SYSTEMATIC REVIEW

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Comparing Tolerability of Olanzapine in Schizophrenia and Affective Disorders

A Meta-Analysis

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Abstract

Background: Olanzapine is prescribed for a number of psychiatric disorders, including schizophrenia, bipolar mania, and unipolar and bipolar depression. Olanzapine treatment is associated with tolerability issues such as metabolic adverse effects (e.g. weight gain, increase in blood glucose, triglycerides and total cholesterol levels), extrapyramidal symptoms [EPS] (e.g. parkinsonism, akathisia, tardive dyskinesia) and sedative adverse effects. Metabolic issues lead to some long-term consequences, which include cardiovascular diseases (CVD) and type 2 diabetes mellitus, and these complications cause high rates of mortality and morbidity among patients with severe mental illnesses. The expanded indications of olanzapine in psychiatry suggest a need to investigate whether there is a difference in the incidence and severity of adverse effects related to category diagnosis. Are the adverse effects expressed differently according to phenotype? Unfortunately, there are no reported studies that investigated these differences in adverse effects associated with olanzapine treatment in psychiatric patients with different phenotypes.

Objective: The aim of the present meta-analysis is to separately examine olanzapine-induced cardiometabolic adverse effects and EPS in patients with schizophrenia and affective disorders.

Data Sources: A search of computerized literature databases PsycINFO (1967–2010), PubMed (MEDLINE), EMBASE (1980–2010) and the clinicaltrials.gov website for randomized clinical trials was conducted. A manual search of reference lists of published review articles was carried out to gather further data.

Study Selection: Randomized controlled trials were included in our study if (i) they assessed olanzapine adverse effects (metabolic or extrapyramidal) in adult patients with schizophrenia or affective disorders; and (ii) they administered oral olanzapine as monotherapy during study.

Data Extraction: Two reviewers independently screened abstracts for choosing articles and one reviewer extracted relevant data on the basis of predetermined exclusion and inclusion criteria. It should be mentioned that

for the affective disorders group we could only find articles related to bipolar disorder.

Data Synthesis: Thirty-three studies (4831 patients) that address olanzapine monotherapy treatment of adults with schizophrenia or bipolar disorder were included in the analysis. The primary outcomes were metabolic adverse effects (changes in weight, blood glucose, low-density lipoprotein, total cholesterol and triglyceride levels). The secondary outcomes of our study were assessing the incidence of some EPS (parkinsonism, akathisia and use of antiparkinson medication). The tolerability outcomes were calculated separately for the schizophrenia and bipolar disorder groups and were combined in a meta-analysis. Tolerability outcomes show that olanzapine contributes to weight gain and elevates blood triglycerides, glucose and total cholesterol levels in both schizophrenia and bipolar disorder patients. However, olanzapine treatment produced significantly more weight gain in schizophrenia patients than in bipolar disorder patients. In addition, increases in blood glucose, total cholesterol and triglyceride levels were higher in the schizophrenia group compared with the bipolar disorder group, even though these differences were not statistically significant. Based on our results, the incidence of parkinsonism was significantly higher in the schizophrenia group than in the bipolar disorder group. Subgroup analysis and logistic regression were used to assess the influence of treatment duration, dose, industry sponsorship, age and sex ratio on tolerability outcome.

Conclusions: Our results suggest that schizophrenia patients may be more vulnerable to olanzapine-induced weight gain. The findings may be explained by considering the fact that in addition to genetic disposition for metabolic syndrome in schizophrenia patients, they have an especially high incidence of lifestyle risk factors for CVD, such as poor diet, lack of exercise, stress and smoking. It might be that an antipsychotic induces severity of adverse effect according to the phenotype.

1. Background

Atypical antipsychotics (second-generation antipsychotics [SGAs]) are widely prescribed for the treatment of multiple psychiatric conditions such as schizophrenia, bipolar disorder, major depressive disorder and anxiety disorder.[1] Olanzapine is an atypical antipsychotic that is prescribed for acute mania,[2,3] bipolar depression,[4] schizophrenia, and bipolar mania.[5,6] It is an antagonist with a moderate to high affinity for the dopamine ($D_{1–5}$), serotonin ($5\text{-}HT_{2A,\ 2B,\ 2C,\ 3,\ 6}$), histamine ($H_1$), α1-adrenergic and muscarinic cholinergic ($M_{1–5}$) receptors.[5]

The main problem regarding the safety of antipsychotics, and particularly olanzapine, is weight gain and metabolic risks that lead to other complications such as diabetes mellitus and cardiovascular diseases (CVD).[7] CVD are already recognized as the leading cause of mortality and morbidity among patients with severe mental illnesses, such as schizophrenia, major depression, and bipolar disorders.[8,9] Risk factors for CVD such as obesity, hypertension, smoking, dyslipidemia and diabetes are more frequent in schizophrenic and bipolar disorder patients than in the general population.[10,11] Furthermore, SGAs may worsen CVD risk factors.[11-13] Diabetes and

CVD can significantly increase the rate of medical morbidity and mortality, affect quality of life and produce additional healthcare costs.[14,15]

Extrapyramidal symptoms (EPS), including dystonia, parkinsonism and akathisia, are other common adverse effects of antipsychotic treatment.[16] Although it is well known that atypical antipsychotics cause fewer EPS compared with typical antipsychotics,[17,18] studies have shown that EPS, including akathisia[19] and tardive dyskinesia,[20] are also observed with some SGAs, and a meta-analysis of head-to-head comparisons by Rummel-Kluge et al.[21] demonstrated differences between the SGAs in inducing EPS. Several studies have reported that acute EPS development is a major risk factor for later development of tardive dyskinesia in schizophrenia patients.[22,23] With the increasing use of SGAs in psychiatry, it is worth examining the incidence of EPS in different mental disorders. The presence of bipolar disease as a risk factor for antipsychotic-induced movement disorders is still unconvincing. Although some reports in the literature suggest that bipolar disorder patients are more likely to develop EPS than schizophrenia patients,[24] the results of the pooled data analysis reported by Cavazzoni et al.[16] showed that these findings may be representative of treatment with haloperidol, but not necessarily of olanzapine treatment. Recently, because of extrapyramidal risks associated with the use of atypical antipsychotics, the combination of mood stabilizers, antidepressants and antipsychotics has become more widely prescribed.

Although the pathophysiology of both disorders remains unclear, in recent years, investigation of the factors that contribute to the different SGA tolerability profiles between schizophrenia and bipolar disorder has just started.[25,26] Given that SGAs are prescribed for different diagnoses, it would be interesting to see whether the adverse effects have a different expression according to phenotype.

