TECHNICAL COMMENTARY

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Treatments for weight and metabolic abnormalities

SCHIZOPHRENIA LIBRARY

Introduction

Many antipsychotic medications are associated with weight gain and metabolic abnormalities, and various adjunctive pharmacological approaches have been investigated for these problems. Effective adjunctive pharmaceutical treatments for side effects increase adherence to antipsychotic medications and reduce the risk of psychotic relapse.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 16 systematic reviews that met our inclusion criteria[3-18].

- Moderate quality evidence finds a benefit of adjunctive metformin for reducing weight in adults or children with schizophrenia. Moderate to low quality evidence finds more weight reduction with metformin plus lifestyle intervention than placebo (less 5.05kg), metaformin alone (less 1.5kg) or lifestyle intervention alone (less 3.30kg). Triglycerides, glucose, insulin and cholesterol levels may also be improved with metformin.
- Moderate quality evidence finds large effects of reduced weight and BMI with topiramate. There were also medium to large effects of improved triglycerides and low-density lipoproteins with topiramate. Lower quality

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evidence finds improvements with topiramate in fasting blood insulin, insulin resistance and systolic blood pressure. There were no improvements over placebo in total cholesterol, high density lipoproteins, leptin, fasting blood glucose and diastolic blood pressure.

- Moderate quality evidence finds more weight reduction with adjunctive reboxetine or sibutramine than placebo. Moderate to low quality evidence also finds benefits of adjunctive amantadine for weight reduction.
- Moderate quality evidence finds glucagon-like peptide-1 receptor agonists reduce weight, waist circumference and BMI, and improves haemoglobin A1c, glucose and visceral adiposity.
- Moderate to low quality evidence finds reduced BMI, but not weight with adjunctive ranitidine.
- Moderate quality evidence suggests switching antipsychotic medications from olanzapine to aripiprazole or quetiapine may reduce weight and blood glucose levels.
- There were no benefits for weight of adjunctive fluoxetine, rosiglitazone famotidine, nizatidine, norepinephrine, orlistat, or metformin + sibutramine, and no benefits for metabolic disturbances of adjunctive melatonin.

Choi Y

Efficacy of Adjunctive Treatments Added to Olanzapine or Clozapine for Weight Control in Patients with Schizophrenia: A Systematic Review and Meta-Analysis

Scientific World Journal 2015; Article ID 970730

View review abstract online

Comparison	**Topiramate (100-300mg/d over 8-12 weeks), metformin (750-2250mg/d over 12 weeks), sibutramine (15mg/d over 12 weeks) or reboxetine (4mg/d over 6 weeks) vs. placebo.**
Summary of evidence	**Moderate quality evidence (small samples, consistent, direct, unable to assess precision) suggests a benefit of adjunctive topiramate, sibutramine, metformin, and reboxetine for weight reduction.**
Weight reduction	
Significant effects of greater weight reduction with topiramate, sibutramine, metformin and reboxetine than with placebo; Topiramate: 2 RCTs, N = 99, mean change from baseline = -2.405kg, $p = 0.004$, $I^2 = 0\%$, $p = 0.86$ Sibutramine: 2 RCTs, N = 58, mean change from baseline = -2.342kg, $p = 0.004$, $I^2 = 0\%$, $p = 0.37$ Metformin: 3 RCTs, N = 160, mean change from baseline = -1.331kg, $p = 0.014$, $I^2 = 44\%$, $p = 0.17$ Reboxetine: 2 RCTs, N = 85, mean change from baseline = -1.862kg, $p = 0.001$, $I^2 = 0\%$, $p = 0.33$	
Risks	Authors report no differences between groups in adverse effects.
Consistency in results‡	Consistent
Precision in results§	Unable to assess, no confidence intervals are reported.
Directness of results‖	Direct

de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R

Metformin in prevention and treatment of antipsychotic induced weight gain: A systematic review and meta-analysis

BMC Psychiatry 2016; 16(341) doi: 10.1186/s12888-016-1049-5

View review abstract online

Comparison	**Metaformin (750 to 2000mg for 12-24 weeks) vs. placebo.** **Studies included people with schizophrenia or schizoaffective disorder.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, direct, unable to assess precision) suggests a benefit of adjunctive metformin compared to adjunctive placebo for weight and BMI reduction in both adults and children. There was also less insulin resistance and no effect on fasting blood sugar levels.**

Weight reduction

Treatment with adjunctive metformin resulted in significantly more weight and BMI loss;

Weight: 12 RCTs, N = 743, MD = -3.27kg, 95%CI -4.66 to -1.89, $p < 0.001$, $I^2 = 82\%$

BMI: 12 RCTs, N = 743, MD = -1.13kg/m_2, 95%CI -1.61 to -0.66, $p < 0.001$, $I^2 = 83\%$

Metabolic indices

Treatment with adjunctive metformin resulted in significantly less insulin resistance;

9 RCTs, N = 499, MD = -1.49, 95%CI -2.40 to -0.59, $p < 0.001$, $I^2 = 86\%$

There were no differences in fasting blood sugar;

10 RCTs, N = 647, MD = -2.48mg/dl, 95%CI -5.54 to 0.57, $p = 0.11$, $I^2 = 71\%$

Subgroup analysis showed a larger effect in first-episode patients than in chronic patients (weight change -5.94kg vs. -2.06kg). Results were similar in both adults and children, and when studies of ethnic Chinese samples were excluded (these showed the largest effect).

