.17 mg/dL); risperidone, 5.57 (4.57) mg/dL (−3.38 to 14.51 mg/dL); aripiprazole, 0.03 (4.55) mg/dL (−8.9 to 8.98 mg/dL); and ziprasidone, −1.52 (5.52) mg/dL (−12.31 to 9.34 mg/dL).

Prolactin

There were insufficient prolactin data on clozapine for this analysis. Furthermore, mean variation in prolactin during trials was poorly reported, except for aripiprazole. The 4 studies examining this compound reported a decrease in prolactin. For the other compounds, we found the percentage of patients judged to have a meaningful increase in prolactin during the trial in each arm and calculated the ORs (95% credible interval) for each compound. This analysis included 12 studies, 26 arms and 1180 patients. Risperidone, olanzapine and ziprasidone significantly increased prolactin levels compared with placebo, as follows: risperidone OR, 38.63 (8.62–125.6); olanzapine OR, 15.6 (4.39–41.1); ziprasidone OR, 9.35 (1.24–37.03); and quetiapine OR, 3.16 (0.13–15.9).

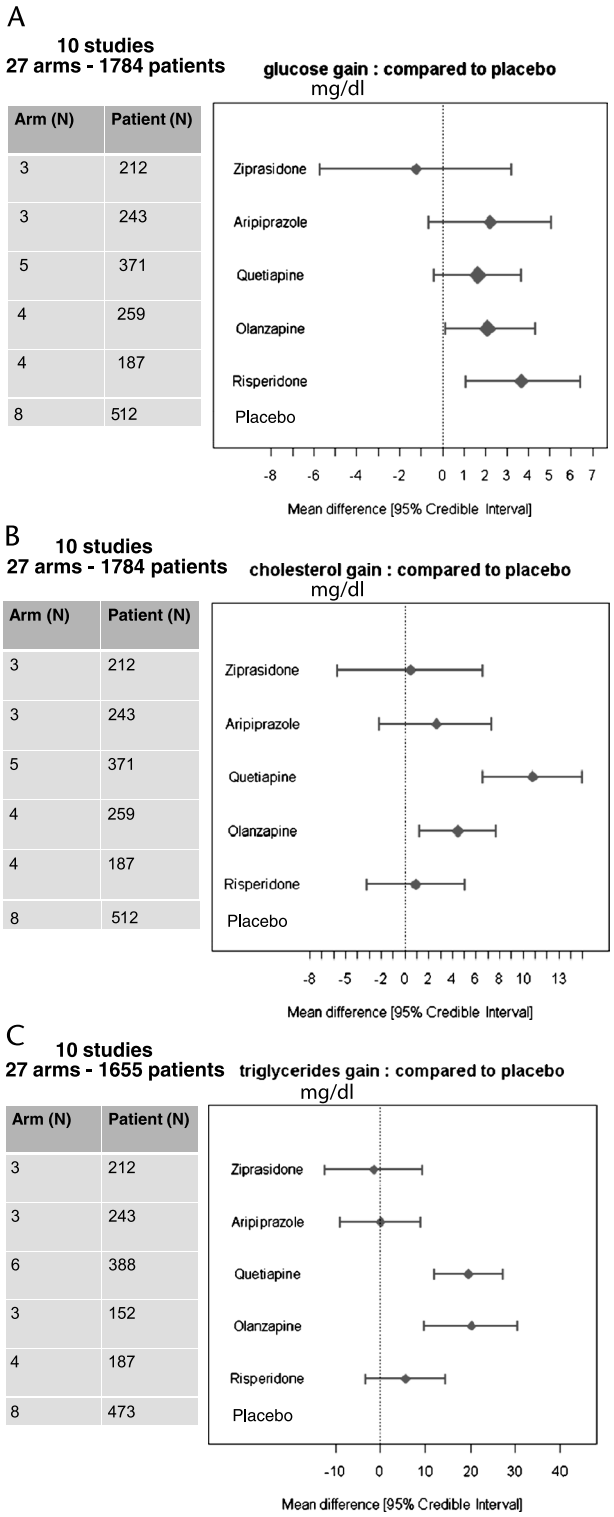


FIGURE 2. Mean increase (95% credible interval) of metabolic parameters in SGA trials for children and adolescents: glucose (A), cholesterol (B), and triglycerides (C). In the 3 metacalculations, all Geweke convergence diagnostic *Z* scores for each treatment variable were included between −1.96 and 1.96. All Raftery and Lewis' dependence factors were less than 5. A sensitivity analysis with different choices of low-information prior distributions showed the robustness of the model.