Some authors indicate possible inherent genetic vulnerability to metabolic irregularity in schizophrenia patients,[27-29] although some other studies are not in line with this suggestion.[30,31] Results from a comprehensive, naturalistic screening programme[26] showed that the prevalence of metabolic syndrome in schizoaffective patients was higher compared with schizophrenia and bipolar disorder patients. They suggest a possible increased inherent genetic vulnerability to metabolic syndrome in schizoaffective patients. Unadjusted odds ratio for metabolic syndrome did not statistically differ between bipolar disorder and schizophrenia patients in their study; however, the differences were statistically significant after adjustment.

If there is a difference, it could mean that a phenotype *per se* influences a medication's safety and tolerability. What might be the biological mechanism involved in these differences? What could we learn about a disease if there is such a difference? Schizophrenia is a polygenic and multifactorial complex disorder in which a myriad of different genes are potentially involved. The phenotypic expression of the disease in conjunction with epigenetic and environmental phenomena needs to be better understood. Bipolar disorders are also heterogeneous and share some genetic features with schizophrenia.[26,32-34]

The objective of this research was to compare the tolerability profiles of olanzapine as prescribed for bipolar disorders and schizophrenia. To the best of our knowledge, no meta-analysis has previously compared the metabolic and extrapyramidal adverse effects of olanzapine for different mental diseases. We therefore conducted a meta-analysis of studies in order to compare olanzapine adverse effects in patients with schizophrenia and bipolar disorders. We hypothesized that phenotype of disease may affect induction and severity of olanzapine adverse effects. With the increasing use of SGAs in psychiatry, this investigation is valuable not only to inform clinicians but also to provide clues to the pathophysiology of schizophrenia and bipolar disorders.

2. Methods

2.1 Data Sources and Search Strategy

A systematic review of the literature on olanzapine for the treatment of schizophrenia and affective disorders that reported randomized controlled trials (RCTs) was performed. The search

engines used were PsycINFO (1967–2010), PubMed (MEDLINE), EMBASE (1980–2010) and the clinicaltrials.gov website. The authors performed a systematic literature review using the Medical Subject Headings (MeSH) terms. The keywords used for the search were 'schizophrenia' or 'affective disorder', 'bipolar disorder', 'major depression', 'bipolar mania', 'unipolar depression' in conjunction with 'olanzapine'. There were no limitations on language. A hand search of published review articles, as well as cross-referencing, was carried out to gather further data.

All search engines were compared together to find and avoid duplicate publications. In addition, preliminary reports or republication of part of the data from an original report were regarded as duplicate. If data were duplicated in more than one study, the most recent study was included in the analysis. The authors of the studies that met inclusion criteria were contacted to provide the unreported or additional data. Two reporters independently checked all reports for inclusion and exclusion criteria.

It is important to mention that at this stage, the authors could not find any articles that reported SGA side effects for both schizophrenia and affective disorder patients; therefore, they searched for articles that reported SGA side effects in either the schizophrenia or affective disorders groups; the results were then compared together.

2.1.1 Inclusion Criteria

Studies were searched and divided into two groups: schizophrenia and bipolar disorder. Inclusion criteria were studies that contained (i) adult patients (18–65 years of age) who had a diagnosis of schizophrenia or affective disorders; (ii) RCTs, open-label or double-blind; (iii) oral monotherapy treatment of olanzapine; (iv) fixed- and flexible-dose studies with a duration of 3 weeks or longer; and (v) reported data on metabolic or extrapyramidal adverse effects with olanzapine treatment.

2.1.2 Exclusion Criteria

Trials in both groups were left out if they contained (i) combination therapy of olanzapine with another agent such as an antimanic, antidepressant or other antipsychotic medication; (ii) psychotic diagnosis other than schizophrenia such as schizoaffective or schizophreniform disorders; (iii) incomplete or unavailable data; (iv) study groups of children or adolescents; (v) non-randomized methods; or (vi) treatment with olanzapine depot injection (because no related study was found in the bipolar disorder group).

2.2 Data Extractions and Outcome Parameters

Two reviewers (HM and ES) independently checked abstracts for each diagnostic group and chose related articles, then one reviewer (HM) extracted data to ensure that they met the inclusion criteria. Trial abstracts were screened initially and then in the second step, full texts were reviewed. Data and articles from the schizophrenia and bipolar disorders group were analysed separately to compare the results of the two groups. The data extractions were separated along two dimensions: (i) clinically important metabolic adverse effects, including change in weight, glucose, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides and total cholesterol levels, were separately assessed in each group. Weight change was reported as the change in kilograms from baseline to endpoint; the changes in other metabolic parameters were defined as the change in mg/dL from baseline to endpoint; and (ii) some EPS-related adverse events were chosen as second outcome. Outcome variables were the incidence of some EPS-related adverse effects (e.g. parkinsonism, antiparkinson medication use and akathisia), as measured by treatment-emergent adverse event data.

2.3 Meta-Analytic Calculations

Continuous outcomes were analysed by estimating means and confidence intervals for each group of subjects: schizophrenia and affective disorders. Using comprehensive meta-analysis (CMA),[35] effect size estimates for continuous outcomes were calculated from the mean, standard deviation (SD) and sample size for each group of subjects. The moderator was diagnostic type,

which varied between studies. Dichotomous outcomes (incidence of akathisia, parkinsonism and use of antiparkinson medication) were estimated based on events and sample size for each group of patients (schizophrenia and affective disorders) and reported as event rates. We then compared the point estimates of each group to see whether the difference between the points was significant or not. The level of significance for the effect size estimates was set at $p = 0.05$. For all analyses, effect size estimates were pooled with the random-effects model, which is more strict than the fixed-effects model and permits population-level inferences as well.[36] We examined the heterogeneity of the study with the I-squared (I^2) statistic, supposing that I^2 statistics more than 50% proposed considerable heterogeneity. Level of significance was set at $p < 0.1$.

2.3.1 Sub-Analyses and Addressing Potential Confounding Factors

Sub-analyses, including between-group differences, were carried out for potential confounding factors in age, sex ratio and daily dose. The effects of treatment duration on the results were examined by performing subgroup analyses, including short-term (≤12 weeks) and longer-term studies, separately. To analyse pharmaceutical company sponsorship effects, a subgroup analysis was also done. Logistic regression analyses were used to determine association of sex ratio with tolerability outcome.

3. Results

3.1 Study Characteristics

The search strategy identified 688 articles that were related to the schizophrenia group, and 255 articles were found for the affective disorders group. Among these, 910 were discarded according to the following criteria: (i) duplication: 317 studies; (ii) type of article/study (e.g. case study, review, letter to the editor and crossover study): 313 studies; (iii) type of population (e.g. non-randomized, non-schizophrenia patients, age range): 108 studies; (iv) treatment type (e.g. combination therapy or depot olanzapine injection): 73 studies; and (v) incomplete or unavailable data: 99 studies. As a result, 33 studies[2,37-68] (n = 4831) were accepted for both groups: for schizophrenia patients N = 19, n = 2389,[1] and for the affective disorders group N = 14, n = 2442. It should be mentioned that for the affective disorders group we could only find articles related to bipolar disorder; we could not find related studies on other affective disorders, considering our inclusion criteria. More information on the sorting process in each group is shown in figure 1. In addition, table I provides details of demographic characteristics among studies included in the meta-analysis.