Risks	One RCT reported more diarrhorea with metformin.
Consistency in results	Inconsistent
Precision in results	Unable to assess MDs
Directness of results	Direct

Fiedorowicz JG, Miller DD, Bishop JR, Calarge CA, Ellingrod VL, Haynes WG

Systematic review and meta-analysis of pharmacological interventions for weight gain from antipsychotics and mood stabilizers

Current Psychiatry Reviews 2012; 8(1): 25-36 View review abstract online	
Comparison	**Adjunctive metformin, topiramate, H2 antagonists (famotidine or nizatidine) or norepinephrine vs. placebo.** **Treatment duration 12-16 weeks.** **Most studies included people with schizophrenia or schizoaffective disorder.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, direct, unable to assess precision) suggests a benefit of adjunctive topiramate for weight reduction. Moderate to low quality evidence (inconsistent or small sample) suggests a benefit of adjunctive metformin, but no benefit of H2 antagonists or norepinephrine for weight reduction.**
Weight reduction	
Significant effects of greater weight reduction with metformin and topiramate than with placebo; Metformin: 7 RCTs, N = 336, MD = -2.93kg, 95%CI -4.89 to -0.97, p = 0.003, I^2 = 91%, p = 0.00001 Topiramate: 3 RCTs, N = 282, MD = -2.98kg, 95%CI -4.14 to -1.83, p = 0.00001, I^2 = 33%, p = 0.22 *No significant differences between groups for;* H2 antagonists: 6 RCTs, N = 352, MD = -1.78kg, 95%CI -4.06 to 0.50, p = 0.13, I^2 = 94%, p = 0.00001 Norepinephrine: 3 RCTs, N = 97, MD = -1.30kg, 95%CI -2.66 to 0.60, p = 0.06, I^2 = 56%, p = 0.11	
Risks	Authors report no differences between groups in adverse effects.
Consistency in results	Consistent for topiramate and norepinephrine, inconsistent for metformin and H2 antagonists.
Precision in results	Unable to assess, confidence intervals are not standardised.
Directness of results	Direct

Goh KK, Chen CH, Lu ML

Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials

International Journal of Psychiatry in Clinical Practice 2019; 23: 14-32

View review abstract online	
Comparison	**Adjunctive topiramate (6 to 24 weeks, 50 to 400 mg/day) vs. control.**
Summary of evidence	**Moderate quality evidence (medium to large samples, mostly inconsistent and imprecise, direct) finds large effects of reduced weight and BMI with topiramate. There were also medium to large effects of improved triglycerides and low density lipoproteins. Lower quality evidence (small sample) finds improvements in fasting blood insulin, insulin resistance and systolic blood pressure. There were no improvements in total cholesterol, high density lipoproteins, leptin, fasting blood glucose and diastolic blood pressure.**
Weight reduction	
A large significant effect of reduced weight with topiramate; 16 RCTs, N = 874, SMD = -0.96, 95%CI -1.22 to -0.69, $p < 0.001$, $I^2 = 68\%$ Subgroup analyses showed double blind RCTs had larger effect sizes than open label RCTs (-1.17 vs. -0.61). Studies from the Middle East and South Asia showed the largest effect sizes, followed by East Asia, then America and Europe (-2.14 vs. -0.74 vs. -0.64). *A large significant effect of reduced BMI with topiramate;* 11 RCTs, N = 608, SMD = -1.02, 95%CI -1.38 to -0.66, $p < 0.001$, $I^2 = 74\%$ Subgroup analyses showed double blind RCTs had larger effect sizes than open label RCTs (-1.08 vs. -0.81). Studies from countries with an overweight population <25% showed more BMI reduction compared with those with an overweight population 25 to 50% or >50% (-2.19 vs. -0.82 vs. -1.03). Studies with baseline BMI <25 kg/m$_2$ had more BMI reduction than those with baseline BMI >25 kg/m$_2$ (-1.21 vs. -0.51). Studies of patients on olanzapine showed better outcomes than clozapine or risperidone. The effects of topiramate increased with baseline psychopathology severity. There were no effects of topiramate dose, illness stage, age, gender, setting, or treatment duration.	
Metabolic abnormalities	
Significant medium to large effects of improved metabolic factors with topiramate for; Triglycerides: 5 RCTs, N = 268, SMD = -0.68, 95%CI -1.24 to -0.13, $p < 0.05$, $I^2 = 79\%$ Low density lipoproteins: 4 RCTs, N = 247, SMD = -0.80, 95%CI -1.06 to -0.53, $p < 0.001$, $I^2 = 0\%$ Fasting blood insulin: 1 RCT, N = 67, SMD = -0.61, 95%CI -1.10 to -0.12, $p = 0.01$ Insulin resistance: 1 RCT, N = 67, SMD = -1.27, 95%CI -1.79 to -0.74, $p < 0.001$ Systolic blood pressure: 1 RCT, N = 67, SMD = -0.78, 95%CI -1.28 to -0.28, $p < 0.01$ *There were no significant differences in;* Total cholesterol: 3 RCTs, N = 187, SMD = -0.75, 95%CI -1.58 to 0.07, $p = 0.07$, $I^2 = 86\%$	

