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SYSTEMATIC REVIEW

Second-Generation Antipsychotic Drugs for Patients with Schizophrenia: Systematic Literature Review and Meta-analysis of Metabolic and Cardiovascular Side Effects

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Abstract

Background and Objectives Second-generation antipsychotics (SGAs) for schizophrenia show different risk profiles, whose evidence has been evaluated through comparative reviews on randomized controlled trials (RCTs) and observational studies.

Methods We performed a systematic review and meta-analysis of weight gains, metabolic and cardiovascular side effects of SGAs, relying on both RCTs and observational studies, by comparing variations between the start of treatment and the end of follow-up. The systematic review refers to papers published from June 2009 to November 2020. PRISMA criteria were followed. No restrictions on heterogeneity level have been considered for meta-analysis. A test for the summary effect measure and heterogeneity (I^2 metric) was used.

Results Seventy-nine papers were selected from 3076 studies (61% RCTs, 39% observational studies). Olanzapine and risperidone reported the greatest weight gain and olanzapine the largest BMI increase. Paliperidone showed the highest increase in total cholesterol, but is the only drug reporting an increase in the HDL cholesterol. Quetiapine XR showed the highest decrease in fasting glucose. Lurasidone showed the lowest increase in body weight and a reduction in BMI and was also the only treatment reporting a decrease in total cholesterol and triglycerides. The highest increase in systolic and diastolic blood pressure was reported by quetiapine XR.

Conclusions Despite some limitations (differences in the mean dosages per patient and other side effects not included) this paper provides the first complete meta-analysis on SGAs in variations on metabolic risk profile between start of treatment and end of follow-up, with useful results for clinical practice and possibly for future economic evaluation studies.

1 Introduction

Schizophrenia is a severe long-term mental health condition that involves cognitive, mood symptoms, behavioral and emotional dysfunctions. The symptoms of schizophrenia are usually classified into positive symptoms—any change in behavior or thoughts, such as hallucinations or delusions—and negative symptoms—where people appear to withdraw from the world around them, take no interest in everyday social interactions, and often appear emotionless and flat. Late adolescence and early adulthood are peak periods for the onset of this disease, that is generally characterized by repeated relapses as well as a worsening of psychopathology and social functioning.

Approximately 1.1% of the adult population is affected and the origin seems to derive from both genetic and environmental factors. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria [1], it is characterized by at least two of the following six symptoms, each present for a significant portion of time during a 1-month period: delusions, hallucinations, disorganized speech (e.g. frequent derailment or inconsistency), grossly organized behavior or catatonic and negative symptoms (e.g. decreased expression of emotions and abulia).

The treatment of schizophrenia includes antipsychotic (or neuroleptic) drugs. The efficacy of neuroleptics has been extensively investigated and the results show, not only a reduction in the risk of relapse, but also a lower risk of hospitalization for the subjects treated. This translates positively into the quality of life of these patients [2].

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Key Points

This study investigated the risk-profile of different second-generation antipsychotics (SGAs) for the treatment of schizophrenia through a meta-analysis by assessing variations between the start of treatment and the end of follow-up.

Olanzapine and risperidone reported the greatest weight gain and olanzapine the largest BMI increase. Paliperidone showed the highest increase in total cholesterol, but is the only drug reporting an increase in the HDL cholesterol. Quetiapine XR showed the highest decrease in fasting glucose. Lurasidone showed the lowest increase in body weight and a reduction in BMI and was also the only treatment reporting a decrease in total cholesterol and triglycerides. The highest increase in systolic and diastolic blood pressure was reported by quetiapine XR.

The evidence on the metabolic risk profile of SGAs may support clinicians in the selection of the appropriate treatment for each patient and the development of economic evaluation studies.

Antipsychotic drugs have been available from the mid-1950s; the older types are called typical or first-generation antipsychotics (e.g. chlorpromazine, haloperidol). In the 1990s, new antipsychotic drugs, called second-generation or "atypical" antipsychotics (SGAs) were developed. The first of these SGAs was clozapine, which was followed by risperidone, olanzapine, ziprasidone, quetiapine, amisulpride, sertindole, lurasidone, paliperidone, iloperidone, asenapine, aripiprazole and, more recently, brexpiprazole, cariprazine and zotepine (not in the USA). Some of these SGAs (e.g. paliperidone, aripiprazole, olanzapine, and risperidone) are also available in long-acting injectable (LAI) formulations. The main guidelines recommend SGAs as first choice in both the first episode and in exacerbations. The recommendations on the use of SGAs are supported by a lower incidence of adverse events [3] and, as a consequence, by low discontinuation of therapy [4]. However, SGAs can cause weight gain and considerable changes in the metabolism, which can increase the risk of diabetes and increase circulating cholesterol levels.

Since many SGAs are available, understanding how the many substances compare with each other is important. Few studies focused on the comparison of antipsychotics with placebo in terms of response [5] or considered the real-world effectiveness in preventing relapses [6]. These studies showed that patients improved with antipsychotics compared with placebo, and that clozapine and long-acting injectable antipsychotic medications were the treatments with the highest rate of prevention of schizophrenia relapse. A more recent study reported no consistent superiority of any SGA across efficacy outcomes [7] and most of the literature showed that the main differences between the diverse compounds arise from the tolerability profiles [5, 8–12], especially in terms of metabolic side effects [13].

