TECHNICAL COMMENTARY

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Dopamine

Introduction

Dopamine is a neurotransmitter that is important for emotional and cognitive processing in the brain, particularly rewarding and pleasurable stimuli or experiences. Alterations of the dopamine system have been suggested in schizophrenia. This may be assessed as changes in levels of dopamine or its metabolites, or as changes in levels or activity of the mechanical components of the dopamine system, such as the receptors that 'receive' dopamine, or the transporters that 'remove' it. Reviews included in this table reflect evidence from functional brain imaging investigations into biochemical activity across the whole brain.

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 have been 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, 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 11 systematic reviews that met our inclusion criteria[3-13].

- Moderate to high quality evidence suggests a large effect of increased striatal presynaptic dopamine function (particularly in associative and sensorimotor regions), and a small effect of increased striatal dopamine receptor availability in people with schizophrenia compared to controls. There were no differences in striatal dopamine transporter levels.

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- Moderate quality evidence suggests no differences in D2/D3 receptor availability in the thalamus and temporal cortex of unmedicated people with schizophrenia compared to controls. Moderate to low quality evidence suggests no differences in D2/D3 receptor availability in the substantia nigra.
- Moderate to low quality evidence suggests an association between dopamine receptor occupancy and clinical improvement on the PANSS following treatment with antipsychotic medications. Greatest D2 receptor occupancy occurs with haloperidol (91.9%), then risperidone, olanzapine, clozapine, quetiapine, aripiprazole, ziprasidone, and then amisulpride (85%).

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Chen KC, Yang YK, Howes O, Lee IH, Landau S, Yeh TL, Chiu NT, Chen PS, Lu RB, David AS, Bramon E

Striatal dopamine transporter availability in drug-naive patients with schizophrenia: a case-control SPECT study with [(99m)Tc]-TRODAT-1 and a meta-analysis

Schizophrenia Bulletin 2013; 39(2): 378-86

View review abstract online

Comparison	**Striatal dopamine transporter availability (measured by SPECT) in drug-naive people with schizophrenia and controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests no difference in striatal dopamine transporter availability between drug-naïve people with schizophrenia and controls.**
Striatal dopamine transporter availability	
No significant difference in striatial dopamine transport availability between drug-naive people with schizophrenia and controls; 6 studies, N = 293, *d* = -0.07, 95%CI -0.31 to 0.18, *p* = 0.60, *b* = 0.07, *p* = 0.61 There was no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Meyer-Lindenberg A

Striatal presynaptic dopamine in schizophrenia, part I: meta-analysis of Dopamine Active Transporter (DAT) density

Schizophrenia Bulletin 2013; 39(1): 22-32

View review abstract online

Comparison	**Density of dopamine transporter (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large sample, inconsistent, precise, direct) suggests no difference in dopamine transporter levels in the striatum of people with schizophrenia compared to controls.**
Presynaptic dopamine transporter density	
No significant difference in dopamine transport density in the striatal pre-synaptic terminals of people with schizophrenia compared to controls; 13 studies, N = 349, *d* = -0.244, 95%CI -0.676 to 0.188, *p* = 0.269, Q = 44.075, *p* < 0.001, I^2 = 75.082% *The results remained non-significant when only studies considering striatal subregions were included:* Caudate: *d* = -0.197, 95%CI -0.564 to 0.133, *p* = 0.431 Putamen: *d* = -0.187, 95%CI -0.661 to 0.153, *p* = 0.549 There were also no significant effects of any potential moderating variables including radiotracer type (*p* = 0.602), year of publication (*p* = 0.927), participant age (*p* = 0.301), duration of illness (*p* = 0.468), symptom severity (*p* = 0.452), antipsychotic exposure (*p* = 0.171), or gender (*p* = 0.389).	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct comparisons and measures of functional activity

Fusar-Poli P, Meyer-Lindenberg A

Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [^{18}F/^{11}C]-DOPA PET studies