High density lipoproteins: 4 RCTs, N = 247, SMD = -0.07, 95%CI -0.58 to 0.44, p = 0.78, I^2 = 75% Leptin: 6 RCTs, N = 345, SMD = -0.64, 95%CI -1.52 to 0.24, p = 0.16, I^2 = 93% Fasting blood glucose: 7 RCTs, N = 369, SMD = -0.43, 95%CI -1.00 to 0.15, p = 0.15, I^2 = 85% Diastolic blood pressure: 1 RCT, N = 67, SMD = -0.45, 95%CI -0.93 to 0.04, p = 0.07	
Risks	There were no significant differences between groups, apart from more paresthesia and psychomotor slowing with topiramate.
Consistency in results	Inconsistent, apart from low density lipoproteins.
Precision in results	Mostly imprecise
Directness of results	Direct

Gu XJ, Chen R, Sun CH, Zheng W, Yang XH, Wang SB, Ungvari GS, Ng CH, Golenkov A, Lok GKI, Li L, Chow IHI, Wang F, Xiang YT

Effect of adjunctive ranitidine for antipsychotic-induced weight gain: A systematic review of randomized placebo-controlled trials

Journal of International Medical Research 2018; 46: 22-32.

View review abstract online

Comparison	**Adjunctive ranitidine (8 to 24 weeks, 150 to 600 mg/day) + olanzapine vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, inconsistent, unable to assess precision, direct) suggests reduced BMI but not weight with adjunctive ranitidine.**
Weight reduction	
A significant effect of reduced BMI with ranitidine; 4 RCTs, N = 312, WMD = -1.08kg/m2, 95%CI -2.15 to -0.01, p = 0.05, I^2 = 94% *No significant difference in weight;* 3 RCTs, N = 260, WMD = -1.54kg, 95%CI -3.13 to 0.04, I^2 = 78%	
Risks	There was less drowsiness with ranitidine. There were no differences in akathisia, rigidity, tremor, dry mouth, headache, and constipation. showed no significant group.
Consistency in results	Inconsistent

Precision in results	Unable to assess; WMD not standardised.
Directness of results	Direct

Igwe SC, Brigo F

Does melatonin and melatonin agonists improve the metabolic side effects of atypical antipsychotics?: A systematic review and meta-analysis of randomized controlled trials

Clinical Psychopharmacology and Neuroscience 2-18; 16: 235-45

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Comparison	**8-12 weeks of melatonin + antipsychotics vs. placebo + antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (small samples, inconsistent, appears imprecise, direct) suggests no benefit of melatonin for metabolic disturbances.**
Metabolic anomalies	
There were no significant differences between groups; Body weight: 2 studies, N = 43, MD = 1.16, 95%CI -7.58 to 9.90, $p > 0.05$ Body mass index: 2 studies, N = 43, MD = 0.43, 95%CI -2.68 to 3.55, $p > 0.05$ Waist circumference: 2 studies, N = 43, MD = 0.44, 95%CI -6.32 to 7.20, $p > 0.05$ Hip circumference: 2 studies, N = 43, MD = -0.39, 95%CI -5.02 to 4.25, $p > 0.05$ Total cholesterol: 2 studies, N = 43, MD = 0.30, 95%CI -50.46 to 51.06, $p > 0.05$ LDL cholesterol: 2 studies, N = 62, MD = 4.79, 95%CI -29.04 to 38.62, $p > 0.05$ HDL cholesterol: 2 studies, N = 43, MD = 0.79, 95%CI -5.33 to 6.90, $p > 0.05$ Trigylcerides: 2 studies, N = 43, MD = -49.32, 95%CI -111.42 to 12.78, $p > 0.05$ Fasting glucose: 2 studies, N = 43, MD = 3.07, 95%CI -4.28 to 10.41, $p > 0.05$	
Consistency in results	Authors report the results are inconsistent.
Precision in results	Appears imprecise.
Directness of results	Direct

Maayan L, Vakhrusheva J, Correll CU

Effectiveness of Medications Used to Attenuate Antipsychotic-Related Weight Gain and Metabolic Abnormalities: A Systematic Review and Meta-Analysis

Neuropsychopharmacology 2010; 35: 1520-1530

View review abstract online

Comparison	**Adjunctive amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, metformin, metformin + sibutramine, nizatidine, orlistat, reboxetine, rosiglitazone, sibutramine, and topiramate vs. placebo.** **Most studies included people with schizophrenia or schizoaffective disorder.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, direct, unable to assess precision) suggests a benefit of adjunctive metformin, topiramate, sibutramine and reboxetine, but no benefit of nizatidine, amantadine, fluoxetine orlistat, or metformin + sibutramine for weight reduction.** **Low quality evidence (very small samples) is unsure of the benefits of D-fenfluramine, dextroamphetamine, famotidine or rosiglitazone for weight reduction.**

Weight reduction

Overall, pharmacologic interventions were associated with a significant weight reduction;

32 studies, N = 1,482, MD = -1.99kg, 95%CI -2.77 to -1.20, $p = 0.00001$, $I^2 = 86\%$, $p = 0.00001$

Significant effects of greater weight reduction with the following agents vs. placebo;

D-fenfluramine: 1 RCT, N = 16, MD = -2.60kg, 95%CI -5.14 to -0.06, $p = 0.04$

Metformin: 7 RCTs, N = 334, MD = -2.94kg, 95%CI -4.89 to -0.99, $p = 0.003$, $I^2 = 91\%$, $p = 0.00001$

Reboxetine: 2 RCTs, N = 79, MD = -1.90kg, 95%CI -3.07 to -0.72, $p = 0.002$, $I^2 = 0\%$, $p = 0.34$

Sibutramine: 2 RCTs, N = 55, MD = -2.56kg, 95%CI -3.91 to -1.22, $p = 0.0002$, $I^2 = 40\%$, $p = 0.20$

