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Risperidone or aripiprazole in children and adolescents with autism and/or intellectual disability: A Bayesian meta-analysis of efficacy and secondary effects

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ABSTRACT

Second-generation antipsychotics (SGAs) induce frequent adverse effects in children and adolescents with each compound appearing to have a specific adverse effect profile. Aripiprazole and risperidone are FDA-approved medications for behavioral disturbances associated with autism and/or intellectual disabilities (ID) in children and adolescents. Using Bayesian meta-analysis of all relevant studies ($N = 8$; 18 arms; 782 patients), we aimed to calculate odds ratios (OR) or mean average effects to assess efficacy, weight gain, metabolic changes, sedation, and extra-pyramidal syndrome (EPS) of the two compounds. Reporting was incomplete to assess metabolic changes. Compared to placebo, significant treatment-related increases were observed for: CGI response with aripiprazole (OR = 6.09, 95% credible interval [2.3–12.63]) and risperidone (12.8 [5.57–27.33]); weight gain with aripiprazole (OR = 6.28 [1.64–17.12]) and risperidone (7.76 [1.88–25.2]); EPS with risperidone (OR = 3.72 [1.73–7.22]); and somnolence/sedation with aripiprazole (OR = 25.76 [1.29–112.3]) and risperidone (9.63 [3.52–22.79]). There were no significant differences between active compounds. We conclude that short term efficacy of risperidone and aripiprazole are similar for behavioral disturbances associated with autism and/or ID, and that secondary effects are frequent. More research should be conducted on metabolic changes as current literature is lacking compared to other indications in youths.

1. Introduction

Atypical or second-generation antipsychotic medications (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 FDA-approved medications for bipolar mania in children and adolescents (age 10–17 years; except olanzapine, age 13–17 years) and for adolescent schizophrenia (age 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 (ID) in children and adolescents (age 6–17 years) (Bonnot & Holzer, 2012). SGAs were developed to limit the frequency of

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extrapyramidal syndrome (EPS). However, comparisons between the two compounds in this last indication lack regarding both efficacy and adverse events. This is unfortunate as we recently have shown that the risk of adverse effects in children and adolescents receiving SGA is frequent and that each compound's adverse effect profile is specific (Cohen, Bonnot, Bodeau, Consoli, & Laurent, 2012). Thus, in performing a Bayesian meta-analysis on 41 short-term controlled studies (93 arms) with children and adolescents ($N = 4015$) treated with SGA we found that olanzapine, clozapine, risperidone, quetiapine, and aripiprazole increased weight gain; risperidone and olanzapine increased glucose levels; quetiapine and olanzapine increased cholesterol and triglyceride levels; risperidone, olanzapine and ziprasidone increased prolactinemia; ziprasidone, olanzapine, aripiprazole, risperidone increased the risk of EPS; finally, all SGAs increased the risk of somnolence/sedation. Since some authors have suggested that individuals with autism and/or ID may be more at risk of adverse effects due to neuro-developmental vulnerabilities (Matson & Hess, 2011; Périsse, Guinchat, Hellings, & Baghdadli, 2012), we aimed to assess efficacy and secondary effects of SGA in treating behavioral disturbances in children and adolescents with autism and/or ID. 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 to include both multi-arm comparative studies and secondary-effect studies (Cohen et al., 2012). We hypothesized that compounds have distinct profiles of secondary effects which should be known and taken into account in treatment decision-making.

2. Methods

2.1. Search and study selection

Study selection is detailed in Cohen et al. (2012). 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 EMEA 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) cross-over; 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 ($\leq$12 weeks); (5) unrelated research questions (e.g., young adult; pharmacovigilance or kinetics studies); (6) literature reviews; (7) data already reported; (8) study duration $\geq$13 weeks; and (9) incomplete reporting of variables of interest (see below). In total; we found 41 short-term studies of the relevant drugs; all published in English. Among these studies 8 reported efficacy and secondary effects of SGA (risperidone: 6 studies; aripiprazole: 2 studies) in children and adolescents with autism and/or ID.

