META-ANALYSIS

Umbrella Review: Association Between Antipsychotic Drugs and Metabolic Syndrome Hallmarks in Children and Adolescents

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Objective: To summarize the available evidence on metabolic parameters indicating metabolic adverse effects and risk of metabolic syndrome in children and adolescents treated with antipsychotics, following a pre-specified protocol (PROSPERO ID 252336).

Method: We searched PubMed, Embase and PsycINFO until May 14, 2021, to identify systematic reviews (SR), meta-analyses (MA) and network meta-analyses (NMA) examining symptoms associated to metabolic syndrome in patients <18 years of age who required treatment with oral antipsychotic drugs. Evidence from quantitative analyses for all outcomes related to anthropometric, glyco-metabolic, and blood pressure parameters (measured from baseline to intervention-end and/or follow-up, in subjects exposed to antipsychotics and placebo) was reported on the basis of their metrics (median difference [medianD], mean difference [MD], standardized mean difference [SMD], odds ratio [OR], risk ratio ([RR]). A qualitative synthesis was also made. A formal quality assessment of the included studies was carried out by using the AMSTAR 2. We also provided a hierarchical stratification of the evidence from meta-analyses based on the class of evidence.

Results: A total of 23 articles (13 MA, 4 NMA and 6 SR) were included for review. As compared with placebo, an increase in triglyceride levels was associated with olanzapine (medianD [95% CI]: 37 [12.27, 61.74] mg/dL; MD [95% CI]: 38.57 [21.44, 55.77] mg/dL) and quetiapine (medianD [95% CI]: 21.58 [95% CI]: 4.27, 38.31 mg/dL; MD [95% CI]: 34.87 [20.08, 49.67] mg/dL; SMD [95% CI]: 0.37 [0.06, 0.068]), whereas decreased triglyceride levels were found for lurasidone. Increased total cholesterol level was associated with asenapine (medianD [95% CI]: 9.1 [1.73, 16.44] mg/dL), quetiapine (medianD [95% CI]: 15.60 [7.30, 24.05] mg/dL; olanzapine (MD [95% CI] from 3.67 [1.43, 5.92] mg/dL to 20.47 [13.97, 26.94] mg/dL]; and lurasidone (medianD [95% CI]: 8.94 [1.27, 16.90] mg/dL). Change in glucose levels did not differ among antipsychotics or placebo. Lurasidone, molindone, and ziprasidone were the best tolerated in terms of weight gain. According to the AMSTAR 2 scoring system, 13 (56.5%) reviews were rated as very low quality. According to classes of evidence, most MA were level 4, especially because of their limited total sample size.

Conclusion: By collating meta-analyses assessing biochemical markers of metabolic syndrome in antipsychotic-treated children, we conclude that olanzapine should not be the antipsychotic of choice in patients at risk for hypertriglyceridemia or hypercholesterolemia. Aripiprazole and lurasidone appear to be better tolerated in terms of metabolic adverse events. Insufficient meta-analytic data are available to provide a precise risk estimate of metabolic syndrome, and, overall, the quality of evidence is low.

Study registration information: Association between the use of antipsychotic drugs and alterations of the parameters defining the Metabolic Syndrome (MetS) in children and adolescents: an umbrella review; https://www.crd.york.ac.uk/prospero/; CRD42021252336.

Key words: antipsychotics; triglycerides; cholesterol; glucose; pediatric

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Antipsychotic drugs (antipsychotics) are increasingly being used in children and adolescents, on and off label, for treating a wide range of acute and chronic psychiatric disorders and for neuropsychiatric rehabilitation.[1] Notwithstanding the well-documented efficacy in several disorders,[2,3] significant evidence supports the notion that antipsychotics may cause metabolic disturbances, with different risk profiles among different drugs.[4-6] Indeed, metabolic adverse events are often treatment limiting and a reason for discontinuation[4,7]; they are difficult to prevent and to treat, and may cause severe long-term outcomes.[8,9] The pathophysiology of metabolic adverse events may involve both neurotransmitter receptors and other mechanisms. Mechanisms based on specific neurotransmitter

receptors include alterations of appetite, of reward gained from eating, and disruption of neurohormonal signals in the hypothalamus (satiety hormones, insulin, others), muscles, liver, fat, gut, and pancreas (glycemic and lipidemic regulation).[10] Mechanisms independent of neurotransmitter receptors involve a direct interference of antipsychotics with sterol trafficking and lipid/sterol metabolism in cells, leading to hyperproduction of lipids and sterols with consequent energy depletion[11]; this activity is based on the chemical nature of antipsychotics as weak base amphiphilic drugs, but its precise mechanism is unclear.

A recent meta-analysis with meta-regression showed in adults that clozapine and olanzapine are associated with the greatest risk of metabolic disturbances related to levels of triglycerides, cholesterols, and glycemic indexes, whereas aripiprazole and ziprasidone showed the lowest risk; the authors also showed that the risk score of antipsychotics for causing glyco-metabolic alterations is correlated with their propensity to remain non-ionized in hydrophobic membranes vs their propensity to become ionized and consequently to be extracted from membranes.[5,11] A recent meta-review highlighted that aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, and risperidone are associated with increased risks of weight gain; aripiprazole, olanzapine, and quetiapine are associated with risk of increased cholesterol, whereas asenapine, olanzapine, and risperidone are associated with risk of glucose increase/diabetes.[6] Whereas the general notion of antipsychotics causing weight gain is well established, in both adults and youth, less is known about the association with metabolic syndrome (MetS) and even less in biochemical parameters that are early predictors of it. As of today, there is no standard definition for MetS in childhood. Pediatricians usually refer to the current Adult Treatment Panel (ATP III) definition of MetS, a constellation of at least 3 of the followiing 5 cardiometabolic risk factors: hypertriglyceridemia, low HDL, high fasting glucose, central obesity (based on waist circumference), and hypertension.[12] In 2004, de Ferranti *et al.* defined criteria for pediatric MetS based on the ATP III, and proposed for diagnosis the presence of 3 or more of the following findings: high fasting triglycerides (>1.1 mmol/L or 100 mg/dL); low HDL (<1.3 mmol/L or 50 mg/dL, except in boys 15 to 19 years of age, in whom the cut-point was <1.2 mmol/L or 45 mg/dL); fasting glucose (>6.1 mmol/L or 110 mg/dL); waist circumference >75th percentile for age and sex; and systolic blood pressure above the 90th percentile for sex, age, and height.[13] In 2012, the US Department of Health and Human Services issued an expert panel report on cardiovascular health for children and adolescents[14] detailing the acceptable, borderline, and elevated levels for all parameters that define MetS in children and adolescents. Desirable BMI, waist circumference, and blood pressure levels should be under the 95th percentile; HDL cholesterol should be higher than 40 mg/dL, LDL cholesterol lower than 110 mg/dL, total cholesterol lower than 170 mg/dL, and triglycerides lower than 75 or 90 mg/dL, respectively for children under or over 10 years of age, and fasting glucose should be lower than 126 mg/dL. With respect to maximal tolerable variations, the panel indicated −5 mg/dL HDL, +20 mg/dL LDL, +30 mg/dL total cholesterol, +25 or +40 mg/dL triglycerides (below or above 10 years of age), and +26 mg/dL fasting glucose, as limits indicating a risk factor for MetS.[14]

Data on adults, although not definitive,[15] suggested that antipsychotics have an impact on all MetS criteria. A comprehensive summary of the available evidence on the youth population is thus needed, to perform a risk assessment on the development of antipsychotic-related MetS.

Despite a comprehensive review providing high-quality evidence on any type of adverse effects following the use of several drug classes (antidepressants, antipsychotics, anti−attention-deficit/hyperactivity medications, and mood stabilizers) in pediatrics that has been recently published,[6] there has been no systematic effort to summarize the currently available evidence from existing systematic reviews and meta-analyses specifically on the wide range of metabolic adverse effects in response to antipsychotics in children and adolescents.[16]

This umbrella review aims to do the following: (1) to appraise and to grade the quality and strength of the evidence from existing meta-analyses (or systematic reviews or network meta-analyses) across metabolic symptoms in the youth population treated with antipsychotics; and (2) to provide a comprehensive summary of the degree of change for each metabolic symptom, to better support the pharmacological management of pediatric patients in clinical practice.

METHOD

This umbrella review was conducted following the protocol CRD42021252336 registered on PROSPERO beforehand.

Inclusion criteria

Patients Included in the Reviews. Participants were children and adolescents <18 years of age who were diagnosed with all psychiatric disorders using any diagnostic criteria and requiring treatment with antipsychotic drugs, regardless of nationality, sex, length/stage of illness, or treatment setting.

Interventions

We included systematic reviews (SR), meta-analyses (MA), and network meta-analyses (NMA) focused on oral antipsychotic drugs (on and off label), regardless of the type, dose, or treatment schedule. We considered antipsychotics compared to placebo and/or to other antipsychotics, or we considered comparisons between baseline and follow-up assessments in the context of treatment with 1 antipsychotic. We included only studies in which all participants were in the age range of interest (<18 years).

Outcomes

We made qualitative and quantitative synthesis of all outcomes related to anthropometric, glyco-metabolic, and blood pressure parameters on the basis of their metrics (median difference [medianD], mean difference [MD], standardized mean difference [SMD], odds ratio [OR], risk ratio [RR]), measured from baseline to intervention end and/or post-intervention follow-up.

Types of Studies

The types of studies included were SR, MA, and NMA that followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

We considered both SR including randomized controlled trials (RCT) and those including other study designs (eg, cohort studies). We included only MA that separately analyzed observational studies and clinical trials. In the case that 2 SR addressed the same psychiatric disorder, treatment, and outcomes, we included the SR reporting the largest amount of data, in terms of the number of studies. Narrative literature reviews were excluded. MA or SR that included long-acting formulations were excluded.

Search Strategy and Selection Criteria

The present umbrella review summarizes the results from NMA, MA, and SR, assessing the association between antipsychotic drugs and alterations of parameters defining the MetS in children and adolescents.

To provide decision makers with all of the known information obtained from systematically performed searches, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[17] as previously used for carrying out similar and recent umbrella reviews[18,19] and a Web-based search in 3 scientific libraries, namely, PubMed, Embase, and APA Psycinfo, was performed, from inception to May 14, 2021.

Our search strategy for PubMed is fully described in Supplement 1, available online; the search strategy was adapted as needed for each database. In brief, we used 3 domains referring to the following: (1) orally administered antipsychotic drugs; (2) pediatric patients; and (3) systematic review/meta-analysis. Psychiatric diagnosis was not a search criterion. There were no language or date restrictions for the inclusion.

