TECHNICAL COMMENTARY

Cardiometabolic and weight changes

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Introduction

Patient populations that are prescribed antipsychotic agents may experience cardio and metabolic side effects. Effects of antipsychotics on the cardiometabolic system may include changes in weight, heart rate, impulse conduction, cardiac rhythm, myocardial contractility, blood pressure, glucose, cholesterol, and triglyceride levels. These changes increase the risk of type 2 diabetes mellitus and cardiovascular diseases.

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, which 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 25 systematic reviews that met inclusion criteria[3-27].

Medicated patients vs. population or healthy controls

- Moderate to high quality evidence suggests a large effect of reduced heart rate variability in people with a schizophrenia spectrum disorder, with no significant effect of medications, apart from clozapine and tricyclic antidepressants.
- Moderate quality evidence suggests a small effect of increased hypertension in people with multi-episode schizophrenia compared to population controls.

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- Moderate quality evidence suggests a medium-sized increased risk of low HDL cholesterol, hypertriglyceridemia, diabetes (small effect), metabolic syndrome and abdominal obesity (large effect) in people with multi-episode schizophrenia compared to population controls.
- Moderate quality evidence suggests first-episode and drug naïve patients may show increased hypertension, but not other cardiometabolic indices, when compared to population controls. After treatment with antipsychotic medications, patients showed increased weight gain in the short and long-term, and increased insulin levels, insulin resistance, cholesterol, triglyceride, leptin, and blood pressure levels in the long-term.

Medicated patients vs. unmedicated patients

- Moderate quality evidence suggests increased rates of diabetes, metabolic syndrome, high triglycerides, low HDL, hyperglycaemia >100 mg/dl and myocardial infaction in medicated patients compared to people in their first-episode of psychosis or unmedicated patients with an established disorder. There was also increased prevalence of high blood pressure in first-episode patients compared to unmedicated patients, and increased waist size in unmedicated patients compared to first-episode patients.
- Moderate quality evidence suggests antipsychotics are associated with increased in body mass index in patients who were antipsychotic naïve pre-treatment.

Any antipsychotic vs. placebo

- High quality evidence shows small effects of increased QTc prolongation with haloperidol, quetiapine, olanzapine, risperidone, and iloperidone compared to placebo. Medium effects were reported with ziprasidone and amisulpride, and a large effect with sertindole. No differences were reported between placebo and lurasidone, aripiprazole, paliperidone, and asenapine.
- High quality evidence shows small effects of more weight gain with aripiprazole, amisulpride, asenapine, and paliperidone compared to placebo. Medium-sized effects were reported with risperidone, quetiapine, sertindole, chlopromazine, iloperidone, clozapine, zotepine, and olanzapine. Moderate quality evidence suggests a small effect with brexpiprazole and lurasidone.
- Moderate quality evidence finds clozapine resulted in the most weight, cholesterol, triglycerides, and glucose increases. Olanzapine resulted in the most BMI increases, and also increases in weight, cholesterol, and triglycerides. Quetiapine increased weight, cholesterol, and triglycerides. Zotepine increased weight, triglycerides, and glucose.
- In children and adolescents with schizophrenia, high quality evidence suggests a medium-sized effect of more weight gain with risperidone than placebo. Moderate to high quality evidence suggests large effects with olanzapine and quetiapine, medium effects with paliperidone, asenapine, and aripiprazole, and no differences between placebo and ziprasidone.

First-generation vs. second-generation antipsychotics

- Moderate quality evidence suggests second-generation clozapine, olanzapine, risperidone, or quetiapine may be associated with a small increased risk of diabetes mellitus when compared to any first-generation antipsychotic.
- Moderate quality evidence suggests more total cholesterol increase with second-generation olanzapine than first-generation haloperidol, and more triglyceride increase with second-generation amisulpride than haloperidol.
- Moderate quality evidence suggests second-generation amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine may be associated with more weight gain than first-generation

haloperidol, but there may be no differences when compared to low-potency first-generation antipsychotics.

Second-generation vs. second-generation antipsychotics

- Moderate quality evidence suggests shorter Bazett's corrected QT interval in patients taking aripiprazole than in patients taking risperidone (favouring aripiprazole). Moderate to low quality evidence suggests shorter Bazett's corrected QT interval in patients taking risperidone than in patients taking sertindole.
- Moderate quality evidence suggests olanzapine produced more weight gain and glucose increase than amisulpride, aripiprazole, quetiapine, risperidone, lurasidone and ziprasidone. Clozapine produced more weight gain than risperidone, risperidone produced more weight gain than amisulpride, and sertindole produced more weight gain than risperidone. Olanzapine produced more cholesterol increase than aripiprazole, risperidone and ziprasidone. Quetiapine produced more cholesterol increase than risperidone and ziprasidone.

Schizophrenia vs. affective disorders

- Moderate quality evidence suggests patients with schizophrenia treated with olanzapine may show more weight gain than patients with bipolar disorder treated with olanzapine, with no differences in cholesterol or blood glucose levels.
- Moderate quality evidence suggests patients with schizophrenia treated with quetiapine may show more cholesterol increase than patients with affective disorder treated with quetiapine, with no differences in blood glucose, triglyceride levels or weight gain.

Alawami M, Wasywich C, Cicovic A, Kenedi C

A systematic review of clozapine induced cardiomyopathy

International Journal of Cardiology 2014; 176: 315-320

View review abstract online

Comparison	**Incidence of cardiomyopathy in people who are taking the antipsychotic clozapine.**
Summary of evidence	**Low quality evidence (small sample, unable to assess precision, appears inconsistent, direct) is uncertain of the incidence of cardiomyopathy in people taking clozapine.**
Cardiomyopathy	
17 studies (N = 26) The mean age at time of cardiomyopathy diagnosis was 33.5 years, and the mean dose of clozapine on presentation was 360mg. Symptoms of cardiomyopathy developed at an average of 14.4 months after initiating clozapine. The clinical presentation was generally consistent with heart failure, including shortness of breath (60%) and palpitations (36%). Echocardiography at presentation showed dilated cardiomyopathy in 39% of cases and was not specified in other cases.	
Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, no measure of precision is reported.
Directness of results‖	Direct

Alvares GA, Quintana DS, Hickie IB, Guastella AJ

Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis

Journal of Psychiatry and Neuroscience 2016; 41(2): 89-104

View review abstract online

Comparison	**Heart rate variability (low variability represents unhealthy autonomic nervous system output) in people with a**

	schizophrenia spectrum disorder vs. controls.
Summary of evidence	**Moderate to high quality evidence (unable to assess consistency, precise, direct, large samples) suggests a large effect of reduced heart rate variability in people with a schizophrenia spectrum disorder, with no significant effect of medications, apart from clozapine and tricyclic antidepressants.**
Heart rate variability	
A large, significant effect of reduced heart rate variability in people with a schizophrenia spectrum disorder compared to controls, with similar effect sizes in medicated and non-medicated patients; All patients: 41 studies, N = 3,373, g = -0.952, 95%CI -1.105 to -0.800, $p < 0.001$ Non-medicated patients: 19 studies, N = 1,799, g = -0.901, 95%CI -1.210 to -0.592, $p < 0.05$ Medicated patients: 21 studies, N = 1,532, g = -1.058, 95%CI -1.353 to -0.763, $p < 0.05$ Assessment of individual antipsychotics indicated clozapine had a significant detrimental effect on heart rate variability (g = -0.643, $p < 0.001$), but not amisulpride, olanzapine or sertindole. Assessment of individual antidepressants indicated tricyclic antidepressants had a significant detrimental effect on heart rate variability (g = -0.454, $p < 0.01$), but not selective serotonin reuptake inhibitors or serotonin−norepinephrine reuptake inhibitors. Many people with a schizophrenia spectrum disorder also had a mood disorder. Authors report possible publication bias.	
Consistency in results	No measure of consistency is reported for the analysis on schizophrenia spectrum disorders.
Precision in results	Precise
Directness of results	Direct