Topiramate: 2 RCTs, N = 133, MD = -2.52kg, 95%CI -4.87 to -0.16, $p = 0.04$, $I^2 = 75\%$, $p = 0.02$

No significant differences between groups in weight reduction;

Amantadine: 2 RCTs, N = 144, MD = -2.27kg, 95%CI -4.77 to 0.23, $p = 0.08$, $I^2 = 40\%$, $p = 0.20$

Dextroamphetamine: 1 RCT, N = 20, MD = 0.82kg, 95%CI -2.49 to 4.13, $p = 0.63$

Famotidine: 1 RCT, N = 14, MD = -0.10kg, 95%CI -2.75 to 2.55, $p = 0.94$ Fluoxetine: 2 RCTs, N = 60, MD = 0.99kg, 95%CI -0.90 to 2.88, $p = 0.31$, $I^2 = 0\%$, $p = 0.61$ Metformin + sibutramine: 1 RCT, N = 28, MD = -1.40kg, 95%CI -3.58 to 0.78, $p = 0.21$ Nizatidine: 4 RCTs, N = 338, MD = -2.07kg, 95%CI -4.58 to 0.45, $p = 0.11$, $I^2 = 95\%$, $p = 0.00001$ Orlistat: 1 RCT, N = 63, MD = -1.69kg, 95%CI -3.69 to 0.31, $p = 0.10$ Rosiglitazone: 1 RCT, N = 19, MD = -1.00kg, 95%CI -1.63 to 3.63, $p = 0.46$ Authors report greatest weight reduction with metformin in chronically treated patients; with reboxetine in prevention trials, in studies lasting <12 weeks, and for both inpatients and first-episode patients; with sibutramine in intervention trials, in studies lasting ≥12 weeks, and for both outpatients and chronically treated patients. Authors report little evidence of publication bias.
Metabolic abnormalities
Few differences were found between groups (agent vs. placebo) for metabolic variables; insulin decreased significantly more with metformin and rosiglitazone; triglyceride levels decreased significantly more with metformin + sibutramine and fluvoxamine; LDL cholesterol was significantly greater with rosiglitazone and significantly lower with sibutramine.

Risks	Authors report no differences between groups in rates of nausea.
Consistency in results	Inconsistent for overall analysis, metformin, topiramate, and nizatidine.
Precision in results	Unable to assess, confidence intervals are not standardised.
Directness of results	Direct

Mizuno Y, Suzuki T, Nakagawa A, Yoshida K, Mimura M, Fleischhacker WW, Uchida H

Pharmacological Strategies to Counteract Antipsychotic-Induced Weight Gain and Metabolic Adverse Effects in Schizophrenia: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2014; doi: 10.1093/schbul/sbu030

View review abstract online

Comparison	**Adjunctive amantadine, aripiprazole, fluoxetine, metformin, nizatidine, reboxetine, rosiglitazone, sibutramine or topiramate**

	vs. placebo. **Treatment duration 6-24 weeks.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, direct, unable to assess precision) suggests a benefit of adjunctive aripiprazole for weight reduction.** **Moderate to low quality evidence (inconsistent *or* small samples) suggests a benefit of adjunctive metformin, topiramate, sibutramine and reboxetine, but no benefit of nizatidine, amantadine, fluoxetine or rosiglitazone for weight reduction.**
Weight reduction	
Significant effects of greater weight reduction with the following agents vs. placebo; Aripiprazole: 3 RCTs, N = 266, MD = -2.13kg, 95%CI -2.87 to -1.39, $p < 0.05$, $I^2 = 0\%$ Metformin: 10 RCTs, N = 711, MD = -3.17kg, 95%CI -4.44 to -1.90, $p < 0.05$, $I^2 = 88\%$ Reboxetine: 2 RCTs, N = 79, MD = -1.90kg, 95%CI -3.07 to -0.72, $p < 0.05$, $I^2 = 0\%$ Sibutramine: 3 RCTs, N = 66, MD = -2.86kg, 95%CI -4.72 to -1.01, $p < 0.05$, $I^2 = 49\%$ Topiramate: 2 RCTs, N = 140, MD = -5.20kg, 95%CI -9.55 to -0.84, $p < 0.05$, $I^2 = 0\%$ *No significant differences between groups;* Amantadine: 2 RCTs, N = 144, MD = -2.27kg, 95%CI -4.66 to 0.23, $p > 0.05$, $I^2 = 40\%$ Fluoxetine: 2 RCTs, N = 60, MD = 0.75kg, 95%CI -1.76 to 3.26, $p > 0.05$, $I^2 = 0\%$ Nizatidine: 4 RCTs, N = 341, MD = -2.03kg, 95%CI -4.53 to 0.47, $p > 0.05$, $I^2 = 97\%$ Rosiglitazone: 2 RCTs, N = 37, MD = 0.26kg, 95%CI -1.83 to 2.35, $p > 0.05$, $I^2 = 0\%$ Subgroup analyses across all agents showed larger effects in treatment trials (MD = -2.28) than in prevention trials (MD = -1.71), in first-episode patients (MD = -3.52) than in more chronic patients (MD = -1.71kg), in outpatient trials (MD = -2.37) than inpatient trials (MD = -1.50). Authors report possible publication bias.	
Consistency in results	Inconsistent for metformin and nizatidine (I^2 >50%).
Precision in results	Unable to assess, confidence intervals are not standardised.
Directness of results	Direct

