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REVIEW
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Topiramate and Metformin Are Effective Add-On Treatments in Controlling Antipsychotic-Induced Weight Gain: A Systematic Review and Network Meta-Analysis

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Background: Antipsychotic drugs may lead to side effects such as obesity, diabetes, dyslipidemia, and cardiovascular disease. The current systematic review and network meta-analysis analyzes and provides an update on the clinical performance of these add-ons in comparison to placebo on body weight and body mass index (BMI) reductions.

Methods: A comprehensive literature search was performed on electronic databases: PubMed (1946-), Embase (1974-), Cochrane library (1992-), and OpenGrey (2000-) until 31 July 2018. Network meta-analyses, comparing the body weight change, BMI change and withdrawn due to adverse events of different pharmacological add-ons, was performed using a multivariate meta-regression model with random-effects, adopting a frequentist approach. To rank the prognosis for all add-ons, we used surface under the cumulative ranking (SUCRA) values.

Outcomes: From 614 potential studies identified, 27 eligible studies (n = 1,349 subjects) were included. All the studies demonstrated low to moderate risk of bias. For the analysis of body weight change, all add-ons except Ranitidine showed significant weight

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reductions comparing to placebo. The effectiveness rank based on SUCRA results from highest to lowest was Sibutramine, Topiramate, Metformin, Reboxetine, Ranitidine, and placebo. A similar pattern was seen for BMI change. The analysis of safety outcome did not detect significantly increased withdrawn number from the add-ons. Current evidence showed relatively good tolerance and safety of using the pharmacological add-ons.

Interpretation: Topiramate and Metformin are effective add-on treatments in controlling antipsychotic-induced weight gain, comparing to placebo. They are well tolerated in short-term period. Although Sibutramine has the highest rank of the effectiveness, its license has been withdrawn in many countries due to its adverse effects. Hence, Sibutramine should not be adopted to treat antipsychotic-induced weight gain.

Keywords: antipsychotic-induced weight gain, network meta-analysis, pharmacological add-ons, topiramate, metformin

INTRODUCTION

Antipsychotic drugs (APDs) may lead to side effects such as obesity, diabetes, dyslipidemia, and cardiovascular disease. This adverse effect cluster presents an obstacle in the treatment and management of patients with schizophrenia or bipolar disorder, and limits patient adherence to medication and consequently adversely impacts treatment outcomes.

To counter the antipsychotic-induced weight gain, various pharmacological add-ons were investigated. Taking antidiabetics or antiobesity drugs as an adjuvant treatment, including metformin, orlistat, sibutramine, and naltrexone, is a popular approach for weight management and has been widely studied (Baptista et al., 2006; Henderson et al., 2007; McElroy et al., 2007; Joffe et al., 2008; Tchoukhine et al., 2011; Tek et al., 2014; Anagnostou et al., 2016; Rado and von Ammon Cavanaugh, 2016; Vishnupriya et al., 2016; Wu et al., 2016; Handen et al., 2017). Most of the studies reported significant reductions in body weight. Gastrointestinal agents, especially antacids like nizatidine, were reported may stop but not reduce the weight gain (Atmaca et al., 2003, 2004; Assuncao et al., 2006). Topiramate, a type of anticonvulsant, shows a negative association with body weight gain and has been found to control antipsychotic-induced weight gain for subjects with schizophrenia or bipolar disorder (McElroy et al., 2007; Afshar et al., 2009; Wozniak et al., 2009; Narula et al., 2010).

Until recently, no study has been published comparing various pharmacological add-ons on antipsychotic-induced weight gain, from both direct and indirect evidence. The current systematic review and network meta-analysis analyzes and provides an update on the clinical effectiveness and safety of these add-ons in comparison to placebo on body weight, body mass index (BMI) reductions and number of withdrawn due to adverse effects.

MATERIALS AND METHODS

Literature Search and Eligibility Criteria

A comprehensive literature search was performed on electronic databases: PubMed (1946-), Embase (1974-), Cochrane library (1992-), and OpenGrey (2000-) until 31 July 2018. The specific concepts used in the search strategy were "antipsychotic agents" and "weight." We conducted literature search using Medical Subject Headings (MeSH) or Emtree, and free text terms. There were no restrictions on language. The bibliography listed in review papers and included publications were also checked.