Bak M, Fransen A, Janssen J, van Os J, Drukker M

Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis

PLoS ONE 2014; 9(4): e94112. doi: 10. 1371/journal.pone.0094112

View review abstract online

Comparison	**Weight changes with antipsychotic use.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, mostly inconsistent, direct) suggests chlorpromazine, clozapine, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine,**

	and risperidone are associated with increases in weight for over 38 weeks. No significant weight changes were found with amisulpride, aripiprazole, asenapine, melperone, sertindole, ziprasidone, or placebo.
Weight change **Data are reported for the largest samples**	
Significant increase in weight from baseline with; Chlorpromazine > 38 weeks: 1 study, N = 169, ES = 1.91, 95%CI 1.20 to 2.62, $p < 0.05$ Clozapine > 38 weeks: 7 studies, N = 553, ES = 7.34, 95%CI 4.48 to 10.19, $p < 0.05$, I^2 98.6%, $p < 0.001$ First-generation antipsychotics combined > 38 weeks: 5 studies, N = 359, ES = 4.86, 95%CI 3.62 to 6.10, $p < 0.05$, I^2 71.9%, $p = 0.007$ Haloperidol > 38 weeks: 14 studies, N = 1104, ES = 3.93, 95%CI 1.39 to 4.47, $p < 0.05$, I^2 91.9%, $p < 0.001$ Olanzapine > 38 weeks: 27 studies, N = 2974, ES = 4.62, 95%CI 3.27 to 5.98, $p < 0.05$, I^2 98.8%, $p < 0.001$ Paliperidone > 38 weeks: 2 studies, N = 895, ES = 0.99, 95%CI 0.67 to 1.31, $p < 0.05$, I^2 0%, $p = 0.54$ Perphenazine > 38 weeks: 2 studie2, N = 17, ES = 1.60, 95%CI 0.10 to 3.10, $p < 0.05$, I^2 0%, $p = 0.47$ Quetiapine > 38 weeks: 6 studies, N = 923, ES = 1.55, 95%CI 0.48 to 2.62, $p < 0.05$, I^2 89.1%, $p < 0.001$ Risperidone > 38 weeks: 26 studies, N = 4382, ES = 2.57, 95%CI 1.98 to 3.10, $p < 0.05$, I^2 91.8%, $p < 0.001$ Second-generation antipsychotics combined > 38 weeks: 1 study, N = 1085, ES = 11.50, 95%CI 9.37 to 13.63 *There was no significant weight change with amisulpride, aripiprazole, asenapine, melperone, sertindole, ziprasidone, or placebo*	
Consistency in results	Inconsistent, apart from paliperidone and perphenazine
Precision in results	Imprecise
Directness of results	Direct

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Chung AKK, Chua S

Effects on prolongation of Bazett's corrected QT interval of seven second-generation antipsychotics in the treatment of schizophrenia: a meta-analysis

Journal of Psychopharmacology 2010; 25(5): 646-666

View review abstract online

Comparison	**Mean change in Bazett's corrected QT interval (QTBc).** **Lengthening of the QTBc has been implicated in cardiac disease. The QT interval represents the time between the Q wave and the T wave in the heart's electrical cycle.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, direct) suggests risperidone lengthened the QTBc interval compared to aripiprazole.** **Moderate to low quality evidence (1 medium-sized RCT) suggests shorter mean QTBc in risperidone vs. sertindole. No other differences in mean QTBc were reported between various other antipsychotics.**

Bazett's corrected QT interval (QTBc)

Mean QT interval at last assessment

Significantly shorter mean QTBc in people receiving risperidone vs. sertindole, favouring risperidone;

1 RCT, N = 174, MD = -18.60, 96%CI -26.94 to -10.26, $p < 0.0001$

No difference between risperidone and haloperidol;

3 RCTs, N = 1,079, MD = 1.93, 95% CI -2.22 to 6.08, $p = 0.36$, $I^2 = 0\%$, $p = 0.80$

Mean QT interval change from baseline

Significantly shorter change in QTBc in people receiving aripiprazole vs. risperidone, favouring aripiprazole;

2 RCTs, N = 283, MD = -7.34, 96%CI -13.85 to -0.83, $p = 0.03$, $I^2 = 0\%$, $p = 0.82$

No significant differences in change in QT interval between;

Risperidone and olanzapine: 2 RCTs, N = 716, MD = -0.20, 95% CI -4.30 to 3.90, $p = 0.92$, $I^2 = 82\%$, $p = 0.02$

Olanzapine and haloperidol: 1 RCTs, N = 111, MD = -1.59, 95% CI -11.28 to 8.10, $p = 0.75$

Olanzapine and placebo: 1 RCT, N = 109, MD = 4.09, 95% CI -4.08 to 12.26, p = 0.33 Aripiprazole and placebo: 1 RCT, N = 204, MD = 1.49, 95% CI -4.41 to 7.39, p = 0.62 Ziprasidone and clozapine: 1 RCT, N = 147, MD = 0.68, 95% CI -1.52 to 2.87, p = 0.16 Olanzapine and aripiprazole combined vs. placebo: 2 RCTs, N = 313, MD = 2.38 95% CI -2.40 to 7.17, p = 0.33, I^2 = 0%, p = 0.61 Olanzapine and risperidone combined vs. first-generation antipsychotics: 3 RCTs, N = 1,159, MD = 2.24, 95% CI -1.41 to 5.89, p = 0.23, I^2 = 2%, p = 0.36 Olanzapine and aripiprazole combined vs. risperidone: 4 RCTs, N = 999, MD = -2.23, 95% CI -5.70 to 1.24, p = 0.21, I^2 = 67%, p = 0.03	
Consistency in results	Mostly consistent
Precision in results	Imprecise
Directness of results	Direct

De Hert M, Yu W, Detraux J, Sweers K, van Winkel R, Correll CU

Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis

CNS Drugs 2012; 26(9): 733-759

View review abstract online

Comparison	**Weight gain and cardiometabolic factors associated with second-generation asenapine, iloperidone, lurasidone, or paliperidone vs. placebo.** **Note: a few studies included patients with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, consistent, direct) suggests asenapine, iloperidone, paliperidone and lurasidone increase weight more than placebo.** **Low quality evidence (unable to assess consistency or precision, differences are not clinically significant) is unable to determine changes in cholesterol, triglycerides and glucose.**
Weight increase ≥ 7% from baseline	
Asenapine, iloperidone and paliperidone showed a significant, medium sized effect of more weight	