3.2 Outcome Results

3.2.1 First Outcome Measure: Metabolic Changes

Weight Gain

Thirty-one studies (n = 4488), 18 for the schizophrenia group (n = 2196) and 13 for the bipolar disorder group (n = 2292), were accepted and checked for changes in weight (kg) in the sample. Analysis revealed an increase in weight in both groups; however, the schizophrenia group showed significantly more weight gain than the bipolar disorder group (3.14 kg vs 2.28 kg, respectively; $p = 0.020$). Details are shown in figure 2.

Cholesterol Change

Thirteen studies (n = 2723), six for the schizophrenia group (n = 1011) and seven for the bipolar disorder group (n = 1712), were examined for changes in blood cholesterol levels (mg/dL). Even though the increase from baseline is clear in both groups, there was no statistically significant difference between the two groups (11.70 mg/dL in the schizophrenia group vs 9.94 mg/dL for the bipolar disorder group; $p = 0.771$) [figure 3].

Glucose Change

Fifteen studies (n = 2825), seven for the schizophrenia group (n = 1105) and eight for the bipolar disorder group (n = 1720), were compared for changes in blood glucose levels (mg/dL). In spite of the fact that olanzapine changed the levels of glucose in both groups, the difference was

1 'N' refers to the number of articles whereas 'n' is the number of patients.

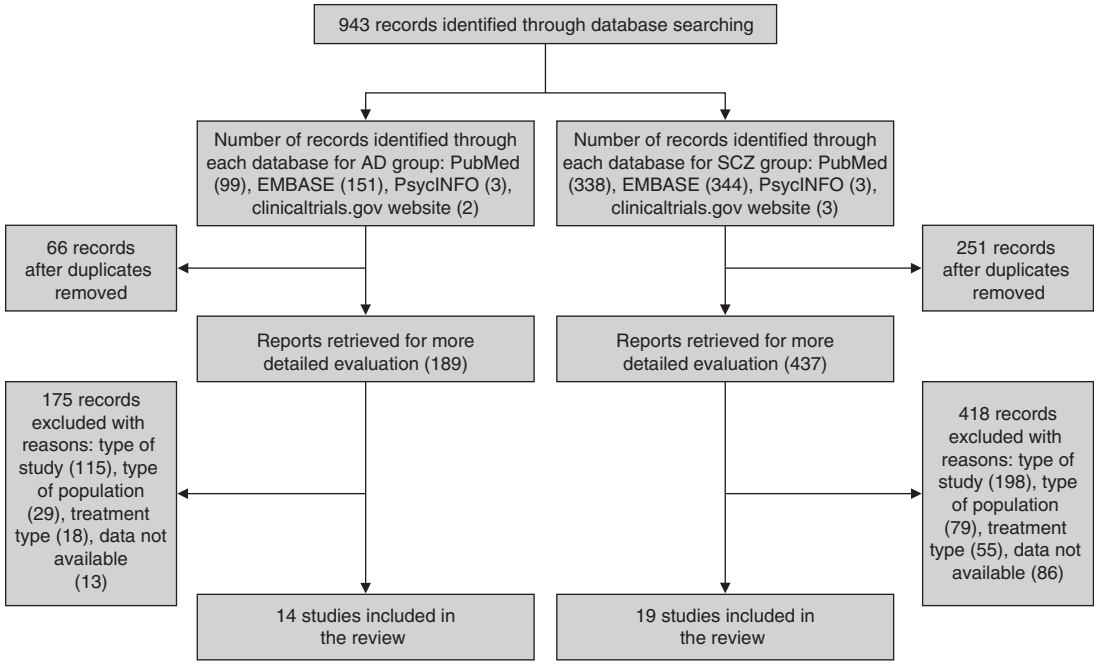

Fig. 1. Flow diagram describing the search process (Quality of Reporting of Meta-analysis [QUORUM]). **AD** = affective disorders; **SCZ** = schizophrenia.

not statistically significant between the schizophrenia and bipolar disorder groups (5.63 vs 2.02 mg/dL, respectively; p = 0.116) [figure 4].

Triglycerides Change

Six studies (n = 1165), two for the schizophrenia group (n = 551) and four for the bipolar disorder group (n = 614), were evaluated for changes in blood triglyceride levels (mg/dL). There was no statistically significant difference between the two groups (38.19 vs 26.12 mg/dL, respectively; p = 0.064), although the levels of triglycerides changed in both groups after olanzapine administration (figure 5).

Low-Density Lipoprotein and High-Density Lipoprotein Change

We could not find enough studies to compare LDL and HDL changes between the two groups.

3.2.2 Second Outcome Measure: Extrapyramidal Adverse Effects

EPS-related adverse event rates and their intensity were low in both groups; however, there were some significant differences in the frequency of parkinsonism between the two groups.

Incidence of Akathisia

The akathisia event rate did not differ significantly between the groups. Based on eight articles included in the bipolar disorder group (n = 1575), the event rate was 6.3%; according to 11 articles in the schizophrenia group (n = 1475), the incidence of akathisia was 7.8% (p = 0.468) [figure 6].

Incidence of Parkinsonism

The incidence of parkinsonism was significantly higher in the schizophrenia group. Based on seven articles included in the bipolar disorder group (n = 1460), the event rate was 3.1%; in six articles in the schizophrenia group (n = 884), the incidence of parkinsonism was 13.9% (p = 0.005) [figure 7].

Antiparkinson Medication Use

Antiparkinson medication use did not differ significantly between two groups. According to four articles included in the bipolar disorder group (n = 926), the event rate was 6.7%; in eight

articles in the schizophrenia group (n = 1099), the use of such medication was 13.7% (p = 0.184) [figure 8].

3.2.3 Heterogeneity

Heterogeneity of all outcomes (metabolic and extrapyramidal) were explored by I^2 statistic; they were all heterogeneous ($I^2 > 50\%$). Sub-analyses were assessed to determine possible sources of heterogeneity in results.