Two investigators (CjZ and QZ) independently screened for eligible studies based on pre-defined eligibility criteria. Randomized controlled trials (RCTs) that examined the pharmacological interventions of weight management for antipsychotics-induced obesity were included. To avoid imprecise estimations, only those add-ons with at least two RCTs studied were included. Non-randomized or observational studies, case reports, commentaries, and letters-to-editors were excluded.

Data Extraction and Quality Assessment

The following data were extracted from the included studies: (1) study characteristics (publication year and patient population); (2) baseline characteristics (mean age, number of males, follow-up time, and ongoing antipsychotic treatment); and (3) outcome events (weight change [kg], BMI change [kg/m^2], and number of withdrawn due to adverse events).

The quality of each study was evaluated, using the Cochrane Collaboration Risk of Bias tool, by two independent investigators (CjZ and QZ). Six domains were assessed for each RCT, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain would be assigned a judgment of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias. Any disagreement in quality assessment was resolved by discussion and consensus.

Statistical Analysis

A network geometry was constructed based on the included studies for each add-on treatment. Each node represented an add-on and its size was weighted by the number of subjects of each add-on. The connecting line between two nodes meant a

direct comparison existed and its thickness was determined by the number of studies included.

Network meta-analysis, comparing the body weight change, BMI change, and number of patients withdrawn due to adverse events among different pharmacological add-ons, was performed using a multivariate meta-regression model with random-effects, adopting a frequentist approach (Higgins et al., 2012; White et al., 2012). The model allows for the inclusion of potential covariates, and accounts for the correlations from multi-arm trials, and mean difference (MD) for weight and BMI change and risk ratio (RR) for number of withdrawn due to adverse events of each add-on treatment was estimated (White, 2011).

To rank the prognosis for all the add-ons, we used surface under the cumulative ranking (SUCRA) values (Salanti et al., 2011). Rank probabilities of all the add-ons were first estimated under a Bayesian framework. A step function was then applied to summarize the cumulative ranking for estimating the SUCRA values of each add-on, ranging from 0 to 1. Thus, large SUCRA values indicated a better prognosis.

The node-splitting approach and inconsistency model were used to test the consistency assumption (Dias et al., 2010). The former method involved fitting a series of node-splitting models, with one model for each add-on pairing for which there was direct and indirect evidence (Donegan et al., 2013). The latter method first fits an inconsistency model and then conduct a Wald test to check whether there is significant inconsistency among the included studies (White, 2015). Sensitivity analysis was conducted by (1) excluding studies with both "blinding of participants and personnel" and "blinding of outcome assessment" ranked as "Unclear" or "High risk," as the outcomes (i.e., measurement of weight and BMI) were likely to be biased due to these two key components, and (2) limiting the analysis on studies with less than 12 months' follow-up.

The network meta-analyses were implemented by Stata/MP 13 with network and network graphs package (Chaimani et al., 2013; StataCorp, 2013; White, 2015).

RESULTS

Study Characteristics and Network Geometry

From 614 potential studies identified from the initial search, 27 randomized controlled trials (n = 1,349 subjects) satisfied inclusion/exclusion criteria and were included in this meta-analysis (**Figure 1** and **Table 1**; Lopez-Mato et al., 2003; Poyurovsky et al., 2003, 2007, 2013; Henderson et al., 2005, 2007; Ko et al., 2005; Nickel et al., 2005; Klein et al., 2006; Baptista et al., 2007, 2008; McElroy et al., 2007; Arman et al., 2008; Wu et al., 2008, 2012; Afshar et al., 2009; Carrizo et al., 2009; Narula et al., 2010; Wang et al., 2012; Chen et al., 2013; Jarskog et al., 2013; Ranjbar et al., 2013; Biedermann et al., 2014; de Silva et al., 2015; Anagnostou et al., 2016; Mehta and Ram, 2016; Rado and von Ammon Cavanaugh, 2016). The mean age was 31.9 years old and 48.6% (n = 655) were males. The follow-up period was relatively short, ranging from 6 to 26 weeks. Among the included studies, one study recruited patients with autism spectrum disorder (ASD), two for patients with bipolar disorder, 20 for patients with schizophrenia and schizophrenic conditions and four for patients with various psychosis. Efficacy results on Topiramate were reported in 4 studies, Metformin in 13 studies, Reboxetine in 3 studies, Ranitidine in 2 studies, and Sibutramine in 4 studies (**Figure 1**).