Other Secondary Effects

We found the percentage of patients complaining of sedation/somnolence during each trial and calculated the ORs (95% credible interval) for each compound. This analysis included 29 studies, 66 arms, and 3348 patients (Fig. 3). All compounds significantly increased the risk of reporting somnolence/sedation compared with placebo: clozapine OR, 54.82 (3.87–259.5); ziprasidone OR, 8.72 (2.71–21.97); olanzapine OR, 8.49 (3.97–16.55); risperidone OR, 7.3 (4.63–11.19); aripiprazole OR, 6.07 (2.79–12.22); and quetiapine OR, 5.44 (2.91–9.26).

We found the percentage of patients showing EPS, including akathisia, during each trial and calculated the ORs (95% credible interval) for each compound. This analysis included 28 studies, 63 arms, and a total of 3258 patients. There was no report of EPS in clozapine studies, but it was not clear whether incidences of EPS were systematically assessed. Thus, clozapine was not included in this analysis. All other SGAs except quetiapine significantly increased the risk of EPS compared with the placebo: ziprasidone OR, 20.56 (3.53–68.94); olanzapine OR, 6.36

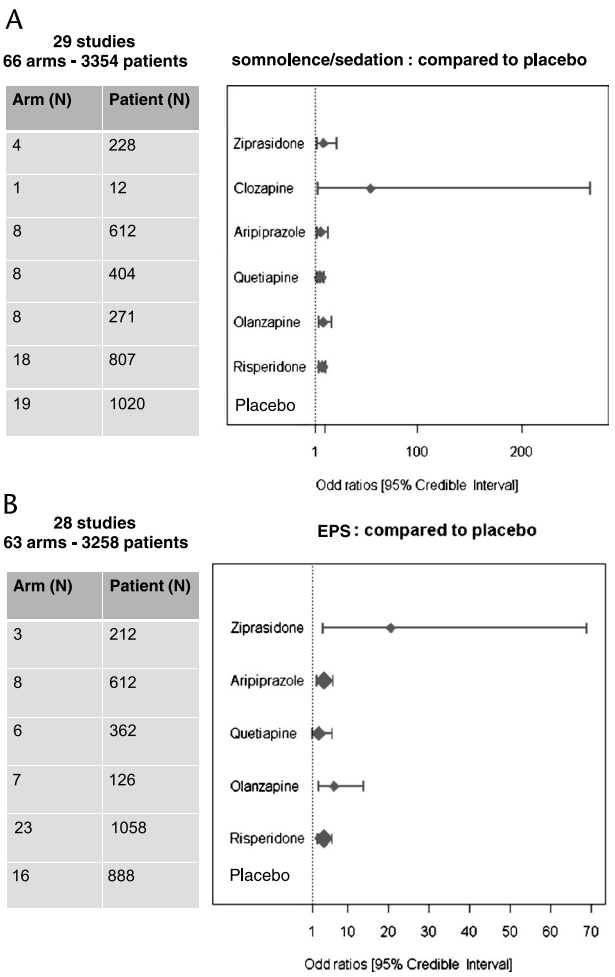


FIGURE 3. Odds ratios (95% credible interval) of patients with somnolence (A) and EPS (B) in SGA trials for children and adolescents. In both metacalculations, all Geweke convergence diagnostic *Z* scores for each treatment variable were included between −1.96 and 1.96. All Raftery and Lewis' dependence factors were less than 5. A sensitivity analysis with different choices of low-information prior distributions showed the robustness of the model.