In the literature there are some systematic reviews comparing side effects, including the metabolic profile of specific oral SGAs in the treatment of schizophrenia. Although most of these studies have been performed in RCT (considered as the gold standard for proving causability), meta-analyses, including observational studies, have been performed as well. The meta-analyses including randomized clinical trials compared the different antipsychotics with placebo [14, 15] or different antipsychotics head-to-head [7, 16] or performed both comparisons [17]. Effect sizes were in general reported as risk ratios for dichotomous outcomes (e.g. sedation) and as standardized mean differences or mean differences for continuous outcomes (e.g. weight gain). Meta-analyses on observational studies carried out comparisons between the various SGA treatments or with placebo in terms of risk of weight gain or risk of developing type 2 diabetes mellitus [18, 19].

The aim of the present paper was to investigate the metabolic and cardiovascular risk profile of the main oral SGAs used in the treatment of adult patients with schizophrenia on the grounds of a systematic review and meta-analysis. In light of the great importance given to the collection and analysis of real-world data for the evaluation of outcomes of new health technologies [20], randomized controlled trials and observational studies have both been considered. Contrary to other published reviews, we assessed the mean variation of the main metabolic parameters between the start of treatment and the end of follow-up for each SGA, reporting detailed results for the different follow-up horizons.

2 Methods

The systematic review of the literature was conducted in November 2020 based on the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [21], starting from a search of the four fundamental elements (population, intervention, comparator, outcomes).

From preliminary research, no studies were found that considered a population to be only European, consequently, no restrictions were imposed on the choice of the base-case population for the analyses.

The drugs taken into consideration were lurasidone, aripiprazole, olanzapine, paliperidone extended release (XR), quetiapine XR and risperidone, which are the products with the highest market share in the major European countries for

the treatment of patients with schizophrenia (IQVIA—data on file [22]). The choice also included lurasidone (recently launched onto the market) as a stabilization drug.

Given that no reliable advantage of any SGA emerged across efficacy outcomes [7], the systematic review of the literature has been focused on metabolic and cardiovascular adverse events. In particular, for each drug, variations from final and baseline values have been retrieved for the following parameters (metabolic profile): body weight, body mass index (BMI), total and high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose, systolic and diastolic blood pressure.

The scientific databases used for the systematic review of the literature were Pubmed and Web of Science. Studies were considered if published in English and related to an adult population (aged ≥ 18 years). The research period has been restricted to the last 10 years. No restrictions were applied to the type of study.

The literature search has been performed according to the following:

"schizophrenia" AND ("lurasidone" OR "quetiapine XR" OR "quetiapine extended release" OR "extended release quetiapine" OR "risperidone" OR "olanzapine" OR "aripiprazole" OR "paliperidone") AND ("fasting glucose" OR "fasting plasma glucose" OR "FPG" OR "weight" OR "BMI" OR "HDL" OR "total cholesterol" OR "triglyceride" OR "blood pressure" OR "hypertension" OR "cardiovascular risk" OR "diabetes").*

Abstract and full-text selection was conducted independently by two expert reviewers (CR, AB). Data were extracted using a customized template developed in Microsoft Excel based on the PICOS statement. Information recorded included study features, participants and treatments characteristics and metabolic profiles.

Data referring to the different treatments were retrieved from all comparative and non-comparative studies identified. Outcomes variations from the different studies, calculated as the difference between the value at the last follow-up and the baseline value, were pooled through a random effect meta-analysis (mean differences) [23] considering the available follow-up. The analyses were performed using Stata® software (StataCorp, version 14) through the "metan" command, which requires two input parameters, effect estimate and standard error. In case the standard deviation was reported for the effect estimate, it was transformed into standard error according to formulas presented in Burns et al. [24].

A test on the summary effect measure is given, as well as a test for heterogeneity, quantified using the I^2 metric [25]: the higher the values (from 0% to 100%) the larger the heterogeneity across studies. For the meta-analyses, a broader inclusion criterion has been applied so no restrictions on heterogeneity level have been considered. Results are displayed in forest plots according to different ranges of follow-up duration: ≤ 6 months, 6 < months ≤ 12, 12 < months ≤ 24 and 24 < months ≤ 36; this will allow further uses of the meta-analysis results in the context of economic evaluations from short to medium time horizons.

An appraisal of the studies included in the analyses has been performed in order to assess their methodological quality and to determine the extent to which the studies addressed the possibility of bias in their design, conduct and analysis. All papers selected for inclusion in the systematic review have been critically evaluated by two appraisers (CR, AB) according to the JBI Critical appraisal tools for randomized controlled trials (RCTs) and cohort studies [26].

The level of evidence (LOE) of the studies was assessed according to a classification provided by the Agency for Healthcare Research and Quality (AHRQ) [27], which considers three categories: high (current evidence derived from RCTs without important limitations), moderate (current evidence derived from RCTs with important limitations or very strong evidence from observational studies or case series), low (current evidence from observational studies, case series or just opinions). In our case, RCTs with lack of double-blinding, failure to adhere to intention-to-treat analysis or methodological flaws (treatment groups dissimilar at the baseline) were considered together with prospective observational trials and pre-post studies as moderate LOE. Retrospective studies and case series were considered low LOE.

Scenario analyses have been performed by considering only RCTs and by removing the low-quality studies according to the LOE to evaluate the robustness of the results.

3 Results

Figure 1 shows the search process according to PRISMA flow-chart. Starting with 3076 identified papers, the analysis focused on 79 that contained useful data for performing the meta-analyses. These were prospective studies (34%, $n = 27$), retrospective studies (5%, $n = 4$) and RCTs (61%, $n = 48$), with a total of 37,467 participants (median 69 participants/arm, range 7–5204). The mean age of the population was 36 ± 7.3 years and 62% were male. The number of studies with each individual SGA were: 49 olanzapine, 27 risperidone, 20 aripiprazole, 19 lurasidone, 13 quetiapine and 6 paliperidone.