Two authors (C.C. and C.S.) independently screened titles and abstracts for eligibility. The full-texts of potentially eligible articles were retrieved. Any disagreement was solved through discussion with a third investigator (M.P.).[20]

Data Extraction and Analysis

V.B. and M.P.R performed the preliminary data extraction. Extracted data were independently further checked by S.R., and disagreements were solved upon reaching a consensus with a third investigator (S.P.), as recommended by the PRISMA criteria.[17] Data were extracted by using prespecified forms that contained the following: (1) general information, including title, author, year published, and health outcome assessed; (2) type of review performed; (3) population assessed; (4) databases screened for the review; (5) date range of publication of the included articles; (6) quality appraisal tool used for bias assessment; (7) results from NMA and MA; (8) results from more than 1 study that were not meta-analyzed but were discussed by the authors.

As recommended by Fusar-Poli and Radua,[21] we did not perform a new meta-analysis of the collated data, as the findings considered in an umbrella review should be limited to those directly obtained from the included studies.[22]

However, we provided a common effect size for each investigated outcome, where possible. Specifically, when only mean differences were reported for a specific investigated outcome, we left them as they were (for example, for BMI); when mean/median differences were reported together with standardized mean/median differences across studies investigating the same outcome, we converted all measures into standardized mean differences; when risk ratios were reported, we converted all into odds ratios (it was not feasible to convert risk difference [RD] to odds ratio; RD was reported in only 1 study[23] evaluating weight change, for the comparison of aripiprazole vs placebo). We have reported these re-calculated effects in a column of Table S1, available online (including other relevant details of all quantitative results) named "conversion to common effect size−CCES." As we found no indication in the literature supporting the use of imputation methods for missing outcomes in the context of NMA, we also preferred not to apply them (affected NMA are by Arango *et al.*[24] and DelBello *et al.*[25]).

Risk-of-Bias Assessment

The methodological quality of a given SR and MA study was independently assessed by 2 authors (C.C. and V.B.) by using the critical appraisal tool for systematic reviews including randomized or nonrandomized studies (AMSTAR 2).[26] Moreover, we distinguished among studies of "very low," "low," "moderate," and "high" quality by using the scheme for interpreting weaknesses detected in critical and non-critical items proposed by Shea *et al.*[26]

If MA and NMA included the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment, the results were extracted and reported accordingly.

Differences Between Protocol and Actual Review

In case 2 SR addressed the same psychiatric disorder, treatment and outcomes, we included the SR reporting the largest number of studies (instead of the most recent review) to provide a more comprehensive picture of the topic.

Because of the limited amount of data, we were unable to perform post hoc analyses (eg, by considering only systematic reviews including clinical studies with a long-term follow-up of greater than 12 months or drug-naive patients or based on the on- or off-label prescription). When not available, we did not perform the GRADE assessment, as data reported in the systematic review were very limited. Furthermore, we provided a hierarchical stratification of the evidence from meta-analyses, applying, for the first time in child and adolescent psychiatry, the recommendations by Fusar-Poli and Radua (reported in the text as class of evidence).[21] Briefly, the system used for classifying the credibility of association stratifies the evidence from MA into 4 categories: class I (convincing) I), class II (highly suggestive), class III (suggestive), and class IV (weak), based on criteria that examine the parameters resulting from each pairwise comparison of MA. Because in NMA the resulting parameters refer to the whole of weighted indirect comparisons, it was not feasible to apply the class of evidence method to score NMA. Therefore, we categorized NMA as significant or not significant based on the reported effect size values.

Overlap of Included Reviews

In order to quantify the amount of overlap between the included reviews, we used the assessment tool proposed by Pieper *et al.*[27] quantifying the Corrected Covered Area (CCA) for the most characterized and therefore the most potentially overlapping outcome, namely, weight gain. CCA takes into account the number of occurrences of the same clinical studies across the publications included in the umbrella review. Resulting CCA values lower than 5 can be considered indicative of a slight overlap, values ranging between 6 and 10 a moderate overlap, values from 11 to 15 a high overlap, and values larger than 15 a very high overlap.

RESULTS

Study Characteristics

The study selection and screening are presented in the PRISMA flow chart (Figure 1). Of the 804 articles retrieved, 317 were from PubMed, 333 from EMBASE, and 154 from Psycinfo; 98 of them met the inclusion criteria for the full-text screening. The 98 reviews were read and classified as meeting or not meeting inclusion criteria; this resulted in 23 reviews being selected for data extraction.

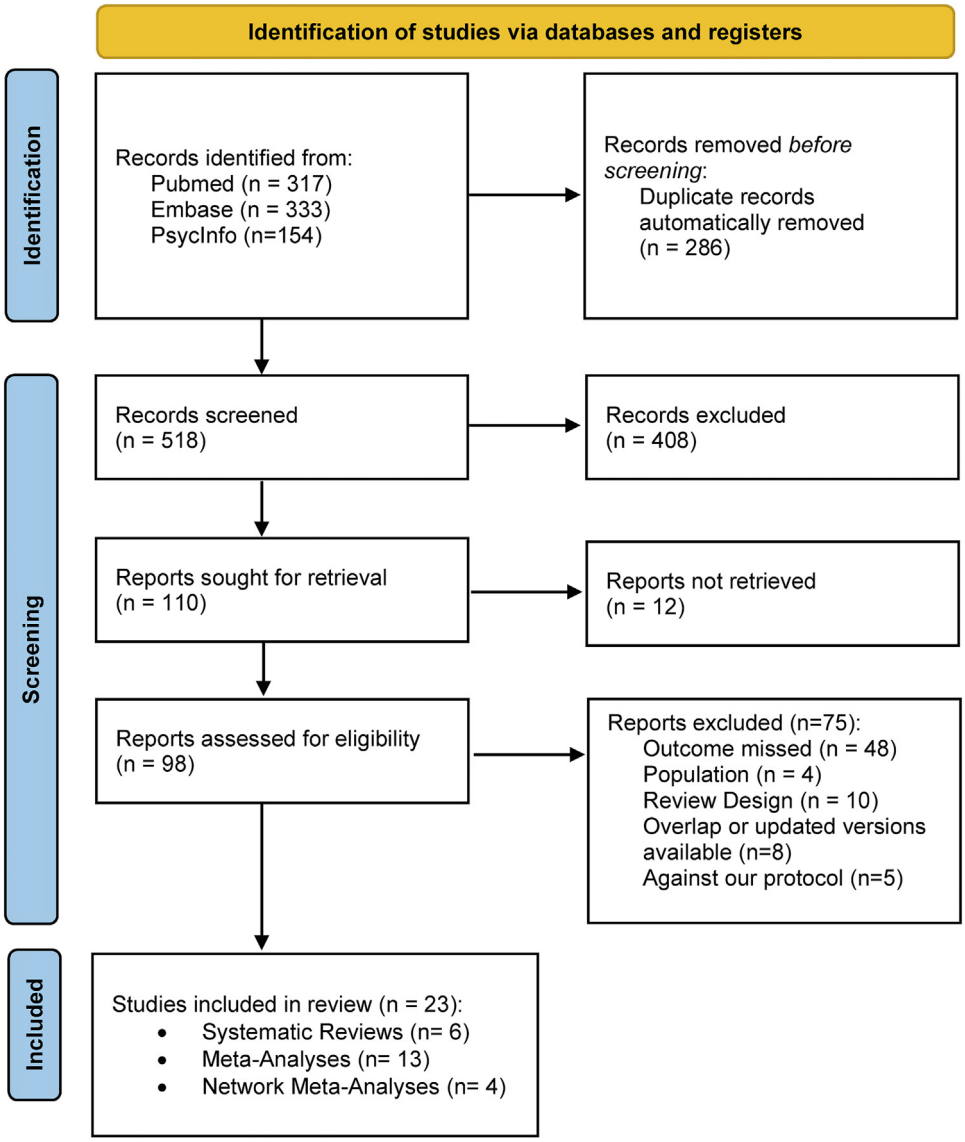
The 23 reviews, published between 2006 and 2021, included 13 MA, 4 NMA and 6 SR without MA. The characteristics of the included SR are summarized in Table 1.[28-47] Of the 23 reviews, 7 (30.4%) included pediatric patients with any psychiatric disorder (ie, conduct disorder, disruptive behavior, autism, pervasive developmental disorder, ADHD, schizophrenia, bipolar disorder, and mania), 6 (26.0%) included subjects with autism spectrum disorders, 6 (26.0%) schizophrenia, 2 (8.6%) bipolar disorders, 1 (4.3%) conduct disorder, and 1 (4.3%) intellectual disability. According to PICO (patient, intervention, comparison, outcome), the majority of the included reviews (16; 69.5%) were focused on the safety of antipsychotic therapy, reporting as outcomes the occurrence of adverse drug reactions; only 4 studies (17.3%) were specifically focused on metabolic outcomes.

According to the AMSTAR 2 scoring system, 2 reviews (8.6%) were high quality, 3 (13.0%) were moderate; 5 (21.7%) low-quality, and 13 (56.5%) very low quality.

The most commonly noted omissions were related to the sources of funding for the studies included in the review (item no. 10; 18 reviews, 78.2%), the study protocol (item no. 2; 13 reviews, 56.5%), data extraction in duplicate (item no. 6; 13 reviews, 56.5%), and the accounting for Risk of Bias (RoB) in primary studies when interpreting or discussing the results of the review (item no. 13; 12 reviews, 52.1%). Figure S1, available online, reports details of the quality assessment that we performed for each study included in the umbrella review.

In view of a more comprehensive framework on the topic that we addressed, we listed in Figure 2 all of the currently available SR, MA and NMA according to the different outcomes of interest that they analyzed; the comprehensive picture highlights a lack of data for most parameters. Of the 23 included studies, no review reported data for waist−hip ratio, insulin, or HbA1c; only 1 MA

FIGURE 1 PRISMA Flow Chart Showing Study Selection and Screening



provided a quantitative analysis on BMI *z* score changes after antipsychotic therapy; 2 MA addressed changes in HDL and LDL; and 3 SR reported changes in blood pressure parameters without providing a quantitative analysis. Conversely, changes in body weight, BMI, blood glucose, triglycerides, and total cholesterol were the subject of several qualitative (13) and quantitative (15) analyses.

Evidence From Quantitative Analyses

Figure 3 providess a comprehensive summary of the change in levels (medianD, MD, and SMD) for each metabolic outcome. Results reporting on risk estimates (OR and RR) are presented separately in Figure S2, available online, because of the low number of analyses available. With the aim of assisting in the interpretation of results from different studies, we provided common effect size values for each drug in relation to placebo, for each metabolic outcome of interest in Table 2. Additional details are reported in Table S1, available online. The sensitivity analysis from which we excluded the only observational study (ie, Pozzi *et al.*[42]) is presented in Figure S3, available online.

All white spaces in figures highlight the absence of data.