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increase ≥ 7% from baseline vs. placebo; Asenapine ≤ 12 weeks: 5 RCTs, N = 1,280, RR = 4.09, 95%CI 2.25 to 7.43, $p < 0.05$, I^2 0%, $p = 0.86$ Asenapine 13-52 weeks: 3 RCTs, N = 502, RR = 2.05, 95%CI 1.21 to 3.46, $p < 0.05$, I^2 0%, $p = 0.47$ Iloperidone ≤ 12 weeks: 4 RCTs, N = 1,727, RR = 3.13, 95%CI 2.08 to 4.70, $p < 0.05$, I^2 not reported Paliperidone ≤ 12 weeks: 12 RCTs, N = 3,773, RR = 2.17, 95%CI 1.64 to 2.86, $p < 0.05$, I^2 0%, $p = 0.90$ Paliperidone 13-52 weeks: 2 RCTs, N = 775, RR = 1.76, 95%CI 1.06 to 2.90, $p < 0.05$, I^2 0%, $p = 0.85$ *No significant differences were reported between lurasidone and placebo;* Lurasidone ≤ 12 weeks: 6 RCTs, N = 1,707, RR = 1.42, 95%CI 0.87 to 2.29, $p > 0.05$, I^2 0%, $p = 0.92$
Total, high-density (HDL) and low-density (LDL) cholesterol
Asenapine showed a significant increase in total cholesterol to over 12 weeks; 1 RCT, N = 194, WMD 6.53mg/dL, 95%CI 1.17 to 11.89, $p < 0.05$ *Iloperidone showed showed a significant increase in total cholesterol, LDL and HDL cholesterol to 12 weeks;* Total cholesterol: 1 RCT, N = 300, WMD 11.60mg/dL, 95%CI 4.98 to 18.22, $p < 0.001$ LDL cholesterol: 1 RCT, N = 300, WMD 10.30mg/dL, 95%CI 4.94 to 15.66, $p < 0.001$ HDL cholesterol: 1 RCT, N = 300, WMD 3.6mg/dL, 95%CI 1.58 to 5.62, $p < 0.001$ *Lurasidone showed more increased HDL cholesterol to 12 weeks;* HDL cholesterol: 5 RCTs, N = 1,004, WMD 1.50mg/dL, 95%CI 0.56 to 2.44, $p < 0.05$ Authors state results were not clinically significant
Glucose
Asenapine showed a significant decrease in glucose levels to 12 weeks; 2 RCTs, N = 379, WMD -3.95mg/dL, 95%CI -7.37 to -0.53, $p < 0.05$ *Iloperidone showed a significant increase in glucose levels from baseline;* 1 RCT, N = 300, WMD 6.90mg/dL, 95%CI 2.48 to 11.32, $p < 0.01$ *Paliperidone showed a significant increase in glucose levels from baseline to > 12 weeks;* 6 RCTs, N = 1,022, WMD 3.39mg/dL, 95%CI 0.42 to 6.36, $p < 0.05$ Authors state results were not clinically significant

Triglycerides	
Paliperidone showed a significant decrease in triglyceride levels from baseline to > 12 weeks; 4 RCTs, N = 791, WMD -0.20mg/dL, 95%CI -0.40 to -0.01, $p < 0.05$ Authors state results were not clinically significant	
Consistency in results	Consistent for weight gain, I^2 not reported for cholesterol, triglycerides or glucose levels.
Precision in results	Imprecise for weight gain.
Directness of results	Direct

Foley DL, Morley KI

Systematic Review of Early Cardiometabolic Outcomes of the First Treated Episode of Psychosis

Archives of General Psychiatry 2011; 68(6): 609-616

View review abstract online

Comparison	**Weight gain and cardiometabolic factors associated with antipsychotic medication in people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, direct, unable to assess consistency or precision) suggests that untreated people with first episode psychosis show no differences in cardiometabolic indices when compared to controls. After treatment with antipsychotic medications, patients showed increased weight gain in the short and long-term, and increased insulin levels, insulin resistance, total and LDL cholesterol, triglyceride, leptin, ghrelin and blood pressure levels in the long-term. There were no consistent differences reported between particular antipsychotic agents.**
Cardiometabolic indices at baseline (no or minimal exposure to antipsychotics)	
3 studies reported a higher waist to hip ratio and 1 study reported more intra-abdominal fat relative to BMI than controls. 2 studies reported higher prevalence of prediabetes than controls, and 1 study found increased rates of diabetes.	

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2 studies found no difference in rates of triglycerides, cholesterol, insulin, adiponectin, leptin, or interleukin 6.

Cardiometabolic indices after exposure to antipsychotics

By 1 to 2 months

The average weight gain reported in 3 studies after 6 to 8 weeks of taking olanzapine was 5 to 6 kg, while 1 study reported the average weight gained while taking risperidone was 4 kg, and haloperidol, 3 kg. 1 study reported a significant increase in fasting and postprandial blood glucose levels, and in the incidence of diabetes after 6 weeks. 1 study reported a significant increase at 8 weeks in insulin levels, insulin resistance, glucose, cholesterol, triglyceride, and C peptide levels following treatment with clozapine, olanzapine, risperidone, and/or sulpiride.

By 3 to 4 months

4 studies reported that weight gain in those taking olanzapine (7-9 kg) or risperidone (5-6kg) were associated with significantly more weight gain than those taking haloperidol (3-4 kg). A significant increase in cholesterol and fasting insulin levels after olanzapine was reported in 1 of 2 studies. No increases were reported for fasting triglyceride, glucose, or leptin levels, but there was a significant increase in percentage of body fat and waist to hip ratio, and C peptide levels while taking olanzapine.

By 12 months

3 studies reported an average 11 to 17 kg weight gain with olanzapine, 1 study reported 10 kg increases with amisulpride, clozapine or quetiapine fumarate. 2 studies reported 8 to 9 kg weight increases with risperidone, 3 studies reported 4-11 kg with haloperidol, 1 study reported 6kg weight increases with chlorpromazine, 5 kg increases with ziprasidone hydrochloride, and 1kg increases with perphenazine.

3 studies reported significant increases in insulin levels, insulin resistance, and total and LDL cholesterol, triglyceride, leptin, and ghrelin levels. 1 study reported an elevation in fasting glucose levels, but this was not reported in 2 studies. 1 study reported that weight gain significantly correlated with insulin and leptin levels. No differences in effect were found between haloperidol, olanzapine, risperidone, amisulpride, quetiapine, or ziprasidone.

However, at 12 months, 1 study reported that olanzapine and quetiapine were associated with a greater elevation in triglyceride levels and systolic blood pressure than risperidone; olanzapine was associated with a greater elevation in diastolic blood pressure than risperidone; quetiapine was associated with a greater elevation in cholesterol levels than risperidone; and olanzapine was associated with a greater reduction in HDL cholesterol levels than quetiapine or risperidone.

By 2 years

1 study reported an average 7 kg weight gain with risperidone, 2 studies reported 6kg weight increases with haloperidol.

1 study reported that orally disintegrating tablets of olanzapine or adjunctive reboxetine were associated with significantly less weight gain than standard tablets.

Baseline predictors of post-treatment cardiometabolic outcomes:

Weight gain after antipsychotic treatment was associated with lower pre-treatment BMI (3 studies), younger age (2 studies), and 1 study reported triglyceride levels, more negative symptoms, and more co-medications including antidepressants.	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Gao K, Fang F, Wang Z, Calabrese JR

Subjective Versus Objective Weight Gain During Acute Treatment With Second-Generation Antipsychotics in Schizophrenia and Bipolar Disorder

Journal of Clinical Psychopharmacology. 2016; 36(6): 637-42

View review abstract online

Comparison	**Subjective (self-report) vs. objective assessments of weight gain in people with schizophrenia on antipsychotics vs. placebo.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests subjectively-rated weight gain was lower than objectively-rated weight gain on people with schizophrenia on antipsychotic medication.**
Weight gain	
17 RCTs, N = 10,230 NNH (the number of patients needed to be treated with antipsychotics) for a 7% or greater weight gain, measured objectively = 5 to 62. NNH for subjectively measured weight gain = 11 to -224. For objectively measured weight gain, aripiprazole, iloperidone, olanzapine, paliperidone, quetiapine immediate release, and risperidone had a significantly higher number of patients with 7% or greater weight gain relative to placebo, with iloperidone having the smallest NNH and paliperidone having the largest NNH. For self-reported weight gain, iloperidone, olanzapine, and risperidone had a significantly higher number of patients with self-reported weight gain relative to placebo.	
Consistency in results	Unable to assess; no measure of consistence is reported.

Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Goetz RL, Miller BJ

Meta-analysis of ghrelin alterations in schizophrenia: Effects of olanzapine

Schizophrenia Research 2019; 206: 21-6

View review abstract online

Comparison	**Ghrelin alterations in people with schizophrenia before and after 12 weeks of olanzapine treatment.**
Summary of evidence	**Moderate quality evidence (small sample, inconsistent, precise, direct) finds a medium-sized effect of decreased blood ghrelin levels after 12 weeks of treatment with olanzapine.**
Ghrelin	
A significant, medium-sized decrease in blood ghrelin levels post-treatment; 6 studies, N = 111, SMD = -0.48, 95%CI -0.88 to -0.08, p = 0.018, I^2 = 53%, $p < 0.05$ Age, sex, baseline BMI, geography, olanzapine dose and duration, year of publication, study quality, inpatient status, and antipsychotic washout did not moderate this association. Authors report that decreased ghrelin is a paradoxical phenomenon known to occur in obesity.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Lancet 2009; 373: 31-41

View review abstract online

Comparison	**Weight gain with first-generation vs. second-generation antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precision, direct) suggests amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine may be associated with more weight gain than haloperidol, but there may be no differences when compared to low-potency first-generation antipsychotics.**
Weight gain	
Amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine were associated with significantly more weight gain than was haloperidol; Amisulpride: 2 RCTs, N = 373, MD 0.9, 95%CI 0.2 to 1.6, $p = 0.012$ Clozapine: 3 RCTs, N = 170, MD 3.4, 95%CI 2.0 to 4.9, $p < 0.0001$ Olanzapine: 9 RCTs, N = 2952, MD 3.3, 95%CI 2.2 to 4.4, $p < 0.0001$ Quetiapine: 3 RCTs, N = 945, MD 1.4, 95%CI 0.7 to 2.1, $p < 0.0001$ Risperidone: 9 RCTs, N = 1,366, MD 1.7, 95%CI 0.9 to 2.4, $p < 0.0001$ Sertindole: 2 RCTs, N = 779, MD 3.3, 95%CI 0.2 to 6.4, $p = 0.040$ Zotepine: 3 RCTs, N = 321, MD 2.7, 95%CI 1.7 to 3.7, $p < 0.0001$ No differences in weight gain were reported compared to low-potency first-generation antipsychotics.	
Consistency in results	Authors report considerable heterogeneity in some analyses
Precision in results	Appears precise
Directness of results	Direct

Leucht S, Cipriani A, Loukia S, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Lancet 2013; 382: 951-962

View review abstract online

Comparison	**Weight gain and QTc prolongation with all antipsychotics vs. placebo for ~ 6 weeks.** **Studies on patients with predominant negative symptoms, concomitant medical illness, treatment resistance, and stable illness were excluded.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows small effects of increased QTc prolongation for haloperidol, quetiapine, olanzapine, risperidone, and iloperidone compared to placebo. Medium effects were reported for ziprasidone and amisulpride, and a large effect for sertindole. No differences were reported for lurasidone, aripiprazole, paliperidone, and asenapine.** **High quality evidence shows small effects of more weight gain for aripiprazole, amisulpride, asenapine, and paliperidone compared to placebo. Medium size effects were reported for risperidone, quetiapine, sertindole, chlopromazine, iloperidone, clozapine, zotepine, and olanzapine. No differences were reported for haloperidol, ziprasidone, and lurasidone.**
QTc prolongation	
Overall, this review includes 212 RCTs, with 43,049 participants. *Significant, small effects of increased QTc prolongation were reported for;* Haloperidol: g = 0.11, 95%CrI, 0.03 to 0.19, $p < 0.05$ Quetiapine: g = 0.17, 95%CrI, 0.06 to 0.29, $p < 0.05$ Olanzapine: g = 0.22, 95%CrI, 0.11 to 0.31, $p < 0.05$ Risperidone: g = 0.25, 95%CrI, 0.15 to 0.36, $p < 0.05$ Iloperidone: g = 0.34, 95%CrI, 0.22 to 0.46, $p < 0.05$ *Significant, medium effects of increased QTc prolongation were reported for;* Ziprasidone: g = 0.41, 95%CrI, 0.31 to 0.51, $p < 0.05$ Amisulpride: g = 0.66, 95%CrI, 0.39 to 0.91, $p < 0.05$ *A significant, large effect of increased QTc prolongation were reported for;* Sertindole: g = 0.90, 95%CrI, 0.76 to 1.02, $p < 0.05$ No significant differences were reported for lurasidone, aripiprazole, paliperidone, and asenapine compared to placebo.	
Weight gain	

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Significant, small effects of more weight gain compared to placebo were reported for; Aripiprazole: g = 0.17, 95%CrI, 0.05 to 0.28, $p < 0.05$ Amisulpride: g = 0.20, 95%CrI, 0.05 to 0.35, $p < 0.05$ Asenapine: g = 0.23, 95%CrI, 0.07 to 0.39, $p < 0.05$ Paliperidone: g = 0.38, 95%CrI, 0.27 to 0.48, $p < 0.05$ *Significant, medium effects of more weight gain compared to placebo were reported for;* Risperidone: g = 0.42, 95%CrI, 0.33 to 0.50, $p < 0.05$ Quetiapine: g = 0.43, 95%CrI, 0.34 to 0.53, $p < 0.05$ Sertindole: g = 0.53, 95%CrI, 0.38 to 0.68, $p < 0.05$ Chlopromazine: g = 0.55, 95%CrI, 0.34 to 0.76, $p < 0.05$ Iloperidone: g = 0.62, 95%CrI, 0.49 to 0.74, $p < 0.05$ Clozapine: g = 0.65, 95%CrI, 0.31 to 0.99, $p < 0.05$ Zotepine: g = 0.71, 95%CrI, 0.47 to 0.96, $p < 0.05$ Olanzapine: g = 0.74, 95%CrI, 0.67 to 0.81, $p < 0.05$ No significant differences between placebo and haloperidol, ziprasidone, or lurasidone.

Consistency in results	Authors report disagreement between direct and indirect estimates (a measure of consistency) was identified in only very few cases; 1/62 for weight gain; 2/35 for QTc prolongation.
Precision in results	Precise
Directness of results	Direct and indirect comparisons, with no consistent differences in results across these comparisons

Mitchell AJ, Vancampfort D, De Hert A, Yu W, van Winkel R, Yu W, De Hert M

Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients

Schizophrenia Bulletin 2013; 39(2): 295-305

View review abstract online

Comparison	**Weight gain and cardiometabolic factors associated in treated, untreated and first-episode patients.**

Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests increased rates of diabetes, metabolic syndrome, high triglycerides, low HDL, and hyperglycaemia > 100 mg/dl in medicated patients compared to people in their first-episode of psychosis, and compared to unmedicated patients with an established disorder. There was also increased prevalence of high blood pressure in first-episode patients compared to unmedicated patients, and increased waist size in unmedicated patients compared to first-episode patients.**
Metabolic syndrome	
Significantly higher prevalence of metabolic syndrome was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients ($p < 0.0001$). No differences were reported between the latter two groups ($p = 0.9755$); Medicated established patients: 78 studies, N = 24,892, 35.3%, 95%CI 32.8% to 37.8% First-episode patients: 14 studies, N = 1,104, 9.9% 95%CI 6.1% to 14.5% Unmedicated patients: 11 studies, N = 702, 9.8%, 95%CI 5.3% to 15.6%	
Waist size in males > 102cm, females > 88cm	
Significantly higher prevalence of increased waist size was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients ($p < 0.0001$). Significantly higher prevalence of increased waist size was reported in unmedicated patients compared to first-episode patients ($p < 0.0072$); Medicated established patients: 58 studies, N = 17,474, 52.7%, 95%CI 48.9% to 56.5% First-episode patients: 17 studies, N = 2,127, 22.0%, 95%CI 15.6% to 29.1% Unmedicated patients: 10 studies, N = 837, 26.6%, 95%CI 15.9% to 38.9%	
Blood pressure > 130/85	
Significantly higher prevalence of high blood pressure was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients ($p < 0.0001$). Significantly higher prevalence of high blood pressure was reported in first-episode patients compared to unmedicated patients ($p < 0.0154$); Medicated established patients: 64 studies, N = 18,202, 39.7%, 95%CI 36.4% to 43.1% First-episode patients: 11 studies, N = 979, 30.4% 95%CI 21.3% to 40.3% Unmedicated patients: 7 studies, N = 454, 24.3%, 95%CI 11.2% to 40.5%	
Triglycerides > 150 mg/dl	
Significantly higher prevalence of high triglycerides was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients ($p <$	

