TECHNICAL COMMENTARY

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BIPOLAR DISORDERS LIBRARY

Pharmaceutical treatments for relapse prevention

Introduction

Bipolar disorder is a disabling condition characterised by episodes of mania or hypomania and depression. Bipolar disorder is associated with an excess mortality including an increased risk of suicide. Adherence to pharmacological treatment is critical for effective control of symptoms as non-adherence increases the risk of relapse and suicide[1].

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics 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[2]. 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)[3]. 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 three reviews that met our inclusion criteria[1, 4, 5].

Medications vs. placebo

Efficacy

- Moderate to high quality evidence suggests fewer relapses to mania with risperidone, olanzapine, and quetiapine. Lower quality evidence suggests fewer relapses to mania with aripiprazole. There were fewer relapses to depression with olanzapine and quetiapine, but not with risperidone or aripiprazole.
- Moderate quality evidence suggests fewer relapses in general with lithium, lithium + imipramine (but not for bipolar I disorder), lithium + oxcarbazepine, lithium + valproate, lamotrigine, lamotrigine + aripiprazole, valproate, and valproate + aripiprazole.

Side effects

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- Moderate to low quality evidence suggests placebo was better tolerated than carbamazepine, lithium, or lithium + valproate. There was greater incidence of prolactin-related adverse events with long-acting injectable risperidone, more weight gain with olanzapine, risperidone, quetiapine and aripiprazole, more tremor with aripiprazole and risperidone, more restlessness with aripiprazole, and more sedation with olanzapine and quetiapine.

Medications vs. other medications

Efficacy

- Moderate to high quality evidence suggests fewer relapses to mania or depression with quetiapine + lithium or valproate compared to placebo + lithium or valproate. Quetiapine alone (vs. lithium or valproate) was only effective for relapse to mania.
- Moderate to low quality evidence suggests fewer relapses to mania with aripiprazole or risperidone + lithium or valproate compared to placebo + lithium or valproate, and fewer relapses in general with olanzapine or ziprazidone + lithium or valproate.
- Moderate quality evidence suggests fewer relapses (any) with olanzapine than with imipramine, paliperidone, or lamotrigine; fewer relapses with quetiapine than with imipramine or lamotrigine; fewer relapses with lithium or lithium + valproate than with imipramine; fewer relapses with aripiprazole + valproate than with imipramine or paliperidone.
- Moderate to low quality evidence suggests fewer relapses, particularly to mania, with long-acting injectable risperidone or flupenthixol decanoate than with any oral medication.

Side effects

- Moderate to low quality evidence suggests lamotrigine was better tolerated than carbamazepine, lithium, or lithium + valproate. Long-acting injectable risperidone was associated with more prolactin-related adverse events than any oral medications.

Kishi T, Oya K, Iwata N

Long-acting injectable antipsychotics for prevention of relapse in bipolar disorder: A systematic review and meta-analyses of randomized controlled trials

International Journal of Neuropsychopharmacology 2016; 19: 1-10

View review abstract online

Comparison 1	**Long-acting injectable risperidone vs. placebo.** **Treatment duration ranged from 18 to 24 months.** **Authors report some risk of bias in primary studies.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, direct, large sample, some risk of bias) suggests a small to medium-sized, significant effect of fewer relapses to any mood or mania episode and fewer mood or mania symptoms with long-acting injectable risperidone.** **Moderate quality evidence (imprecise) suggests no differences between groups for relapses to depression, although depression scale scores showed greater improvement with long-acting injectable risperidone.** **Moderate quality evidence (imprecise) suggests long-acting injectable risperidone was associated with large effects of higher incidence of prolactin-related adverse events and weight gain, but less use of benzodiazapines (small effect).**

Relapse to any mood episode or symptoms

A small, significant effect of fewer relapses to any mood episode and fewer mood symptoms with long-acting injectable risperidone;

Study-defined relapse rates: 2 RCTs, N = 567, RR = 0.63, 95%CI 0.51 to 0.77, $p < 0.0001$, $I^2 = 13\%$, $p = 0.28$

Clinical Global Impressions: 2 RCTs, N = 532, WMD = -0.76, 95%CI -1.03 to -0.50, $p < 0.00001$, $I^2 = 0\%$, $p > 0.05$