3.3 Sub-Analyses

3.3.1 Age

All studies reported mean age (SD) of participants; no difference was observed between the

Table I. Demographic characteristics among bipolar and schizophrenic studies included in the meta-analysis

Diagnostic type	Age (y; mean ± SD)	Dose (mg/day; mean ± SD)	Treatment duration (wk)	Male/female (N)
Bipolar disorder				
McIntyre et al.[48]	39.6 ± 11.9	5–20	12	135/94
Tohen et al.[56]	41.4 ± 12.1	11.8 ± 7.5	12	87/138
Tohen et al.[61]	39.5 ± 11.9	11.4 ± 2.49	3	99/116
Tohen et al.[60]	42.2 ± 12.5	9.7	8	141/229
Tohen et al.[2]	39.5 ± 11	14.9 ± 5	3	35/35
Tohen et al.[58]	38.3 ± 10.7	16.4 ± 4.2	4	27/28
Sanger et al.[54]	39.1 ± 10.9	5–20	3	10/9
Tohen et al.[59]	39.5 ± 10.9	5–20	48	29/47
McIntyre et al.[47]	40.1 ± 11.3	15.8 ± 2.3	3	114/76
McIntyre et al.[49]	38.4 ± 10.4	15.9 ± 2.5	3	117/88
McIntyre et al.[50]	38.7 ± 12.4	15.7 ± 4.1	40	68/39
Tohen et al.[57]	41 ± 13	11.4 ± 5.3	12	86/148
NCT00510146[a][66]	35.93 ± 11.13	5–20	6	138/205
NCT00129220[a][68]	43.12 ± 12	5–20	6	49/55
Schizophrenia				
McQuade et al.[51]	38.2 ± 11	16.5	26	115/46
Kane et al.[44]	38.3 ± 10.5	16.7	28	194/87
Wu et al.[63]	34.2 ± 10.3	10–20	6	25/11
Bhowmick et al.[39]	31.4 ± 7.7	10–20	12	20/18
Saddichha et al.[53]	26.7 ± 6.4	17 ± 5	8	94/46
Beasley et al.[38]	38 ± 9.3	10	8	16/19
Riedel et al.[52]	34.47 ± 11.6	15.82 ± 5.44	8	11/6
Chan et al.[42]	40.8 ± 11.5	11.72 ± 4.87	8	14/10
Lieberman et al.[46]	40.8 ± 10.8	20.1	72	244/92
Sirota et al.[55]	36.2 ± 10.9	16 ± 3.3	11	17/4
Dollfus et al.[43]	39 ± 9	5–15	6	11/18
Bitter et al.[40]	37.6 ± 9.3	17.2 ± 4.8	18	46/30
Breier et al.[41]	40.1 ± 11.6	15.27 ± 4.52	28	180/97
Alvarez et al.[37]	37 ± 10.6	12.2 ± 5.8	52	85/39
Lecrubier et al.[45]	37.25 ± 10.75	5, 20	24	37/13
Vanelle et al.[62]	36.5 ± 8	11.4 ± 2.8	8	23/17
NCT00320489[a][65]	40.12 ± 10.84	5–20	104	177/83
NCT00645099[a][64]	37.5 ± 11.4	10–15	24	133/87
NCT00145496[a][67]	42.8 ± 11.27	5–20	24	170/54

a Unpublished studies.

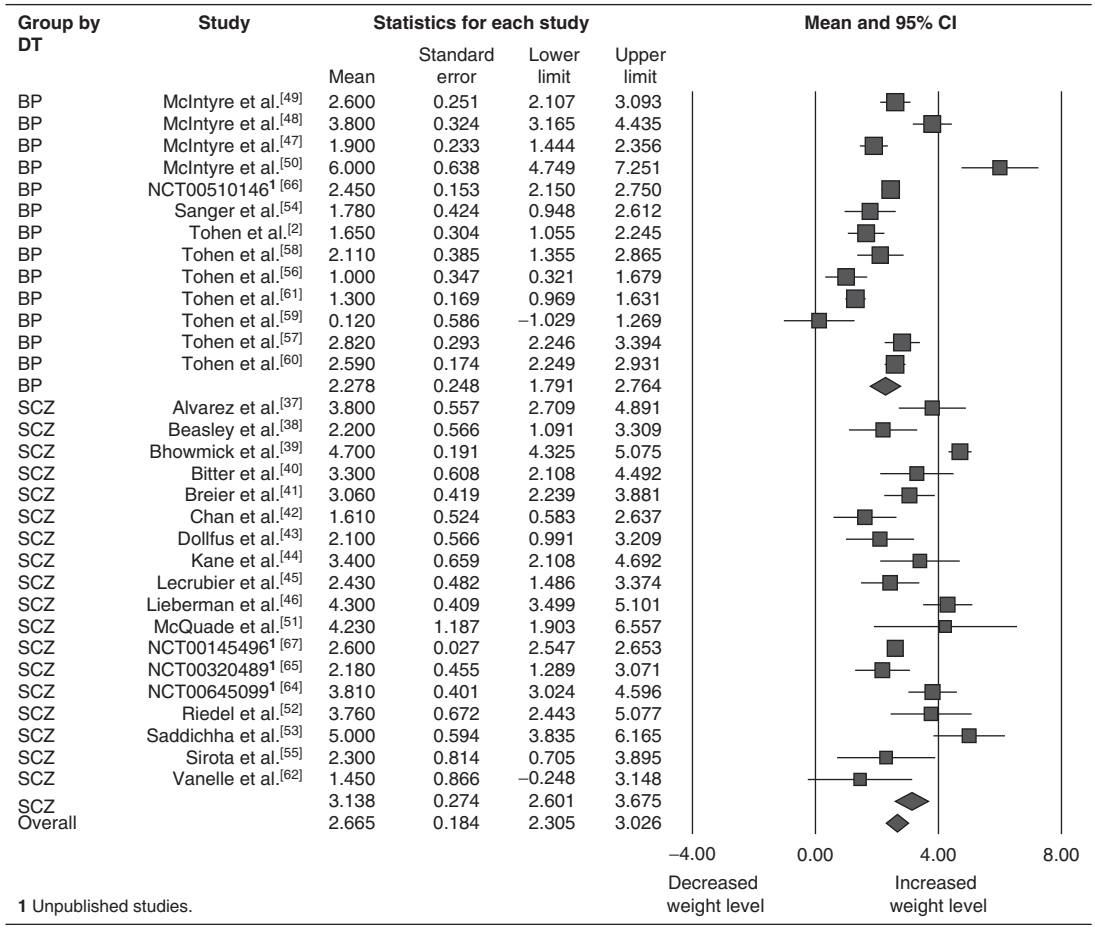

Fig. 2. Forest plot of the effect size estimates of weight changes (kg) in schizophrenia patients compared with bipolar disorder patients ($p = 0.020$). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

two groups: 38.9 (11) and 39.7 (11.9) years for studies in the schizophrenia and bipolar disorder groups, respectively. See table I for more information on demographic characteristics among studies included in the meta-analysis.

3.3.2 Sex Ratio

Sex ratio was also reported in all studies. Significantly more males participated in schizophrenia studies compared with bipolar disorders studies; percentage of males was significantly higher in the schizophrenia group than in the bipolar group (1612/2389 [67.5%] vs 1135/2442 [46.5%], respectively; $p < 0.001$).