2.2. Data extraction and pertinent criteria

Two co-authors (DC and OB) independently extracted the relevant data from the original selected reports. Extracted data were compared to ensure accuracy. In case of disagreements, we checked original report for relevant data. Given the Bayesian statistics performed, the authors decided not to impute missing data with replacement values. Rather, 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 standard deviation) and 0 when data were incomplete or absent; the adverse effect quality score (AEQS) was the sum. It could range from 1 to 13 (Cohen et al., 2012). We did not use a "classic" quality score (e.g., criteria of Detsky, Naylor, O'Rourke, McGeer, & L'Abbe, 1992) 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 reflect 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) percentage of responders using the Clinical Global Improvement (CGI) scale; (2) 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%); (3) the percentage of subjects reporting *somnolence/sedation*; (4) the percentage of subjects with clinical *EPS and/or akathisia*. Analyses for the percentage of subjects with clinically significant increase of cholesterol, triglyceride, glucose, and prolactine and for change in body mass index were not conducted as these variables were poorly reported across studies. Similarly, weight (kg), glucose (mg/dl); cholesterol (mg/dl); (4) triglycerides (mg/dl); prolactin (ng/dl) changes were not conducted as these variables were poorly reported for risperidone.

2.3. Statistical analysis

Given that data were available from double-blind, placebo-controlled trials and from naturalist controlled trials comparing one or more compounds, we used a Bayesian method to keep the maximum amount of information in the meta-analysis (Caldwell, Ades, & Higgins, 2005; Lu & Ades, 2004). As stated previously, to limit bias, we decided not to impute missing data

with replacement values as is the case in many meta-analysis using more classical calculation, in particular regarding standard deviation that are not systematically reported in studies. We used a logistic regression model as all our data were binary outcome variables. The Bayesian model was implemented using WinBUGS version 1.4 (BUGS, 2010), a software used to analyze complex statistical models with Markov chain Monte Carlo methods (Lunn et al., 2000), using Gibbs sampling (Casella & George, 1992; German & Derman, 1984) and the Metropolis algorithm (Metropolis, Rosenbluth, Teller, & Teller, 1953) 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 (R Development Core Team, 2010) using the R2WinBUGS package (BUGS, 2010; Sturtz, Ligges, & Gelman, 2005).

For each variable, we estimated the mean effect of each compound compared to 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 standard deviations. We then constructed posterior distributions of the treatment effects from two 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 non-autocorrelation and the convergence of each chain. Those criteria were checked using the CODA package (Plummer, Best, Cowles, & Vines, 2006). Convergence was assessed using Geweke's convergence diagnostic (Z-score), and the non-autocorrelation 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.

3. 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 and/or ID, Tourette syndrome and conduct disorder. Among these studies, 8 trials investigated SGA for behavioral disturbances in children and adolescents with autism and/or ID. In total, the meta-analysis consisted of 18 arms, including 782 children and adolescents who received aripiprazole (4 arms, $N = 213$), risperidone (6 arms, $N = 226$), or placebo (8 arms, $N = 343$). Efficacy and secondary effects occurring with aripiprazole and risperidone were compared to those occurring in children and adolescents treated with a placebo. Table 1 summarized the main characteristics of the studies. Reporting was incomplete to assess metabolic changes in studies with risperidone. No meta-calculations were therefore possible for these variables.

3.1. Efficacy (Fig. 1)

Efficacy was assessed using the percentage of patients who had meaningful response according to clinical global impression. Both aripiprazole and risperidone were superior to placebo: OR = 6.09, 95% credible interval [2.3–12.63] and 12.8