Schizophrenia Bulletin 2013; 39(1): 33-42

View review abstract online

Comparison	**Presynaptic dopamine synthesis capacity (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample,**

	consistent, precise, direct) shows increased presynaptic dopamine synthesis capacity in the striatum of people with schizophrenia compared to controls.
Presynaptic dopamine synthesis capacity	
Large effect size suggests a significant increase in dopamine synthesis capacity in the striatal pre-synaptic terminals of people with schizophrenia compared to controls; 11 studies, N = 244, d = 0.867, 95%CI 0.594 to 1.140, p < 0.001, Q = 19.19, p = 0.078, I^2 = 39.17% *This difference remained when only studies considering striatal sub-regions were included:* Caudate: d = 0.569, 95%CI 0.176 to 0.961, p = 0.005 Putamen: d = 0.643, 95%CI 0.098 to 1.189, p = 0.021 There were also no significant effects of any potential moderating variables including radiotracer type (p = 0.701), year of publication (p = 0.727), participant age (p = 0.856), duration of illness (p = 0.736), symptom severity (p = 0.783), antipsychotic exposure (p = 0.501), or gender (p = 0.299).	
Consistency in results	Consistent
Precision in results	Mostly precise
Directness of results	Direct comparisons and measures of functional activity

Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S

The nature of dopamine dysfunction in schizophrenia and what this means for treatment: Meta-analysis of imaging studies

Archives of General Psychiatry 2012; 69(8): 776-786

View review abstract online

Comparison	**Striatal dopamine function (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests a large effect of increased striatal presynaptic dopamine function, and a small effect of increased receptor availability in people with schizophrenia compared to controls. There are no difference in dopamine transporter levels.**

Presynaptic dopamine function	
Large effect size suggests significantly elevated dopamine activity in schizophrenia patients compared to controls; 17 studies, N = 482, *d* = 0.79, 95%CI 0.52 to 1.07, *p* < 0.001, I^2 = 39.92% *The results did not differ when the analysis was conducted only on drug-free or drug-naïve patients;* *d* = 0.69, 95%CI 0.36 to 1.01, *p* = 0.001, I^2 = 46.46%	
Dopamine transporter levels	
Small effect size suggests no significant difference in dopamine transporter levels between schizophrenia and controls; 11 studies, N = 284, *d* = -0.34, 95%CI -0.75 to 0.07, *p* = 0.10, I^2 = 64%	
Dopamine receptor availability	
Small effect size suggests significantly elevated dopamine receptor levels in unmedicated schizophrenia patients compared to controls; 22 studies, N = 661, *d* = 0.26, 95%CI 0.001 to 0.52, *p* = 0.049, I^2 = 63.93%	
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Kambeitz J, Abi-Dargham A, Kapur S, Howes OD

Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: Systematic review and meta-analysis of imaging studies

British Journal of Psychiatry 2014; 204(6): 240-249

View review abstract online

Comparison	**Cortical and extrastriatal D2/D3 receptor availability (measured by PET or SPECT) in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, some inconsistency and imprecision, direct) suggests no differences in**

	D2/D3 receptor availability in the thalamus and temporal cortex of people with schizophrenia compared to controls. **Moderate to low quality evidence (medium-sized samples, inconsistent, imprecise, direct) also suggests no differences in D2/D3 receptor availability in the substantia nigra.**
D2/D3 receptor availability **Binding potential relative to the non-displaceable compartment**	
Thalamus *No significant differences between groups in D_2/D_3 receptor availability;* 8 studies, N = 264, *d* = -0.32, 95%CI -0.68 to 0.03, *p* = 0.07, I^2 = 49% Authors report that the effect became significant when the only 2 studies with positive effect sizes were excluded from the analysis. Subgroup analysis of 5 studies of participants with previous exposure to antipsychotic medication showed a non-significant effect size (*d* = -0.34). There were too few studies of drug-naïve patients for meta-analysis (k = 3), and effect sizes from these studies ranged from -0.77 to 0.35. Temporal cortex *No significant differences between groups in D_2/D_3 receptor availability;* 6 studies, N = 170, *d* = -0.23, 95%CI -0.54 to 0.07, *p* = 1.00, I^2 = 0% Effect sizes in studies of drug-free or drug-naïve patients ranged from -0.42 to 0.49. Substantia nigra *No significant differences between groups in D_2/D_3 receptor availability;* 5 studies, N = 143, *d* = 0.04, 95%CI -0.92 to 0.99, *p* = 0.90, I^2 = 85% Excluding one study of drug-naïve patients did not substantially change the effect (*d* = -0.04). Meta-regression showed no effect of publication year, gender, or age in any analysis. There was no evidence of publication bias. Authors report that the evidence for other measures and regions is limited because of the small number of studies and some inconsistent findings, although individual studies have found significant differences in D2/D3 receptors in the cingulate and uncus, in D1 receptors in the prefrontal cortex, and in dopamine transporter availability in the thalamus.	
Consistency in results	Some inconsistency.
Precision in results	Some imprecision.
Directness of results	Direct

Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K

Estimating dopamine D2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis

Journal of Clinical Psychopharmacology 2013; 33(5): 675-81

View review abstract online

Comparison	**Dopamine D2 receptor occupancy (measured by PET/SPECT) according to antipsychotic type.**
Summary of evidence	**Moderate quality evidence (large sample, direct, inconsistent, unable to assess precision) suggests greatest D2 receptor occupancy with haloperidol (91.9%), then risperidone, olanzapine, clozapine, quetiapine, aripiprazole, ziprasidone, and then amisulpride (85%).**
D2 receptor occupancy	
51 studies, N = 606 *Maximum occupancy for;* Haloperidol: 91.9%, 95%CI 86.1 to 97.8 Risperidone: 92.4%, 95%CI 81.8 to 100 Olanzapine: 96.5%, 95%CI 85.8 to 100 Clozapine: 61.7%, 95%CI 49.2 to 74.2 Quetiapine: 49.1%, 95%CI 18.7 to 79.6 Aripiprazole: 86.9%, 95% CI 78.2 to 95.7 Ziprasidone: 82.9%, 95%CI 44.9 to 100 Amisulpride: 85.0%, 95%CI 68.5 to 100 Authors report that age, sex, and imaging method did not explain the heterogeneity observed across study results.	
Consistency in results	Authors report inconsistent results for haloperidol, risperidone, olanzapine, clozapine and amisulpride.
Precision in results	No measure of precision is reported.
Directness of results	Direct

McCutcheon R, Beck K, Jauhar S, Howes OD

Defining the Locus of Dopaminergic Dysfunction in Schizophrenia: A Meta-analysis and Test of the Mesolimbic Hypothesis

Schizophrenia Bulletin 2018; 44: 1301-11

View review abstract online

Comparison	**Presynaptic dopamine functioning (measured by PET) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests a medium-sized increase in presynaptic dopamine functioning in the striatum of people with schizophrenia, particularly in associative and sensorimotor regions.**

Presynaptic dopamine functioning

A significant, medium-sized increase in presynaptic dopamine functioning in the striatum of people with schizophrenia;

21 studies, N = 582, g = 0.68, 95%CI 0.44 to 0.91, $p < 0.001$, $I^2 = 42.5\%$

There were similar increases in associative and sensorimotor, but not limbic, brain regions.

There were no moderating effects of medication status, patient age, or symptom severity.

Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Stone JM, Davis JM, Leucht S, Pilowsky LS

Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs--an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature

Schizophrenia Bulletin 2009; 35(4): 789-797 View review abstract online	
Comparison	**Comparison of dopamine D2/D3 receptor occupancy (measured by PET/SPECT) in the striatum and temporal cortex of people with schizophrenia compared to healthy controls following first and second generation antipsychotic medication. Indirectly compared to efficacy measurements of antipsychotics in separate patient groups.**
Summary of evidence	**Low quality evidence (indirect, small samples or unable to assess sample size, precision and consistency) is unclear about the relationship between receptor occupancy and drug effectiveness, side effects or measurement type. Single ligands had significantly higher occupancy than dual ligands. Significant difference in occupancy rates between first and second generation antipsychotics was reported, when controlling for ligand type and modelling method.**
D2/D3 receptor occupancy	
Fifteen studies were pooled to estimate the dopamine receptor occupancy; Striatal occupancy following first generation antipsychotic administration: N = 28, 74% ± 12% Striatal occupancy following second generation antipsychotic administration: N = 115, 49% ± 21% t = 8.8, $p < 4x10^{-13}$ Temporal cortex occupancy following first generation antipsychotic administration: N not reported, 77% ± 12% Temporal cortex occupancy following second generation antipsychotic administration: N not reported, 67% ± 19% t = 3.5, $p = 0.001$ Ratio of striatal/temporal occupancy for first generation antipsychotics: 96 ± 24% Ratio of striatal/temporal occupancy for second generation antipsychotics: 74 ± 35% t = 3.7, $p < 0.001$	
Subgroup analysis 1: correlation to clinical efficacy *Indirect comparison using dose-response curve calculated from separate efficacy studies into first and second generation antipsychotics;* Occupancy correlated strongly with drug efficacy for temporal D2/D3: $r = 0.95$, $p < 0.001$ Also correlated striatal occupancy with drug efficacy: $r = 0.76$, $p = 0.046$	