Considering the significant difference in sex ratio between the schizophrenia and bipolar disorder patient groups, this variable was included in the statistical analysis as a regressor. By doing this meta-regression on weight gain and parkinsonism incidence, we found that in the schizophrenia patients' group, weight gain and parkinsonism incidence were inversely related to male ratio.

3.3.3 Dose

Based on eight studies in the bipolar disorder group and eight in the schizophrenia group which specified mean daily dose (SD), no difference was

observed between the two groups: schizophrenia group 14.6 (4.9) mg/day and bipolar disorder group 13.5 (5) mg/day.

3.3.4 Company Sponsorship

The studies were stratified based on industry sponsorship. By considering only the studies with industry sponsorship, 14 studies were found in the bipolar disorder group and 13 in the schizophrenia group. By running meta-analysis between the stratified bipolar disorder and schizophrenia groups, outcomes remained the same as the main analysis for levels of blood total cholesterol levels and weight gain, and the incidence of akathisia and antiparkinson medication use. In addition, we observed significantly higher glucose levels in the schizophrenia group compared with the bipolar disorder group (7.5 mg/mL vs 2.6 mg/dL, respectively; p = 0.01). It should be mentioned that we could not find non-sponsored studies for the bipolar disorder group.

3.3.5 Treatment Duration

We stratified the studies based on treatment duration. Short-term studies (between 3 and 12 weeks) showed that the results of primary and secondary outcomes remained the same as the main analysis for levels of total cholesterol and glucose, and the incidence of akathisia, antiparkinson medication use and parkinsonism. The results for weight gain were, however, different. Overall, 19 studies, 11 for the bipolar disorder group (n = 2231) and 8 for the schizophrenia group (n = 262), in which weight changes have been reported for short-term treatment, were compared. Even though weight gain was higher in the schizophrenia group, this difference was no longer statistically significant (2.18 vs 2.94 kg, respectively; p = 0.226). For studies of more than 12 weeks, we did not have enough data in the bipolar disorder group.

4. Discussion

Metabolic syndrome is a significant public health problem in patients with mental illnesses and particularly schizophrenia. Recently, atypical antipsychotic agents have been linked to several forms of morbidity, including obesity, hyperlipidemia, and type 2 diabetes, which predict meta-

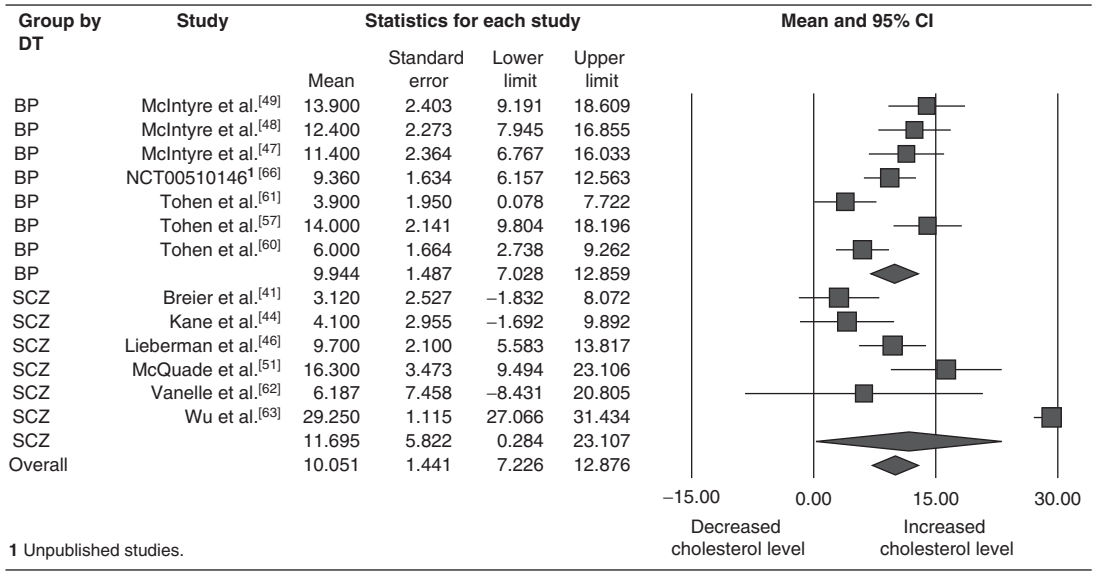

Fig. 3. Forest plot of the effect size estimates of cholesterol changes (mg/dL) in schizophrenia patients compared with bipolar disorder patients (p = 0.771). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

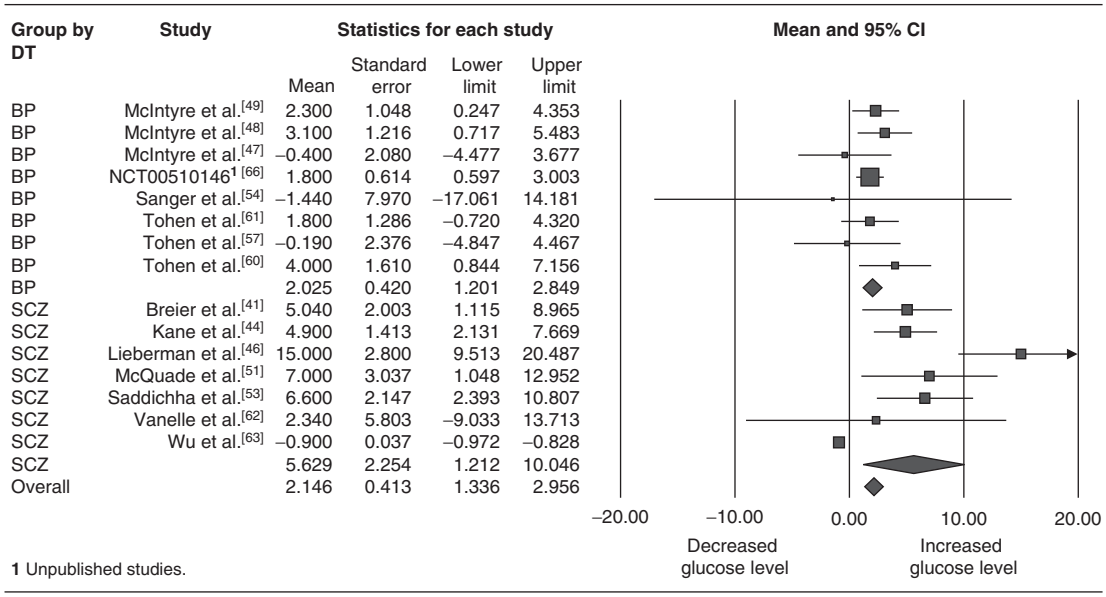

Fig. 4. Forest plot of the effect size estimates of glucose changes (mg/dL) in schizophrenia patients compared with bipolar disorder patients ($p = 0.116$). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

bolic syndrome, cardiovascular morbidity and malignancy.[62,69,70] The mechanisms responsible for an association between schizophrenia, antipsychotic treatment and metabolic syndrome still remain unclear.[71]

The aim of our meta-analysis was to investigate the difference between olanzapine adverse effects in schizophrenia and bipolar disorder patients. To our knowledge, this is the first meta-analysis comparing schizophrenia and bipolar disorder patients with regard to metabolic and extrapyramidal adverse effects of olanzapine in RCTs. Based on the different phenotypes of these mental illnesses and the frequent use of SGAs to treat these illnesses, studying the degree of sensitivity and tolerability of SGAs in bipolar disorder and schizophrenia patients seems essential. Our results revealed that all metabolic parameters increased from baseline for both groups. Furthermore, these changes were statistically significant for mean weight gain in the schizophrenia group compared with the bipolar disorder group.