The network geometry was constructed (**Figure 2**). Most of the studies demonstrated low to moderate risk of bias in the six domains assessed. However, due to missing information or inappropriate methods on randomization, four studies were ranked as "Unclear" or "High risk" in "Random sequence generation" (**Supplementary Figure S1**).

Effectiveness on Body Weight Change

For outcome of body weight change, 27 studies were included in the analysis. All the add-ons, except Ranitidine, showed significant weight reductions compared to placebo. Topiramate showed the lowest mean difference (MD) −3.07 kg (95% CI: −5.57, −0.48), followed by Sibutramine MD = −2.97 kg (95% CI: −4.18, −1.77), Metformin MD = −2.50 kg (95% CI: −3.21, −1.80), and Reboxetine MD = −2.25 kg (95% CI: −3.54, −0.95) (**Table 2**). Results from both the node-splitting method and inconsistency model showed no evidence on the violation of consistency assumption between direct and indirect comparisons. As shown in **Supplementary Figure S2**, the pooled estimates were quite similar between consistency model (red diamonds) and inconsistency model (green diamonds), indicating that inconsistency covariates did not yield a significantly better fitting. The p-value = 0.166 from the Wald test further confirmed that there is no evidence on the violation of consistency assumption.

To confirm the rank of effectiveness on body weight reduction, SUCRA values were calculated, and the rank from highest to lowest was Sibutramine, Topiramate, Metformin, Reboxetine, Ranitidine, and placebo (**Table 3**).

In the sensitivity analysis by excluding the eight studies, similar pooled estimates were obtained and the rank order remained the same. Further sensitivity analysis by excluding studies with less than 12 months' follow-up showed that metformin, sibutramine and topiramate were consistently significant with a reduction in body weight at −2.54 (95% CI: −3.29, −1.79), −2.98 (95% CI: −4.34, −1.62), and −2.95 (95% CI: −5.87, −0.03), respectively. Ranitidine did not show any significant reduction in body weight, which was consistent to the main result as well. However, Reboxetine was reported only in studies with less than 12 months' follow-up, we were unable to check its sensitivity results.

Effectiveness on BMI Change

For the BMI change outcome, 24 studies were included in the analysis. A similar pattern was seen for BMI change, where all add-ons except cardiac Ranitidine showed statistically significant BMI reductions comparing