0.0001). No differences were reported between the latter two groups (p = 0.1063); Medicated established patients: 69 studies, N = 19,388, 41.4%, 95%CI 36.5% to 45.7% First-episode patients: 17 studies, N = 1,950, 19.6% 95%CI 13.1% to 27.0% Unmedicated patients: 9 studies, N = 730, 16.9%, 95%CI 7.6% to 29.0%
HDL in males < 40 mg/dl, females < 50 mg/dl
Significantly higher prevalence of low HDL was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.4043); Medicated established patients: 68 studies, N = 18,837, 44.7%, 95%CI 41.2% to 48.2% First-episode patients: 16 studies, N = 1,950, 21.9% 95%CI 15.6% to 28.9% Unmedicated patients: 9 studies, N = 730, 20.4%, 95%CI 9.8% to 33.7%
Hyperglycaemia > 110 mg/dl
Significantly higher prevalence of hyperglycaemia (> 110 mg/dl) was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients (p < 0.0001); Medicated established patients: 41 studies, N = 13,214, 18.1%, 95%CI 15.5% to 20.7% First-episode patients: 5 studies, N = 240, 6.9% 95%CI 5.0% to 19.9%
Hyperglycaemia >100 mg/dl
Significantly higher prevalence of hyperglycaemia (> 100 mg/dl) was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.162); Medicated established patients: 26 studies, N = 6,798, 27.8%, 95%CI 23.0% to 32.9% First-episode patients: 7 studies, N = 788, 8.7% 95%CI 5.2% to 12.9% Unmedicated patients: 3 studies, N = 390, 6.4%, 95%CI 2.2% to 12.7%
Diabetes
Significantly higher prevalence of diabetes was reported in medicated patients who were not in their first episode of psychosis, compared to first-episode patients and unmedicated patients (p < 0.0001). No differences were reported between the latter two groups (p = 0.31); Medicated established patients: 12 studies, N = 2,098, 12.8%, 95%CI 8.44% to 17.9% First-episode patients: 9 studies, N = 8,075, 1.3% 95%CI 0.4% to 2.4% Unmedicated patients: 4 studies, N = 7,618, 2.1%, 95%CI 0.5% to 4.8%

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness in results	Direct

Moteshafi H, Stip E

Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: a meta-analysis

Expert Opinion on Drug Safety 2012; 11(5): 713-732

View review abstract online

Comparison	**Weight gain and cardiometabolic factors in people with schizophrenia vs. affective disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests patients with schizophrenia treated with quetiapine may show significantly higher total and LDL cholesterol than patients with affective disorder treated with quetiapine, with no differences in blood glucose, triglyceride levels or weight gain. No differences between groups on aripiprazole for any measure.**
Cholesterol, triglycerides, blood glucose levels and weight gain	
Quetiapine increased total and LDL cholesterol levels in the schizophrenia group, while reducing total and LDL cholesterol levels in the affective disorder group; this difference was significant (p = 0.000); Schizophrenia: 4 studies, N = 1,473, mean change total cholesterol = 8.053, LDL = 5.008 Affective disorder: 7 studies, N = 2,433, mean change total cholesterol = -2.765, LDL = -2.762 No differences were reported for aripiprazole, which decreased the levels of cholesterol in both groups. No differences were reported for triglyceride, blood glucose or weight gain.	
Consistency in results	Authors report inconsistency in results (I^2 > 50%).
Precision in results	Unable to assess (no CIs reported).
Directness of results	Direct

Moteshafi H, Zhornitsky S, Brunelle S, Stip E

Comparing Tolerability of Olanzapine in Schizophrenia and Affective disorders: a meta-analysis

Drug Safety 2012; 35(10): 819-836 View review abstract online	
Comparison	**Weight gain and cardiometabolic factors in people with schizophrenia vs. affective disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests patients with schizophrenia treated with olanzapine may show significantly more weight gain than patients with bipolar disorder treated with olanzapine, with no differences in cholesterol or blood glucose levels.**
Cholesterol, blood glucose and weight gain	
Affective disorder patients treated with olanzapine showed significantly less weight gain than schizophrenia patients treated with olanzapine (p = 0.020); Schizophrenia: 18 RCTs, N = 2,196, mean weight gain: 3.138 Bipolar disorder: 13 RCTs, N = 2,212, mean weight gain: 2.278 No differences in cholesterol and blood glucose levels.	
Consistency in results	Authors report inconsistency in results (I^2 > 50%).
Precision in results	Unable to assess (no CIs reported).
Directness of results	Direct

Ormerod S, McDowell SE, Coleman JJ, Ferner RE

Ethnic differences in the risks of adverse reactions to drugs used in the treatment of psychoses and depression: a systematic review and meta-analysis.

Drug Safety 2008; 31(7): 597-607 View review abstract online	
Comparison	**Cardiometabolic side effects in different ethnic groups.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) no differences in hyperglycemia and diabetes mellitus between Black and non-Black patients on antipsychotic**

	medications. **Low quality evidence (very imprecise) is unable to determine ethnic differences in cardiovascular mortality rates.**
Hyperglycemia	
No differences between Black and non-Black populations; 3 studies, RR 1.60, N = 375, 95%CI 0.95 to 2.05, $p = 0.08$, $I^2 = 0\%$, $p = 0.53$ Authors report that the studies were of medium quality.	
Diabetes Mellitus	
No differences between Black and non-Black populations. 3 studies, RR 1.35, N = 653, 95%CI 0.95 to 1.92, $p = 0.09$, $I^2 = 51.1\%$, $p = 0.13$ Authors report that the studies were of medium quality.	
Cardiovascular mortality	
Increased rates of cardiovascular mortality in Hispanic vs. White populations; Hispanic vs. White: 1 study, RR 11.30, N = 653, 95%CI 1.10 to 118.1, $p < 0.05$ *Differences were not significant in Black vs. White comparison;* Black vs. White: 1 study, OR 7.20, N = 653, 95%CI 0.70 to 69.9, $p > 0.05$	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU, Christensen R

Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56(3): 191-202

View review abstract online

Comparison 1	**Antipsychotics vs. placebo in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large sample) suggests a medium-sized effect of more increase in weight gain with risperidone than placebo in children and adolescents with schizophrenia. Moderate to high quality evidence (medium-sized samples) suggests large effects with olanzapine and quetiapine, medium effects with paliperidone, asenapine and aripiprazole, and no differences between placebo and ziprasidone.**
Weight gain	
Significant, large effects of increased weight were found for; Olanzapine: 1 RCT, N = 106, SMD = 1.32, 95%CI 0.88 to 1.77, $p < 0.00001$ Quetiapine: 1 RCT, N = 222, SMD = 0.80, 95%CI 0.51 to 1.09, $p < 0.00001$ *Significant, medium-sized effects of increased weight were found for;* Paliperidione: 1 RCT, N = 147, SMD = 0.57, 95%CI 0.23 to 0.92, $p = 0.001$ Asenapine: 1 RCT, N = 292, SMD = 0.44, 95%CI 0.20 to 0.69, $p = 0.0004$ Risperidone: 2 RCTs, N = 417, SMD = 0.43, 95%CI 0.23 to 0.62, $p < 0.0001$, $I^2 = 0\%$ Aripiprazole: 1 RCT, N = 290, SMD = 0.38, 95%CI 0.14 to 0.63, $p = 0.002$ *No difference in weight was found between placebo and;* Ziprasidone: 1 RCT, N = 186, SMD = -0.04, 95%CI -0.36 to 0.28, $p = 0.79$	
Consistency in results	Consistent where applicable (risperidone [>1 RCT]).
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Antipsychotics vs. antipsychotics in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (mostly unclear sample sizes, precise, indirect) suggests olanzapine and quetiapine are associated more increases in weight than other antipsychotics.**
Weight gain	
Olanzapine showed large effects of more weight gain than; Risperidone 2 RCTs, N = 96, SMD = -0.93, 95%CI -1.24 to -0.47, $p = 0.004$, $I^2 = 0\%$	