Relapse to mania or mania symptoms

A medium-sized, significant effect of fewer relapses to mania and fewer mania symptoms with long-acting injectable risperidone;

Study-defined relapse rates: 2 RCTs, N = 537, RR = 0.42, 95%CI 0.29 to 0.61, $p < 0.00001$, $I^2 = 38\%$, $p = 0.20$

Young Mania Rating Scale: 2 RCTs, N = 532, WMD = -5.80, 95%CI -7.57 to -4.04, $p < 0.00001$, $I^2 =$

0%, $p > 0.05$	
Relapse to depression or depression symptoms	
No significant differences in relapses to depression, but a significant effect of reduced depression symptoms with long-acting injectable risperidone; Study-defined relapse rates: 2 RCTs, N = 537, RR = 1.21, 95%CI 0.81 to 1.81, $p = 0.35$, $I^2 = 0\%$, $p > 0.05$ Montgomery-Asberg Depression Scale: 2 RCTs, N = 532, WMD = -1.76, 95%CI -3.23 to -0.28, $p = 0.02$, $I^2 = 0\%$, $p > 0.05$	
Risks	*Long-acting injectable risperidone was associated with higher incidence of prolactin-related adverse events and weight gain, and less use of benzodiazapines than placebo;* Prolactin-related: 2 RCTs, N = 570, RR = 4.82, 95%CI 1.88 to 12.40, $p = 0.001$, $I^2 = 0\%$ Weight gain: 2 RCTs, N = 570, RR = 3.80, 95%CI 2.00 to 7.21, $p < 0.0001$, $I^2 = 0\%$ Use of benzodiazapines: 2 RCTs, N = 570, RR = 0.54, 95%CI 0.32 to 0.91, $p = 0.02$, $I^2 = 0\%$ There were no differences between groups in rates of somnolence, insomnia, anxiety, headache or diabetes.
Consistency in results‡	Consistent
Precision in results§	Precise for mood and mania symptoms only.
Directness of results‖	Direct
Comparison 2	**Long-acting injectable risperidone (6 trials) or flupenthixol decanoate (1 trial) vs. oral medications (antidepressants, antipsychotics or mood stabilisers).** **Treatment duration ranged from 6 to 18 months.**
Summary of evidence	**Moderate to low quality evidence (large samples, inconsistent, imprecise, indirect, some risk of bias) suggests a small, significant effect of fewer relapses to any mood episode and fewer mood symptoms with long-acting injectable risperidone or flupenthixol decanoate over oral medications. There was a small, significant effect of fewer relapses to mania and fewer mania symptoms with long-acting injectable risperidone over oral medications, but no differences in levels of depression.** **Long-acting injectable risperidone was associated with a medium-sized effect of more prolactin-related adverse events.**

Any mood symptoms	
A small, significant effect of fewer relapses to any mood episode and fewer mood symptoms with long-acting injectable risperidone or flupenthixol decanoate than with oral medications; Study-defined relapse rates: 6 RCTs, N = 560, RR = 0.87, 95%CI 0.56 to 1.35, $p = 0.53$, $I^2 = 74\%$, $p = 0.002$ Clinical Global Impressions: 5 RCTs, N = 507, WMD = -0.15, 95%CI -0.68 to 0.38, $p = 0.57$, $I^2 = 77\%$, $p < 0.05$	
Mania or mixed symptoms	
A small, significant effect of fewer relapses to mania and fewer mania symptoms with long-acting injectable risperidone than with placebo; Study-defined relapse rates: 3 RCTs, N = 424, RR = 0.66, 95%CI 0.28 to 1.56, $p = 0.35$, $I^2 = 74\%$, $p = 0.02$ Young Mania Rating Scale: 5 RCTs, N = 507, WMD = -1.03, 95%CI -3.24 to -1.18, $p = 0.36$, $I^2 = 63\%$, $p < 0.05$	
Depression symptoms	
No significant differences between groups; Study-defined relapse rates: 3 RCTs, N = 424, RR = 1.25, 95%CI 0.60 to 2.59, $p = 0.55$, $I^2 = 55\%$, $p < 0.05$ Montgomery-Asberg Depression Scale: 4 RCTs, N = 478, WMD = 1.27, 95%CI -0.59 to 3.12, $p = 0.18$, $I^2 = 37\%$, $p > 0.05$	
Risks	*Long-acting injectable risperidone was associated with higher incidence of prolactin-related adverse events;* 4 RCTs, N = 480, RR = 2.66, 95%CI 1.12 to 6.33, $p = 0.03$, $I^2 = 0\%$
Consistency in results	Inconsistent, apart from Montgomery-Asberg Depression Scale and prolactin-related adverse events.
Precision in results	Imprecise
Directness of results	Indirect (mixed comparisons).