Table 1 presents the characteristics of the studies included in the quantitative synthesis, which presents only study arms whose drugs are considered in the present study, regardless of whether they were compared with other treatments or placebo, while Table 2 presents the metabolic parameters extracted. Parameter variations for total and HDL cholesterol, triglycerides and fasting glucose were expressed in mg/dL. To convert millimoles per liter to milligrams per deciliter, we multiplied total and HDL cholesterol values

by 38.6, triglycerides values by 88.6 and fasting glucose values by 18.

Supplementary Table 1 reports metabolic parameters derived by the considered studies while the Supplementary material shows a detailed analysis of results according to the forests plots for the different treatments, follow-up periods and parameters considered. A summary of the main findings considering the complete follow-up horizon of studies is presented in Table 2. The appraisal of the studies according to the risk of bias and LOE is reported in Supplementary Table 2.

From the meta-analyses, lurasidone was shown to be the treatment with a lower increase in body weight (0.43 kg) and with a decrease in BMI (− 0.10 kg/m^2); it was also the only treatment reporting a decrease in total cholesterol (− 8.01 mg/dL) and triglycerides (− 5.33 mg/dL) and the highest decrease in HDL cholesterol (− 2.05 mg/dL).

Olanzapine and risperidone reported the largest weight gain of 4.52 and 4.19 kg, respectively, with significant differences compared with the other treatments. Olanzapine also reported the greatest variation in BMI (1.59 kg/m^2) compared with the other SGAs and significant effects on the variation of triglycerides (33.10 mg/dL) and fasting glucose (6.24 mg/dL). Paliperidone showed the highest increase in total cholesterol (14.69 mg/dL) but reported a positive increase in the HDL cholesterol (0.57 mg/dL). Aripiprazole was another treatment showing a large increase in triglycerides (18.63 mg/dL).

The assessment of the variations in diastolic blood pressure was not possible for paliperidone due to lack of data. The highest increase in systolic and diastolic blood pressure was reported by quetiapine XR—2.60 and 2.77 mm Hg, respectively. Quetiapine XR was also the only drug reporting a decrease in fasting glucose (− 0.59 mg/dL).

The parameters reporting the higher heterogeneity ($I^2 > 50\%$) were body weight (aripiprazole, olanzapine, risperidone), BMI (aripiprazole, olanzapine), HDL cholesterol (olanzapine, risperidone), total cholesterol (olanzapine, risperidone), triglycerides (olanzapine, paliperidone, risperidone), fasting glucose (aripiprazole, olanzapine, risperidone), systolic blood pressure (olanzapine) and diastolic blood pressure (olanzapine, risperidone).

The scenario analysis performed considering only data from RCTs (see Supplementary Table 3) confirmed in