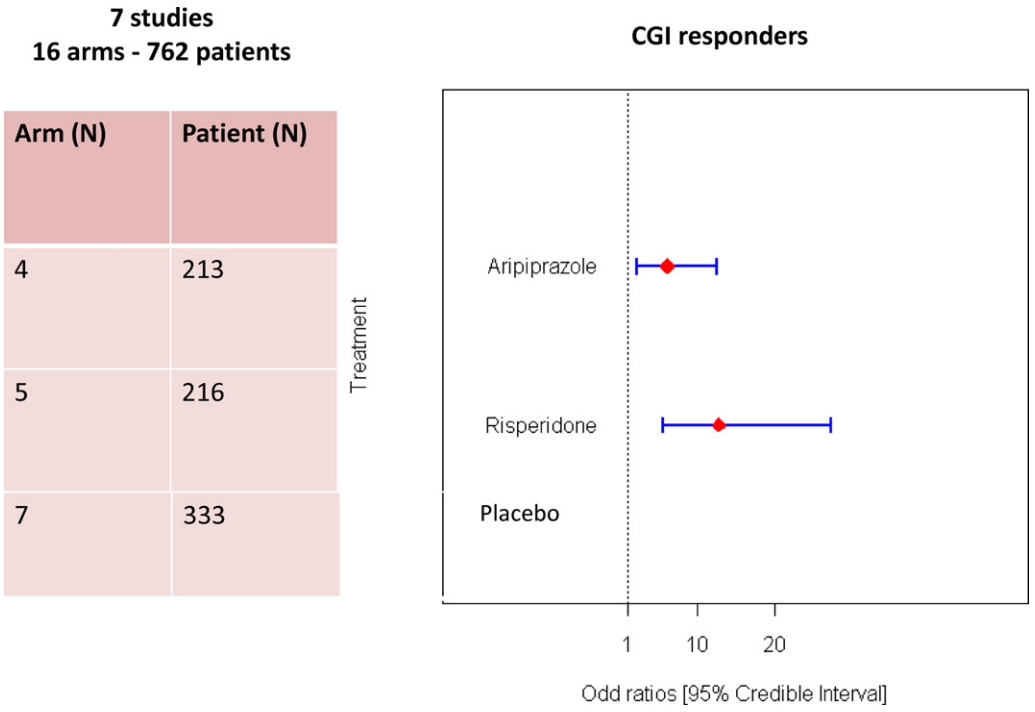

Fig. 1. Odds ratios (95% credible interval) of patients with significant clinical response (define as very much or much improved using the clinician global impression (CGI) scale) in risperidone and aripiprazole trials for behavioral disturbances of children and adolescents with autism and/or intellectual disability.

Table 1
Short term studies with atypical antipsychotics in children and adolescents with PDD and/or ID and behavioral disturbances: main characteristics.

Author(s) (year)	Arm	Subjects (*N*)	Dose (mg)	Adolescent only	Mean age	Duration (weeks)	Random	Male (%)	White (%)	Sites (N)	US only	Washout	Industry funded	AEQS	CGI (%RES)	Weight (%CME)	Sedation (%CME)	EPS (%CME)
Owen et al. (2009)	Aripiprazole	47	2/15	No	9.7	8	Yes	89.4	80.4	20	Yes	Yes	Yes	6	67	14	17	14.9
	Placebo	51			8.8			86.3	68.1						16	3	4	8
Marcus et al. (2009)	Aripiprazole	53	5	No	9	8	Yes	88.7	69.8	37	Yes	Yes	Yes	8	78	17	1.9	23.1
	Aripiprazole	59	10		10			84.7	69.5						80	9	6.8	22
	Aripiprazole	54	15		9.5			92.6	77.8						83	16	3.7	22.2
	Placebo	52			10.2			92.3	67.3						50	4	0	11.8
RUPPAN (2002)	Risperidone	49	1.8	No	8.8	8	Yes	80	66	5	Yes	Yes	No	4	75.5	5	59	34
	Placebo	52			8.8			83	66						11.5	1	27	10
Shea, Turgay, Carroll, et al. (2004)	Risperidone	40	1.17	No	7.6	8	Yes	72.5	67.5		No	No	Yes	3	54	NR	72.5	12.8
	Placebo	39			7.3			82.1	71.8						18	NR	7.7	27.5
Aman, De Smedt, Derivan, Lyons, and Findling (2002)	Placebo	63		No	8.1	6	Yes	79	62	11	Yes	Yes	Yes	4	7.9	1	10	0
	Risperidone	55	1.16		8.7			85	51						53.8	8	54	4
Snyder, Turgay, Aman, et al (2002)	Placebo	57		No	8.8	6	Yes	73.7	73.7	11	Yes	Yes	Yes	4	10.6	0	14	5
	Risperidone	53	0.98		8.6			77.4	78.8						32.1	4	41	13.2
Findling, McNamara, Branicky, et al. (2000)	Placebo	10		No	9.2	10	Yes	95	NR	1	Yes	No	Yes	3	NR	NR	20	0
	Risperidone	10	4.1		9.2			95	NR						NR	NR	30	0
Buitelaar, van der Gaag, Cohen-Kettenis, and Melman (2001)	Risperidone	19	2.9	Yes	14	6	Yes	89	NR	2	No	Yes	Yes	3	68	9	5	26
	Placebo	19			13.7			84	NR						5	6	58	18