(2.43–13.84); aripiprazole OR, 3.79 (2.17–6.17); risperidone OR, 3.71 (2.18–6.02); and quetiapine OR, 2.54 (0.88–6.07).

DISCUSSION

In this meta-analysis of relevant short-term controlled studies of children and adolescents treated with SGAs, secondary effects occurred with a significant frequency for each of the 6 studied compounds, as summarized in Table 1. It appears that (1) most SGAs induce EPS in children and adolescents with rather low frequency, with the notable exception of ziprasidone (OR, ≈20), which shows a more "typical" profile, and (2) as hypothesized, different SGAs have quite different secondary-effect profiles.

Somnolence/sedation effects are the "norm" with all SGAs but are particularly common with clozapine. The severity of the problem of weight gain with SGAs has been discussed in several reports.[5,21–23] Mean weight gain in children and adolescents over as few as 3 to 12 weeks is almost 4 kg with olanzapine and almost 2 kg with risperidone, quetiapine, and clozapine. Ziprasidone (and to a lesser extent, aripiprazole) has shown a better profile.

Second-generation antipsychotics differ also in their cardiometabolic effects. Olanzapine and quetiapine have the most severe effects, with increases of 5 to 10 mg/dL in total cholesterol and 20 mg/dL in triglycerides. It is noteworthy that although too few studies reported on clozapine mean triglyceride increase, analysis of percentage of patients with a clinically significant triglyceride increase (11 studies, 26 arms, and 1668 patients) suggested that clozapine's OR was comparable to that of olanzapine and quetiapine (respectively, OR, 12; 95% credible interval [0.93–48.2]; OR, 7.3 [1.8–20.2]; OR, 28.8 [2.5–133.3]), although sample size for clozapine was small (n = 30), and the increase was not statistically significant. There were small but significant increases in blood glucose for risperidone and olanzapine (2–4 mg/dL). The increases in lipid and glucose levels were of moderate clinical significance.[4] However, we cannot exclude the possibilities that (1) long-term metabolic effects may be more clinically meaningful and may correlate with duration of SGA treatment, and (2) some patients appear to experience dramatic increases in some of these variables, whereas we considered only mean changes.

Finally, risperidone, olanzapine, and ziprasidone significantly increase the risk of clinically meaningful hyperprolactinemia, with ORs ranging from 10 to 40. Some large studies[24–27] described hyperprolactinemia as a function of sex and suggested that the prolactin increase doubles for females compared with males. Given that the risk of osteoporosis is higher for women and for those with chronic hyperprolactinemia, this issue may be a major concern for girls treated with risperidone, olanzapine, or ziprasidone and should be investigated in follow-up studies.[28] The question of whether moderators, other than sex, contribute to a drug's secondary-effect profile is a challenging issue. There has been only an inconsistent association of drug dosage with weight gain,[5,25–27] whereas the association of drug dosage with EPS appears to be consistent in the case of aripiprazole.[24,29–31] A given diagnosis per se does not seem to influence weight gain and metabolic changes.[32] Given the limited data, more research is needed in this field.

Although the Pediatric Research Equity Acts and the Best Pharmaceuticals for Children Act have clearly increased the number of studies on treatment of children with SGAs, we were struck by several points while reviewing this literature. (1) The language of most of these reports focuses on efficacy rather than adverse effects. (2) Quality of reporting is moderate because we had AEQS mean equal to 5.46 (SD, 3.32) (maximum score, 13). However, AEQS was correlated with the year of publication (Spearman $r = 0.53$), meaning that reporting of adverse effects improved in the recent years. (3) The large, industry-funded studies of quetiapine and olanzapine, which have more severe effects on weight gain and lipid profiles, were shorter (3–6 weeks) than those of aripiprazole and risperidone (4–8 weeks)(see Supplemental Table 1, Supplemental Digital Content 3), whereas longer studies of the former compounds would be more useful for assessing risks. (4) Few studies reported actual increases in prolactin levels rather than percentage of subjects with "clinically meaningful" increases, which made it difficult to assess these effects objectively. For example, only 6 of 24 risperidone studies included more detailed data. (5) The tendency to deemphasize adverse effects was not limited to industry-sponsored trials—studies of clozapine (none of which were industry sponsored) provided the least information about secondary effects. We recommend that journal editors and reviewers as well as government agencies should set higher standards for reporting adverse effects of these compounds in children and adolescents, so that clinicians can make judgments based on a more balanced risk-benefit analysis.