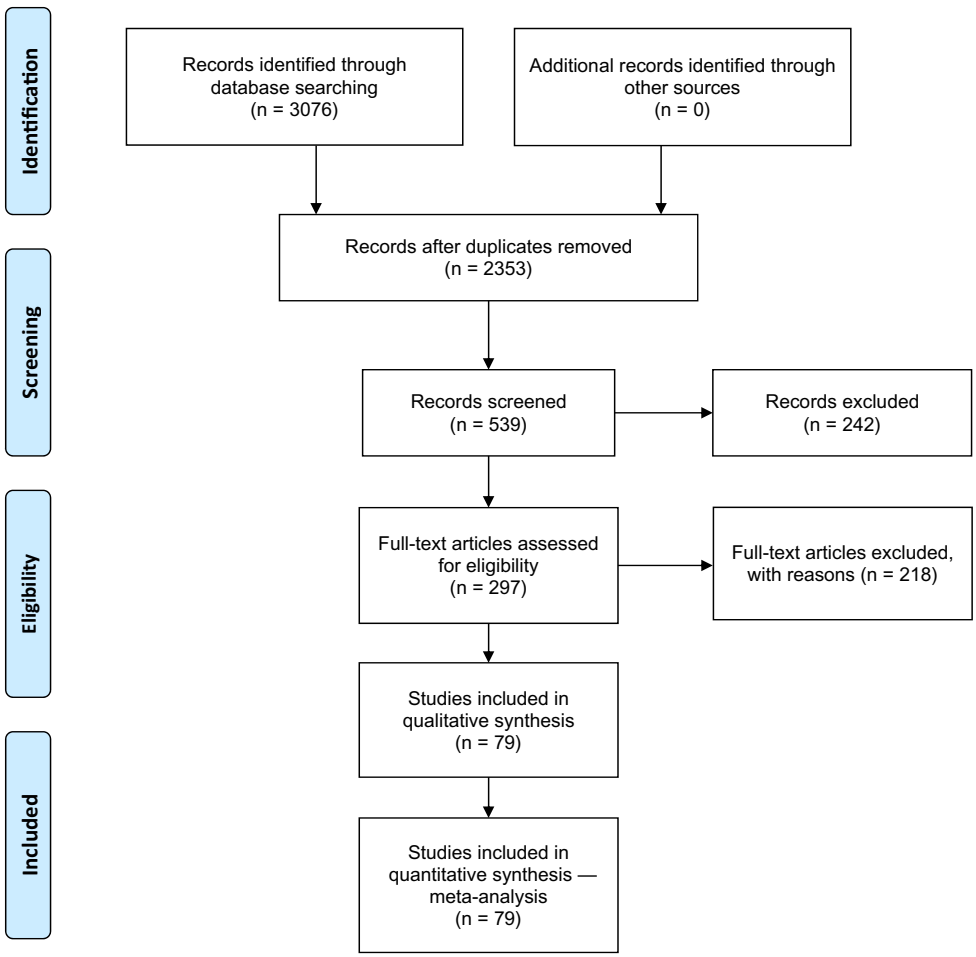

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart

Table 1 Studies characteristics

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Aripiprazole	2010	Josiassen 2010 [28]	Naturalistic, single-blind design	2 m	USA	19	74	23
Aripiprazole	2010	Lee 2010 [29]	Prospective study	2 m	Korea	21	62	33
Aripiprazole	2011	Lee 2011 [30]	Retrospective analysis	4 m	Korea	66	47	37
Aripiprazole	2012	Zhang 2012 [31]	Prospective, observational study	12 m	China	71	63	26
Aripiprazole	2013	Takekita 2013 [32]	Randomized open-label study	3 m	Japan	49	47	41
Aripiprazole	2013	Jindal 2013 [33]	Randomized, double-blind controlled trial	6 w	India	30	63	NA
Aripiprazole	2014	Li 2014 [34]	Multicenter, randomized, double-blind, double-dummy, parallel-group clinical study	6 w	China	139	49	34
Aripiprazole	2014	Adams 2014 [35]	Multicenter, randomized, double-blind, Phase 3 study	6 m	USA	161	66	43
Aripiprazole	2014	Gupta 2014 [36]	Prospective study	4 m	India	210	NA	NA
Aripiprazole	2014	Zhang 2014 [37]	Randomized clinical trial	2 m	China	50	62	42
Aripiprazole	2014	Perez-Iglesias 2014 [38]	Randomized open-label study	3 m	Spain	68	52	32
Aripiprazole	2016	Gründer 2016 [39]	Multicenter, double-blind, double-dummy, randomized study	6 m	Germany	73	62	35
Aripiprazole	2016	Malla 2016 [40]	Open-label prospective study	12 m	Canada	68	76	25
Aripiprazole	2016	Kishi 2016 [41]	Rater-masked, randomized trial	6 m	Japan	22	32	42
Aripiprazole	2017	Kumar 2017 [42]	Non-randomized, naturalistic, rater-blinded, prospective, comparative trial	2 m	India	13	62	29
Aripiprazole	2019	Turangan 2019 [43]	Comparative pre-post study	6 w	Indonesia	44	NA	NA
Aripiprazole	2019	Cheng 2019 [44]	Open-label randomized study	8 w	China	162	46	24.8
Aripiprazole	2019	Mustafa 2019 [45]	Prospective cohort, multi-site study	12 m	17 sites in Canada	199	67.50	32.9
Aripiprazole	2020	Vazquez-Bourgon 2020 [46]	Randomized open label study	36 m	Spain	59	48.70	32.6
Aripiprazole	2020	Gao 2020 [47]	Retrospective study	24 w	China	47	64	23.15
Lurasidone 120 mg	2011	Meltzer 2011a [48]	Prospective, multicenter, randomized parallel-group study	6 w	USA, Colombia, Lithuania, Asia	118	79	38
Lurasidone 120 mg	2011	Potkin 2011 [49]	Randomized, double-blind, fixed-dose, parallel group study	3 w	USA	150	70	42
Lurasidone 120 mg	2013	Ogasa 2013 [50]	Multicenter, randomized, fixed-dose, double-blind, parallel-group, placebo-controlled study	6 w	USA	49	73	41
Lurasidone 120 mg	2013	Nasrallah 2013 [51]	Randomized, fixed-dose, double-blind, placebo-controlled, multiregional, parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Malaysia, France	124	74	38

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Lurasidone 160 mg	2013	Loebel 2013a [52]	Multiregional, prospective, randomized parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Colombia	121	68	38
Lurasidone 20 mg	2015	Potkin 2015 [53]	Randomized, double-blind, placebo-controlled study	6 w	USA	71	72	41
Lurasidone 40 mg	2011	Meltzer 2011a [48]	Prospective, multicenter, randomized parallel-group study	6 w	USA, Colombia, Lithuania, Asia	119	78	38
Lurasidone 40 mg	2013	Ogasa 2013 [50]	Multicenter, randomized, fixed-dose, double-blind, parallel-group, placebo-controlled study	6 w	USA	50	72	40
Lurasidone 40 mg	2013	Nasrallah 2013 [51]	Randomized, fixed-dose, double-blind, placebo-controlled, multiregional, parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Malaysia, France	122	67	40
Lurasidone 40 mg	2015	Potkin 2015 [53]	Randomized, double-blind, placebo-controlled study	6 w	USA	67	69	42
Lurasidone 40 mg	2019	Higuchi 2019 [54]	Prospective, multicenter, parallel-group study	6 w	Japan, South Korea, Malaysia and Taiwan	150	55	42
Lurasidone 80 mg	2013	Loebel 2013a [52]	Multiregional, prospective, randomized parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Colombia	125	77	36
Lurasidone 80 mg	2013	Nasrallah 2013 [51]	Randomized, fixed-dose, double-blind, placebo-controlled, multiregional, parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Malaysia, France	119	64	39
Lurasidone 80 mg	2015	Potkin 2015 [53]	Randomized, double-blind, placebo-controlled study	6 w	USA	71	73	42
Lurasidone 80 mg	2019	Higuchi 2019 [54]	Prospective, multicenter, parallel-group study	6 w	Japan, South Korea, Malaysia and Taiwan	154	53	44
Lurasidone 80 mg	2020	Jena 2020 [55]	Randomized, open-label, active-controlled, parallel design clinical trial	6 w	India	50	50	33.88
Lurasidone flexible dose (40-160 mg/day)	2013	Loebel 2013b [56]	Double-blind, parallel-group study	12 m	USA, Russia, India, Ukraine, Romania, Colombia	78	72	37
Lurasidone flexible dose (40-120 mg/day)	2016	Correll 2016 [57]	Open-label extension study	22 m	USA, Russia, India, Ukraine, Romania, Malaysia, France	191	62	38
Lurasidone flexible-doses (37–111 mg/day)	2020	Patel 2020 [58]	Double-blind active control trial	12 m	Argentina, Brazil, Chile, Croatia, Israel, South Africa, Thailand, USA	391	74.20	41.9
Olanzapine	2009	Karagianis 2009 [59]	Prospective, multicenter, observational study	12 m	Canada	249	54	42