PDD, pervasive developmental disorder; ID, intellectual disability; RUPPAN, research units on pediatric psychopharmacology autism network; AEQS, adverse effect quality score; %CME, % clinically meaningfull events; EPS, extra pyramidal syndrome; CGI, clinical global impression; %RES, % of responders; Random, randomization.
As we could not control for study characteristics that may have differed from one study to another and within a specific trial from one arm to another, we checked whether study characteristics differed according drug exposure. Using Kruskal–Wallis test, we found no significant differences for the number of subjects per arm, mean age, gender distribution, and study duration according to drug/placebo exposure ($p = 0.072$, 0.192, 0.118, 0.121, respectively).

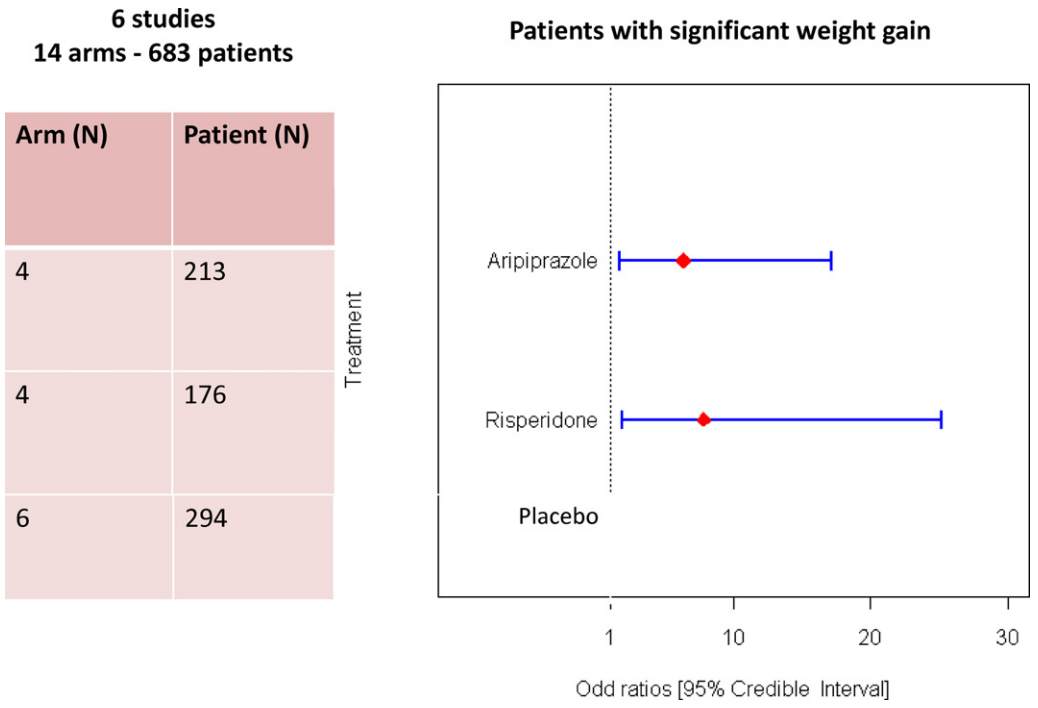

Fig. 2. Odds ratios (95% credible interval) of patients with significant weight gain in risperidone and aripiprazole trials for children and adolescents with autism and/or intellectual disability.