Mukundan A, Faulkner G, Cohn T, Remington G

Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems

Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD006629. DOI: 10.1002/14651858.CD006629.pub2

View review abstract online

Comparison 1	**Switching from fluphenazine decanoate to haloperidol decanoate.**
Summary of evidence	**Low quality evidence (very small sample) is unclear about the benefit of switching from fluphenazine decanoate to haloperidol decanoate for weight reduction.**
Weight reduction	
No significant differences between groups in mean body weight; 1 RCT, N = 19, MD = -2.80kg, 95%CI -7.04 to 1.44, *p* = 0.20	
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise for global/mental state and study attrition, unable to assess MD.
Directness of results	Direct
Comparison 2	**Switching from olanzapine to aripiprazole or quetiapine.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, consistent, direct, unable to assess precision) suggests switching from olanzapine to aripiprazole or quetiapine may reduce weight and blood glucose levels.**
Weight reduction	
Trend effect of reduction in mean body weight with aripiprazole or quetiapine vs. olanzapine; Mean body weight: 2 RCTs, N = 287, MD = -1.94kg, 95%CI -3.90 to 0.08, *p* = 0.06, I^2 = 0%	
Metabolic abnormalities	
Significant effect of reduction in blood glucose with aripiprazole or quetiapine vs. olanzapine; Fasting blood glucose: 2 RCTs, N = 280, MD = -2.53kg, 95%CI -2.94 to -2.11, *p* = 0.00001, I^2 = 0%	
Risks	No significant difference between groups in risk of treatment-emergent adverse effects (2 RCTs, N = 302, RR = 1.07, 95%CI 0.92

	to 1.24, p = 0.38, I^2 = 0%).
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Precise for adverse events, imprecise for mental state, unable to assess MDs.
Directness of results	Direct

Praharaj SK, Jana AK, Goyal N, Sinha VK

Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis

British Journal of Clinical Pharmacology 2011; 71(3): 377-82

View review abstract online

Comparison	**Adjunctive metformin (750-2550mg/day) + olanzapine vs. placebo + olanzapine.** **Treatment duration 12-14 weeks.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, direct, unable to assess precision) suggests metformin may reduce body weight and BMI levels.**
Weight reduction	
Significant effect of reduced body weight and BMI with metformin; Body weight: 4 RCTs, N = 210, WMD = -5.02kg, 95%CI -6.10 to -3.93, p = 0.00001, I^2 = 0%, p = 0.45 BMI: 4 RCTs, N = 210, WMD = -1.82kg/m^2, 95%CI -2.19 to -1.44, p = 0.00001, I^2 = 0%, p = 0.52 *No significant differences between groups for waist circumference;* 4 RCTs, N = 210, WMD -1.42cm, 95%CI -3.13 to 0.29, p = 0.10, I^2 = 85.1%, p = 0.00002	
Consistency in results	Consistent for body weight and BMI, inconsistent for waist circumference.
Precision in results	Unable to assess WMDs (not standardised).
Directness of results	Direct

Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S

Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis

PLoS ONE 2016; 11(6): e0156208

View review abstract online

Comparison	**Adjunctive metformin (250-5000mg/day) + clozapine vs. placebo + clozapine.** **Treatment duration 12 weeks to 6 months.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, mostly consistent, direct, unable to assess precision) suggests metformin reduces body weight, BMI, waist circumference, triglycerides, glucose and insulin.**

Weight reduction

Significant effect of reduced body weight, BMI, and waist circumference with metformin;

Weight change: 7 RCTs, N = 305, MD = -3.12kg, 95%CI -4.88 to -1.37, $p = 0.0005$, $I^2 = 20\%$, $p = 0.28$

BMI: 6 RCTs, N = 306, MD = -1.18kg/m^2, 95%CI -1.76 to -0.61, $p = 0.0001$, $I^2 = 32\%$, $p = 0.19$

Waist circumference: 5 RCTs, N = 303, MD -1.69cm, 95%CI -3.06 to 0.32, $p = 0.02$, $I^2 = 0\%$, $p = 0.68$

Authors report no differences in results for weight measures according to study quality, study duration or presence of psychosocial interventions.

Metabolic abnormalities

Significant effect of improved metabolic factors with metformin;

Blood glucose: 8 RCTs, N = 478, MD = -0.60mg/dL, 95%CI -1.03 to -0.17, $p = 0.006$, $I^2 = 86\%$, $p < 0.00001$

Triglycerides: 4 RCTs, N = 282, MD = -0.17mmol/L, 95%CI -0.30 to -0.03, $p = 0.02$, $I^2 = 0\%$, $p = 0.80$

Insulin: 4 RCTs, N = 266, MD = -5.63mu/L, 95%CI -9.57 to -1.68, $p = 0.005$, $I^2 = 75\%$, $p = 0.007$

HOMA: 3 RCTs, N = 245, MD = -0.89, 95%CI -1.06 to -0.72, $p < 0.0001$, $I^2 = 0\%$, $p = 0.44$

No significant differences between groups for;

HDL cholesterol: 4 RCTs, N = 282, MD = 0.07mmol/L, 95%CI -0.02 to 0.16, $p = 0.14$, $I^2 = 61\%$, $p = 0.05$

LDL cholesterol: 3 RCTs, N = 227, MD = -0.10mmol/L, 95%CI -0.30 to 0.09, $p = 0.30$, $I^2 = 0\%$, $p =$