Subgroup analysis 2: correlation to extrapyramidal side effects *Indirect comparison using dose-response curve calculated from separate efficacy studies into first and second generation antipsychotics;* Dose was correlated linearly with occupancy in the striatum, $r = 0.59$, $p = 0.004$, but not with temporal $r = 0.38$, p not significant EPSE are known to increase with dose and so are likely to be associated more with striatal dopamine	
Subgroup analysis 3: controlling for assessment method; Simplified Reference Tissue Modelling vs. Ratio modelling Significant difference in the two methods was seen in the temporal cortex, ratio modelling estimated 61% occupancy, SRTM estimated 78%. $F = 21.3$, $p = 0.04$ No significant difference was found in the occupancy estimates of both methods in the striatum The association of measurement method and drug type (typical vs. atypical) was zero for both regions	
Subgroup analysis 4: single vs. dual ligands Single ligand studies assess striatal and extrastriatal antipsychotic binding simultaneously, whereas dual ligand studies assess striatal and extrastriatal binding with different tracers on separate occasions In the striatum, single ligand binding had an 18% lower (95%CI 10 to 25%) occupancy estimate than dual ligands. $F = 22$, $p = 0.000007$ In the temporal cortex, single ligand binding had a 13% higher (95%CI 6 to 21%) occupancy estimate than dual ligands. $F = 13$, $p = 0.0006$	
Subgroup analysis 5: Occupancy ANCOVA with ligand type and modelling method covariates In the striatum, occupancy was estimated at 74%, 95%CI 66 to 82% for first generation antipsychotics. For second generation antipsychotics, occupancy was estimated at 47%, 95%CI 44 to 54% This is a significant difference of 27%, 95%CI 18 to 36% between the two classes of antipsychotics $F = 37$, $p = 0.00000005$	
Consistency in results	No measure of consistency is reported.
Precision in results	Confidence intervals are not reported for all outcomes, precise for subgroup analyses 4 and 5.
Directness of results	Direct comparison of receptor occupancy, indirect comparison of antipsychotic doses.

Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K, Mamo DC

Dopamine D2 Receptor Occupancy and Clinical Effects

Journal of Clinical Psychopharmacology 2011; 31(4): 497-502

View review abstract online

Comparison	**Dopamine (D2) receptor occupancy and association with treatment response in people with schizophrenia.**
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency or precision, direct) is uncertain as to D2 receptor occupancy rates and relationship with treatment response.**
Dopamine receptor occupancy	
Dopamine D2 receptor occupancy was significantly higher in patients with extrapyramidal side effects than in patients without extrapyramidal side effects; 12 studies, N = 82, 77 ± 9% vs. 63 ± 17%, *p* = 0.011 *Patients with a 25% reduction in the PANSS or BPRS scores showed higher dopamine D2 receptor occupancy than those without;* 12 studies, N = 82, 66 ± 14% vs 58 ± 19%, *p* = 0.054	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	Unable to assess (no confidence intervals).
Directness of results	Direct

Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K, Mamo DC

Predicting Dopamine D2 Receptor Occupancy From Plasma Levels of Antipsychotic Drugs. A Systematic Review and Pooled Analysis

