TECHNICAL COMMENTARY

Diabetes mellitus

Introduction

People with schizophrenia are often reported to have increased rates of co-occurring illnesses, including diabetes mellitus. Diabetes is a state of impaired insulin function, either as a result of reduced insulin production (type I diabetes) or reduced insulin responsiveness (type II diabetes). Insulin regulates blood glucose levels, and reduced insulin function effectively increases blood glucose levels (hyperglycaemia). This is a dangerous state in the long term, and can ultimately damage the retina, kidneys, nerves and blood vessels. Consequently, effective management of diabetes is crucial.

It is unclear if any increased risk in people with schizophrenia is purely a consequence of biological risk, the metabolic impact of antipsychotic administration, or unhealthy lifestyle choices, but it is likely a combination of many factors.

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 randomized 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, there is a dose dependent response or if results are reasonably 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 ten systematic reviews that met our inclusion criteria[3-12].

- Moderate quality evidence shows people with multi-episode schizophrenia have

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increased rates of diabetes compared to age and gender-matched population controls, although when type 1 diabetes was assessed separately, there were no differences found. People with multi-episode schizophrenia have similar rates of diabetes as people with first-episode psychosis (9.5% vs. 8.7%), while drug naïve patients have slightly lower rates (6.4%).

- Moderate quality evidence finds a medium to large effect of increased odds of type 2 diabetes in patients with a family history of type 2 diabetes compared to patients without a family history of type 2 diabetes.
- Moderate to high quality evidence finds a large increase in 2-hour oral glucose tolerance test results in unmedicated patients with first-episode psychosis or first-episode mood disorder compared to controls. There were significant, medium-sized increases in insulin levels and insulin resistance in first-episode psychosis patients compared to controls, but no differences between controls and patients with a mood disorder. There were no significant differences in fasting glucose or haemoglobin A1c.
- High quality evidence finds small effects of more impaired global cognition and memory, and a medium-sized effect of more impaired processing speed in people with schizophrenia and diabetes compared to people with schizophrenia without diabetes.
- Moderate to high quality evidence suggests second generation antipsychotics clozapine, olanzapine, risperidone and quetiapine may be associated with a small increased risk of diabetes mellitus when compared to first generation antipsychotics.
- Moderate to high quality evidence suggests a small effect of greater adherence to diabetes medication in people with schizophrenia than in people without schizophrenia (approximately 17 more days per year).
- Moderate quality evidence suggests access to treatments for diabetes was not significantly different for people with schizophrenia.

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TECHNICAL COMMENTARY

Diabetes mellitus

Bora E, Akdede BB, Alptekin K

The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis

Psychological Medicine 2017; 47: 1030-40

View review abstract online

Comparison	**Cognitive functioning in people with schizophrenia and diabetes vs. people with schizophrenia without diabetes.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct,) suggests small effects of more impaired global cognition and memory, and a medium-sized effect of more impaired processing speed in people with schizophrenia and diabetes.**

Cognitive functioning

Significant, small to medium-sized effects of more impaired cognition in people with schizophrenia and diabetes;

Global cognition: 6 studies, N = 2,897, d = 0.28, 95%CI 0.18 to 0.38, $p < 0.001$, $I^2 = 0\%$, $p = 0.89$

Memory: 5 studies, N = 2,480, d = 0.22, 95%CI 0.12 to 0.33, $p < 0.001$, $I^2 = 0\%$, $p = 0.39$

Processing speed: 5 studies, N = 2,480, d = 0.44, 95% CI 0.3 to 0.55, $p < 0.001$, $I^2 = 0\%$, $p = 0.49$

The effect size for global cognition was similar in the subgroup analyses of studies that were matched for gender (d = 0.30), and in studies that included only people with type 2 diabetes (d = 0.27).

Authors report no evidence of publication bias.