In the following paragraphs, we report in detail the statically significant results for each outcome, based on their metrics (MD, SMD, medianD, and OR). In addition, we have calculated the overlap of the included reviews following the approach suggested by Pieper *et al.*[27] Regarding our most characterized outcome weight gain,

TABLE 1 Characteristics of the Included Studies

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
Alfageh, 2019[28]	SR and MA	Cochrane Library MEDLINE Embase PsycINFO	**P:** ASD **I:** antipsychotics **C:** placebo, other tx, no tx **O:** adverse events	RCT; OBS	1997-2017	ASD	Mean age (min-max): 4-15 (RCT) 5-15 (OBS)	ROB mNOS	Moderate
Almandil, 2013[29]	SR and MA	EMBASE PubMed BIOSIS IPA Cochrane Library clinicaltrials.gov mRCT ICTRP-WHO PsycINFO	**P:** pediatric patients **I:** SGA **C:** placebo **O:** weight gain and/or metabolic adverse effects	RCT	2000-2009	Conduct disorder Disruptive behavior ASD PDD ADHD SCZ BD Mania	Min-max: 2-17	JADAD	Low
Alonso-Pedrero, 2019[30]	SR	PubMed	**P:** users of antipsychotic or antidepressant drugs **I:** antipsychotics or antidepressants **C:** / **O:** weight gain	OBS	2009-2016	Any mental disorder requiring treatment with antipsychotics	NA	NOS	Very low
Arango 2020[24]	SR and NMA	Embase MEDLINE Cochrane Library	**P:** adolescents (13-17 y) with SCZ **I:** lurasidone **C:** placebo or other SGA **O:** efficacy, tolerability	RCT	NA	SCZ	NA	NA	Very Low
Armenteros, 2006[31]	SR and MA	PsychINFO MEDLINE	**P:** adolescent and children (5-18 y) with SCZ **I:** antipsychotics **C:** / **O:** response to tx	OBS	1967-2003	SCZ	Min-max: 5-18 Mean age (min-max): 9-16	JADAD	Very low

(*continued*)

TABLE 1 Continued

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
Channing, 2018[32]	SR	PubMed PsycINFO EMBASE MEDLINE clinicaltrials.gov WOS	**P:** adolescents and children **I:** lurasidone **C:** / **O:** pharmacokinetics, efficacy, safety	Any type	2014-2017	Any mental disorder requiring treatment with antipsychotics	Min-max: 5-17	NA	Very low
DelBello, 2021[25]	SR and NMA	Embase MEDLINE Cochrane Library clinicaltrials.gov Databases of gray literature (not specified)	**P:** pediatric patients with bipolar disorder or bipolar depression **I:** antipsychotics **C:** monotherapy, combination, placebo **O:** efficacy, metabolic and safety outcomes	RCT	2009-2017	BD	Min-max: 10-18 Mean age (min-max): 14-16	ROB	Low
Hirsch, 2016[33]	SR and MA	Cochrane Library Ovid Medline Embase CINAHL PsycINFO CPCI-S Autism data, ZETOC WorldCat, clinicaltrials.gov ICTRP-WHO	**P:** individuals with ASD **I:** aripiprazole **C:** placebo **O:** adverse events	RCT	2009-2014	ASD	Min-max: 6-17	ROB	High
Jensen, 2007[34]	SR	MEDLINE Embase	**P:** pediatric patients **I:** SGA **C:** / **O:** /	CT	1994; 2006	Any mental disorder requiring treatment with antipsychotics	Min-max: 5-17 Mean age (min-max): 9-15	NA	Very low

(*continued*)

TABLE 1 Continued

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
Khan, 2019[35]	SR and MA	MEDLINE OVID EMBASE Cochrane Library	**P:** pediatric patients **I:** SGA **C:** / **O:** /	RCT	2000;2014	Conduct disorders	Min-max: 5-17	NA	Very low
Krause, 2018[36]	SR and NMA	MEDLINE EMBASE PsycINFO Cochrane Library PubMed Biosis ClinicalTrials.gov	**P:** pediatric patients with SCZ, schizofreniform and SZA **I:** antipsychotics **C:** placebo, antipsychotics **O:** efficacy, acceptability, tolerability	RCT	1967-2017	SCZ SFD SZA	Min-max: 8-18 Mean age (min-max): 8-18	ROB	Very low
Liu, 2011[37]	SR and MA	PubMed	**P:** pediatric patients **I:** pharmacotherapy for bipolar disorder **C:** placebo, antipsychotics **O:** efficacy and safety	CT	1994-2011	BD	Min-max: 4-18 Mean age (min-max): 5-18	NA	Very low
Maneeton, 2018[38]	SR and MA	Scopus PubMed CINAHL Cochrane Library clinicaltrial.gov EudraCT	**P:** pediatric patients with ASD **I:** aripiprazole **C:** placebo **O:** efficacy, safety	RCT	2009-2017	ASD	Min-max: 6-17	ROB	Low
Maneeton, 2018b[39]	SR and MA	Scopus PubMed CINAHL Cochrane Library clinicaltrial.gov EudraCT	**P:** pediatric patients with ASD **I:** risperidone **C:** placebo **O:** efficacy, safety	RCT	2002-2013	ASD	Min-max: 2.5-17	ROB	Very low
McQuire, 2015[40]	SR and MA	Embase Medline PsycINFO Cochrane Library	**P:** pediatric patients with intellectual disabilities and challenging	RCT	2001-2013	ASD ID	Min-max: 7-11 Mean age: 9	ROB	Moderate

(*continued*)

TABLE 1 Continued

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
		ERIC BEI IBSS SSCI clinicaltrials.gov	behavior **I:** pharmacological intervention **C:** placebo, other tx **O:** efficacy, safety						
Pagsberg, 2017[41]	SR and NMA	Cochrane library PubMed clinicaltrials.gov	**P:** pediatric patients with SCZ **I:** antipsychotics **C:** placebo, antipsychotics **O:** efficacy, tolerability	RCT	2006-2015	SCZ	Min-max: 8-19 Mean age (min-max): 11-16	ROB	High
Pozzi, 2020[42]	SR and MA	PubMed	**P:** pediatric patients **I:** antipsychotics **C:** controls **O:** safety	OBS	1998-2019	Any mental disorder requiring treatment with antipsychotics	Min-max: 2-20 Mean age (min-max): 4.6-17.3	NOS	Very low
Pringsheim, 2011[43]	SR and MA	MEDLINE Embase	**P:** pediatric patients **I:** SGA **C:** placebo, SGA **O:** metabolic and neurological adverse effects	RCT	1996-2009	Any mental disorder requiring treatment with antipsychotics	Min-max: 0-18	USPSTF criteria	Low
Rodrigues, 2021[23]	SR and MA	MEDLINE EMBASE CINAHL PsycINFO ERIC Cochrane Library WOS Clinicaltrials.gov ICTRP — WHO	**P:** children and youth (< 25) diagnosed with pervasive developmental disorder or autism spectrum disorder **I:** pharmacological intervention **C:** placebo, pharmacological intervention, behavioral therapy **O:** efficacy, tolerability, QoL	RCT	2000-2018	ASD	Min-max: 0-25 Mean age (min-max): 4.8-10.7	ROB	Low

(*continued*)

TABLE 1 Continued

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
Schneider, 2014[44]	SR	PubMed MEDLINE	**P**: children or adolescents with early onset SCZ **I**: clozapine **C**: antipsychotic **O**: efficacy, tollerability	CT OBS Case report	1994-2009	SCZ or psychosis	Min-max: 9-21 Mean age (min-max): 11-19	NA	Very low
Stafford, 2015[45]	SR and MA	Embase MEDLINE PreMEDLINE PsycINFO EI AMED ASSIA BEI Cochrane Library CINAHL ERIC IBSS SSA SSCI HMIC PsycBOOKS PsycEXTRA	**P**: children, adolescent or young adults with psychosis or SCZ **I**: antipsychotics **C**: placebo, psychological intervention, antipsychotics **O**: efficacy, safety	RCT	1976-2012	SCZ or psychosis	Mean age (min-max): 11-24.5	ROB	Moderate
Unwin, 2011[46]	SR	PsychINFO MEDLINE Embase CINAHL	**P**: children or adolescent with intellectual disability and problem behaviors **I**: SGA	RCT	2001-2005	ID	Min-max: 5-18	JADAD	Very low

(*continued*)

TABLE 1 Continued

First author, year, reference	Review design	Literature databases searched to conduct SR	PICO	Type of study	Range (y) of included studies	Diagnosis	Age (y)	ROB	AMSTAR 2
			C: placebo O: efficacy						
Zuddas, 2011[47]	SR	MEDLINE PubMed	P: children or adolescent with psychiatric disorders different from SCZ I: antipsychotic C: placebo or antipsychotics O: efficacy, tolerability	RCT	2000-2009	Psychiatric disorders different from SCZ	Min-max: 2-18	NA	Very low

Note: *ADHD = attention-deficit/hyperactivity disorder; EI = Australian Education Index; AMED = allied and complementary medicine; ASD = autism spectrum disorders; ASSIA = Applied Social Services Index and Abstracts; BD = bipolar disorder, BEI = British Education Index; CINAHL= Cumulative Index to Nursing and Allied Health Literature; CT = clinical trials; ERIC = Sociological Abstracts, Social Services Abstracts, Education Resources Information Centre; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; HMIC = Health Management Information Consortium; IBSS = International Bibliography of the Social Sciences; ICTRP-WHO = International Clinical Trials Registry Platform–World Health Organization; ID = intellectual disability; IPA= International Pharmaceutical Abstracts; MA = meta-analysis; mNOS = modified Newcastle–Ottawa Scale; mRCT = metaRegister of Controlled Trials; NA = not available; NMA = network meta-analysis; NOS = Newcastle–Ottawa Scale; OBS = observational studies; PDD = pervasive developmental disorder; QoL = quality of life; RCT = randomized controlled trials; ROB = Risk of Bias; SCZ = schizophrenia; SFD = schizophreniform disorder; SGA = second-generation antipsychotics; SSCI = Social Sciences Citation Index; SR = systematic reviews; tx = treatment; SSA = Social Services Abstracts; SZA = schizoaffective disorder; USPSTF = US Preventive Services Task Force; WOS = Web of Science.*

FIGURE 2 List of the Currently Available Systematic Reviews (SR), Meta-Analyses (MA), and Network Meta-Analyses (NMA), According to the Different Outcomes of Interest That They Analyzed

