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 ± 4.2 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

A typical 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 and in Europe. The risk of adverse effects (weight gain, somnolence, and EPS) with olanzapine was reported to be significantly increased in young patients compared with adults, leading to concerns about the use of SGAs in children. Emerging findings indicate that children and adolescents are more vulnerable to weight gain, cardiometabolic effects (increase in glucose, triglycerides, and cholesterol levels), and hyperprolactinemia. 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.

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, 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...
us to include both multimodal comparative studies and secondary-effect studies (eg, see Correll et al and Sikich et al). 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) 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 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 sampling15,16 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 2.11.018 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 1.29 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).

**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).
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
(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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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,\textsuperscript{5,25–27} whereas the association of drug dosage with EPS appears to be consistent in the case of aripiprazole.\textsuperscript{24,29–31} A given diagnosis per se does not seem to influence weight gain and metabolic changes.\textsuperscript{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 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**

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<th>Aripiprazole</th>
<th>Clozapine</th>
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*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. This may have introduced bias in metacalculations. 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. 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). 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. 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. 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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AUTHOR DISCLOSURE INFORMATION

Dr Cohen reported past consultation for or the receipt of honoraria from Schering-Plough, Bristol-Myers Squibb, Otsuka, Janssen, and Sanofi-Aventis. Dr Consoli reported receiving travel support from Bristol-Myers Squibb. Dr Bonnot reported receiving travel support from Actelion. No other authors reported financial disclosure or conflict of interest.

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