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Chung J, Miller BJ

Meta-analysis of comorbid diabetes and family history of diabetes in non-affective psychosis

Schizophrenia Research 2019; 216: 41-47

View review abstract online	
Comparison	**Rates of type 2 diabetes in people with schizophrenia who have a family history of type 2 diabetes vs. people with schizophrenia with no family history of type 2 diabetes.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds a medium to large effect of increased odds of type 2 diabetes in patients with a family history of type 2 diabetes.**
Type 2 diabetes	
A medium to large effect of increased odds of type 2 diabetes in patients with a family history of type 2 diabetes; 10 studies, N = 3,780, OR = 4.3, 95%CI 2.9 to 6.4, $p < 0.001$, $I^2 = 58\%$, $p < 0.001$ Meta-regression showed older mean study age was associated with increased effect sizes. There were no associations with sex, BMI, geographic region, study quality, or year of publication.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Cullen AE, Holmes S, Pollak TA, Blackman G, Joyce DW, Kempton MJ, Murray RM, McGuire P, Mondelli V

Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis

Biological Psychiatry 2019; 85: 35-48

View review abstract online

Comparison	**Rates of diabetes in people with schizophrenia or other psychotic disorders vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds no increases in rates of type 1 diabetes in people with schizophrenia or other psychotic disorders.**
Type 1 diabetes	

No significant differences between groups; 8 population-level studies, OR = 0.79, 95%CI 0.43 to 1.46, $p = 0.46$, $I^2 = 97\%$, $p < 0.001$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Gorczynski P, Firth J, Stubbs B, Rosenbaum S, Vancampfort D

Are people with schizophrenia adherent to diabetes medication? A comparative meta-analysis

Psychiatry Research 2017; 250: 17-24

View review abstract online

Comparison	**Rates of adherence to diabetes medication in people with schizophrenia compared to people without schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample size, inconsistent, precise, direct) suggests a small effect of more adherence to diabetes medication in people with schizophrenia than people without schizophrenia.**
Adherence to diabetes medication	
More people with schizophrenia adhered to diabetes medication than those without schizophrenia; 10 studies, N = 33,680, OR = 1.34, 95%CI 1.18 to 1.52, $p < 0.01$ *People with schizophrenia adhered to medication on 77.3% of days prescribed;* 7 studies, N = 32,080, 95%CI 73.6% to 81%, $I^2 = 99\%$ *People with schizophrenia adhered to medication on 4.6% more days per year than those without schizophrenia;* 4 studies, N = 190,220, 95%CI 2.4% to 6.7%, $p < 0.01$, $I^2 = 92\%$ Equating to approximately 17 more days per year adherent to medication. Factors associated with diabetes medication adherence were older age, number of outpatient visits, along with multiple medication administration variables.	
Consistency in results	Inconsistent where reported.

Precision in results	Precise for OR.
Directness of results	Direct

Greenhalgh AM, Gonzalez-Blanco L, Garcia-Rizo C, Fernandez-Egea E, Miller B, Arroyo MB, Kirkpatrick B

Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naive patients with nonaffective psychosis

Schizophrenia Research 2017; 179: 57-63

View review abstract online

Comparison	**Glucose and insulin levels in unmedicated people with first-episode psychosis vs. controls.** **All patients had a maximum lifetime antipsychotic exposure of one week and no antipsychotic use in the 30 days prior to the study.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds small to medium-sized effects of increased fasting glucose, glucose intolerance, insulin resistance and fasting insulin in unmedicated people with first-episode psychosis.**
Glucose metabolism	

A significant, small increase in fasting glucose in unmedicated patients with first-episode psychosis;

Fasting glucose: 19 studies, N = 1,781, g = 0.21, 95%CI 0.11 to 0.31, $p < 0.001$, I^2 = 55%, p = 0.002

After removal of an outlier, heterogeneity reduced to 36.5% (p = 0.062) and the effect size reduced slightly (g = 0.16, p = 0.002).

There were no moderating effects of age, body mass index, cortisol, family history exclusions, or smoking.

Significant, medium-sized increase in the oral glucose tolerance test in unmedicated patients with first-episode psychosis;

2-hour glucose tolerance test: 4 studies, N = 426, g = 0.58, 95%CI 0.38 to 0.78, $p < 0.001$, I^2 = 83%, $p < 0.001$

A significant, small effect of more insulin resistance in unmedicated patients with first-episode psychosis;

Insulin resistance: 9 studies, N = 913, g = 0.30, 95%CI 0.17 to 0.44, $p < 0.001$, I^2 = 64%, p = 0.005

After removal of an outlier, heterogeneity reduced to 9% (p = 0.359) and the effect size increased to medium (g = 0.44, $p < 0.001$).