As many studies indicate, SGA medications are associated with weight gain, and our findings are consistent in this regard. In a meta-analysis comparing all SGAs head-to-head, weight gain was seen significantly more with clozapine and olanzapine treatment than with other antipsychotics[11] These results are generally similar to the findings of a systematic review reporting metabolic adverse effects among different SGAs in children and adolescents, showing that olanzapine was the most likely to lead to weight gain.[72] Another randomized comparative study also reported that olanzapine produced more weight and glucose level changes compared with amisulpride during a 6-month trial.[73] The mechanism of olanzapine-induced weight gain remains obscure at present; however, several factors could account for this, such as a high affinity of this medication to H_1, 5-HT_{2c} and M_1 receptors.[51,74-77] Olanzapine's high affinity to these receptors is associated with appetite changes, increased food intake and sedation. Genetic data also propose a role of leptin receptor activity, G-protein signalling, cannabinoid receptor activity and promelanin-concentrating hormone signalling in weight gain associated with the SGAs.[78,79]

We also examined the mean changes in lipid profile and glucose level in both patient groups. Our meta-analysis showed increases in the mean level of blood glucose, total cholesterol and triglycerides in both groups. These changes happened more in the schizophrenia group compared with the bipolar disorder group; however, the difference between these groups was not statistically significant.

Even though the mechanism for olanzapine's effect on glucose level and insulin resistance is poorly understood, there is some indication that the long-term use of olanzapine may decrease insulin secretion, which may lead to hyperglycemia.[80] A proposed mechanism for hyperglycaemia is related to the drug's affinity for the H_1, M_3 and 5-HT_{2C} receptors, which is correlated with an increased risk of diabetes.[81] Another possible mechanism by which olanzapine may cause increased insulin resistance could be by impairing the ability of insulin to stimulate glucose uptake into peripheral tissues such as skeletal muscle and adipose tissue. There is recent evidence indicating that polymorphism in the 5-HT_{2A} and 5-HT_{2C} receptor coding genes, *HTR2A* and *HTR2C*, seems to be associated with development of metabolic abnormalities such as C-peptide and insulin elevation during olanzapine and clozapine treatment.[82-84]

Some SGAs are associated with dyslipidemia, including increased levels of LDL, total cholesterol and triglycerides, which can result in CVD.[85] At present, the exact mechanism underlying changes in lipids due to certain SGA treatments is unknown. Several hypotheses have been proposed regarding biological factors such as weight gain, dietary changes and the development of glucose intolerance to explain the high frequency of dyslipidemia with specific antipsychotic medications.[86,87]

Albaugh et al.[88] recently proposed an interesting mechanism to explain why olanzapine contributes to metabolic adverse effects leading to obesity and diabetes. In their animal model, they found that long-term administration of olanzapine has at least five effects on predisposing male rats to increased adiposity. These effects are decreased physical activity, impaired glucose and insulin tolerance, increased tendency to ^{14}C-2-deoxyglucose and free fatty acid uptake into fat depots, increased adipose tissue lipogenesis and impaired lipolysis. Recently, results of a 3-month, prospective, open-label study showed a significant decline in adiponectin levels, an adipocyte-derived hormone that increases insulin sensitivity, for olanzapine-treated patients compared with risperidone-treated patients.[89] The observed reduction in plasma adiponectin levels in olanzapine-treated patients may suggest a direct effect

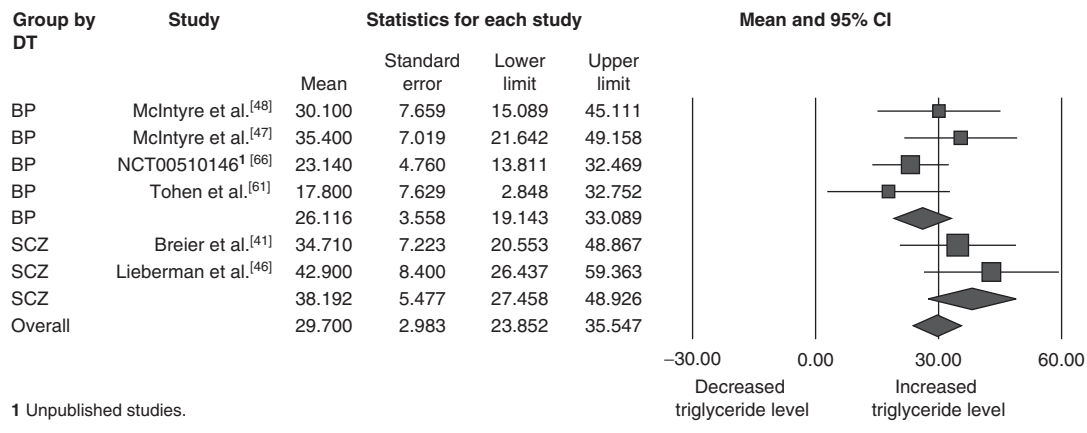

Fig. 5. Forest plot of the effect size estimates of triglyceride changes (mg/dL) in schizophrenia patients compared with bipolar disorder patients (p = 0.064). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