0.95 Systolic blood pressure: 3 RCTs, N = 146, MD = 0.07, 95%CI -0.51 to 0.96, p = 0.80, I^2 = 0%, p = 0.71 Dystolic blood pressure: 3 RCTs, N = 146, MD = -0.23, 95%CI -0.79 to 0.33, p = 0.43, I^2 = 0%, p = 0.77 Authors report no differences in results for weight measures according to study quality, study duration or presence of psychosocial interventions.	
Consistency in results	Consistent apart from glucose, insulin and HDL cholesterol.
Precision in results	Unable to assess MDs (not standardised).
Directness of results	Direct

Siskind D, Hahn M, Correll CU, Fink-Jensen A, Russell AW, Bak N, Broberg BV, Larsen J, Ishoy PL, Vilsboll T, Knop FK, Kisely S, Ebdrup BH

Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: A systematic review and individual participant data meta-analysis

Diabetes, Obesity and Metabolism 2019; 21: 293-302

View review abstract online

Comparison	**Glucagon-like peptide-1 receptor agonists (1.8-2.00mg/day, 12-24 weeks weeks) vs. controls.** **Individual participant data from studies** **randomizing patients to GLP-1RA or control were meta-analysed** **Treatment duration 12 weeks to 6 months.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, direct, unable to assess precision) finds glucagon-like peptide-1 receptor agonists reduce body weight, waist circumference and BMI, and improves haemoglobin A1c, glucose and visceral adiposity.**
Weight reduction	
A significant effect of more weight loss with glucagon-like peptide-1 receptor agonists; Body weight: 3 RCTs, N = 168, MD = -3.71kg, 95%CI 2.44 to 4.99kg, p < 0.001, Q-test p = 0.43	

Waist circumference: 3 RCTs, N = 167, MD = -3.00cm, CI not reported, $p < 0.001$, Q-test $p = 0.13$ Body mass index: 3 RCTs, N = 168, MD = -1.19kg/m^2, CI not reported, $p < 0.001$, Q-test $p = 0.33$ Weight loss with glucagon-like peptide-1 receptor agonists was greater for clozapine/olanzapine-treated patients than other antipsychotics. Sex, age, psychosis severity, nausea, any adverse effect, and agent did not significantly impact outcomes.
Metabolic abnormalities
Significant effect of improved metabolic factors with glucagon-like peptide-1 receptor agonists; Haemoglobin A1c: 3 RCTs, N = 166, MD = -3.25IFCC, CI not reported, $p < 0.001$, Q-test $p = 0.28$ Fasting glucose: 3 RCTs, N = 166, MD = -0.45mmol/L, CI not reported, $p < 0.001$, Q-test $p = 0.22$ Visceral adiposity: N = 97, MD = -177.51gm, CI not reported, $p = 0.011$, Q-test $p = 0.09$ There were no significant differences in diastolic blood pressure, high-density lipoprotein cholesterol, homeostatic model assessment insulin, low-density lipoprotein cholesterol, systolic blood pressure and triglycerides.

Risks	Nausea was more common with glucagon-like peptide-1 receptor agonists.
Consistency in results	Consistent
Precision in results	Unable to assess MDs (not standardised and Cis not reported).
Directness of results	Direct

Zheng W, Li X, Tang Y, Xiang Y, Wang C, de Leon J

Metformin for Weight Gain and Metabolic Abnormalities Associated With Antipsychotic Treatment Meta-Analysis of Randomized Placebo-Controlled Trials

Journal of Clinical Psychopharmacoly 2015; 35: 499-509

View review abstract online

Comparison	**Adjunctive metformin (250-2550mg/day) vs. placebo.** **Treatment duration 6-24 weeks.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, direct) suggests medium-sized effects of improved weight, BMI, waist circumference, triglycerides, glucose, insulin and total cholesterol with metformin.**

Weight reduction
Medium-sized, significant effects of reduced body weight, BMI, and waist circumference with metformin; Body weight: 19 RCTs, N = 1,279, SMD = -0.61, 95%CI -0.77 to -0.44, $p < 0.00001$, $I^2 = 51\%$, $p = 0.005$ BMI: 18 RCTs, N = 1,228, SMD = -0.69, 95%CI -0.91 to -0.46, $p < 0.00001$, $I^2 = 73\%$, $p < 0.00001$ Waist circumference: 9 RCTs, N = 575, SMD = -0.35, 95%CI -0.66 to -0.04, $p = 0.03$, $I^2 = 69\%$, $p = 0.001$ Subgroup analyses found no differences in study results for weight measures according to age, publication language (Chinese vs. English), treatment style (intervention vs. prevention), dose (≤ 750mg/d vs. > 750mg/d), study duration (≤ 12 weeks vs. > 12 weeks) study quality (low vs. high), and antipsychotic type (olanzapine vs. clozapine).
Metabolic abnormalities
Medium-sized, significant effects of improved metabolic factors with metformin; Fasting glucose: 17 RCTs, N = 1,281, SMD = -0.65, 95%CI -0.95 to -0.35, $p < 0.0001$, $I^2 = 85\%$, $p < 0.00001$ Fasting insulin: 11 RCTs, N = 787, SMD = -0.64, 95%CI -1.03 to -0.25, $p = 0.001$, $I^2 = 85\%$, $p < 0.00001$ HOMA: 11 RCTs, N = 680, SMD = -0.75, 95%CI -1.11 to -0.40, $p < 0.0001$, $I^2 = 79\%$, $p < 0.00001$ Glycosylated hemoglobin A1c: 4 RCTs, N = 383, SMD = -0.38, 95%CI -0.69 to -0.07, $p = 0.02$, $I^2 = 53\%$, $p = 0.10$ Triglycerides: 11 RCTs, N = 856, SMD = -0.56, 95%CI -0.98 to -0.13, $p = 0.01$, $I^2 = 89\%$, $p < 0.00001$ Total cholesterol: 8 RCTs, N = 628, SMD = -0.51, 95%CI -0.82 to -0.20, $p = 0.001$, $I^2 = 72\%$, $p = 0.0007$ *A trend effect for improved HDL cholesterol with metformin;* HDL cholesterol: 7 RCTs, N = 542, SMD = 0.45, 95%CI 0.00 to 0.90, $p = 0.05$, $I^2 = 84\%$, $p < 0.00001$ *No significant differences between groups for LDL cholesterol;* LDL cholesterol: 5 RCTs, N = 433, SMD = -0.03, 95%CI -0.41 to 0.35, $p = 0.86$, $I^2 = 73\%$, $p = 0.006$