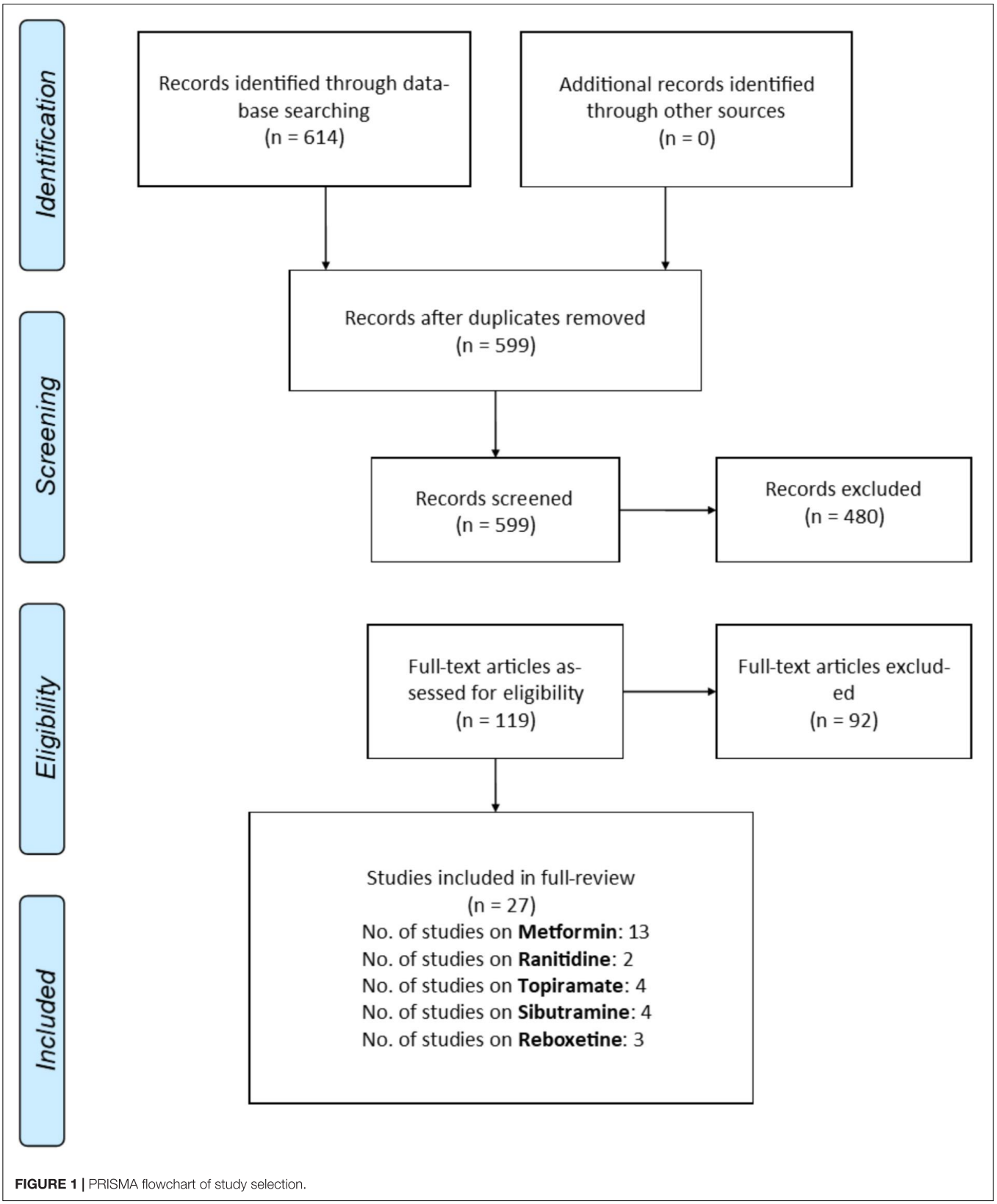

FIGURE 1 | PRISMA flowchart of study selection.

TABLE 1 | Summary of study characteristics of included study.