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Olanzapine	2009	Novick 2009 [60]	Prospective, observational study	36 m	Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK	2701	57	40
Olanzapine	2009	Smith 2009 [61]	Randomized open-label study	5 m	USA	23	100	41
Olanzapine	2010	Gilles 2010 [62]	Case series	6 w	Germany	14	79	29
Olanzapine	2010	Josiassen 2010 [28]	Naturalistic, single-blind design	2 m	USA	14	57	22
Olanzapine	2010	Chiu 2010 [63]	Open-label, prospective, multicenter study	2 m	Taiwan	33	64	38
Olanzapine	2010	Bushe 2010 [64]	*Post hoc* analysis from a randomized, controlled study	6 m	USA	171	67	42
Olanzapine	2010	Smith 2010 [65]	Randomized open-label study	5 m	USA	23	100	41
Olanzapine	2011	Krakowski 2011 [66]	Double-blind randomized prospective	3 m	USA	30	80	35
Olanzapine	2011	Grootens 2011 [67]	Double-blind, parallel group, randomized, controlled multicenter trial	2 m	The Netherlands and Belgium	35	86	23
Olanzapine	2011	Meltzer 2011b [68]	Open-label prospective study	12 m	USA	82	57	40
Olanzapine	2011	Fernandez-Egea 2011 [69]	Open-label trial	4 m	Spain	30	67	27
Olanzapine	2011	Meltzer 2011a [48]	Prospective, multicenter, randomized parallel-group study	6 w	USA, Colombia, Lithuania, Asia	122	78	38
Olanzapine	2011	Raposo 2011 [70]	Randomized, naturalistic study	9 m	Brazil	18	100	35
Olanzapine	2011	Lee 2011 [30]	Retrospective analysis	2 m	Korea	363	44	36
Olanzapine	2012	Paslakis 2012 [71]	Open prospective clinical trial	3 w	Germany	7	86	29
Olanzapine	2012	Kusumi 2012 [72]	Open-label, multicenter, randomized, flexible-dose study	12 m	Japan	57	61	44
Olanzapine	2012	Novick 2012 [73]	Prospective, observational study	12 m	10 European countries	5204	59	40
Olanzapine	2012	Kaushal 2012 [74]	Prospective, randomized, comparative, open-label clinical study	2 m	India	30	47	29
Olanzapine	2012	Schreiner 2012 [75]	Prospective, randomized, controlled, open-label, parallel-group study	6 m	Argentina, Egypt, Estonia, France, Greece, Italy, Jordan, Latvia, Lebanon, Lithuania, Romania, Slovakia, South Africa, Spain, and Turkey	220	60	37
Olanzapine	2012	Buchanan 2012 [76]	Randomized double-blind study	6.5 m	Australia, the Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Poland, Romania, Russia, South Africa, Spain, Sweden, and the UK	240	68	40

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Olanzapine	2012	Buchanan 2012 [76]	Randomized double-blind study	6.5 m	Brazil, Canada, Chile, Mexico, and the USA	224	76	43
Olanzapine	2012	Schloemaker 2012 [77]	Randomized double-blind study	12 m	Australia, Belgium, Czech Republic, France, Germany, Poland, Russia, South Africa, and Spain	150	59	36
Olanzapine	2012	Alvarez 2012 [78]	Randomized, double-blind, parallel-group study	6 m	Spain	23	65	36
Olanzapine	2012	Li 2012 [34]	Randomized, open-label, parallel-design, controlled trial	6 w	China	40	70	24
Olanzapine	2013	Ou 2013 [79]	Multicenter, open-label, parallel-group, randomized, trial	6 w	China	130	57	28
Olanzapine	2013	Hu 2013 [80]	Prospective, randomized, open-label, flexible-dose, parallel-group study	3 m	China	23	74	29
Olanzapine	2013	Jindal 2013 [33]	Randomized, double-blind controlled trial	6 w	India	30	50	NA
Olanzapine	2014	Salviato 2014 [81]	longitudinal study	12 m	Brazil	30	47	28
Olanzapine	2014	Choure 2014 [82]	Open-label, observational, non-interventional, prospective longitudinal study	2.5 m	India	32	50	NA
Olanzapine	2014	Gupta 2014 [36]	Prospective study	4 m	India	210	NA	NA
Olanzapine	2014	Zhang 2014 [37]	Randomized clinical trial	2 m	China	50	68	41
Olanzapine	2015	Fabrazzo 2015 [83]	Retrospective study	12 m	Italy	67	60	39
Olanzapine	2016	Gründer 2016 [39]	Multicenter, double-blind, double-dummy, randomized study	6 m	Germany	73	62	35
Olanzapine	2016	Singh 2016 [84]	Prospective, randomized, observational study	6 m	India	31	87	29
Olanzapine	2016	Kumar 2016 [85]	Randomized, double-blind, parallel group comparison	12 m	India	36	69	42
Olanzapine	2017	Lin 2017 [86]	Prospective randomized, double-blind trial	6 w	Taiwan	44	41	39
Olanzapine	2018	Huang 2018 [87]	Randomized active-controlled treatment	13 w	China	29	69	24
Olanzapine	2018	Ullah 2018 [88]	Randomized clinical trial	1 m	Pakistan	8	NA	NA
Olanzapine	2018	Osborn 2018 [89]	Retrospective cohort study	24 m	UK	2789	100	49
Olanzapine	2018	Osborn 2018 [89]	Retrospective cohort study	24 m	UK	3549	0	53
Olanzapine	2019	Cheng 2019 [44]	Open-label randomized study	8 w	China	158	51	24.6