A significant, small effect of increased fasting insulin in unmedicated patients with first-episode psychosis;

Fasting insulin concentration: 10 studies, N not reported, g = 0.28, 95%CI 0.15 to 0.42, $p < 0.001$, I^2 = 77%, $p < 0.001$

After removal of an outlier, heterogeneity reduced to 40% (p = 0.103) and the effect size increased to medium (g = 0.46, $p < 0.001$).

Consistency in results	Inconsistent, apart from outlier analyses.
Precision in results	Precise
Directness of results	Direct

Kucukgoncu S, Kosir U, Zhou E, Sullivan E, Srihari VH, Tek C

Glucose metabolism dysregulation at the onset of mental illness is not limited to first episode psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 2019; 13: 1021-31

View review abstract online

Comparison	**Glucose and insulin in unmedicated people with first episode psychosis or a mood disorder vs. controls.**

	All patients were either antipsychotic-naïve or had life-time prior treatment of less than 2 weeks.
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds a large increase in oral glucose tolerance test results in unmedicated patients compared to controls, with no significant differences between first-episode psychosis and mood disorders. There were significant, medium-sized increases in insulin levels and insulin resistance in first-episode psychosis, but not in mood disorders compared to controls. There were no differences in fasting glucose or haemoglobin A1c in either disorder.**
Glucose metabolism	
Significant, large increase in the oral glucose tolerance test results in unmedicated patients compared to controls; All patients: 6 studies, N = 621, g = 0.94, 95%CI 0.59 to 1.29, $p < 0.05$, I^2 = 81%, $p < 0.001$ *The effect sizes were similar in subgroup analysis of psychosis and mood disorders;* Psychosis: 4 studies, N = 426, g = 0.62, 95%CI 0.11 to 1.12, $p < 0.05$, I^2 = 84%, $p < 0.001$ Mood disorders: 2 studies, N = 195, g = 1.22, 95%CI 0.75 to 1.70, $p < 0.05$, I^2 = 0.01%, p = 0.44 Q_B = 2.929, p = 0.08 *There were no significant differences in fasting glucose compared to controls;* All patients: 31 studies, N = 2,817, g = 0.10, 95%CI -0.03 to 0.23, $p > 0.05$, I^2 = 57%, $p < 0.001$ *The effect sizes were similar in subgroup analysis of psychosis and mood disorders;* Psychosis: 24 studies, N = 2,603, g = 0.12, 95%CI -0.02 to 0.27, $p > 0.05$, I^2 = 63%, $p < 0.001$ Mood disorders: 8 studies, N = 1,575, g = 0.02, 95%CI -0.25 to 0.29, $p > 0.05$, I^2 = 32%, p = 0.17 Q_B = 0.30, p = 0.58 Meta-regressions found only increased patient age was associated with increased effect size in the mood disorders subgroup analysis. *There were no significant differences in insulin levels compared to controls;* All patients: 19 studies, N = 1,710, g = 0.21, 95%CI -0.24 to 0.67, $p > 0.05$, I^2 = 77%, $p < 0.001$ *Significant, medium-sized increase in insulin levels in the subgroup analysis of psychosis, but not mood disorders;* Psychosis: 15 studies, N = 1,297, g = 0.40, 95%CI 0.16 to 0.64, $p < 0.05$, I^2 = 73%, $p < 0.001$ Mood disorders: 4 studies, N = 413, g = -0.06, 95%CI -0.54 to 0.40, $p > 0.05$, I^2 = 66%, p = 0.03 Q_B = 3.35, p = 0.06 *There were no significant differences in insulin resistance compared to controls;* All patients: 16 studies, N = 1,534, g = 0.24, 95%CI -0.08 to 0.56, $p > 0.05$, I^2 = 47%, p = 0.018	