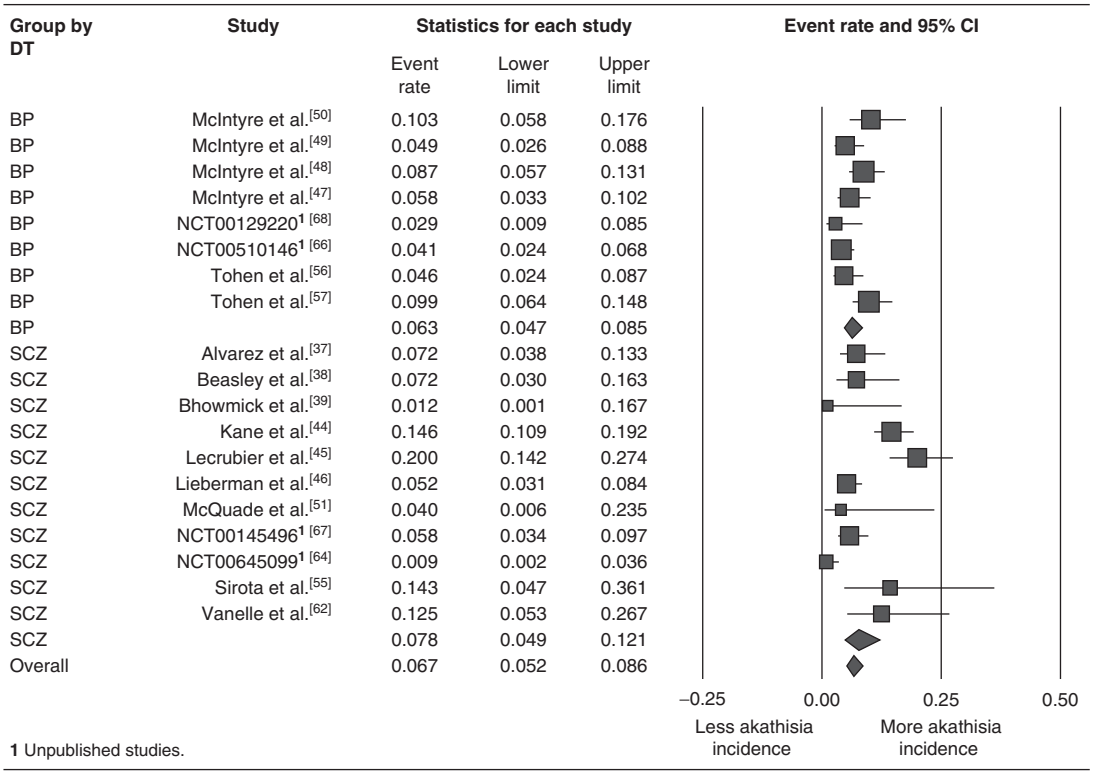

Fig. 6. Forest plot of the effect size estimates of akathisia incidence in schizophrenia patients compared with bipolar disorder patients (p = 0.468). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

of olanzapine on the adipose tissue and explain partially the increased metabolic risk in these patients.

As our second outcome, we examined EPS related to olanzapine treatment between schizophrenia patients and those with bipolar disorder. Most published placebo-controlled studies show that the rate of akathisia is similar for olanzapine and placebo in both schizophrenia and bipolar disorder,[19] which is consistent with our results. The difference found between the two groups for the incidence of akathisia was not significant. Our results revealed that even with the low incidence of parkinsonism in patients treated with olanzapine, parkinsonism occurred significantly more in the schizophrenia group than in the bipolar disorder group. The use of antiparkinson medication was also checked and was higher in the schizophrenia group; however, this difference was not significant.

Cavazzoni and his research group[16] compared olanzapine-induced EPS in bipolar mania and schizophrenia patients in a pooled analysis. They found the same results as us. Namely, that parkinsonism in schizophrenia patients was more frequent than in bipolar patients; however, the usage of antiparkinson medication was similar for both groups.

The reduced incidence of EPS during treatment with atypical antipsychotic agents is thought to happen because of their unique receptor-binding profiles.[90] In a review by Gao et al.[91] it is mentioned that olanzapine did not produce more akathisia, parkinsonism or use of antiparkinson medication in bipolar groups compared with schizophrenia groups.

As expected, effect size estimates were heterogeneous across studies. A secondary objective was, therefore, established to identify the factors contributing to this heterogeneity. Because of concerns that sociodemographic characteristics among different studies included in our meta-analysis might have influences on our results and cause heterogeneity, we conducted logistic regression assessing the effect of various baseline characteristics (sex ratio, age, daily dose, and industry sponsorship) on weight gain and parkinsonism incidence. In the bipolar disorder patients' group, none of these baseline variables had any noticeable effect on parkinsonism incidence. In the schizophrenia group, however, parkinsonism incidence and weight gain showed a reversed dependency on the sex ratio, by using a meta-regression. As weight gain and parkinsonism incidence were significantly higher in schizophrenia, and male percentage was also higher in this group, outcome differences between the two groups still remain significant.

As mentioned earlier, we also stratified the studies based on treatment duration. Short-term studies showed that parkinsonism incidence was observed significantly more in the schizophrenia group. Weight gain level was also increased in the schizophrenia patients; however, this difference was no longer statistically significant. For studies of more than 12 weeks' duration, data unavailability in the bipolar disorder group prevented us from performing the same analysis. Conducting studies on the long-term safety of antipsychotic drugs should be considered a priority in psychopharmacology, as treatment with antipsychotics is often continued for a long period of time or even for the patients' whole life.

Taken together, these results do not suggest that population differences in sex ratio, age and daily dose significantly influenced our results. Furthermore, as no non-sponsored study was available for the bipolar disorder group, we could not assess the industry-sponsorship effects in this group; however, by comparing the industry-sponsored studies between the two groups of patients, weight gain, glucose level and parkinsonism incidence happened significantly more in

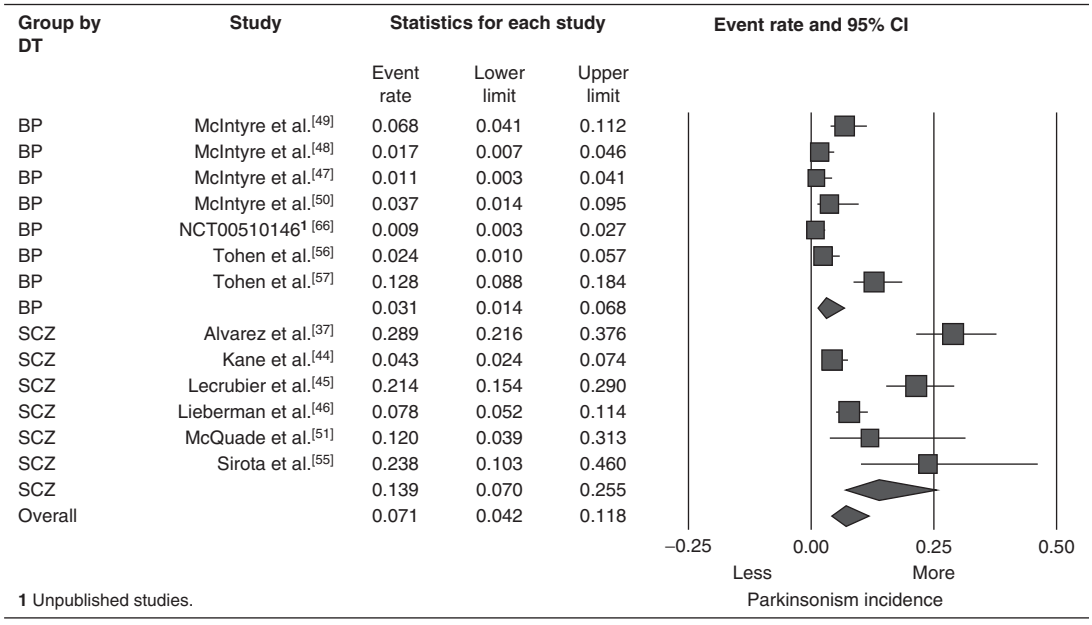

Fig. 7. Forest plot of the effect size estimates of parkinsonism incidence in schizophrenia patients compared with bipolar disorder patients (p = 0.005). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