Molindone: 1 RCT, N = 75, SMD = -1.77, 95%CI -2.31 to -1.23, $p < 0.00001$ Quetiapine: unclear sample size, SMD = -1.23, 95%CI -1.79 to -0.68, $p < 0.05$ Paliperidone: unclear sample size, SMD = -1.07, 95%CI -1.61 to -0.53, $p < 0.05$ Asenapine: unclear sample size, SMD = 0.83, 95%CI 0.29 to 1.36, $p < 0.05$ Ziprasidone: unclear sample size SMD = 1.25, 95%CI 0.77 to 1.74, $p < 0.05$ Aripiprazole: unclear sample size, SMD = -0.94, 95%CI -1.37 to -0.52, $p < 0.05$ *Quetiapine showed medium-sized effects of more weight gain than;* Ziprasidone: unclear sample size, SMD = 0.89, 95%CI 0.46 to 1.32, $p < 0.05$ Aripiprazole: unclear sample size, SMD = -0.58, 95%CI -0.94 to -0.22, $p < 0.05$ Risperidone: unclear sample size, SMD = 0.44, 95%CI 0.08 to 0.79, $p < 0.05$ Asenapine: unclear sample size, SMD = -0.40, 95%CI -0.78 to -0.03, $p < 0.05$ *Paliperidone showed medium-sized effects of more weight gain than;* Aripiprazole: 1 RCT, N = 226, SMD = -0.50, 95%CI -0.76 to -0.23, $p = 0.0002$ Ziprasidone: unclear sample size, SMD = 0.73, 95%CI 0.33 to 1.14, $p < 0.05$ *Risperidone showed a medium-sized effect of more weight gain than;* Ziprasidone: unclear sample size, SMD = 0.46, 95%CI 0.08 to 0.83, $p < 0.05$ *Asenapine showed a medium-sized effect of more weight gain than;* Ziprasidone: unclear sample size, SMD = 0.49, 95%CI 0.09 to 0.89, $p < 0.05$	
Consistency in results	Consistent where applicable (risperidone [>1 RCT]).
Precision in results	Mostly precise
Directness of results	Direct for molindone vs. olanzapine, molindone vs. risperidone, risperidone vs. olanzapine, and aripiprazole vs. paliperidone. Indirect for all other comparisons.

Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, Beck K, Natesan S, Efthimiou O, Cipriani A, Howes OD

Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis

The Lancet Psychiatry 2020; 7: 64-77

View review abstract online	
Comparison	**Metabolic functioning in people with schizophrenia on 6 weeks of antipsychotic treatment vs. placebo controls.**
Summary of evidence	**Moderate quality evidence (large overall sample, some inconsistencies, unable to assess precision, direct) finds clozapine resulted in the most weight gain, cholesterol, triglycerides, and glucose increases. Olanzapine resulted in the most BMI increases, and also increased weight, cholesterol, and triglycerides. Quetiapine increased weight, BMI, cholesterol, and triglycerides. Zotepine increased weight, triglycerides, and glucose. Sertindole, risperidone, and paliperidone increased weight and BMI. Brexpiprazole, asenapine, and iloperidone increased weight, while lurasidone increased BMI.**
Metabolic factors	
100 RCTs, N = 25,952 *The following antipsychotics showed significantly greater increases in weight;* Brexpiprazole: 0.88 kg Asenapine: 1.17 kg Risperidone and Paliperidone: 1.28 kg Quetiapine: 1.56 kg Iloperidone: 1.77 kg Sertindole: 2.37 kg Olanzapine: 2.73 kg Zotepine: 2.80 kg Clozapine: 3.01 kg *The following antipsychotics showed significantly greater increases in BMI;* Lurasidone: 0.24 kg/m^2 Risperidone and Paliperidone: 0.56 kg/m^2 Quetiapine: 0.70 kg/m^2 Sertindole: 0.76 kg/m^2 Clozapine: 1.02 kg/m^2 Olanzapine: 1.07 kg/m^2 *The following antipsychotics showed significantly greater increases in total cholesterol;* Quetiapine: 0.31 mmol/L	

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Olanzapine: 0.40 mmol/L Clozapine: 0.56 mmol/L Non-white ethnicity was associated with greater increases in total cholesterol. *The following antipsychotics showed significantly greater increases in triglycerides;* Quetiapine: 0.32 mmol/L Olanzapine: 0.46 mmol/L Zotepine: 0.92 mmol/L Clozapine: 0.98 mmol/L *The following antipsychotics showed significantly greater increases in glucose;* Zotepine: 0.99 mmol/L Clozapine: 1.05 mmol/L Greater increases in glucose were predicted by higher baseline weight and male sex. Improvements in symptom severity were associated with increases in weight, BMI, and total cholesterol.	
Consistency in results	Some inconsistencies
Precision in results	Unable to assess; mean differences not standardised
Directness of results	Direct

Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Asenjo Lobos C, Kissling W, Davis JM, Leucht S

Head-to-head comparisons of metabolic side effects of second-generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2010; 123: 225-233

View review abstract online

Comparison	**Weight gain and cardiometabolic factors associated with second-generation vs. other second-generation antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent or unable to assess, imprecise, direct) suggests olanzapine produced more weight gain and glucose than amisulpride, aripiprazole, quetiapine, risperidone, and ziprasidone. Clozapine**

	produced more weight gain than risperidone, risperidone more than amisulpride, and sertindole more than risperidone. Olanzapine produced more cholesterol increase than aripiprazole, risperidone and ziprasidone. Quetiapine produced more cholesterol increase than risperidone and ziprasidone.
Weight gain	
Olanzapine produced more weight gain than; Amisulpride: 3 RCTs, N = 671, MD 2.11kg, 95%CI 1.29 to 2.94, $p < 0.0001$ Aripiprazole: 2 RCTs, N = 656, MD 3.9kg, 95%CI 1.62 to 6.19, $p = 0.0008$ Quetiapine: 7 RCTs, N = 1,173, MD 2.68kg, 95%CI 1.10 to 4.26, $p = 0.0009$ Risperidone: 16 RCTs, N = 2,302, MD 2.44kg, 95%CI 1.61 to 3.27, $p < 0.0001$ Ziprasidone: 5 RCTs, N = 1,659, MD 3.82kg, 95%CI 2.96 to 4.69, $p < 0.0001$ *Clozapine produced more weight gain than;* Risperidone: 4 RCTs, N = 459, MD 2.86kg, 95%CI 1.07 to 4.65, $p = 0.002$ *Risperidone produced more weight gain than;* Amisulpride: 3 RCTs, N = 585, MD 0.99kg, 95%CI 0.37 to 1.61, $p = 0.002$ *Sertindole more weight gain than;* Risperidone: 2 RCTs, N = 328, MD 0.99kg, 95%CI 0.12 to 1.86, $p = 0.03$ Meta-regressions suggest part of the heterogeneity was explained by longer study duration, higher dose of antipsychotics and study sponsorship being related to increased (study duration, dose) or decreased weight (study sponsorship by pharmaceutical company). No consistent relationships were reported for sex, washout period, or ethnicity.	
Cholesterol change	
Olanzapine produced more cholesterol increase than; Aripiprazole: 2 RCTs, N = 789, MD 15.35mg/dl, 95%CI 9.08 to 21.62, $p < 0.0001$ Risperidone: 9 RCTs, N = 1,802, MD 12.92mg/dl, 95%CI 8.22 to 17.62, $p < 0.0001$ Ziprasidone: 4 RCTs, N = 1,502, MD 15.83mg/dl, 95%CI 5.95 to 25.72, $p = 0.002$ *Quetiapine produced more cholesterol increase than;* Risperidone: 5 RCTs, N = 1,433, MD 8.61mg/dl, 95%CI 4.66 to 12.56, $p < 0.0001$ Ziprasidone: 2 RCTs, N = 754, MD 16.01mg/dl, 95%CI 8.57 to 23.46, $p < 0.0001$	
Glucose	