Risks	Authors report significantly higher frequencies of nausea/vomiting and diarrhoea with metformin, and no differences for any other adverse effect.
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct

Zheng W, Wang S, Ungvari GS, Ng CH, Yang XH, Gu YH, Li M, Xiang YQ, Xiang YT

Amantadine for Antipsychotic-Related Weight Gain: Meta-Analysis of Randomized Placebo-Controlled Trials

Journal of Clinical Psychopharmacology 2017; 37: 341-6

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Comparison	**Adjunctive amantadine (100-400mg/day, mean 8.2 weeks) vs. placebo.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, unable to assess precision, direct) finds more weight reduction with amantadine.**
Weight reduction	
A significant effect of more weight reduction with amantadine; 3 RCTs, N = 205, WMD = -2.22kg, 95%CI -3.58 to -0.86, p = 0.001, I^2 = 45%, p = 0.16	
Risks	There were no differences in adverse events apart from more insomnia with amantadine.
Consistency in results	Consistent
Precision in results	Unable to assess (WMDs not standardised).
Directness of results	Direct

Zheng W, Zhang QE, Cai DB, Yang XH, Ungvari GS, Ng CH, Wu RR, Xiang YT

Combination of Metformin and Lifestyle Intervention for Antipsychotic-Related Weight Gain: A Meta-Analysis of Randomized Controlled Trials

Pharmacopsychiatry 2019; 52: 24-31

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Comparison 1	**Metformin plus lifestyle intervention (250-1500mg/day, mean 12-24 weeks) vs. metformin alone.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, some inconsistency, unable to assess precision, direct) finds more weight reduction with metformin plus lifestyle intervention than metformin alone (1.50kg).**
Weight reduction	
Significant effects of more weight loss and reduced BMI with metformin plus lifestyle intervention; Body weight: 1 RCT, N = 64, WMD = -1.50kg, 95%CI -2.98 to -0.02, $p = 0.05$ BMI: 2 RCTs, N = 191, WMD = -1.08kg/m^2, 95%CI -1.97 to -0.19, $p = 0.02$, $I^2 = 84\%$ There were no significant differences in waist circumference.	
Risks	There were no differences in all cause discontinuation.
Consistency in results	Inconsistent where applicable.
Precision in results	Unable to assess (WMDs not standardised).
Directness of results	Direct
Comparison 2	**Metformin plus lifestyle intervention (250-1500mg/day, mean 12-24 weeks) vs. lifestyle intervention alone.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, unable to assess precision, direct) finds more weight reduction with metformin plus lifestyle intervention than lifestyle intervention alone (3.30kg).**
Weight reduction	
Significant effects of more weight loss, reduced BMI, and reduced waist circumference with metformin plus lifestyle intervention; Body weight: 1 RCT, N = 64, WMD = -3.30kg, 95%CI -4.78 to -1.82, $p < 0.0001$ BMI: 3 RCTs, N = 343, WMD = -1.45kg/m^2, 95%CI -1.93 to -0.97, $p < 0.00001$, $I^2 = 0\%$ Waist circumference: 3 RCTs, N = 343, WMD = -2.10cm, 95%CI -2.83 to -1.38, $p < 0.00001$, $I^2 = 0\%$	
Risks	There were no differences in all cause discontinuation, lack of energy, loss of appetite and nausea.
Consistency in results	Consistent

Precision in results	Unable to assess (WMDs not standardised).
Directness of results	Direct
Comparison 3	**Metformin plus lifestyle intervention (250-1500mg/day, mean 12-24 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, consistent, unable to assess precision, direct) finds more weight reduction with metformin plus lifestyle intervention than placebo (5.05kg).**
Weight reduction	
Significant effects of more weight loss and reduced BMI with metformin plus lifestyle intervention; Body weight: 3 RCTs, N = 244, WMD = -5.05kg, 95%CI -7.92 to -2.18, p = 0.0006, I^2 = 92% BMI: 3 RCTs, N = 244, WMD = -2.85kg/m^2, 95%CI -4.47 to -1.22, p = 0.0006, I^2 = 97%	
Risks	There were no differences in all cause discontinuation, or adverse effects.
Consistency in results	Inconsistent
Precision in results	Unable to assess (WMDs not standardised).
Directness of results	Direct

Zhuo C, Xu Y, Liu S, Li J, Zheng Q, Gao X, Li S, Jing R, Song X, Yue W, Zhou C, Upthegrove R