Author	Anthropometric parameters					Glucose				Lipids				CV
	BW	BMI	WC	Waist-hip ratio	BMI z-score	Blood glucose	HOMA-IR	Insulin	HbA1c	TG	TC	HDL	LDL	BP
Alfageh 2019[39]	✓	✗	✗	✗	✗	○	○	✗	✗	✗	✗	✗	✗	✗
Almandil 2013[34]	✓	✗	✗	✗	✗	○	✗	✗	✗	○	○	✗	✗	✗
Alonso Pedrero 2019[47]	○	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Arango 2020[29]	✓	✗	✗	✗	✗	✓	✗	✗	✗	✓	✓	✗	✗	✗
Armenteros 2006[48]	○	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Channing 2018[46]	○	✗	✗	✗	✗	○	✗	✗	✗	○	○	✗	✗	✗
DelBello 2021[30]	✓	✗	✗	✗	✗	✓	✗	✗	✗	✓	✓	✓	✓	✗
Hirsch 2016[32]	✓	✓	✗	✗	✗	✓	✗	✗	✗	✓	✗	✓	✓	✗
Jensen 2007[49]	○	✗	✗	✗	✗	○	✗	✗	✗	✗	✗	✗	✗	✗
Khan 2019[40]	✓	✗	✗	✗	✗	✗	✗	✗	✗	○	○	✗	✗	✗
Krause 2018[33]	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Liu 2011[43]	○	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Maneeton 2018a[35]	✓	✗	✗	✗	✗	○	✗	✗	✗	✓	✗	✗	✗	✗
Maneeton 2018b[36]	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
McQuire 2015[41]	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Pagsberg 2017[28]	✓	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Pringsheim 2011[31]	✓	✓	✗	✗	✗	○	✗	✗	✗	✓	✓	○	○	○
Pozzi 2020[42]	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Rodrigues 2021[37]	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Schneider 2014[44]	○	○	✗	✗	✗	✗	✗	✗	✗	○	○	✗	✗	○
Stafford 2015[38]	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Unwin 2011[50]	○	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Zuddas 2011[45]	○	○	○	✗	✗	○	✗	✗	✗	○	✗	○	○	○

Note: *BMI = body mass index; BP = blood pressure; BW = body weight; CV = cardiovascular; HbA1C = glycosylated hemoglobin; HOMA-IR = homeostatic model for the assessment of insulin resistance; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; O = only qualitative synthesis; TC = total cholesterol; TG = triglycerides; WC = waist circumference; V = quantitative synthesis; X = no data.*

therefore potentially the most overlapping, we included in our overview a total of 15 MA or NMA, resulting in 98 original studies and 180 studies including duplications. By calculating the CCA, we found a score of 5.9, suggesting a slight to moderate overlap.

Triglyceride Levels

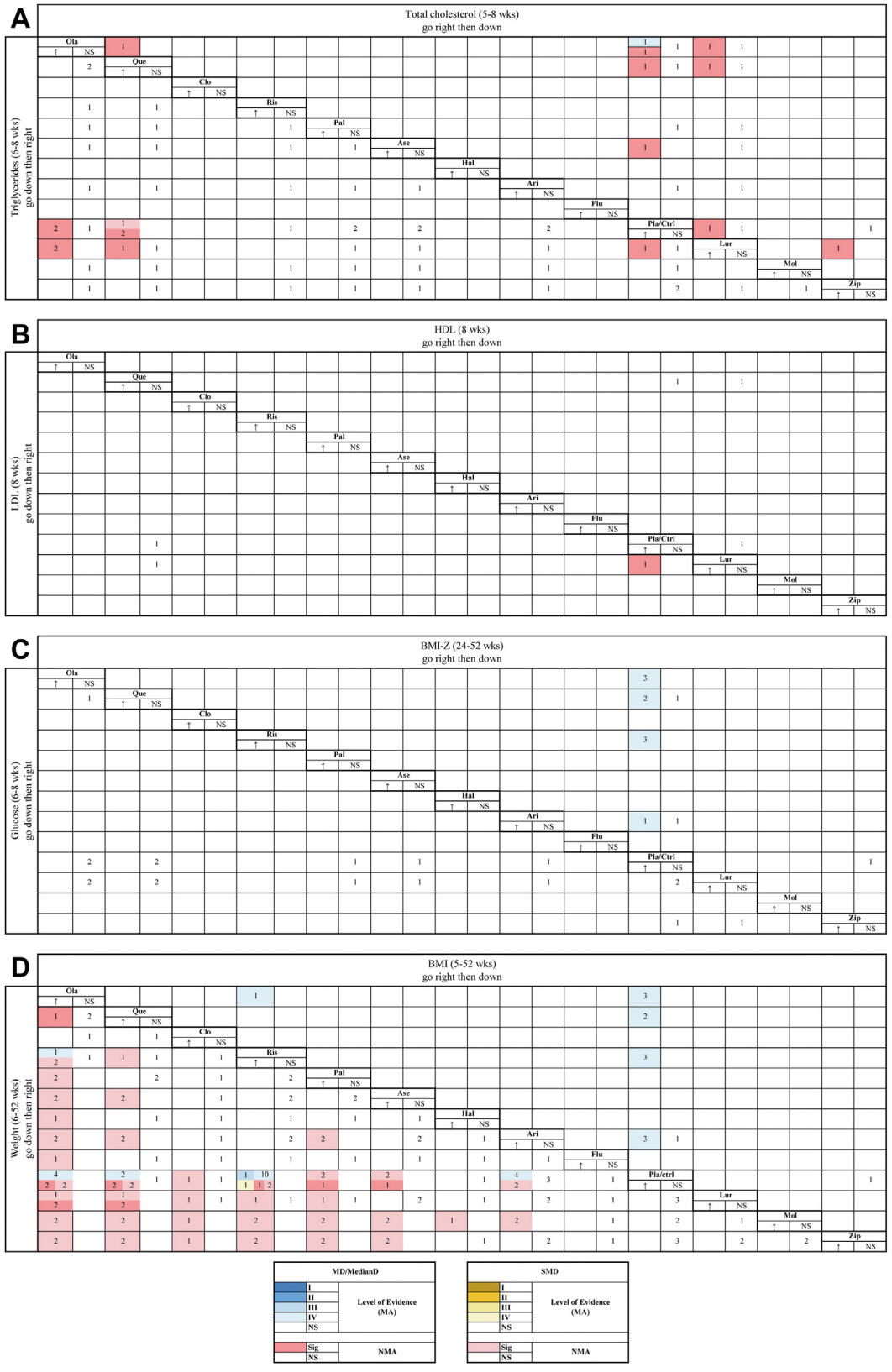
Triglyceride levels are shown in Figure 3A. Data were extracted from 3 NMA of RCT.[24,25,41] As compared with placebo, data for lurasidone showed no difference in 1 NMA[24] and decreased triglyceride levels in another one (MD [95% CI]: −13.43 (−26.63, −0.25] mg/dL).[25] For olanzapine, a median (95% CI) of 37 (12.27, 61.74) mg/dL[24] and an MD (95% CI) of 38.57 (21.44, 55.77) mg/dL[25] were found. For quetiapine, a median (95% CI) of 21.58 (95% CI: 4.27, 38.31) mg/dL was found[24]; for MD (95% CI): 34.87 (20.08, 49.67) mg/dL[25]; and for SMD (95% CI): 0.37 (0.06, 0.068).[41] For the remaining drugs, data indicated no significant difference as compared with placebo.

Two NMA reported significant comparisons between drugs.[24,25] As compared with lurasidone, quetiapine showed an MD (95% CI) of 48.3 (28.51, 68.03)[25] and 1 non-significant result,[24] whereas olanzapine resulted in a median (95% CI) of 32.75 (4.19, 61.30)[24] and MD (95% CI) of 52 (30.25, 73.62) mg/dL.[25] For the remaining drugs, data indicated no significant difference as compared with other antipsychotics.[24,25,41] Odds ratios were in line with the above results (Figure S2, available online).

Total Cholesterol Levels

Total cholesterol levels are shown in Figure 3A. These levels were retrieved from 2 NMA[24,25] and 1 MA[43] of RCT: as compared with placebo, asenapine was associated with an increased total cholesterol level (median [95% CI]: 9.1 (1.73, 16.44] mg/dL).[24] No difference was found in 1 analysis for olanzapine,[24] but increased levels were reported in 2 other analyses: direct and indirect comparisons of 2 studies resulted in an MD (95% CI) of 3.67 (1.43, 5.92) mg/dL,[43] class of evidence IV, and 20.47 (13.97, 26.94) mg/dL.[25] No difference was observed for quetiapine in 1 analysis,[25] whereas another reported a significant increase, with a median (95% CI) of 15.60 (7.30, 24.05) mg/dL.[24] Similar results were retrieved for lurasidone, not significant in 1 analysis[25] but significant in another (median [95% CI] = 8.94 [1.27, 16.90] mg/dL).[24] Paliperidone, aripiprazole, and ziprasidone were found to be non-significantly different from placebo.[24]

FIGURE 3 Comprehensive Summary of the Change in Levels or of the Risk of Change for Each Metabolic Outcome and Antipsychotic Drug, as Reported in Quantitative Assessments



Note: *For each drug/drug intersection, numbers report on how many meta-analyses and network meta-analyses found any differences between treatment effects on each specific outcome. All comparisons are to be read top-left to bottom-right.*

TABLE 2 Common Effect Size Values for Each Drug in Relation to Placebo, for Each Metabolic Outcome of Interest

Triglycerides change	**Effect metrics: SMD**	
Drugs	**Random effect (95% CI)**	**Reference**
Aripiprazole	0.06 (−0.29, 0.42)	Pagsberg, 2017[41]
Asenapine	0.11 (−0.13, 0.34)	Pagsberg, 2017[41]
Molindone	−0.16 (−0.75, 0.43)	Pagsberg, 2017[41]
Olanzapine	0.40 (−0.01, 0.80)	Pagsberg, 2017[41]
Paliperidone	0.22 (−0.23, 0.67)	Pagsberg, 2017[41]
Quetiapine	**0.37 (0.06, 0.68)**	Pagsberg, 2017[41]
Risperidone	0.12 (−0.07, 0.32)	Pagsberg, 2017[41]
Ziprasidone	0.09 (−0.25, 0.43)	Pagsberg, 2017[41]
Triglycerides levels increased	**Effect metrics: OR**	
Aripiprazole	1.59 (0.60, 4.20)	Hirsh, 2016[33]
	1.550 (0.61, 3.95)	Maneeton, 2018[39]
Olanzapine	**5.13 (2.78, 9.45)**	Pringsheim, 2011[43]
Total cholesterol, change	**Effect metrics: MedianD**	
Drugs	**Random effect (95% CI)**	**Reference**
Quetiapine	**15.60 (7.30, 24.05)**	Arango, 2020[24]
Asenapine	**9.10 (1.73, 16.44)**	Arango, 2020[24]
Lurasidone	**8.94 (1.27, 16.90)**	Arango, 2020[24]
Paliperidone	9.83 (−0.76, 20.45)	Arango, 2020[24]
Olanzapine	8.54 (−1.09, 18.18)	Arango, 2020[24]
Aripiprazole	4.26 (−3.01, 11.51)	Arango, 2020[24]
Ziprasidone	−2.98 (−11.49, 5.48)	Arango, 2020[24]
LDL, change	**Effect metrics: MD**	
Drugs	**Random effect (95% CI)**	**Reference**
Lurasidone	**−5.90 (−10.51, −1.309**	Delbello, 2021[25]
Quetiapine	−0.69 (−6.21, 4.82)	Delbello, 2021[25]
LDL levels increased	**Effect metrics: OR**	
Aripiprazole	3.26 (0.13, 81.98)	Hirsh, 2016[33]
HDL, change	**Effect metrics: MD**	
Drugs	**Random effect (95% CI)**	**Reference**
Lurasidone	2.30 (−0.07, 4.67)	Delbello, 2021[25]
Quetiapine	−0.39 (−2.75, 1.96)	Delbello, 2021[25]
HDL levels increased	**Effect metrics: OR**	
Aripiprazole	0.94 (0.11, 8.43)	Hirsh, 2016[33]
Blood glucose, change	**Effect metrics: MedianD**	
Drugs	**Random effect (95% CI)**	**Reference**
Aripiprazole	3.53 (−1.66, 8.84)	Arango, 2020[24]
Asenapine	3.56 (−1.38, 8.54)	Arango, 2020[24]
Lurasidone	1.67 (−3.50, 6.88)	Arango, 2020[24]
Olanzapine	4.51 (−1.70, 10.72)	Arango, 2020[24]
Paliperidone	6.11 (−1.57, 14.00)	Arango, 2020[24]
Quetiapine	0.85 (−4.21, 5.98)	Arango, 2020[24]
Ziprasidone	−5.93 (−13.23, 1.37)	Arango, 2020[24]
Blood glucose levels increased	**Effect metrics: OR**	
Aripiprazole	1.57 (0.07, 33.34)	Hirsh, 2016[33]