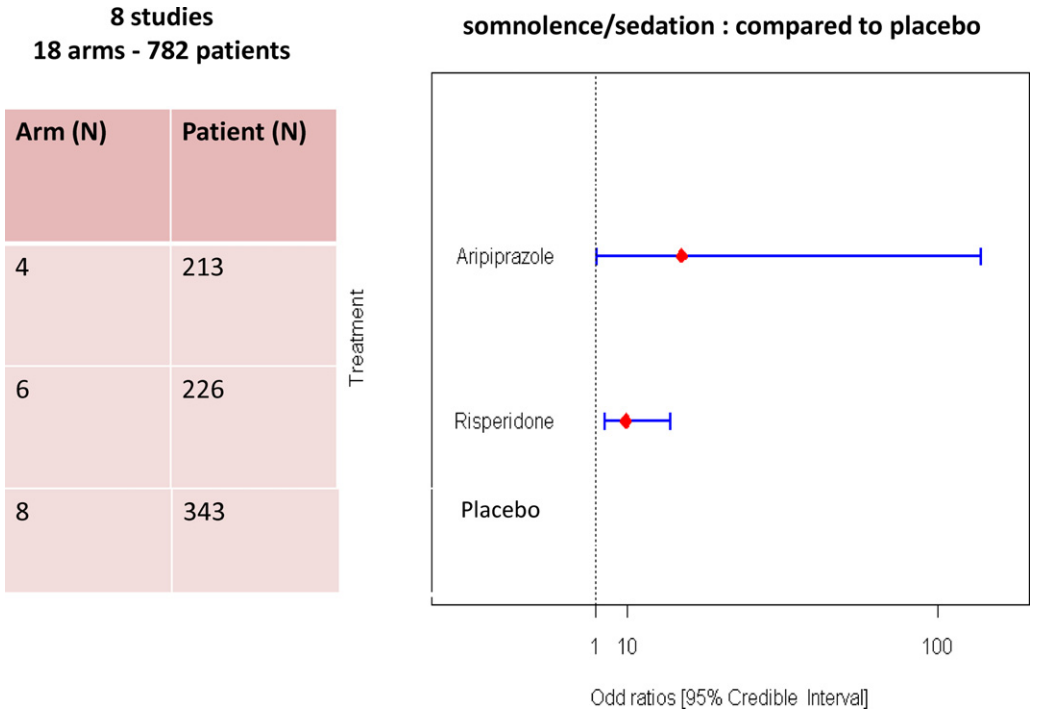

Fig. 3. Odds ratios (95% credible interval) of patients with somnolence in risperidone and aripiprazole trials for children and adolescents with autism and/or intellectual disability.

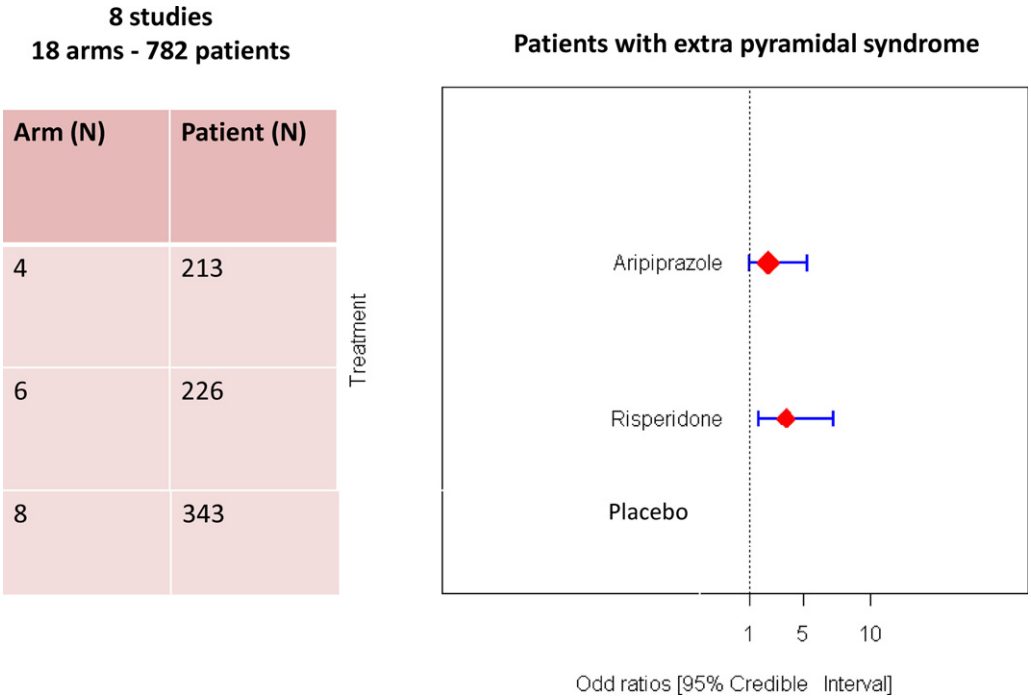

Fig. 4. Odds ratios (95% credible interval) of patients with extrapyramidal syndrome (EPS) in risperidone and aripiprazole trials for children and adolescents with autism and/or intellectual disability.