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Olanzapine	2019	Martin 2019 [90]	Randomized Phase 2 study	12 w	International, multicenter (not specified countries)	75	70.70	40.3
Olanzapine	2020	Moghimi Sarani 2020 [91]	Double-blind placebo controlled clinical trial	12 w	Iran	39	71	32.6
Olanzapine	2020	Huang 2020 [92]	Observational cohort prospective study	12 w	China	33	36	23.5
Olanzapine	2020	de Almeida 2020 [93]	Open-label non-randomized study	6 w	Brazil	17	47	37
Olanzapine	2020	Potkin 2020 [94]	Randomized double blind	4 w	USA and Europe	133	60.90	41.5
Olanzapine	2020	Jena 2020 [55]	Randomized, open-label, active-controlled, parallel design clinical trial	6 w	India	51	65	31.59
Olanzapine	2020	Guan 2020 [95]	Two-stage case–control study	10 w	China	813	49	35
Paliperidone XR	2012	Na 2012 [96]	Multicenter, open-label, non-comparative clinical trial	6 m	Korea	225	43	37
Paliperidone XR	2012	Zhang 2012 [31]	Prospective, observational study	12 m	China	63	56	27
Paliperidone XR	2012	Schreiner 2012 [75]	Prospective, randomized, controlled, open-label, parallel-group study	6 m	Argentina, Egypt, Estonia, France, Greece, Italy, Jordan, Latvia, Lebanon, Lithuania, Romania, Slovakia, South Africa, Spain, and Turkey	239	56	39
Paliperidone XR	2013	Hu 2013 [80]	Prospective, randomized, open-label, flexible-dose, parallel-group study	3 m	China	33	64	25
Paliperidone XR	2015	Ucok 2015 [97]	Non-randomized, single-arm, multicenter clinical trial	12 m	Turkey	84	76	28
Paliperidone XR	2018	Chen 2018 [98]	Open-label, single-arm, multicenter, Phase IV trial	6 m	Taiwan	297	46	40
Quetiapine XR	2009	Karagianis 2009 [59]	Prospective, multicenter, observational study	12 m	Canada	63	54	42
Quetiapine XR	2009	Novick 2009 [60]	Prospective, observational study	36 m	Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK	350	54	40
Quetiapine XR	2010	Josiassen 2010 [28]	Naturalistic, single-blind design	2 m	USA	11	64	22
Quetiapine XR	2010	Bushe 2010 [64]	*Post hoc* analysis from a randomized, controlled study	6 m	USA	175	65	40
Quetiapine XR	2011	Chen 2011 [99]	Prospective study	2 m	Taiwan	17	65	36
Quetiapine XR	2012	Novick 2012 [73]	Prospective, observational study	12 m	10 European countries	760	53	41
Quetiapine XR	2013	Loebel 2013b [56]	Double-blind, parallel-group study	12 m	USA, Russia, India, Ukraine, Romania, Colombia	33	61	38