(continued)

TABLE 2 Continued

BMI, change	**Effect metrics: MD**	
Drugs	**Random effect (95% CI)**	**Reference**
Aripiprazole	**0.40 (0.18, 0.63)**	Rodrigues, 2021[23]
	0.44 (−0.27, 1.16)	Hirsch, 2016[33]
	0.27 (0.11, 0.42)[a]	Pringsheim, 2011[43]
Olanzapine	**1.28 (0.96, 1.59)**	Pringsheim, 2011[43]
Weight, change	**Effect metrics: SMD**	
Drugs	**Random effect (95% CI)**	**Reference**
Aripiprazole	**0.68 (0.42, 0.93)**	Hirsch, 2016[33]
	0.45 (0.24, 0.66)	Maneeton, 2018[39]
	0.44 (0.24, 0.64)	Rodrigues, 2021[23]
	0.43 (0.28, 0.58)[a]	Pringsheim, 2011[43]
	0.43 (0.30, 0.57)	Almandil, 2013[29]
	0.27 (0.05, 0.48)	Pagsberg, 2017[41]
Asenapine	**0.45 (0.20, 0.69)**	Pagsberg, 2017[41]
Molindone	−0.38 (−0.86, 0.09)	Pagsberg, 2017[41]
	−0.35 (−0.84, 0.15)	Krause, 2018[36]
Olanzapine	**1.51 (1.23, 1.80)**[a]	Pringsheim, 2011[43]
	1.50 (1.22, 1.78)	Almandil, 2013[29]
	1.21(0.84, 1.58)	Pagsberg, 2017[41]
Paliperidone	**0.69 (0.44, 0.94)**	Pagsberg, 2017[41]
Quetiapine	**1.00 (0.51, 1.48)**[a]	Pagsberg, 2017[41]
	0.85 (0.56, 1.14)	Pringsheim, 2011[43]
Risperidone	**0.77 (0.53, 1)**	Pringsheim, 2011[43]
	0.80 (0.62, 0.98)	Pringsheim, 2011[43]
	0.78 (0.61, 0.95)	Almandil, 2013[29]
	0.88 (0.61, 1.14)	Maneeton, 2018[38]
	0.45 (0.10, 0.80)	Maneeton, 2018[38]
	0.97 (0.73, 1.20)	Alfageh, 2019[28]
	2.34 (−0.91, 5.60)	Khan, 2019[35]
	0.71 (0.47, 0.96)	Rodrigues, 2021[23]
	0.82 (0.57, 1.06)	McQuire, 2015[40]
	0.41 (0.21, 0.62)	Pagsberg, 2017[41]
Ziprasidone	−0.04 (−0.36, 0.27)	Pagsberg, 2017[41]
	−0.04 (−0.36, 0.28)	Krause, 2018[36]
Weight increased	**Effect metrics: OR**	
Aripiprazole	**3.66**[b]	Pringsheim, 2011[43]
	2.34 (0.47, 11.64)	Pagsberg, 2017[41]
	4.82 (2.09, 11.15)	Hirsch, 2016[33]
Asenapine	2.82 (0.38, 20.89)	Pagsberg, 2017[41]
Lurasidone	0.82 (0.22, 2.13)	Delbello, 2021[25]
Molindone	2.09 (0.16, 26.72)	Pagsberg, 2017[41]
Olanzapine	**10.66** [b]	Pringsheim, 2011[43]
	17.34 (3.97, 75.65)	Pagsberg, 2017[41]
	44.81 (11.19, 147.70)	Delbello, 2021[25]
Paliperidone	3.47 (0.69, 17.50)	Pagsberg, 2017[41]
Quetiapine	**8.40 (1.58, 44.82)**	Pagsberg, 2017[41]
	2.59 (0.79, 6.74)	Delbello, 2021[25]
Risperidone	2.9[b]	Pringsheim, 2011[43]

(continued)

TABLE 2 Continued

Weight increased	**Effect metrics: OR**	
	9.01 (2.10, 38.69)	Pagsberg, 2017[41]
Ziprasidone	0.45 (0.04, 5.49)	Pagsberg, 2017[41]

Note: The measure reported for each common effect size was chosen so that the largest number of data could be converted into it. Significant results are reported in boldface type. MD = mean difference; OR = odds ratio; SMD = standardized mean difference.
[a]*Fixed effect.*
[b]*Not clear whether random or fixed effect.*

Comparisons between drugs were available with respect to lurasidone. Both olanzapine and quetiapine resulted in 1 analysis with no significant difference[24] and another with a significant increase (MD [95% CI]: 25.36 [16.93, 33.82] mg/dL and 10.29 [2.12, 18.50] mg/dL, respectively)[25]; 1 analysis showed no significant difference for lurasidone vs paliperidone or asenapine, but increased levels against ziprasidone (medianD [95% CI]: 11.97 [0.46, 23.65] mg/dL).[24] In addition, 1 analysis showed a significant increase for olanzapine vs quetiapine (MD [95% CI]: 15.07 [6.18, 23.93] mg/dL.[25]

LDL Cholesterol Levels

LDL cholesterol levels are shown in Figure 3B. Mean change in LDL levels was available only in 1 recent NMA[25] of 4 RCT. As compared with placebo, no significant difference was reported for quetiapine,[25] whereas decreased LDL levels were found for lurasidone (MD [95% CI]: −5.9 [−10.51, −1.30] mg/dL).[25] As compared with lurasidone, quetiapine showed no difference.[25] One non-significant relative risk for aripiprazole vs placebo (Figure S2, available online) was measured in an MA by Hirsch *et al.*[33]

HDL Cholesterol Levels

Figure 3B shows HDL cholesterol levels. Mean change in HDL levels was available only in 1 recent NMA[25] of 4 RCT. Quetiapine and lurasidone were associated with no significant difference vs placebo[25] and no significant difference was reported between quetiapine and lurasidone.[25] One non-significant relative risk for aripiprazole vs placebo (Figure S2, available online) was measured in an MA by Hirsch *et al.*[33]

Glucose Levels

Glucose levels are shown in Figure 3C. Two NMA of RCT found non-significant changes for olanzapine,[24,25] quetiapine[24,25], paliperidone[24], asenapine[24], aripiprazole,[24] lurasidone,[24,25] and ziprasidone[24] vs placebo.

No significant difference was also reported for olanzapine,[24,25] quetiapine,[24,25] paliperidone,[24] asenapine,[24] aripiprazole,[24] and ziprasidone[24] against lurasidone and for olanzapine against quetiapine.[24]

Risk ratio values from 1 MA[33] resulted in no difference between aripiprazole and placebo (Figure S2, available online).

BMI z Values

Figure 3C shows BMI z values. Only 1 MA of the observational studies included BMI z scores[42]: as compared with no treatment, BMI z scores were increased with olanzapine (from MD [95% CI] of 0.89 [0.21, 1.57] kg/m^2 to 0.98 [0.46, 1.58] kg/m^2, depending on duration of use), quetiapine (non-significant, and MD [95% CI] of 0.54 [0.20, 0.88] kg/m^2 and 0.57 [0.40, 0.74] kg/m^2, depending on duration of use), risperidone (from MD [95% CI] of 0.48 [0.3, 0.66] kg/m^2 to 0.62 [0.45, 0.79] kg/m^2, depending on duration of use), and aripiprazole (non-significant, and MD [95% CI] of 0.31 [0.14, 0.48] kg/m^2, depending on duration of use). No significant difference was found for ziprasidone.

Body Mass Index

Body mass index is shown in Figure D. Three MA of RCT[23,33,43] and 1 MA of observational studies[43] reported data on BMI score changes. Compared with placebo, an increased BMI was reported for olanzapine (MD [95% CI] = +1.28 [0.96, 1.59] kg/m^2, class of evidence IV][43]; for aripiprazole, 1 MA reported non-significant changes[33] and 2 reported significant increases (MD [95% CI] of 0.27 [0.11, 0.42] kg/m^2 [43] and 0.40 [0.18, 0.63] kg/m^2, [23] class of evidence IV).

Significant increases were found also in observational studies for aripiprazole (MD [95% CI] of 1.7 [0.28, 3.12] kg/m^2, class of evidence IV),[42] quetiapine (MD [95% CI] of 1.50 [0.37, 2.62] kg/m^2 and 1.82 [0.53, 3.11] kg/m^2 , depending on duration of use)[42], risperidone (from MD [95% CI] of 2.00 [1.40, 2.60] kg/m^2 to 2.16 [1.00, 3.32]

kg/m^2, depending on duration of use),[42] and olanzapine (MD [95% CI] of 3.42 [2.10, 4.75] kg/m^2 and 3.47 [2.21, 4.72] kg/m^2, depending on duration of use, class of evidence IV).[42] However, as compared to controls, no significant difference was found for ziprasidone.[42] The only available comparison between drugs showed that the change in BMI was greater with olanzapine than with risperidone (MD [95% CI]: 0.90 (0.42, 1.38) kg/m^2, class of evidence IV).[43]

Weight

Figure 3D summarizes subjects' weight. Four NMA[24,25,36,41] and 11 MA analyzed weight changes.[23,28,29,33,35,38-40,42,43,45]

As compared with placebo, olanzapine was associated with increased body weight, with MD (95% CI) values of 3.45 (2.93, 3.98) kg[29] and 3.47 (2.94, 3.99) kg,[43] class of evidence IV. Metrics from 4 NMA were the following: median (95% CI): 3.83 (2.38, 5.24) kg[24]; MD (95% CI): 3.9 (3.2, 4.60) kg[25]; and SMD (95% CI): 1.21 (0.84, 1.58)[41] and 1.24 (0.91, 1.57).[36]

The risk of weight change (OR [95% CI]) ranged from 10.66 (not reported)[43] to 44.81 (11.19, 147.70)[25] (Figure S2, available online). MD values from 1 MA of observational studies ranged, depending on duration of use, from 10.70 (3.98, 17.42) kg to 10.91 (6.68, 15.13) kg,[42] with class of evidence IV.