The results from this meta-analysis need to be interpreted within its limitations: (1) the variable reporting of secondary-effect data, which is evidenced by the fact that only 3 studies contributed to all metacalculations presented here. (2) The numbers of study arms and patients treated were low for clozapine and ziprasidone, explaining the large 95% credible intervals for these 2 compounds. More studies are needed before we can conclude that ziprasidone has a better metabolic profile, although preliminary studies are promising. (3) All studies were controlled, but we included nonrandomized studies in order to (i) consider as many studies as possible, and (ii) keep some important naturalistic studies as these are usually more informative on adverse

TABLE 1. Summary of SGAs' Secondary Effects Reported in Controlled Short-Term Studies

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
↗ Weight	+	++++	++++	+++	++	+/−
↗ Glucose	+/−	?	+	+/−	++	0
↗ Cholesterol	0	?	+++	++++	0	0
↗ Triglycerides	0	+++*	++++	++++	+/−	0
Hyperprolactinemia	0	?	+++	+/−	++++	++
Sedation	++	++++	++	+	++	++
EPS	+	0?	++	+/−	+	++++

*Based on the calculation of ORs for the percentage of patients with a significant increase in triglycerides. This analysis included 11 studies, 26 arms, and 1668 patients, including 30 treated with clozapine (data not shown).

? indicates unknown.

effects.[5] This may have introduced bias in metacalculations.[10] However, one should note that nonrandomized studies (n = 7; 17.1%) accounted for 392 patients (9.76%) only; that metacalculations performed on randomized controlled trials yielded mainly the same results: similar significant differences with the placebo except for clozapine mean weight gain and olanzapine mean glucose gain (because in both calculations less arms were included); and that similar mean effects or ORs were found for most calculations (detailed comparative data are given in Supplemental Table 3, Supplemental Digital Content 6, http://links.lww.com/JCP/A126). (4) Although the figures show the mean effects and ORs for the compounds in parallel, the metacalculations reported here are the comparisons for each compound and the placebo. There are no comparisons between active compounds. (5) We could not control for concomitant medications, which are usually authorized in most studies, or for characteristics (eg, study duration, age, sex distribution) that may have differed from one study to another and within a specific trial from one arm to another. (6) Authors who extracted the data were not blinded as to authors, institutions, or journals, a potential source of bias. (7) The short-term study durations could result in underestimation of secondary effects. We had hoped to include long-term studies, but we found that most such studies are follow-up from industry-funded acute-phase, randomized, placebo-controlled trials, so that patients with the most serious adverse effects are excluded before the longer open phase, biasing the secondary-effect profile. Although it is the nature of clinical care to not treat patients for extended periods if they cannot tolerate a treatment acutely, we found no statistical way to take into account discontinuity between acute and follow-up phases. There is an urgent need for long-term, multiarm comparative studies of SGAs in child and adolescent patients, investigating both efficacy and adverse effects, as has been done in studies of first psychotic episodes in young adults.[33] In children and adolescents, the TEOSS (Treatment of Early-Onset Schizophrenia Spectrum) study (comparing molindone, risperidone, and olanzapine in early-onset schizophrenia) tried to achieve these goals, but only 46% (54/116) of the subjects entered the maintenance treatment after the acute phase (molindone, n = 20; olanzapine, n = 13; risperidone, n = 21).[34] The lack of statistical power led to cautious interpretation of the data.