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Quetiapine XR	2013	Chue 2013 [100]	Multicenter, open-label, prospective study	6 m	Canada, Australia, Hong Kong and Republic of Korea	295	62	38
Quetiapine XR	2013	Loebel 2013a [52]	Multiregional, prospective, randomized parallel-group study	6 w	USA, Russia, India, Ukraine, Romania, Colombia	119	65	37
Quetiapine XR	2014	Gupta 2014 [36]	Prospective study	4 m	India	210	NA	NA
Quetiapine XR	2014	Zhang 2014 [37]	Randomized clinical trial	2 m	China	50	66	40
Quetiapine XR	2014	Perez-Iglesias 2014 [38]	Randomized open-label study	3 m	Spain	47	52	32
Quetiapine XR	2016	Gründer 2016 [39]	Multicenter, double-blind, double-dummy, randomized study	6 m	Germany	73	62	35
Risperidone	2009	Karagianis 2009 [59]	Prospective, multicenter, observational study	12 m	Canada	104	46	44
Risperidone	2009	Novick 2009 [60]	Prospective, observational study	36 m	Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK	1020	58	40
Risperidone	2009	Smith 2009 [61]	Randomized open-label study	5 m	USA	23	96	43
Risperidone	2010	Josiassen 2010 [28]	naturalistic, single-blind design	2 m	USA	16	81	24
Risperidone	2010	Smith 2010 [65]	Randomized open-label study	5 m	USA	23	96	43
Risperidone	2010	Lin 2010 [101]	Randomized, double-blind, fixed-dose trial	6 w	Taiwan	42	58	38
Risperidone	2011	De Hert 2011 [102]	Multinational, multicenter, parallel-group, random allocation, open-label study	12 m	NA	130	46	37
Risperidone	2011	Meltzer 2011b [68]	Open-label prospective study	12 m	USA	78	49	40
Risperidone	2011	Xiang 2011 [103]	Prospective study	15 m	China	129	62	34
Risperidone	2011	Lee 2011 [30]	Retrospective analysis	3 m	Korea	128	52	39
Risperidone	2012	Paslakis 2012 [71]	Open-label prospective clinical trial	3 w	Germany	7	43	43
Risperidone	2012	Novick 2012 [73]	Prospective, observational study	12 m	10 European countries	1863	58	40
Risperidone	2012	Kaushal 2012 [74]	Prospective, randomized, comparative, open-label clinical study	2 m	India	30	47	29
Risperidone	2014	Li 2014 [34]	Multicenter, randomized, double-blind, double-dummy, parallel-group clinical study	6 w	China	140	55	31
Risperidone	2014	Choure 2014 [82]	Open-label, observational, non-interventional, prospective longitudinal study	2.5 m	India	32	50	NA
Risperidone	2014	Song 2014 [104]	Prospective observational study	6 m	China	62	53	25
Risperidone	2014	Gupta 2014 [36]	Prospective study	4 m	India	210	NA	NA

Table 1 (continued)

Drug	Year	Study	Study type	Duration	Country	No. of patients	Males %	Age (years)
Risperidone	2016	Kumar 2016 [85]	Randomized, double-blind, parallel group comparison	12 m	India	35	66	40
Risperidone	2017	Kumar 2017 [42]	Non-randomized, naturalistic, rater-blinded, prospective, comparative trial	2 m	India	22	59	29
Risperidone	2018	Yuan 2018 [105]	Prospective observational study	6 m	China	41	56	23
Risperidone	2018	Osborn 2018 [89]	Retrospective cohort study	24 m	UK	2819	100	57
Risperidone	2018	Osborn 2018 [89]	Retrospective cohort study	24 m	UK	3737	0	62
Risperidone	2019	Cheng 2019 [44]	Open-label randomized study	8 w	China	157	52	24.9
Risperidone	2020	de Almeida 2020 [93]	Open-label non-randomized study	6 w	Brazil	23	74	39
Risperidone	2020	Gao 2020 [47]	Retrospective study	24 w	China	46	63	23.19
Risperidone	2020	Guan 2020 [95]	Two-stage case–control study	10 w	China	772	48	35
Risperidone flexible doses (2–6 mg/day)	2020	Patel 2020 [58]	Double-blind active-control trial	12 m	Argentina, Brazil, Chile, Croatia, Israel, South Africa, Thailand, USA	190	63.70	41.1

NA not available, *m* months, *w* weeks, *XR* extended release

Table 2 Parameter variations according to meta – analysis results (values are expressed as mean change and 95% CI)

Parameter	Drug					
	Aripiprazole	Lurasidone	Olanzapine	Paliperidone XR	Quetiapine XR	Risperidone
Δ Weight (kg)	2.73* (0.53, 4.94)	0.43 (– 0.93, 1.79)	4.52* (3.62, 5.42)	0.88 (– 0.75, 2.51)	1.83* (0.37, 3.29)	4.19* (3.30, 5.07)
Δ BMI (kg/m^2)	1.48 (– 0.04, 3.00)	– 0.10 (– 0.35, 0.16)	1.59* (0.97, 2.21)	0.59 (– 0.34, 1.53)	0.74 (– 0.36, 1.85)	0.61* (0.53, 0.69)
Δ Total cholesterol (mg/dL)	11.67 (– 0.01, 23.35)	– 8.01 (– 9.45, – 6.57)	13.07* (9.60, 16.53)	14.69 (– 1.54, 30.92)	10.55 (– 0.33, 21.43)	4.40 (– 4.46, 13.26)
Δ Cholesterol HDL (mg/dL)	– 0.62 (– 2.15, 0.90)	– 2.05 (– 2.47, – 1.63)	– 1.25 (– 2.73, 0.23)	0.57 (– 1.05, 2.19)	– 1.74* (– 2.92, – 0.56)	– 1.08 (– 2.84, 0.67)
Δ Triglycerides (mg/dL)	18.63* (1.67, 35.58)	– 5.33* (– 6.55, – 4.10)	33.10* (21.93, 44.27)	7.15 (– 14.96, 29.25)	14.25* (2.92, 25.59)	9.39 (– 7.77, 26.54)
Δ Fasting glucose (mg/dL)	0.19 (– 4.22, 4.59)	1.78 (– 18.39, 21.96)	6.24* (4.38, 8.10)	3.20* (0.10, 6.29)	– 0.59 (– 5.37, 4.18)	2.97* (0.30, 5.64)
Δ Systolic blood pressure (mm Hg)	0.84 (– 3.25, 4.93)	– 0.61 (– 1.32, 0.10)	1.64 (– 1.43, 4.72)	1.29 (– 1.48, 4.06)	2.60* (0.04, 5.16)	1.07 (– 1.12, 3.26)
Δ Diastolic blood pressure (mm Hg)	1.00 (– 3.01, 5.01)	0.13 (– 0.24, 0.50)	0.55 (– 1.08, 2.18)	–	2.77* (0.35, 5.19)	1.35 (– 1.48, 4.18)

*Statistical significance

BMI body mass index, *CI,* confidence interval, *HDL* high-density lipoprotein, *XR* extended release

general the results of the base-case analysis, with the exception of aripiprazole, which showed an increase in cholesterol HDL (0.59 vs – 0.62 mg/dL) and risperidone, which reported a decrease in triglycerides (– 3.69 vs 9.39 mg/dL) and in systolic blood pressure (– 2.33 vs 1.07 mm Hg). The scenario analysis conducted excluding low-quality studies (see Supplementary Table 4) showed only small variations in a limited set of parameters compared with the base case.