With regard to risperidone, we found 8 MA included in 6 publications,[23,28,29,35,38,43] with MD (95% CI) ranging from 1.36 (1.05, 1.67) kg[28] to 2.37 (0.26, 4.49) kg[35] and 1 MA with SMD (95% CI) of 0.82 (0.57, 1.06),[40] class of evidence IV; and 3 NMA with a median (95% CI) of 1.50 (0.33, 2.75) kg,[24] and SMD (95% CI) values of 0.41 (0.21, 0.62[41]) and 0.61 (0.32,0.89).[36] However, OR values were discordant (2 non-significant results[23,43] and 1 OR [95% CI] of 9.01 [2.10, 38.69])[41] (Figure S2, available online). Findings from the only MA evaluating observational studies ranged from MD (95% CI) of 4.47 (2.71, 6.23) kg to 9.51 (2.01, 17.01) kg, depending on duration of use.[42]

Although 1 MA reported non-significant weight gain for risperidone compared to olanzapine,[45] 3 analyses found a significant difference between these 2 drugs: MD (95% CI) of 2.41 (0.98, 3.83)[43] with class of evidence IV, and 2 SMD from NMA with SMD (95% CI) of 0.63 (0.34, 0.93)[36] and 0.80 (0.42, 1.18).[41]

Compared to placebo, an increased body weight for quetiapine was found in 1 MA of RCT (MD [95% CI]: 1.41 [1.01, 1.81]),[43] 1 MA of observational studies (MD [95% CI]: 5.84 [2.54, 9.13]),[42] and 4 NMA (median [95% CI]: 2.41 (1.06, 3.74), MD [95% CI]: 1.13 [0.78, 1.47], SMD [95% CI]: 0.85 (0.56, 1.14) and 0.85 [0.61, 1.09].[24,25,36,41]

Compared to placebo, an increased body weight was also found for paliperidone (median [95% CI]: 1.25 [0.12, 2.35] kg,[24] SMD [95% CI]: 0.69 [0.44, 0.94][41] and 0.73 [0.48, 0.97],[36] and asenapine (median [95% CI]: 1.21 [0.32, 2.17],[24] SMD [95% CI]: 0.43 [0.19, 0.68][36] and 0.45 [0.20, 0.69]).[41]

Significant weight increase was found for aripiprazole, with 4 MA with MD (95% CI) ranging from 0.85 (0.57, 1.13) kg[43] to 1.13 (0.71, 1.54) kg,[33] and 2 NMA with SMD (95% CI) of 0.27 (0.05, 0.48)[41] and 0.29 (0.10, 0.49).[36] The remaining analyses found no significant difference.[24,39]

For clozapine, 1 NMA found a non-significant difference from placebo,[24] and 1 NMA indicated a significant increase (SMD [95% CI]: 0.92 [0.22, 1.61).[36] Data indicated no significant difference for haloperidol,[36] fluphenazine,[36] lurasidone,[24,25,36] molindone,[36,41] and ziprasidone.[24,36,41] Comparisons between drugs showed a general weight increase with olanzapine vs all of the other antipsychotics, followed by quetiapine, paliperidone, risperidone, and clozapine (Figure 3).

Evidence From Qualitative Analyses

Evidence from qualitative analyses for outcomes and/or drug comparisons not included in meta-analyses (Table 3) can be useful when quantitative evidence is too limited or absent.[8,25,29-32,34,37,39,41-44,46,47] Although qualitative data do not add much regarding changes in weight and BMI,[37,41-44,47] they can provide useful information regarding other outcomes.

With regard to changes in triglyceride and total/LDL/HDL cholesterols levels as compared with placebo, lurasidone, albeit of minor impact comparing to quetiapine and olanzapine,[25] also determines change in lipids.[32] Aripiprazole did not cause significant changes compared to placebo.[29,44] Regarding risperidone, data are less clear: Almandil *et al.*[29] report a comparable impact on lipids between aripiprazole and risperidone, with no significant changes compared to placebo. Schneider *et al.*[44] report a higher lipid impact of risperidone than placebo. Olanzapine caused a significant increase in lipids,[29] greater than reported for quetiapine[8]; clozapine appears to have more impact on lipids than olanzapine and risperidone.[44]

Regarding changes in glycemic levels as compared to placebo, aripiprazole did not cause significant changes,[29,39,43] whereas lurasidone caused minimal changes of glycemia.[32] Olanzapine appears to have a higher impact on glycemic levels than risperidone,[43] quetiapine, and lurasidone.[43]

TABLE 3 Evidence From Qualitative Analyses for Outcomes and/or Drug Comparisons Not Included in the Meta-analysis

Author, year, reference	Study type	Diagnosis	Change in weight and BMI	Change in lipids	Change in glycemia	Change in blood pressure
Alfageh, 2019[28]	RCT	ASD	SGA long-term therapy associated with more WG leading to discontinuation	—	SGA use associated with hyperglycemia and insulin resistance	—
Almandil, 2013[29]	RCT	BD, SCZ	—	RIS/ARI ~ Pla OLA >> Pla	RIS/ARI ~ Pla OLA > Pla	—
Alonso Pedrero, 2019[30]	OBS	Any mental disorder requiring AP	RIS/OLA/QUE: significant increase	—	—	—
Armenteros, 2006[31]	CT	SCZ	SGA > FGA	—	—	—
Channing, 2018[32]	CT	SCZ	LUR > Pla	LUR ~ Pla	LUR ~ Pla	—
DelBello, 2021[25]	RCT	BD I and II	OLA > QUE > LUR	OLA > QUE > LUR	OLA > QUE > LUR	—
Hirsch, 2016[33]	RCT	ASD	ARI >> Pla	—	—	—
Jensen, 2007[34]	CT	DBD, PDD, tic/Tourette syndrome, SCZ, BD	SGA: significant increase in short-term periods	—	SGA: hyperglycemia and diabetes	—
Khan, 2019[35]	RCT	CD	RIS >> Pla	RIS>Pla	—	—
Krause, 2018[36]	RCT	SCZ, SSD, psychotic disorder	OLA>>MOL	—	—	—
Liu, 2011[37]	CT	BD	OLA/QUE>>ARI/RIS	—	—	—
Maneeton, 2018[39]	RCT	ASD	-	ARI ~ Pla	ARI ~ Pla	—
Pagsberg, 2017[41]	RCT	SCZ, SSDs	OLA/QUE/RIS> ASE/PAL/ARI>MOL/ZIP	QUE > Pla	—	—
Pozzi, 2020[42]	OBS	Any mental disorder requiring AP	OLA>>QUE/RIS>>CTRL	—	—	—
Pringsheim, 2011[43]	RCT	SCZ, BD, PDD	OLA/CLO>RIS>>FGA	CLO/OLA/QUE> RIS ARI~Pla	CLO/OLA>RIS ARI~Pla	RIS~Pla OLA> Pla QUE ? Pla
Schneider, 2014[44]	OBS	SCZ, psychosis	OLA>CLO/RIS	—	—	CLO ? OLA
Unwin, 2011[46]	RCT	ID	RIS>>Pla	—	—	—
Zuddas, 2011[47]	RCT	BD, PDD, ADHD, DBD, CD	OLA>ARI/RIS>>Pla QUE? Pla	—	—	OLA>>Pla

Note: *Drugs are ranked based on a greater change in metabolic parameters, according to evidence from systematic reviews only. ~ = Non-significant changes; > = minimal change; >> = significant increase; ? = inconsistent data; ADHD = attention-deficit/hyperactivity disorder antipsychotics; AP = antipsychotics; ARI = aripiprazole; ASD = autism spectrum disorder; ASE = asenapine; BD = bipolar disorder; CD = conduct disorder; CLO = clozapine; CT = clinical trial; CTRL = controls; DBD = disruptive behavior disorders; FGA = first-generation antipsychotics; ID = intellectual disability; LUR = lurasidone; MOL = molindone; OBS = observational study; OLA = olanzapine; PAL = paliperidone; PDD = pervasive developmental disorders; Pla = placebo; QUE = quetiapine; RCT = randomized controlled trial; RIS = risperidone; SCZ = schizophrenia; SGA = second-generation antipsychotics; SSD = schizophrenia spectrum disorders; sy = syndrome; WG = weight gain; ZIP = ziprasidone.*

Only 2 studies reported changes in blood pressure parameters following antipsychotic therapy[43,47]; a significant increase in blood pressure was found in only 1 study with olanzapine vs placebo.[43]

DISCUSSION

This umbrella review provides, for the first time, a state-of-the-art analysis of the impact of antipsychotic therapy on the development of MetS in children and adolescents. We specifically summarized findings from MA, NMA, and SR and included alongside biochemical parameters all available metabolic and cardiovascular outcomes of interest for the development of MetS.

We found compelling evidence especially regarding triglyceride levels and weight gain, whereas for other outcomes of interest, meta-analytic data are currently limited or even totally unavailable and should be explored in future studies to draw conclusions.

Regarding triglyceride levels, the clearest pattern of results is available for olanzapine and quetiapine. Most systematic analyses, with the exception of 1 NMA[41] have shown both drugs to increase triglycerides. The magnitude of triglycerides increase is of clinical interest (up to +38.6 mg/dL for olanzapine and up to +34.8 mg/dL for quetiapine), considering the +25 mg/dL threshold suggested by the 2011 US Government recommendations, although a second higher threshold (+40 mg/dL) has been also suggested by the same document[14]; treatment with these drugs may raise a normal level of triglycerides to above the diagnostic threshold for MetS. Other antipsychotics, including paliperidone, ziprasidone, asenapine, and aripiprazole, affect triglyceride levels less, although they may still contribute to increasing levels above the recommended threshold value; some evidence of no effect for risperidone and molindone and a possible lowering effect for lurasidone have been reported. Of interest, no meta-analytic data about their impact on triglycerides are available for haloperidol and clozapine. Based on these considerations, olanzapine and quetiapine should be avoided in patients at risk for hypertriglyceridemia (eg, those at familial risk, those who begin antipsychotic treatment with borderline value, etc), whereas lurasidone may be suggested. The present findings on triglycerides have not been previously reported in the large, comprehensive, systematic meta-review by Solmi *et al.*,[6] probably because of different inclusion criteria.