Topiramate and metformin are effective add-on treatments in controlling antipsychotic-induced weight gain: A systematic review and network meta-analysis

Frontiers in Pharmacology 2018; 28(9): 1393

View review abstract online

Comparison	**Adjunctive topiramate, metaformin, reboxetine, sibutramine or ranitidine vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample sizes, consistent, unable to assess precision, direct) finds more weight reduction with adjunctive topiramate, metaformin, reboxetine, and**

	sibutramine.
Weight reduction	
The following adjunctive treatments showed greater reduction in weight than placebo; Topiramate: 4 studies, N = not reported, MD = -3.07kg, 95%CI -5.67 to -0.48, $p < 0.05$ Sibutramine: 4 studies, N = not reported, MD = -2.97kg, 95%CI -4.18 to -1.77, $p < 0.05$ Metformin: 13 studies, N = not reported, MD = -2.50kg, 95%CI -3.21 to -1.80, $p < 0.05$ Reboxetine: 3 studies, N = not reported, MD = -2.25kg, 95%CI -3.54 to -0.95, $p < 0.05$ There were no significant differences between groups for Ranitidine. A similar pattern was found for BMI change.	
Risks	There were no differences in adverse events.
Consistency in results	Authors report results are consistent.
Precision in results	Unable to assess (MDs not standardised).
Directness of results	Direct

Explanation of acronyms

BMI = Body Mass Index, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions Scale, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), GAF = Global Assessment of Functioning, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, HOMA = Homeostatic Model Assessment, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MADRS = Montgomery–Åsberg Depression Rating Scale, MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, TD = tardive dyskinesia, TDRS = Tardive Dyskinesia Rating Scale, vs. = versus, WMD = weighted mean difference

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[19].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[19].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[20]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[19];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[21].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Choi YJ (2015): Efficacy of adjunctive treatments added to olanzapine or clozapine for weight control in patients with schizophrenia: A systematic review and meta-analysis. *Scientific World Journal* 2015.
4. Fiedorowicz JG, Miller DD, Bishop JR, Calarge CA, Ellingrod VL, Haynes WG (2012): Systematic review and meta-analysis of pharmacological interventions for weight gain from antipsychotics and mood stabilizers. *Current Psychiatry Reviews* 8: 25-36.
5. Mizuno Y, Suzuki T, Nakagawa A, Yoshida K, Mimura M, Fleischhacker W*, et al.* (2014): Pharmacological Strategies to Counteract Antipsychotic-Induced Weight Gain and Metabolic Adverse Effects in Schizophrenia: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin* doi:10.1093/schbul/sbu030.
6. Maayan L, Vakhrusheva J, Correll CU (2010): Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 35: 1520-30.
7. Mukundan A, Faulkner G, Cohn T, Remington G (2010): Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database of Systematic Reviews*: CD006629.
8. Praharaj SK, Jana AK, Goyal N, Sinha VK (2011): Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology* 71: 377-82.
9. Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S (2016): Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis. *PLoS ONE* 11: e0156208.
10. Zheng W, Li XB, Tang YL, Xiang YQ, Wang CY, De Leon J (2015): Metformin for Weight Gain and Metabolic Abnormalities Associated with Antipsychotic Treatment: Meta-Analysis of Randomized Placebo-Controlled Trials. *Journal of Clinical Psychopharmacology* 35: 499-509.
11. Igwe SC, Brigo F (2018): Does melatonin and melatonin agonists improve the metabolic side effects of atypical antipsychotics?: A systematic review and meta-analysis of randomized controlled trials. *Clinical Psychopharmacology and Neuroscience* 16: 235-45.
12. Goh KK, Chen CH, Lu ML (2019): Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. *International Journal of Psychiatry in Clinical Practice* 23: 14-32.
13. Gu XJ, Chen R, Sun CH, Zheng W, Yang XH, Wang SB*, et al.* (2018): Effect of adjunctive ranitidine for antipsychotic-induced weight gain: A systematic review of randomized placebo-controlled trials. *Journal of International Medical Research* 46: 22-32.
14. Siskind D, Hahn M, Correll CU, Fink-Jensen A, Russell AW, Bak N*, et al.* (2019): Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: A systematic review and individual participant data meta-analysis. *Diabetes, Obesity and Metabolism* 21: 293-302.
15. Zheng W, Wang S, Ungvari GS, Ng CH, Yang XH, Gu YH*, et al.* (2017): Amantadine for Antipsychotic-Related Weight Gain: Meta-Analysis of Randomized Placebo-Controlled Trials. *Journal of Clinical Psychopharmacology* 37: 341-6.
16. Zheng W, Zhang QE, Cai DB, Yang XH, Ungvari GS, Ng CH*, et al.* (2019): Combination of Metformin and Lifestyle Intervention for Antipsychotic-Related Weight Gain: A Meta-Analysis of Randomized Controlled Trials. *Pharmacopsychiatry* 52: 24-31.
17. Zhuo C, Xu Y, Liu S, Li J, Zheng Q, Gao X*, et al.* (2018): Topiramate and metformin are effective add-on treatments in controlling antipsychotic-induced weight gain: A systematic review and network meta-analysis. *Frontiers in Pharmacology* 28: 1393.

18. de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R (2016): Metformin in prevention and treatment of antipsychotic induced weight gain: A systematic review and meta-analysis. *BMC Psychiatry* 16: doi: 10.1186/s12888-016-1049-5.
19. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
20. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
21. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*