Study	Country	Main diseases	Sample size	Mean age (SD)	Ongoing treatment	Intervention and control	Follow-up (weeks)
Afshar et al., 2009	Iran	Schizophrenia	I: 16 (9, 56%) C: 16 (11, 69%)	I: 37.5 (5.7) C: 38.1 (4.6)	Clo	I: Topiramate C: Placebo	8
Anagnostou et al., 2016	Canada	ASD	I: 28 (21, 75%) C: 32 (24, 75%)	I: 12.9 (2.85) C: 12.7 (2.64)	Mixed	I: Metformin C: Placebo	16
Arman et al., 2008	Iran	Schizophrenia	I: 16 (11, 69%) C: 16 (10, 63%)	I: 11.25 (2.46) C: 8.93 (4.28)	Ris	I: Metformin C: Placebo	12
Baptista et al., 2007	Canada	Schizophrenia	I: 36 (23, 64%) C: 36 (19, 53%)	I: 43.8 (11.4) C: 44.5 (12.0)	Ola	I: Metformin C: Placebo	12
Baptista et al., 2008	Canada	Schizophrenia	I: 13 (6, 46%) C: 15 (8, 53%)	I: 45.6 (8.0) C: 49.4 (12.3)	Ola	I: Metformin C: Placebo	12
Biedermann et al., 2014	Austria	Schizophrenia	I: 6 (, 0%) C: 5 (, 0%)	I: 19-65 C: 19-65	Mixed	I: Sibutramine C: Placebo	24
Carrizo et al., 2009	Venezuela	Schizophrenia	I: 24 (, 0%) C: 30 (, 0%)	I: 39.6 (9.7) C: 38.3 (8.7)	Clo	I: Metformin C: Placebo	14
Chen et al., 2013	Taiwan	Schizophrenia	I: 28 (13, 46%) C: 27 (15, 56%)	I: 41.8 (7.2) C: 41.4 (10.2)	Clo	I: Metformin C: Placebo	24
de Silva et al., 2015	Sri Lanka	Schizophrenia	I: 34 (6, 18%) C: 32 (8, 25%)	I: 33.5 (9.9) C: 35.3 (10.7)	Mixed	I: Metformin C: Placebo	26
Henderson et al., 2005	United States	Schizophrenia	I: 19 (12, 63%) C: 18 (11, 61%)	I: 43.2 (10.6) C: 40.7 (9.9)	Ola	I: Sibutramine C: Placebo	12
Henderson et al., 2007	United States	Schizophrenia	I: 11 (8, 73%) C: 10 (8, 80%)	I: 41.0 (10.0) C: 39.0 (10.0)	Clo	I: Sibutramine C: Placebo	12
Jarskog et al., 2013	United States	Schizophrenia	I: 75 (52, 69%) C: 71 (49, 69%)	I: 41.4 (11.5) C: 45.0 (10.3)	Mixed	I: Metformin C: Placebo	16
Klein et al., 2006	United States	BPD	I: 18 (9, 50%) C: 20 (12, 60%)	I: 12.9 (2.4) C: 13.3 (2.4)	Mixed	I: Metformin C: Placebo	16
Ko et al., 2005	Korea	Schizophrenia	I: 17 (7, 41%) C: 20 (12, 60%)	I: 35.3 (9.75) C: 37.6 (7.98)	Mixed	I: Topiramate C: Placebo	12
Lopez-Mato et al., 2003	Spain	Mixed	I: 29 C: 28	I: NA C: NA	Ola	I: Ranitidine C: Placebo	16
McElroy et al., 2007	United States	BPD	I: 18 (4, 22%) C: 28 (7, 25%)	I: 40.6 (13.9) C: 41.7 (11.8)	Mixed	I: Sibutramine C: Topiramate	24
Mehta and Ram, 2016	India	Schizophrenia	I: 25 (22, 88%) C: 25 (23, 92%)	I: 30.3 (7.4) C: 32.2 (8.3)	Ola	I: Ranitidine C: Placebo	8
Narula et al., 2010	India	Schizophrenia	I: 33 (22, 67%) C: 34 (22, 65%)	I: 31.2 (9.7) C: 31.0 (10.1)	Ola	I: Topiramate C: Placebo	12
Nickel et al., 2005	Germany	Mixed	I: 25 (0, 0%) C: 18 (0, 0%)	I: 35.2 (8.2) C: 34.5 (9.2)	Ola	I: Topiramate C: Placebo	10
Poyurovsky et al., 2007	Israel	Schizophrenia	I: 31 (23, 74%) C: 28 (15, 54%)	I: 30.3 (8.5) C: 29.5 (7.2)	Ola	I: Reboxetine C: Placebo	6
Poyurovsky et al., 2013	Israel	Schizophrenia	I: 29 (23, 79%) C: 14 (12, 86%)	I: 33.2 (9.7) C: 31.0 (8.2)	Ola	I: Reboxetine C: Placebo	6
Poyurovsky et al., 2003	Israel	Schizophrenia	I: 10 (6, 60%) C: 10 (5, 50%)	I: 34.6 (13.0) C: 26.5 (6.7)	Ola	I: Reboxetine C: Placebo	6
Rado and von Ammon Cavanaugh, 2016	United States	Mixed	I: 12 (7, 58%) C: 13 (5, 38%)	I: 33.5 (10.1) C: 39.08 (8.62)	Ola	I: Metformin C: Placebo	24
Ranjbar et al., 2013	Iran	Schizophrenia	I: 25 (16, 64%) C: 27 (17, 63%)	I: 38.5 (11.2) C: 37.7 (11)	Ola	I: Ranitidine C: Placebo	16
Wang et al., 2012	China	Schizophrenia	I: 32 (15, 47%) C: 34 (19, 56%)	I: 26.8 (4.2) C: 25.6 (4.6)	Mixed	I: Metformin C: Placebo	12
Wu et al., 2012	China	Schizophrenia	I: 42 (0, 0%) C: 42 (0, 0%)	I: 25.7 (4.8) C: 27.1 (4.2)	Mixed	I: Metformin C: Placebo	24
Wu et al., 2008	China	Schizophrenia	I: 18 (10, 56%) C: 19 (10, 53%)	I: 25.4 (3.9) C: 24.8 (3.5)	Ola	I: Metformin C: Placebo	12

Clo, clozapine; Ola, olanzapine; Ris, risperidone.

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