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Significant, medium-sized increase in insulin resistance in the subgroup analysis of psychosis, but not mood disorders; Psychosis: 15 studies, N = 1,317, g = 0.36, 95%CI 0.21 to 0.52, $p < 0.05$, I^2 = 43%, p = 0.04 Mood disorders: 2 studies, N = 218, g = 0.02, 95%CI -0.22 to 0.44, $p > 0.05$, I^2 = 0.01%, p = 0.47 Q_B = 2.64, p = 0.10 *There were no significant differences in haemoglobin A1c compared to controls;* All patients: 6 studies, N = 486, g = 0.15, 95%CI -0.07 to 0.37, $p > 0.05$, I^2 = 49%, p = 0.08 *The effect sizes were similar in subgroup analysis of psychosis and mood disorders;* Psychosis: 4 studies, N = 272, g = 0.04, 95%CI -0.22 to 0.30, $p > 0.05$, I^2 = 15%, p = 0.32 Mood disorders: 2 studies, N = 214, g = 0.40, 95%CI -0.001 to 0.80, $p > 0.05$, I^2 = 46%, p = 0.17 Q_B = 2.12, p = 0.14	
Consistency in results	Inconsistent, apart from most mood disorders subgroup analyses and all haemoglobin A1c analyses.
Precision in results	Precise
Directness of results	Direct

Mitchell AJ, Malone D, Doebbeling CC

Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies

The British Journal of Psychiatry 2009; 194: 491-499

View review abstract online

Comparison	**Quality of medical care for comorbid diabetes in people with schizophrenia.** **Note: results are reported only for defined schizophrenia spectrum disorder samples presented separately to other psychiatric illnesses.**
Summary of evidence	**Moderate quality evidence (medium to large samples, unable to assess consistency or precision, direct) suggests access to treatments for diabetes was not significantly different for people with schizophrenia.**
Quality of medical care for diabetes	

Quality of care reported for various comorbid conditions in people with schizophrenia;

One study (N = 200) reported on the quality of general medical care (assessed as self-reported service use and perceived barriers, compared to healthy controls from national survey data) and found that compared to controls, people with schizophrenia were more likely to have visited a doctor (OR = 2.00); had a full physical exam (OR = 2.69); but less likely to visit a dentist (OR = 0.46). Patients were more likely to report perceived barriers to medical care (OR > 3).

One study (N = 199) reported on the quality of medical care for diabetes in schizophrenia spectrum compared to non-psychiatric control with diabetes, and found that patients with schizophrenia were less likely to receive diabetes education (p = 0.002). People with schizophrenia had significantly better levels of a diabetes health marker (HbA_{1c}) than controls (p < 0.01). There was no difference in the number of outpatient visits, emergency visits or hospitalisations.

One study (N = 3,808), including 214 with a schizophrenia spectrum disorder, reported on the quality of medical care for diabetes in schizophrenia spectrum compared to non-psychiatric control, and found that people with schizophrenia were slightly more likely than control to be on insulin therapy (OR = 1.44, p = 0.08, not significant). Those with schizophrenia were significantly more likely to receive an older treatment prescription for hyperlipidaemia (OR = 1.85, p < 0.05) and be referred for nutritional counselling. People with schizophrenia were significantly more likely to miss at least one outpatient appointment (p < 0.001).

One study (N = 11,043) included 705 schizophrenia patients compared to bipolar disorder and non-psychiatric controls with diabetes, and found that those with mental illness were more likely to have better levels of a diabetes health marker (HbA_{1c}) than controls (no statistics reported).

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

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	**First generation vs. second generation antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests second generation antipsychotics clozapine, olanzapine, risperidone and quetiapine may be associated with a small increased risk of diabetes mellitus when**

	compared to any first generation antipsychotic.
Diabetes	
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

Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Hert A, Probst M, De Hert A

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

World Psychiatry 2013; 12: 240-250

View review abstract online

Comparison	**Rates of diabetes in people with chronic schizophrenia vs. age and gender-matched population controls, and vs. patients with first-episode schizophrenia or those who are drug-naïve.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, mostly imprecise, direct) suggests people with chronic schizophrenia have increased rates of diabetes compared to age and gender-matched population controls, with similar rates in first-episode patients (9.5% vs. 8.7%). Drug naïve patients had lower rates of diabetes (6.4%).**