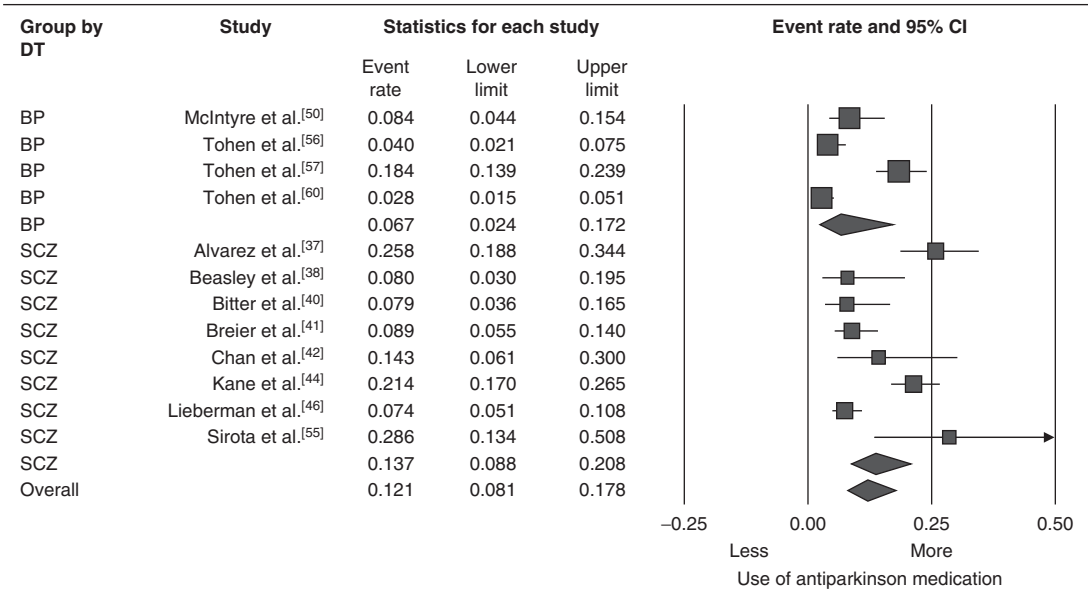

Fig. 8. Forest plot of the effect size estimates of antiparkinson medication use in schizophrenia patients compared with bipolar disorder patients (p = 0.184). **BP** = bipolar disorder patients; **DT** = diagnostic type; **SCZ** = schizophrenia patients.

the schizophrenia group. Treatment duration was also considered and discussed above. The remaining heterogeneity of effect size estimates across studies, even after performing numerous sub-analyses, raises the possibility that factors such as lifestyle and disease phenotype in our comparison groups may contribute to these results.

Some limitations affect this meta-analysis, which may confound our results and determine the necessity to interpret the current results with caution. In particular, the meta-analysis is limited by the fact that relatively few studies were available for direct comparison of SGA adverse effects among bipolar disorder patients versus schizophrenia patients; therefore, we obtained data from articles focusing on either schizophrenia or bipolar disorder patients and compared the results of both groups. In addition, in our comparison there was no placebo control group, which may restrict the interpretation of our results. To cope with this limitation, prospective controlled trials are required specifically to determine a possible relationship between psychiatric diagnosis and olanzapine-induced adverse effects. Second, due to the retrospective nature of this analysis, information on the severity of psychiatric illness could not be considered in this analysis. Another limitation of this meta-analysis was the unavailability of data for depot administration of olanzapine in the bipolar disorder group; in our study only oral monotherapy of olanzapine was included. Finally, we did not examine the impact of previous exposure to antipsychotic treatment, race/ethnicity and initial weight in both groups, which may impact the generalizability of our findings. These variables should be more deeply considered in future studies.

5. Conclusions

Adverse effects are important to consider for prescribers because the efficacy of treatment may be reduced due to the presence of certain adverse effects. The results of our meta-analysis suggest that schizophrenia patients may be more vulnerable to olanzapine-induced weight gain. This meta-analysis proposes that factors such as lifestyle and disease phenotype may contribute to

this susceptibility in the schizophrenia group. Patients with severe mental illnesses need to be informed of the different adverse effects induced by olanzapine, and they should be monitored regularly, especially for metabolic issues. In several domains, the results suggest that we can only say that metabolic adverse effects are lower in the bipolar disorder group compared with the schizophrenia group. But what does that mean for a patient and how does it change our follow-up? It is also important to consider that bipolar disorder patients are more prone to receive polypharmacy (a combination of mood stabilizers, antidepressants and antipsychotics) compared with schizophrenia patients. Therefore, clinicians should take into account the increased risk of metabolic adverse effects associated with antipsychotic drugs (which is confirmed in our meta-analysis) when prescribing atypical antipsychotics for bipolar disorder patients. In a recent review, Taylor et al.[92] emphasized the necessity of respecting guidelines for screening and monitoring metabolic adverse effects in patients with severe mental illnesses, since physical health problems are one of the most common causes of premature death in people with chronic mental illnesses.

Compared with the general population, people with schizophrenia and bipolar disorder have an increased risk of obesity.[79] Our results are consistent with other studies which show that weight gain and increase in blood glucose, total cholesterol and triglyceride levels also occur in the bipolar disorder group receiving olanzapine treatment.[13,93] Our study supports the recommendation of regular screening and accurate monitoring of the patient. Furthermore, appropriate psychoeducation on lifestyle modification programmes, including weight control, healthy diet and increased physical activity, are important to prevent and treat the metabolic syndrome and CVD in patients with severe mental disorders.

As mentioned previously in the Cacabelos et al.[94] review, structural and functional variations in genomes cause proteomic and metabolomic imperfections associated with the disease phenotype. Genetic polymorphism may be an important factor that contributes to metabolic adverse effects of SGAs between schizophrenia and affective disorders patients. In addition to a genetic predisposition for metabolic syndromes among schizophrenic patients, lifestyle risk factors such as stress, poor diet, lack of exercise and smoking are common in these patients.[82,95]

In order to achieve a mature discipline of pharmacogenomics of schizophrenia and bipolar disorder it would be relevant to promote the education of prescribers and the public for the use of genomic screening in clinical practice; pharmacogenomic protocols need to be validated according to drug category and phenotype in order to optimize efficiency. Obviously, these findings need further investigation and the variable confounders are still to be clarified.

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