[5.57–27.33], respectively. There were no significant differences between active compounds. This analysis included 7 studies, 16 arms and 762 patients.

3.2. Secondary effects (Figs. 2–4)

For weight gain, we considered the percentage of patients who had meaningful weight gain during the trial and calculated the odds ratios [95% credible interval] for each compound. This analysis included 6 studies, 14 arms and 683 patients. Both compounds significantly increased the risk of meaningful weight gain: aripiprazole (OR = 6.28 [1.64–17.12]) and risperidone (7.76 [1.88–25.2]). There were no significant differences between active compounds.

We found the percentage of patients complaining of sedation/somnolence during each trial and calculated the odds ratios [95% credible interval] for each compound. This analysis included 8 studies, 18 arms and 782 patients. Both compounds significantly increased the risk of reporting somnolence/sedation compared to placebo: aripiprazole OR = 25.76 [1.29–112.3] and risperidone OR = 9.63 [3.52–22.79]. There were no significant differences between active compounds.

We found the percentage of patients showing EPS, including akathisia, during each trial and calculated the odds ratios [95% credible interval] for each compound. This analysis included 8 studies, 18 arms and a total of 782 patients. Only risperidone significantly increased the risk of EPS compared to the placebo: risperidone OR = 3.72 [1.73–7.22] and aripiprazole OR = 2.44 [0.99–5.26] ($p > 0.05$). However, there were no significant differences between active compounds.

4. Discussion

Although the Pediatric Research Equity Acts and the Best Pharmaceuticals for Children Act have clearly increased the number of studies of treatment of children with SGAs, it appears that few controlled studies have been conducted in children with AD and/or ID and these were limited to two compounds risperidone and aripiprazole. We were struck by several points while reviewing this literature. (1) The results of most of these reports focus on efficacy rather than adverse effects. (2) The quality of reporting is poor as shown by AEQS mean (±SD) equal to 4.37 (±2.12) [maximum score = 13]. However, AEQS was correlated with the year of publication (Spearman $r = 0.88$) meaning that reporting of adverse effects has improved in the recent years. (3) All but one study (RUPPAN, 2002) were industry-funded. (4) No studies with risperidone reported treatment increases in prolactin levels nor in glucose, triglyceride or cholesterol changes. (5) The tendency to de-emphasize adverse effects was not limited to industry-sponsored trials since it was also the case for the RUPPAN study (2002). 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 with autism and/or ID to enable clinicians to make judgments based on a more balanced risk/benefit analysis.

In this meta-analysis of relevant short-term controlled studies of children and adolescents treated with SGAs for behavioral disturbances associated with autism and/or ID, efficacy of risperidone and aripiprazole was comparable and both compounds significantly decreased behavioral symptoms as assessed by the number of responders. However, secondary effects occurred with a significant frequency for both risperidone and aripiprazole. Somnolence/sedation effects were the most frequently reported adverse event and should be considered carefully as it may impact learning in children and adolescents with autism and/or ID. The severity of the problem of weight gain with most SGAs has been discussed in several reports (Correll, Manu, Olshanskiy, et al., 2009; Fleischhaker, Heiser, Hennighausen, et al., 2007; Ratzoni, Gothelf, Brand-Gothelf, et al., 2002) with the exception of aripiprazole that, according to EMEA SmPC, "has not been shown to induce clinically relevant weight gain". In children and adolescents with autism and/or ID, this is not the case as we found a significant increase in the percentage of patients with a meaningful weight gain at the end of the study for both aripiprazole and risperidone. Regarding EPS, only risperidone significantly increased the risk of EPS compared to the placebo in children and adolescents with autism and/or ID. This might be explained by the specific profile of aripiprazole that exhibit both dopamine receptors agonist and antagonist properties (Tadori, Forbes, McQuade, & Kikuchi, 2011).