Regarding total cholesterol, olanzapine and quetiapine quantitatively were the antipsychotics with the highest propensity to determine its increase, although their maximal reported effect seems not to be sufficient on its own to shift the total cholesterol levels from the recommended threshold to the above maximal tolerable one. Milder effects were found for paliperidone, asenapine, and lurasidone. Data indicate that aripiprazole and ziprasidone cause no effect. Comparing our findings to the meta-review by Solmi *et al.*,[6] results are similar with regard to olanzapine and quetiapine; however, Solmi *et al.*[6] found a significant increase in cholesterol levels related to the administration of aripiprazole. This contrasting result can be explained considering that Solmi *et al.*[6] refer to a meta-analysis[48] that did not meet our inclusion criteria; our results come from a different NMA,[24] which reported no significant risk of dyslipidemia with aripiprazole as compared with placebo.

Considering the differences that we found in the magnitude of effect on cholesterol across antipsychotics, they are not as large as on triglycerides; however, in patients at risk for hypercholesterolemia, data support the preferential use of aripiprazole or ziprasidone, and the opportunity to avoid olanzapine and quetiapine.

Choosing the best antipsychotic for patients with altered cholesterol levels is difficult because very few meta-analytic data report on total, HDL, or LDL cholesterol. The literature indicates a beneficial effect of lurasidone in reducing LDL and increasing HDL, although to a non−clinically significant extent, and no effect for quetiapine and aripiprazole. No meta-analytical results for other antipsychotics are available, with limited evidence to support appropriate clinical advice.

Data from qualitative analyses are overall consistent with those from NMA/MA, with the noticeable exception of some SR reporting an increase in lipids for risperidone and not for aripiprazole.

In terms of glucose levels, available data suggest that antipsychotics may produce little (olanzapine, paliperidone, asenapine, aripiprazole) or negligible (lurasidone, quetiapine, ziprasidone) differences as compared to placebo. Indeed, clinical trials conducted in pediatric patients rarely reported alterations of glycemic levels, possibly because children and adolescents are intrinsically more resistant to hyperglycemia than adults and because antipsychotics may only promote hyperglycemia and type 3 diabetes in the long term[49,50]; an early effect of antipsychotics may be the increase in insulin levels that suggests the future development of insulin resistance,[5] as shown by qualitative results on olanzapine and quetiapine.[28] These findings highlight the need for future clinical trials to obtain longer-term data using a comprehensive panel of glycemic parameters in addition to fasting glucose and glycated hemoglobin, such as insulin, C peptide levels, and others.[51,52]

Results from our umbrella review confirm that most antipsychotics induce weight gain and BMI increase, except for ziprasidone, molindone, and lurasidone. The magnitude

of change has been extensively described in previous studies in youths[6] and adults,[5] and qualitative data are consistent.

We found no meta-analysis that focused on waist circumference and blood pressure. These measures are a relevant part of the diagnostic criteria for MetS, and the lack of data highlights the need to include these outcomes in future studies. Although waist circumference may, in part, be inferred by weight and BMI increase, blood pressure is almost completely absent in the literature on pediatric patients. Having high blood pressure since a young age is clearly associated with future adult hypertension, and, in turn, adults with uncontrolled hypertension are at increased risk for cardiovascular and metabolic diseases.[53] Thus, blood pressure must be an outcome of interest when assessing the safety of antipsychotics. In this regard, a very recent individual study assessed cardiac function and structure in children exposed to second-generation antipsychotics.[54] The authors found no difference between second-generation antipsychotics users or patients naive on several cardiac outcomes; nevertheless, the sample was exposed to risperidone, aripiprazole, and quetiapine, and follow-up controls were scattered (from 3 to 96 months); thus, it is not possible to draw conclusions regarding other antipsychotics or based on treatment duration. The few available qualitative data based on a systematic review were reported in the present review, and showed an increasing effect for olanzapine. A substantial amount of clinical and possibly meta-analytic data is needed to provide conclusive clinical advice; however, monitoring blood pressure seems advisable.

This umbrella review presents the first comprehensive critical appraisal of published SR, MA, and NMA specifically reporting metabolic adverse effects to antipsychotics in children and adolescents. In view of a more comprehensive framework on the topic, we included comparisons among antipsychotics and with placebo or no treatment, and provide a summary of the degree of change for each metabolic symptom, to better support the pharmacological management of pediatric patients in clinical practice.

Some methodological issues should be addressed in future umbrella reviews: attempting to better stratify the evidence, together with the quality rating, we also applied criteria for the robustness of findings based on recent recommendations by Fusar Poli and Radua.[21] According to these recommendations, most MAs were class of evidence IV, especially because of their limited total sample size. Whether these criteria can be meaningfully applied to papers concerning child and adolescent psychiatry remains to be determined, because of the intrinsic characteristics of patient populations. Criteria for evaluating specifically NMA should also be provided.

Limitations of our work should be considered. First, this review relies on literature searches, quality assessments, and conclusions provided by the authors of the included SR and MA. We did not re-evaluate these aspects. Similarly, we could not estimate a unique MetS risk, as results of included meta-analyses were most often reported using different metrics, including mean difference, standardized mean difference, and odds ratio.

An intrinsic limitation of our umbrella review is the lack of studies investigating MetS symptoms in pediatric patients: a considerable number of included studies did not report on total cholesterol, blood glucose levels, waist circumferences, and blood pressure.

We included 1 meta-analysis of observational studies; however, evidence from the study by Pozzi *et al.*[42] was in line with the overall picture from the systematic review including only RCT. As reported in the sensitivity analysis (Figure S3, available online) in which we excluded this study, results did not change significantly. Although it may be inadequate to collate RCT and observational studies in the same MA, we believe that long-term studies are required to draw clinically relevant conclusions on the MetS symptoms, and that clinical trials are most often not suitable to reach such an aim, rendering observational studies indispensable.

Most of the existing studies are also rated as low quality when applying the criteria suggested by AMSTAR 2 (18 of 23; 78.2%), highlighting several potential biases. This evidence is driven mainly by missing information in item 10 (the sources of funding for the studies included), 6 (data extraction in duplicate), 2 (protocol published before the MA), and 13 (the accounting for RoB in primary studies when interpreting or discussing results).

To make up for this lack of data, we used less stringent inclusion criteria, by including SR in addition to MA, which focused also on observational studies in addition to interventional studies only, and on patients with any type of psychiatric diagnoses requiring treatment with antipsychotics. Therefore, the considerable heterogeneity of results that we collected partially limited our possibility to draw generalizable conclusions.

Another aspect that we could not address in this umbrella review, because of the lack of source data, was the influence of age, drug dose, treatment duration, and baseline psychopathology (and of other factors) on the induction of metabolic alterations by antipsychotics. Although factors such a psychiatric diagnosis or demographics may not be likely to influence the overall results of an umbrella review, other factors such as ethnicity, drug dose, or treatment duration may indeed have an effect. A relationship between daily dose and weight gain or cholesterol increase, at least

for risperidone, was recently reported.[55] In this regard, we highlight the need for studies that aim to include dose and treatment duration and weight gain in predictive models.

Because of the limited size of the available datasets, we were unable to perform post hoc analyses, for example, by considering only those MA including observational studies with a long-term follow-up of greater than 12 months (or drug-naive patients). Despite the fact that many adverse outcomes cannot be addressed in RCT and that observational research represents the most feasible approach for detecting rare and long-term adverse effects of drugs, only 1 MA reporting evidence from observational studies was considered eligible for inclusion in our umbrella review.[42] Finally, as commonly done in previous umbrella reviews,[56,57] when more than 1 work examined the same treatment and outcomes, the one with the largest number of relevant studies was included.

In conclusion, clinical recommendations emerging from our umbrella review are that, from a metabolic perspective, olanzapine should not be the antipsychotic of choice for chronic treatment in youths, and should be avoided in patients at risk for hypertriglyceridemia and hypercholesterolemia; if olanzapine is chosen as a second- or third-line medication, weight gain as well as all metabolic parameters should be actively monitored. Its use could be considered in the short term, when rapid titration is needed to achieve a prompt response; soon afterward, however, the need for continuation should be assessed and the shift to another antipsychotic always considered. To a lesser extent, quetiapine shows a similar high propensity to cause lipid disturbances, but appears to cause less weight gain. Aripiprazole and especially lurasidone show a more neutral metabolic profile, whereas evidence regarding other antipsychotics is less clear in suggesting their risk or safety of use.

Taken together, available meta-analytic data appear insufficient to provide a precise risk estimate regarding MetS. Outcomes of interest for the diagnosis of MetS are lacking or underreported for several antipsychotics. Thus, the present umbrella review should be viewed as a first attempt to inform clinicians in the process of decision making when selecting a specific antipsychotic based on a patient's metabolic status.

This suggests that a comprehensive research agenda should be endorsed, planning long-term studies on the missing variables (ie, glycemic indices as insulin, C-peptide levels, waist size, as well as long-term changes in blood pressure) leading to high AMSTAR grade meta-analyses able to draw a more precise risk estimate for MetS for each single antipsychotic medication. Head-to head trials and individual patient data NMA will be needed to provide evidence that can truly inform personalized psychiatry approaches. In the meantime, a thorough monitoring of all metabolic parameters, following existing guidelines,[58,59] is warranted.