Despite these caveats, this meta-analysis supports recent concerns regarding the secondary-effect profiles of SGAs in children and adolescents.[5,9] Guidelines for SGAs in children and adolescents should recommend careful monitoring of secondary effects, including clinical (weight, EPS, somnolence) and biological (glucose, lipids, and prolactin) assessments. Guidelines should also recommend cautious prescribing limited in most cases to evidence-based indications, to prevent what seems to be an inappropriate increase in the use of SGAs for a wide range of disorders.[7] The meta-analysis supports the view that SGAs as a class have substantial adverse effects and that each compound has a specific secondary-effect profile that should be taken into account in treatment decision making.

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REFERENCES

1. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry.* 2006;63:679–685.
2. Acquaviva E, Legleye S, Auleley GR, et al. Psychotropic medication in the French child and adolescent population: prevalence estimation from health insurance data and national self-report survey data. *BMC Psychiatry.* 2009;9:72.
3. Woods SW, Martin A, Spector SG, et al. Effects of development on olanzapine-associated adverse events. *J Am Acad Child Adolesc Psychiatry.* 2002;41:1439–1446.
4. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601.
5. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302:1765–1773.
6. Bonnot O, Inaoui R, Lloret C, et al. Surveillance of metabolic syndrome, hyperprolactinemia and cardiac side effects in children and adolescent treated with antipsychotic. Actuality and recommendations. *Neuropsychiatr Enfance Adolesc*. 2010;58:431–438.
7. Governale L, Mehta H. Outpatient use of atypical antipsychotic agents in the pediatric population: years 2004–2008. 2009. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM193204.pdf. Accessed July 26, 2010.
8. Cohen D. Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned? *Psychother Psychosom*. 2007;76:5–14.
9. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry.* 2008;165:1420–1431.
10. Detsky AS, Naylor CD, O'Rourke K, et al. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol*. 1992;45:255–265.
11. Caldwell D, Ades A, Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897–900.
12. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105–3124.
13. BUGS. The BUGS project. 1996–2008. Available at: http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml. Accessed July 28, 2010.
14. Lunn DJ, Thomas A, Best N, et al. WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput*. 2000;10:325–337.
15. Casella G, George E. Explaining the Gibbs sampler. *Am Stat*. 1992;167–174.
16. German S, Derman D. Stochastic relaxation, Gibbs distributions and the Bayesian restoration of images. *IEEE Trans Pattern Anal Machine Intell*. 1984;6:721–741.
17. Metropolis N, Rosenbluth A, Teller H, et al. Equation of state calculations by fast computing machines. *J Chem Physics*. 1953;21:1087–1092.