Olanzapine produced more glucose increase than; Amisulpride: 2 RCTs, N = 406, MD 7.3mg/dl, 95%CI 6.99 to 7.62, $p < 0.0001$ Aripiprazole: 3 RCTs, N = 1,487, MD 4.13mg/dl, 95%CI 1.68 to 6.58, $p = 0.0009$ Quetiapine: 4 RCTs, N = 986, MD 9.32mg/dl, 95%CI 0.82 to 17.82, $p = 0.03$ Risperidone: 9 RCTs, N = 1,303, MD 5.94mg/dl, 95%CI 2.59 to 9.3, $p = 0.0005$ Ziprasidone: 4 RCTs, N = 1,420, MD 8.25mg/dl, 95%CI 2.77 to 13.72, $p = 0.003$	
Consistency in results	Inconsistent for weight gain, consistency not reported for cholesterol or glucose.
Precision in results	Appears imprecise.
Directness of results	Direct

Shah P, Iwata Y, Caravaggio F, Plitman E, Brown EE, Kim J, Chan N, Hahn M, Remington G, Gerretsen P, Graff-Guerrero A

Alterations in body mass index and waist-to-hip ratio in never and minimally treated patients with psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; 208: 420-9

View review abstract online

Comparison	**BMI and waist-to-hip ratio in people with schizophrenia (mostly first-episode) who have never taken antipsychotics or who have less than < 2 weeks of lifetime use vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) suggests antipsychotic-naïve people with schizophrenia or those who have less than < 2 weeks of lifetime use show lower BMI, but higher waist-to-hip ratio, than people without schizophrenia.**
BMI and waist-to-hip ratio	

A small, significant effect showed BMI was lower in patients; 23 studies, N = 2,563, SMD = -0.19, 95%CI -0.34 to -0.05, $p = 0.009$, $I^2 = 65\%$ *A small, significant effect showed waist-to-hip ratio was elevated in patients;* 5 studies, N = 783, SMD = 0.34, 95%CI 0.14 to 0.55, $p = 0.001$, $I^2 = 36\%$ *There were no significant differences in waist circumference;* 9 studies, N = 963, SMD = -0.07, 95%CI -0.17 to 0.32, $p = 0.55$, $I^2 = 69\%$ These differences remained after analyses were restricted to patients matched with controls for age, sex, and ethnicity; to antipsychotic-naive patients; and to patients with schizophrenia-related diagnoses (some studies included people with bipolar disorder). Authors report that weight-to-hip ratio, a measure of abdominal body fat, is a better predictor of cardiovascular disease than BMI, which is a marker of overall body fat.

Consistency in results	Consistent for waist-to-hip ratio only.
Precision in results	Precise
Directness of results	Direct

Siskind D, Sidhu A, Cross J, Chua YT, Myles N, Cohen D, Kisely S

Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy

Australian and New Zealand Journal of Psychiatry 2020; 54(5): 467-481

View review abstract online

Comparison	**Rates of myocarditis and cardiomyopathy in people with schizophrenia taking clozapine.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests rates of myocarditis and cardiomyopathy are similar in people taking clozapine, with incidence between 0.6 and 0.7%.**
Myocarditis and cardiomyopathy	
Myocarditis: 24 studies, N = 256,635, 0.007 (incidence = 0.7%), 95%CI 0.003 to 0.016, $I^2 = 98\%$ Cardiomyopathy: 16 studies, N = 220,493, 0.006, (incidence = 0.6%), 95%CI 0.002 to 0.023, $I^2 = 98\%$	

Consistency in results	Inconsistent
Precision in results	Unable to assess (CIs not standardised).
Directness of results	Direct

Smith M, Hopkins D, Peveler RC, Holt RIG, Woodward M, Ismail K

First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis

The British Journal of Psychiatry 2008; 192: 406-411

View review abstract online

Comparison	**Risk of diabetes associated with first-generation vs. second-generation antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests clozapine, olanzapine, risperidone or quetiapine may be associated with a small increased risk of diabetes mellitus when compared to any first-generation antipsychotic.**
Diabetes mellitus	
11 observational studies (N ~87,000) with median duration of follow-up of 12 months, showed a small increased risk of diabetes mellius in patients prescribed second-generation antipsychotics clozapine, olanzapine, risperidone or quetiapine vs. any first-generation antipsychotic; All antipsychotics: 11 studies, RR 1.32, 95%CI 1.15 to 1.51, $p < 0.05$, $I^2 = 80\%$, $p < 0.001$ Risperidone: 6 studies, RR 1.16, 95%CI 0.99 to 1.35, $p = 0.05$, I^2 not reported Quetiapine: 3 studies, RR 1.28, 95%CI 1.14 to 1.45, $p < 0.05$, I^2 not reported Olanzapine: 8 studies, RR 1.28, 95%CI 1.12 to 1.45, $p < 0.05$, I^2 not reported Clozapine: 7 studies, RR 1.39, 95%CI 1.24 to 1.55, $p < 0.05$, I^2 not reported	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D

Weight gain in antipsychotic-naive patients: a review and meta-analysis

Psychological Medicine 2010; 40: 187-200

View review abstract online

Comparison	**Pre- vs. post-medication weight gain in antipsychotic naïve patients.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests antipsychotics are associated with increased in body mass index in patients who were antipsychotic naïve.**
Body Mass Index	
Antipsychotic use was associated with a significant BMI increase pre- to post-treatment; 9 studies, N = 1,378, WMD 1.97, 95%CI 1.81 to 2.12, $p < 0.00001$, $p < 0.00001$ Subgroup analyses revealed no substantial differences on the effect size excluding studies with adjunctive therapies, those with non-hospitalised patients, those with physical co-morbidity, and sponsored studies. Subgroup analyses of study duration showed a steady rise in BMI from 4 to 48 weeks.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Vancampfort D, Wampers M, Mitchell A, Correll CU, De Herdt A, Probst M, De Herdt M

A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls

World Psychiatry 2013; 12: 240-250

View review abstract online

Comparison	**Weight gain and cardiometabolic factors in people with schizophrenia spectrum disorder vs. population controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of increased hypertension in patients with multi-episode schizophrenia compared to population controls.** **Moderate to low quality evidence (imprecise) suggests a medium-sized, increased risk of low HDL cholesterol, hypertriglyceridemia, diabetes (small effect), metabolic syndrome and abdominal obesity (large effect) in medicated patients with multi-episode schizophrenia compared to population controls.**
Hypertension	
Overall prevalence of hypertension in people with schizophrenia is around 36%; 57 studies, N = 113,286, 36.3%, 95%CI 30.9% to 42.1%, Q = 12262.5, $p < 0.001$ Prevalence did not differ significantly between multi-episode patients (37.3%), first-episode patients (41.1%), and drug-naïve patients (31.6%). *Compared with matched general population controls (N = 732,965), multi-episode patients (N = 2,410) had a small, significant increased risk of hypertension;* 4 studies, OR 1.36, 95%CI 1.21 to 1.53, $p < 0.001$	
High-density lipoprotein (HDL) cholesterol	
Overall prevalence of low HDL cholesterol in people with schizophrenia is around 37.5%; 58 studies, N = 20,907, 37.5%, 95%CI 34.3% to 40.8%, Q = 1118.4, $p < 0.001$ Rates did not differ significantly between first-episode patients (16%) and drug-naïve patients (24.2%), however multi-episode patients had significantly increased prevalence (41.7%) compared to the other groups combined ($p < 0.001$). *Compared with matched general population controls (N = 6,016), multi-episode patients (N = 647) had a medium-sized, significant increased risk of low HDL cholesterol;* 4 studies, OR 2.35, 95%CI 1.78 to 3.10, $p < 0.001$	
Triglycerides	
Overall prevalence of hypertriglyceridemia in people with schizophrenia is around 34.5%; 58 studies, N = 20,996, 34.5%, 95%CI 30.7% to 38.5%, Q = 1641.2, $p < 0.001$ Rates did not differ significantly between first-episode patients (10.5%) and drug-naïve patients (23.3%), however multi-episode patients had significantly increased prevalence (39%) compared to	