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REFERENCES

1. Olfson M, Druss BG, Marcus SC. Trends in mental health care among children and adolescents. N Engl J Med. 2015;372(21):2029-2038. https://doi.org/10.1056/NEJMsa1413512
2. Fraguas D, Correll CU, Merchán-Naranjo J, *et al*. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. Eur Neuropsychopharmacol. 2011;21(8):621-645. https://doi.org/10.1016/j.euroneuro.2010.07.002
3. Correll CU, Cortese S, Croatto G, *et al*. Efficacy and acceptability of pharmacological, psychosocial, and brain stimulation interventions in children and adolescents with mental

disorders: an umbrella review. World Psychiatry. 2021;20(2):244-275. https://doi.org/10.1002/wps.20881

4. Pisano S, Catone G, Veltri S, *et al*. Update on the safety of second generation antipsychotics in youths: a call for collaboration among pediatricians and child psychiatrists. Ital J Pediatr. 2016;42(1):51. https://doi.org/10.1186/s13052-016-0259-2
5. Carnovale C, Lucenteforte E, Battini V, et al. Association between the glyco-metabolic adverse effects of antipsychotic drugs and their chemical and pharmacological profile: a network meta-analysis and regression [published online ahead of print February 24, 2021]. Psychol Med. https://doi.org/10.1017/S0033291721000180
6. Solmi M, Fornaro M, Ostinelli EG, *et al*. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020;19(2):214-232. https://doi.org/10.1002/wps.20765
7. Pozzi M, Pisano S, Bertella S, *et al*. Persistence in therapy with risperidone and aripiprazole in pediatric outpatients: a 2-year naturalistic comparison. J Clin Psychiatry. 2016;77(12):e1601-e1609. https://doi.org/10.4088/JCP.15m10247
8. de Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2):114-126. https://doi.org/10.1038/nrendo.2011.156
9. Correll CU, Sikich L, Reeves G, *et al*. Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. World Psychiatry. 2020;19(1):69-80. https://doi.org/10.1002/wps.20714
10. Ballon JS, Pajvani U, Freyberg Z, Leibel RL, Lieberman JA. Molecular pathophysiology of metabolic effects of antipsychotic medications. Trends Endocrinol Metab. 2014;25(11):593-600. https://doi.org/10.1016/j.tem.2014.07.004
11. Vantaggiato C, Panzeri E, Citterio A, Orso G, Pozzi M. Antipsychotics promote metabolic disorders disrupting cellular lipid metabolism and trafficking. Trends Endocrinol Metab. 2019;30(3):189-210. https://doi.org/10.1016/j.tem.2019.01.003
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-3421.
13. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. Circulation. 2004;110(16):2494-2497. https://doi.org/10.1161/01.CIR.0000145117.40114.C7
14. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. Pediatrics. 2011;128(Suppl 5):S213-S256. https://doi.org/10.1542/peds.2009-2107C
15. Meyer JM, Davis VG, Goff DC, *et al*. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. Schizophr Res. 2008;101(1-3):273-286. https://doi.org/10.1016/j.schres.2007.12.487
16. Libowitz MR, Nurmi EL. The burden of antipsychotic-induced weight gain and metabolic syndrome in children. Front Psychiatry. 2021;12:623681. https://doi.org/10.3389/fpsyt.2021.623681
17. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
18. Uljarević M, Billingham W, Cooper MN, Condron P, Hardan AY. Examining effectiveness and predictors of treatment response of pivotal response treatment in autism: an umbrella review and a meta-analysis. Front Psychiatry. 2022;12:766150. https://doi.org/10.3389/fpsyt.2021.766150
19. Fullana M, Tortella-Feliu M, Fernández de la Cruz L, *et al*. Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses. Psychol Med. 2020;50(8):1300-1315. https://doi.org/10.1017/S0033291719001247
20. Calati R, Filipponi C, Mansi W, *et al*. Cancer diagnosis and suicide outcomes: umbrella review and methodological considerations. J Affect Disord. 2021;295:1201-1214. https://doi.org/10.1016/j.jad.2021.08.131
21. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evid-Based Ment Health. 2018;21(3):95-100. https://doi.org/10.1136/ebmental-2018-300014
22. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid-Based Healthcare. 2015;13(3):132-140. https://doi.org/10.1097/XEB.0000000000000055
23. Rodrigues R, Lai MC, Beswick A, *et al*. Practitioner review: pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. J Child Psychol Psychiatry Allied Discip. 2021;62(6):680-700. https://doi.org/10.1111/jcpp.13305
24. Arango C, Ng-Mak D, Finn E, Byrne A, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for adolescent schizophrenia: a systematic literature review and network meta-analysis. Eur Child Adolesc Psychiatry. 2020;29(9):1195-1205. https://doi.org/10.1007/s00787-019-01425-2
25. DelBello MP, Kadakia A, Heller V, *et al*. Systematic review and network meta-analysis: efficacy and safety of second-generation antipsychotics in youths with bipolar depression. J Am Acad Child Adolesc Psychiatry. 2022;61(2):243-254. https://doi.org/10.1016/j.jaac.2021.03.021
26. Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clin Res Ed). 2017;358:j4008. https://doi.org/10.1136/bmj.j4008
27. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-375. https://doi.org/10.1016/j.jclinepi.2013.11.007
28. Alfageh BH, Wang Z, Mongkhon P, *et al*. Safety and tolerability of antipsychotic medication in individuals with autism spectrum disorder: a systematic review and meta-analysis. Pediatr Drugs. 2019;21(3):153-167. https://doi.org/10.1007/s40272-019-00333-x
29. Almandil NB, Liu Y, Murray ML, Besag FMC, Aitchison KJ, Wong ICK. Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. Pediatric Drugs. 2013;15(2):139-150. https://doi.org/10.1007/s40272-013-0016-6
30. Alonso-Pedrero L, Bes-Rastrollo M, Marti A. Effects of antidepressant and antipsychotic use on weight gain: a systematic review. Obes Rev. 2019;20(12):1680-1690. https://doi.org/10.1111/obr.12934
31. Armenteros JL, Davies M. Antipsychotics in early onset schizophrenia: systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2006;15(3):141-148. https://doi.org/10.1007/s00787-005-0515-2
32. Channing J, Mitchell M, Cortese S. Lurasidone in children and adolescents: systematic review and case report. J Child Adolesc Psychopharmacol. 2018;28(7):428-436. https://doi.org/10.1089/cap.2018.0046
33. Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). Cochrane Datab Syst Rev. 2016;2016(6):CD009043. https://doi.org/10.1002/14651858.CD009043.pub3
34. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. Eur Child Adolesc Psychiatry. 2007;16(2):104-120. https://doi.org/10.1007/s00787-006-0580-1
35. Khan S, Down J, Aouira N, *et al*. Current pharmacotherapy options for conduct disorders in adolescents and children. Expert Opin Pharmacother. 2019;20(5):571-583. https://doi.org/10.1080/14656566.2018.1561862
36. Krause M, Zhu Y, Huhn M, *et al*. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: a network meta-analysis. Eur Neuropsychopharmacol. 2018;28(6):659-674.
37. Liu HY, Potter MP, Woodworth KY, *et al*. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2011;50(8):749-762. https://doi.org/10.1016/j.jaac.2011.05.011
38. Maneeton N, Maneeton B, Putthisri S, Woottiluk P, Narkpongphun A, Srisurapanont M. Risperidone for children and adolescents with autism spectrum disorder: a systematic review. Neuropsychiatr Dis Treat. 2018;14:1811-1820. https://doi.org/10.2147/NDT.S151802
39. Maneeton N, Maneeton B, Putthisri S, Suttajit S, Likhitsathian S, Srisurapanont M. Aripiprazole in acute treatment of children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2018;14:3063-3072. https://doi.org/10.2147/NDT.S174622
40. McQuire C, Hassiotis A, Harrison B, Pilling S. Erratum to: Pharmacological interventions for challenging behavior in children with intellectual disabilities: a systematic review and meta-analysis. BMC Psychiatry. 2016;16:2. https://doi.org/10.1186/s12888-015-0704-6
41. Pagsberg AK, Tarp S, Glintborg D, *et al*. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: a systematic review and network meta-analysis. J Am Acad Child Adolesc Psychiatry. 2017;56(3):191-202. https://doi.org/10.1016/j.jaac.2016.12.013
42. Pozzi M, Ferrentino RI, Scrinzi G, *et al*. Weight and body mass index increase in children and adolescents exposed to antipsychotic drugs in non-interventional settings: a meta-analysis and meta-regression. Eur Child Adolesc Psychiatry. 2022;31(1):21-37. https://doi.org/10.1007/s00787-020-01582-9
43. Pringsheim T, Lam D, Ching H, Patten S. Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. Drug Saf. 2011;34(8):651-668. https://doi.org/10.2165/11592020-000000000-00000
44. Schneider C, Corrigall R, Hayes D, Kyriakopoulos M, Frangou S. Systematic review of the efficacy and tolerability of clozapine in the treatment of youth with early onset schizophrenia. Eur Psychiatry. 2014;29(1):1-10. https://doi.org/10.1016/j.eurpsy.2013.08.001

45. Stafford MR, Mayo-Wilson E, Loucas CE, *et al*. Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117166. https://doi.org/10.1371/journal.pone.0117166
46. Unwin GL, Deb S. Efficacy of atypical antipsychotic medication in the management of behavior problems in children with intellectual disabilities and borderline intelligence: a systematic review. Res Dev Disabil. 2011;32(6):2121-2133. https://doi.org/10.1016/j.ridd.2011.07.031
47. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: a review of the randomized controlled studies. Eur Neuropsychopharmacol. 2011;21(8):600-620. https://doi.org/10.1016/j.euroneuro.2011.04.001
48. Seida JC, Schouten JR, Mousavi SS, *et al*. First- and second-generation antipsychotics for children and young adults. Agency for Healthcare Research and Quality (US); 2012. Feb. Report No.: 11(12)-EHC077-EF. PMID: 22439156. Accessed June 29, 2023. https://pubmed.ncbi.nlm.nih.gov/22439156/
49. Bobo WV, Cooper WO, Stein CM, *et al*. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry. 2013;70(10):1067-1075. https://doi.org/10.1001/jamapsychiatry.2013.2053
50. Galling B, Roldán A, Nielsen RE, *et al*. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. JAMA Psychiatry. 2016;73(3):247-259. https://doi.org/10.1001/jamapsychiatry.2015.2923
51. Vedal TSJ, Steen NE, Birkeland KI, *et al*. Adipokine levels are associated with insulin resistance in antipsychotics users independently of BMI. Psychoneuroendocrinology. 2019;103:87-95. https://doi.org/10.1016/j.psyneuen.2019.01.001
52. Pisano S, Coppola G, Catone G, *et al*. Differences in metabolic factors between antipsychotic-induced weight gain and non-pharmacological obesity in youths. Clin Drug Invest. 2018;38(5):457-462. https://doi.org/10.1007/s40261-018-0627-3
53. Flynn JT, Kelber DC, Baker-Smith CM, *et al*. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3). https://doi.org/10.1542/peds.2017-1904
54. Henderson AM, Islam N, Sandor GGS, Panagiotopoulos C, Devlin AM. Greater arterial stiffness in children with or without second-generation antipsychotic treatment for mental health disorders: Rigidité artérielle plus importante chez les enfants avec ou sans traitement par antipsychotiques de la deuxième génération pour des troubles de santé mentale. Can J Psychiatry. 2021;66(7):667-676.
55. Piras M, Dubath C, Gholam M, *et al*. Daily dose effects of risperidone on weight and other metabolic parameters: a prospective cohort study. J Clin Psychiatry. 2022;83(4):21m14110.
56. Belbasis L, Bellou V, Evangelou E, Ioannidis JPA, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol. 2015;14(3):263-273. https://doi.org/10.1016/S1474-4422(14)70267-4
57. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. Parkinsonism Relat Disord. 2016;23:1-9. https://doi.org/10.1016/j.parkreldis.2015.12.008
58. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. J Can Acad Child Adolesc Psychiatry. 2011;20(3):218-233.
59. American Academy of Child and Adolescent Psychiatry. Practice parameter for the use of atypical antipsychotic medications in children and adolescents. Accessed June 16, 2023. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_antipsychotic_Medications_Web.pdf