Journal of Clinical Psychopharmacology 2011; 31(3): 318-325

View review abstract online

Comparison	**Dopamine D2 receptor occupancy levels of risperidone, clozapine, olanzapine, haloperidol, and ziprasidone predicted from**

	antipsychotic plasma levels in people with schizophrenia.
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency or precision, direct) is uncertain as to the predictive ability of dopamine D2 receptor occupancy levels in antipsychotuc plasma of people with schizophrenia.**
Dopamine receptor occupancy	
The mean prediction errors (measure of bias) and root mean squared prediction errors (measure of precision) were low, indicating good prediction of dopamine D2 receptor occupancy levels of the following antipsychotic drugs, from patients' peripheral plasma or serum levels; Risperidone (N = 98) Mean prediction error = 0.0, 95%CI -1.8 to 1.8 Root mean squared prediction error = 8.9, 95%CI 7.6 to 10.2 Clozapine (N = 75) Mean prediction error = 0.0, 95%CI -3.5 to 3.5 Root mean squared prediction error = 15.1, 95%CI 12.9 to 17.3 Olanzapine (N = 42) Mean prediction error = -0.1, 95%CI -1.2 to 1.2 Root mean squared prediction error = 4.6, 95%CI 3.5 to 5.8 Haloperidol (N = 35) Mean prediction error = 0.1, 95%CI -3.4 to 3.5 Root mean squared prediction error = 9.9, 95%CI 7.3 to 12.5 Ziprasidone (N = 31) Mean prediction error = -0.1, 95%CI -3.3 to 3.1 Root mean squared prediction error = 12.3, 95%CI 8.8 to 15.7	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	Unable to assess; not standardised measure.
Directness of results	Direct

Yilmaz Z, Zai CC, Hwang R, Mann S, Arenovich T, Remington G, Daskalakis ZJ

Antipsychotics, dopamine D2 receptor occupancy and clinical

improvement in schizophrenia: a meta-analysis

Schizophrenia Research 2012; 140(1-3): 214-220

View review abstract online

Comparison	**Association between dopamine (D_2) receptor occupancy (measured by PET/SPECT) and clinical improvement following antipsychotic administration (olanzapine, risperidone, zotepine, haloperidol, ziprasidone, quetiapine, raclopride, aripiprazole, amisulpride, or clozapine) for at least 2 weeks.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, direct) suggests there may be an association between D_2 receptor occupancy (measured by SPECT alone) and clinical improvement on PANSS, following treatment with antipsychotic medications.**

Dopamine receptor occupancy

16 studies undertook PET/SPECT analysis following at least 2 weeks of antipsychotic medication.

Pre-post analysis of the effects of antipsychotic medications showed medications were associated with a large improvement in clinical symptoms;

PANSS: 17 effect sizes, N = 178, d = 1.36, 95%CI 1.13 to 1.60, p not reported

BPRS: 7 effect sizes, N = 78, d = 1.25, 95%CI 0.61 to 1.89, p not reported

D2 receptor occupancy did not predict antipsychotic response based on PANSS change scores;

17 effect sizes, N = 178, r = -0.067, CI not reported, p = 0.511

Exclusion of studies using clozapine,quetiapine and one outlier with D2 occupancy of over 80%, resulted in a significant relationship between D2 occupancy and greater PANSS improvement;

13 effect sizes, N unclear, r = 0.400, CI not reported, p < 0.001

D2 receptor occupancy did not predict antipsychotic response based on BPRS scores;

7 effect sizes, N = 78, r = 0.169, CI not reported, p = 0.092

This result did not change when one study using clozapine was excluded.

For those studies using SPECT only, a significant large correlation was found between D_2 receptor occupancy and better PANSS scores (excluding studies using clozapine, quetiapine and those reporting >80% occupancy);

7 effect sizes, r = 0.593, p < 0.001

No studies (15 effect sizes) using PET found any correlation between D_2 receptor occupancy and PANSS change scores.

Dopamine

Consistency in results	No measured of heterogeneity is provided.
Precision in results	Precise for PANSS, unable to assess correlation outcomes.
Directness of results	Direct measures and comparisons.

Explanation of acronyms

ANCOVA = analysis of covariance statistical test, BPRS = Brief psychiatric rating scale, CI = confidence interval, D_2 = dopamine receptor, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, F = ratio of between sample variance and within sample variance, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = positive and negative syndrome scale, PET = positron emission tomography, *r* = correlation coefficient, SPECT = single-photon emission computed tomography, 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 which involves the selective reporting of results; publication bias - trials which 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.

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† Different effect measures are reported by different reviews.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect [14].

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).

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[15]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an 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

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independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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.

‡ Inconsistency refers to differing estimates of treatment 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;

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

§ 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, this criteria should be relaxed[16].

‖ 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 so is 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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