4 Discussion and Conclusion

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. If left untreated, the symptoms of schizophrenia can be persistent and disabling. Despite its low prevalence (about 1% of the population) it has great health, social and economic burdens not only for patients but also for families, caregivers, and society. Comorbidities related to metabolic disorders and cardiovascular diseases, such as diabetes, hypertension, metabolic syndrome, and obesity are excessively prevalent among patients with schizophrenia. Compared with the general population, schizophrenia patients have nearly twice the risk of diabetes and metabolic syndrome [106] and an increased risk of mortality for cardiovascular disease, with patients' life expectancy reduced by about 15 years [107]. Although some modifiable cardiovascular disease risk factors, such as sedentary lifestyle, may be associated with schizophrenia, several antipsychotics have been associated with an increased risk of weight gain and other metabolic abnormalities.

The literature reports some meta-analyses [7, 14–19] based on RCTs or observational studies which compared antipsychotics with each other and possibly with placebo in terms of relative risks or differences for the considered parameters. In contrast to these studies, the present work considered both RCTs and observational studies in order to provide results that may be also be extended to clinical practice contexts. Moreover, for each SGA we assessed the mean variation of the metabolic parameters between the start of treatment and the end of follow-up, thus providing immediate and clinically tangible results.

The analyses showed that metabolic effects are not statistically different across medicines although presenting great variations. For weight and BMI gain, respectively, olanzapine and risperidone and olanzapine alone reported significant differences compared with the other SGAs. In particular, olanzapine and risperidone reported a weight gain of 4.52 and 4.19 kg, respectively, while olanzapine reported an increase in BMI of 1.59 kg/m^2. From the meta-analyses, lurasidone was shown to be the treatment with the lowest increase in body weight (0.43 kg) and with a decrease in BMI (– 0.10 kg/m^2). These results are in line with a recent published study that provided a systematic review and

meta-analysis of randomized trials lasting at least 6 months comparing SGAs head-to-head in schizophrenia and related disorders [7]. The paper reported that weight gain was greater with olanzapine than with all other non-clozapine SGAs and risperidone was significantly worse than several other SGAs. Olanzapine and clozapine have also been reported as the drugs causing greater weight gain compared with most other agents in another recent narrative review [108]. Huhn and colleagues [15] showed that placebo was preferred to olanzapine and risperidone when considering weight increase (mean difference, olanzapine: 2.78 kg, 95% CI 2.44–3.13; risperidone 1.44 kg, 95% CI 1.05–1.83).

The results on total cholesterol and fasting glucose are in line with those reported by Rummel-Kluge and colleagues [16] who showed that olanzapine produced a greater cholesterol increase than aripiprazole and risperidone, while cholesterol increase with quetiapine was greater than with risperidone. From our meta-analyses lurasidone showed a decrease in total cholesterol (− 8.01 mg/dL) and triglycerides (− 5.33 mg/dL) and a moderate variation in fasting glucose (1.78 mg/dL). Concerning fasting glucose, olanzapine produced the highest increase compared with the other drugs. Our data are in accordance with those derived from the meta-analysis of RCTs and observational studies [14, 18, 19, 109].

The present study has some limitations. First, changes in patients' metabolic profiles have been derived from studies that reported, for each drug, different mean dosages per patient, highlighting that the dose is personalized according to patients' characteristics. Second, the study focused on the analysis of metabolic side effects, without considering the impact of different side effects on patients' quality of life. However, this was out of the scope of the analysis and, furthermore, there are difficulties in assessing the quality of life of patients with schizophrenia because of their cognitive impairments and lack of insight into their disease [110]. Third, the study focused on the analysis of metabolic effects due to the different treatments and did not consider the management of other adverse events.

Despite these limitations, this paper provides evidence on differences in the metabolic effects of SGAs, in a context where recent indications showed no consistent differences in their relative effectiveness.

These findings have important implications not only for clinical practice but also for health economics studies. On the one hand, because currently available antipsychotics vary more with regard to adverse effects than with efficacy, the selection of the appropriate treatment should do no harm to the patient, being mindful that untreated disease can commonly have greater adverse effects than medications. On the other hand, this analysis summarized the evidence on the metabolic impact of SGAs that could be the benchmarks for drugs launched into the market for the same indication, thus integrating the treatment cost with the cost for the management of the metabolic effects. Our findings could be used to perform cost-effectiveness or cost-utility analyses comparing new options with existing treatments and the budget impact of new treatments. A budget impact analysis could also be carried out to estimate the economic impact of a change of prescription mix for current treatment options.

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Declarations

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Authors' contribution CJ: Conceptualization; CR, AB: Data curation; CR: Formal analysis; CJ: Funding acquisition; CR, AB: Investigation; CR: Methodology; CJ: Project administration; CJ: Supervision; CJ, CR, AB: Writing—review & editing.

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