18. R Development Core Team. A language and environment for statistical computing. 2010. Available at: http://www.R-project.org. Accessed July 28, 2010.
19. Sturtz S, Ligges U, Gelman A. R2WinBUGS: a package for running WinBUGS from R. *J Stat Software*. 2005;12:1–16.
20. Plummer M, Best N, Cowles K, et al. CODA: convergence diagnosis and output analysis for MCMC. *R News*. 2006;6:7–11.
21. Fleischhaker C, Heiser P, Hennighausen K, et al. Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents. *J Neural Transm*. 2007;114:273–280.
22. Ratzoni G, Gothelf D, Brand-Gothelf A, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *J Am Acad Child Adolesc Psychiatry.* 2002;41:337–343.
23. 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.
24. Findling RL, Nyilas M, Forbes RA, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2009;70:1441–1451.
25. Haas M, Delbello MP, Pandina G, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. *Bipolar Disord*. 2009;11:687–700.
26. Haas M, Unis AS, Armenteros J, et al. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol*. 2009;19:611–621.
27. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry.* 2007;164:1547–1556.
28. Bonnot O, Inaoui R, Raffin-Viard M, et al. Children and adolescents with severe mental illness need Vitamin D supplementation regardless of disease or treatment *J Child Adolesc Psychopharmacol*. 2011;21:157–161.
29. Findling RL, Robb A, Nyilas M, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry.* 2008;165:1432–1441.
30. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry.* 2009;48:1110–1119.
31. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533–1540.
32. Moreno C, Merchan-Naranjo J, Alvarez M, et al. Metabolic effects of second-generation antipsychotics in bipolar youth: comparison with other psychotic and nonpsychotic diagnoses. *Bipolar Disord*. 2010;12:172–184.
33. McEvoy JP, Lieberman JA, Perkins DO, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry.* 2007;164:1050–1060.
34. Findling RL, Johnson JL, McLellan J, et al. Double-blind maintenance safety and effectiveness findings from the Treatment of Early-Onset Schizophrenia Spectrum (TEOSS) study. *J Am Acad Child Adolesc Psychiatry.* 2010;49:583–594.
35. Pavuluri MN, Henry DB, Findling RL, et al. Double-blind randomized trial of risperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disord*. 2010;12:593–605.
36. Wozniak J, Mick E, Waxmonsky J, et al. Comparison of open-label, 8-week trials of olanzapine monotherapy and topiramate augmentation of olanzapine for the treatment of pediatric bipolar disorder. *J Child Adolesc Psychopharmacol*. 2009;19:539–545.
37. Tramontina S, Zeni CP, Ketzer CR, et al. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *J Clin Psychiatry.* 2009;70:756–764.
38. Delbello M. Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children (REACH): a double-blind, randomized, placebo-controlled study of the efficacy and safety of risperidone for the treatment of acute mania in bipolar I disorder. 2005. Available at: http://download.veritasmedicine.com/PDF/CR003631_CSR.pdf. Accessed July 28, 2010.
39. Haas M, Eerdekens M, Kushner S, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. *Br J Psychiatry.* 2009;194:158–164.
40. Biederman J, Mick E, Hammerness P, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-age children. *Biol Psychiatry.* 2005;58:589–594.
41. Division of Psychiatry Products H. Statistical review and evaluation on ziprasidone NDA/serial no. 20-825 (SE5-032). 2009. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM193492.pdf. Accessed July 28, 2010.
42. 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.
43. DelBello MP, Kowatch RA, Adler CM, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry.* 2006;45:305–313.
44. DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disord*. 2009;11:483–493.
45. Rak IW. Seroquel® (quetiapine fumarate) for treatment of pediatric patients with bipolar mania (10–17 years) or schizophrenia (13–17 years). 2009. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM177104.pdf. Accessed July 28, 2010.
46. Research Units in Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;(347):314–321.
47. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634–e641.
48. Aman MG, De Smedt G, Derivan A, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. *Am J Psychiatry.* 2002;159:1337–1346.
49. Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison. *Biol Psychiatry.* 2008;63:524–529.
50. Sporn AL, Bobb AJ, Gogtay N, et al. Hormonal correlates of clozapine-induced weight gain in psychotic children: an exploratory study. *J Am Acad Child Adolesc Psychiatry.* 2005;44:925–933.
51. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry.* 2000;39:292–299.

52. Snyder R, Turgay A, Aman M, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. *J Am Acad Child Adolesc Psychiatry.* 2002;41:1026–1036.

53. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry.* 1996;53:1090–1097.

54. 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.

55. Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry.* 2000;39:509–516.

56. DelBello MP, Versavel M, Ice K, et al. Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. *J Child Adolesc Psychopharmacol*. 2008;18:491–499.

57. Gaffney GR, Perry PJ, Lund BC, et al. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry.* 2002;41:330–336.

58. Barzman DH, DelBello MP, Adler CM, et al. The efficacy and tolerability of quetiapine versus divalproex for the treatment of impulsivity and reactive aggression in adolescents with co-occurring bipolar disorder and disruptive behavior disorder(s). *J Child Adolesc Psychopharmacol*. 2006;16:665–670.

59. Buitelaar JK, van der Gaag RJ, Cohen-Kettenis P, et al. A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with subaverage cognitive abilities. *J Clin Psychiatry.* 2001;62:239–248.

60. Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia: a double-blind, randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry.* 2006;63:721–730.

61. Jensen JB, Kumra S, Leitten W, et al. A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders. *J Child Adolesc Psychopharmacol*. 2008;18:317–326.

62. Mozes T, Ebert T, Michal SE, et al. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. *J Child Adolesc Psychopharmacol*. 2006;16:393–403.