the other groups combined ($p < 0.001$). *Compared with matched general population controls (N = 6,016), multi-episode patients (N = 647) had a medium-sized, significant increased risk of hypertriglyceridemia;* 4 studies, OR 2.73, 95%CI 1.95 to 3.83, $p < 0.001$
Diabetes
Overall prevalence of diabetes in people with schizophrenia is around 9%; 41 studies, N = 161,886, 9%, 95%CI 7.3% to 11.1%, Q = 3718.8, $p < 0.001$ Rates did not differ significantly between multi-episode patients (9.5%), first-episode patients (8.7%), and drug-naïve patients (6.4%). *Compared with matched general population controls (N = 3,891,899), multi-episode patients (N = 106,720) had a small to medium-sized, significant increased risk of diabetes;* 15 studies, OR 1.99, 95%CI 1.55 to 2.54, $p < 0.001$
Metabolic syndrome
Overall prevalence of metabolic syndrome in people with schizophrenia is around 31%; 117 studies, N = 28,729, 31.1%, 95%CI 28.9% to 33.4%, Q = 1470.4, $p < 0.001$ Rates did not differ significantly between first-episode patients (15.9%) and drug-naïve patients (10%), however multi-episode patients had significantly increased prevalence (34.2%) compared to the other groups combined ($p = 0.007$). *Compared with matched general population controls (N = 6,632), multi-episode patients (N = 868) had a medium-sized, significant increased risk of metabolic syndrome;* 4 studies, OR 2.35, 95%CI 1.68 to 3.29, $p < 0.001$
Abdominal obesity
117 studies, N = 28,729 Multi-episode patients had significantly increased prevalence (50%) compared to drug-naïve group (16.6%, $p < 0.001$). *Compared with matched general population controls (N = 6,632), multi-episode patients (N = 868) had a medium to large, significant increased risk of abdominal obesity;* 5 studies, OR 4.43, 95%CI 2.52 to 7.82, $p < 0.001$

Consistency in results	Inconsistent
Precision in results	Precise for hypertension ORs, imprecise for cholesterol, triglycerides, diabetes, metabolic syndrome and obesity ORs, unable to assess overall prevalence.

Directness of results	Direct

Yu Z-H, Jiang H-Y, Shao L, Zhou Y-Y, Shi H-Y, Ruan B

Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis

British Journal of Clinical Pharmacology 2016; 82: 624-32

View review abstract online

Comparison	**Myocardial infarction in patients with schizophrenia taking antipsychotics vs. patients not taking antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests a medium-sized increased risk of myocardial infarction in patients taking antipsychotics.**
Myocardial infarction	
A medium-sized, significant increased risk of myocardial infarction in people taking antipsychotics; 3 studies, N = unclear, OR = 2.48, 95%CI 1.66 to 3.69, $p < 0.05$, $I^2 = 95\%$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Zhang J, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU

Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2013; 16: 1205-1218

View review abstract online

Comparison	**Weight gain and cardiometabolic factors associated with first-generation vs. second-generation antipsychotics for people with**

	first-episode psychosis.
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests more total cholesterol increase with olanzapine compared to haloperidol, and more triglyceride increase with amisulpride compared to haloperidol.** **Moderate quality evidence (imprecise) suggests olanzapine and risperidone may cause more weight gain than haloperidol.** **Low quality evidence (very small samples) is unable to determine differences in cholesterol, glucose or triglycerides for other comparisons.**
Cholesterol	
Olanzapine resulted in more total cholesterol increase than molindone; 1 RCT, N = 35, *g* 1.02, 95%CI 1.30 to 1.75, *p* < 0.01 *Olanzapine resulted in more total cholesterol increase than sulpiride;* 1 RCT, N = 53, *g* 5.12, 95%CI 4.01 to 6.23, *p* < 0.01 *Olanzapine resulted in more total cholesterol increase than haloperidol;* 3 RCTs, N = 501, *g* 0.17, 95%CI 0.00 to 0.35, *p*= 0.05 *Risperidone resulted in less total cholesterol increase than sulpiride;* 1 RCT, N = 58, *g* -1.36, 95%CI -1.93 to -0.80, *p* < 0.01	
Triglycerides	
Olanzapine resulted in more triglyceride increase than sulpride; 1 RCT, N = 53, *g* 3.32, 95%CI 2.49 to 4.15, *p* < 0.01 *Clozapine resulted in more triglyceride increase than sulpride;* 1 RCT, N = 59, *g* 5.02, 95%CI 3.98 to 6.05, *p* < 0.01 *Sulpride resulted in more triglyceride increase than risperidone;* 1 RCT, N = 58, *g* -1.18, 95%CI -1.74 to -0.63, *p* < 0.01 *Amisulpride resulted in more triglyceride increase than haloperidol;* 1 RCT, N = 207, *g* 0.34, 95%CI 0.06 to 0.61, *p* < 0.05	
Glucose	
Significant, small effects of less glucose change with olanzapine, risperidone and clozapine compared to sulpride;	

Olanzapine: 1 RCT, N = 53, *g* = -1.21, 95%CI -1.79 to -0.63, *p* < 0.01 Risperidone: 1 RCT, N = 58, *g* = -1.99, 95%CI -2.61 to -1.36, *p* < 0.01 Clozapine: 1 RCT, N = 59, *g* = -1.54, 95%CI -2.12 to -0.97, *p* < 0.01
Weight gain
A significant, small effect of more weight gain for risperidone compared to haloperidol; 2 RCTs, N = 485, RR 1.61, 95%CI 1.25 to 2.09, *p* < 0.01 *A significant, medium effect of more weight for olanzapine compared to haloperidol;* 2 RCTs, N = 362, RR 3.31, 95%CI 1.83 to 5.98, *p* < 0.01 Larger differences in weight gain were associated with shorter follow-up time, smaller sample size, younger age, female sex and schizophrenia diagnosis.

Consistency in results	Authors report inconsistency in results.
Precision in results	Imprecise, apart from olanzapine vs. haloperidol for cholesterol and amisulpride vs. haloperidol for triglycerides.
Directness of results	Direct

Zhang Y, Liu Y, Su Y, You Y, Ma Y, Yang G, Song Y, Liu X, Wang M, Zhang L, Kou C

The metabolic side effects of 12 antipsychotic drugs used for the treatment of schizophrenia on glucose: a network meta-analysis

BMC Psychiatry 2017; 17: 373

View review abstract online

Comparison	**Glucose levels in people with schizophrenia on antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (large sample, some inconsistency, unable to assess precision, indirect) finds increased glucose levels with olanzapine compared to placebo, ziprasidone, lurasidone and risperidone.**
Glucose	
47 studies, N = 9,846	

Olanzapine was associated with significantly increased glucose levels compared to; Placebo: MD = 3.95, 95%CI 0.14 to 7.76, $p < 0.05$ Ziprasidone: MD = 5.51, 95%CI 1.62 to 9.39, $p < 0.05$ Lurasidone: MD = 5.58, 95%CI 0.53 to 10.64, $p < 0.05$ Risperidone: MD = 3.05, 95%CI 0.87 to 5.22, $p < 0.05$ There were no significant differences between other antipsychotics (aripiprazole, amisulpride, quetiapine, paliperidone, asenapine, haloperidol, sertindole, or clozapine).	
Consistency in results	Authors report the results are mostly consistent.
Precision in results	Unable to assess MDs (not standardised).
Directness of results	Indirect – network meta-analysis.

Explanation of acronyms

CI = confidence interval, *g* = Hedges *g,* standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, MD = mean difference, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, vs. = versus

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[28].

† 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[28].

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[29]. 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.

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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[28];

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data 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[30].

‖ 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.

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