Although we could not perform meta-calculations for metabolic and hormonal changes in the subgroup of patients with autism and/or ID because of lack of reporting in risperidone studies, we should recall here the results obtained whatever the indication (Cohen et al., 2012). Risperidone and aripiprazole differ also in their metabolic effects. We found a small but significant increase in blood glucose for risperidone (mean increase: 3.7 ± 1.36 mg/dl). However, we cannot exclude the possibilities that (1) long-term metabolic effects may be more clinically meaningful and may correlate with duration of risperidone treatment and (2) some patients appear to experience dramatic increases in some of these variables, whereas we considered only mean changes. Also, risperidone significantly increased the risk of clinically meaningful hyperprolactinemia with an OR above 30: OR = 38.63 (95% Credible Interval: 8.62–125.6). Some large studies (Findling, Nyilas, Forbes, et al., 2009; Haas, Delbello, Pandina, et al., 2009; Haas, Unis, Armenteros, et al., 2009) described hyperprolactinemia as a function of gender and suggested that the prolactin increase doubles for females compared to 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 with autism and/or ID treated with risperidone and should be investigated in follow-up studies (Bonnot, Inaoui, Raffin-Viard, et al. 2011).

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 (Correll et al., 2009; Haas, Delbello, et al., 2009), whereas the association of drug dosage with EPS appears to be consistent in the case of aripiprazole (Findling, Robb, Nyilas, et al., 2008; Marcus, Owen, Kamen, et al., 2009; Owen, Sikich, Marcus, et al., 2009). A diagnosis of autism and/or ID seems to influence weight gain for aripiprazole, but we cannot exclude that age is a confounding factor as studies conducted on bipolar disorder and schizophrenia included older patients, mainly adolescents (Cohen et al., 2012). Given the limited data, more research is needed in this field. Table 2 summarizes risperidone and aripiprazole secondary effect profiles in treating behavioral disturbances of children and adolescents with autism and/or ID.

The results from this meta-analysis need to be interpreted within its limitations: (1) the variable reporting of secondary effect data. (2) The numbers of study arms and patients treated were low explaining the large 95% credible intervals. (3) Although the figures show the mean effects and ORs for the compounds in parallel, the meta-calculations reported here are the comparisons for each compound and the placebo. (4) We could not control for concomitant medications, which are authorized in most studies, or for characteristics (e.g., study duration; age; gender distribution) that may have differed from one study to another and within a specific trial from one arm to another. (5) Authors who extracted the data were not blinded as to authors, institutions, or journals, a potential source of bias. (6) 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 of time 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, multi-arm comparative studies of SGAs in child and adolescent patients with autism and/or ID, investigating both efficacy and adverse effects, as has been done in studies of first psychotic episodes in young adults (McEvoy, Lieberman, Perkins, et al., 2007). In children and adolescents, the TEOSS study (comparing molindole, 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, $n = 21$) (Findling, Johnson, McLellan, et al., 2010). 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 and specifically, risperidone and aripiprazole in children and adolescent with autism and/or ID (Correll et al., 2009; Sikich, Frazier, McClellan, et al., 2008). 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 (Bonnot, Inaoui, Lloret, & Cohen, 2010). 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 including autism and/or ID (Governale & Mehta, 2010). The meta-analysis supports the view that risperidone and aripiprazole have substantial adverse effects and that each compound has a specific secondary effect profile that should be taken into account in treatment decision-making.

Table 2
Summary of risperidone and aripiprazole secondary effects reported in controlled short-term studies for behavioral disturbances in children and adolescents with autism and/or ID.

	Aripiprazole	Risperidone
↗ Weight	++	++
↗ Glucose[a]	+/−	++
↗ Cholesterol[a]	0	0
↗ Triglycerides[a]	0	+/−
Hyperprolactinemia[a]	0	++++
Sedation	++++	++
Extrapyramidal syndrome	+/−	+

ID, intellectual disability.
[a] Based on the calculation of odds ratios or mean changes conducted in Cohen et al. report (2012) that assessed SGA adverse effects whatever the indication.

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