Diabetes	
Patients with multi-episode schizophrenia were at increased risk for diabetes compared to matched population controls; 15 studies, N = 3,998,469, OR = 1.99, 95%CI 1.55 to 2.54, $p < 0.001$, Q = 3718.8, $p < 0.001$ Multi-episode patients (N = 116,751; 9.5%) had similar rates of diabetes as first-episode (N = 1,033; 8.7%) and drug-naïve patients (N = 346; 6.4%), $p = 0.56$.	
Consistency in results	Inconsistent
Precision in results	Precise for hypertension only
Directness of results	Direct

Vancampfort D, Correll CU, Galling B, Probst M, De Hert M, Ward PB, Rosenbaum S, Gaughran F, Lally J, Stubbs B

Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis

World Psychiatry 2016; 15(2): 166-174

View review abstract online

Comparison	**Risk of type 2 diabetes in people with schizophrenia vs. controls and vs. schizophrenia spectrum disorders (schizoaffective disorder, schizophreniform disorder, related psychoses), bipolar disorder, and major depressive disorder.**
Summary of evidence	**Moderate quality evidence (large samples, some inconsistency, imprecise, direct) suggests a medium-sized effect of increased risk of type 2 diabetes in people with multi-episode, but not first-episode, schizophrenia compared to controls, with no differences compared to people with bipolar disorder or major depressive disorder.**
Type 2 diabetes	
A medium-sized, significant effect suggests patients with schizophrenia are at increased risk of type 2 diabetes compared to controls; 29 studies, N = 115,538, RR = 2.04, 95%CI 1.69 to 2.49, $p < 0.001$, $I^2 = 97.8\%$, $p < 0.001$ *A small, significant effect suggests patients with bipolar disorder are at increased risk of type 2*	

diabetes compared to controls; 6 studies, N = 54,688, RR = 1.89, 95%CI 1.29 to 2.77, $p < 0.001$, $I^2 = 7.3\%$, $p = 0.34$ *A small, significant effect suggests patients with major depressive disorder are at increased risk of type 2 diabetes compared to controls;* 3 studies, N = 10,895, RR = 1.43, 95%CI 0.88 to 2.25, $p = 0.029$, (I^2 not reported), Q-value for I^2 = 2.15, $p = 0.34$ *A small, significant effect suggests patients with multi-episode schizophrenia are at increased risk of type 2 diabetes compared to controls;* 38 studies, N = 5,756,134, RR = 1.85, 95%CI 1.45 to 2.37, $p < 0.001$, (I^2 not reported), Q-value for I^2 = 1302.0, $p < 0.001$ *There were no significant differences in risk of type 2 diabetes between patients with first-episode schizophrenia and controls;* 3 studies, N not reported, RR = 4.64, 95%CI 0.73 to 29.3, $p = 0.10$, (I^2 and Q-value not reported), p for $I^2 = 0.23$ *There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with schizophrenia spectrum disorders;* 3 studies, N = 60,657, OR = 0.80, 95%CI 0.52 to 1.25, $p = 0.33$, $I^2 = 24.9\%$, $p = 0.26$ *There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with bipolar disorder;* 6 studies, N = 109,143, OR = 1.22, 95%CI 0.84 to 1.77, $p = 0.28$, $I^2 = 70.8\%$, $p = 0.004$ *There were no significant differences in risk of type 2 diabetes between patients with schizophrenia and patients with depressive disorder;* 2 studies, N = 11,804, OR = 1.27, 95%CI 0.96 to 1.68, $p = 0.10$, $I^2 = 0\%$, $p = 0.80$	
Consistency in results	Consistent apart from schizophrenia vs. controls, multi-episode schizophrenia vs. controls, and schizophrenia vs. bipolar disorder.
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d or g* = Cohen's d or 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), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q_B = heterogeneity statistic between subgroups, RR = relative risk, 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[13].

† Different effect measures are reported by different reviews.

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[14]. 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.

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 randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that 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. 0.2 represents a small

effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[13].

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. Unstandardized (*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. Standardized 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[13];

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

§ 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[15].

‖ 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 that 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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