Lindstrom L, Lindstrom E, Nilsson M, Hoistad M

Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis

Journal of Affective Disorders 2017; 213: 138-50

View review abstract online	
Comparison	**Second-generation antipsychotics aripiprazole, olanzapine, quetiapine or risperidone vs. placebo.** **Follow-up ranged from 6 months to 2 years.** **Note that for the olanzapine and quetiapine side effects comparisons, some of the sample were taking lithium or valproate.** **Authors report some risk of bias in primary studies.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, direct, large samples, some risk of bias) suggests small to medium-sized effects of fewer relapses to mania with olanzapine, risperidone, and quetiapine compared to placebo. Moderate quality evidence (imprecise, medium-sized samples) also suggests fewer relapses to mania with aripiprazole.** **Moderate to high quality evidence suggests small effects of fewer relapses to depression with olanzapine and quetiapine than with placebo, with no differences in depression relapses between risperidone or aripiprazole and placebo.** **Moderate to high quality evidence suggests medium-sized effects of less insomnia with olanzapine and quetiapine than with placebo, with no differences in rates of insomnia between aripiprazole or risperidone and placebo.** **Moderate to low quality evidence (very imprecise) suggests medium-sized effects of more weight gain with olanzapine, risperidone, quetiapine or aripiprazole than with placebo. There were medium-sized effects of more tremor with aripiprazole and risperidone than with placebo, with no differences in rates of tremor between olanzapine or quetiapine and placebo. There was a medium-sized effect of more restlessness with aripiprazole than with placebo, with no differences in rates of restlessness between risperidone, olanzapine or quetiapine and placebo. There were medium-sized effects of more sedation with olanzapine and quetiapine than with placebo, with no differences between aripiprazole, risperidone or ziprasidone and placebo.**
Any relapse	
Significant, small effects of fewer relapses with olanzapine, risperidone, quetiapine and aripiprazole; Olanzapine: 2 RCTs, N = 627, RR = 0.52, 95%CI 0.38 to 0.71, $p < 0.0001$, $I^2 = 66\%$, $p = 0.09$ Risperidone: 2 RCTs, N = 542, RR = 0.61, 95%CI 0.47 to 0.80, $p = 0.0002$, $I^2 = 43\%$, $p = 0.18$ Quetiapine: 2 RCTs, N = 1392, HR = 0.37, 95%CI 0.31 to 0.45, $p < 0.05$, I^2 not reported	

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Aripiprazole: 1 RCT, N = 161, RR = 0.56, 95%CI 0.35 to 0.89, *p* = 0.01	
Mania symptoms	
Significant, medium-sized effects of fewer relapses to mania with olanzapine, risperidone, quetiapine and aripiprazole; Olanzapine: 2 RCTs, N = 627, RR = 0.37, 95%CI 0.27 to 0.51, *p* < 0.00001, I^2 = 0%, *p* = 0.96 Risperidone: 2 RCTs, N = 542, RR = 0.42, 95%CI 0.28 to 0.62, *p* < 0.0001, I^2 = 45%, *p* = 0.18 Quetiapine: 2 RCTs, N = 1392, HR = 0.38, 95%CI 0.29 to 0.50, *p* < 0.05, I^2 not reported Aripiprazole: 1 RCT, N = 160, RR = 0.34, 95%CI 0.14 to 0.81, *p* = 0.01	
Depression symptoms	
Significant, small effects of fewer relapses to depression with olanzapine and quetiapine, with no significant differences between risperidone and aripiprazole and placebo; Olanzapine: 2 RCTs, N = 627, RR = 0.73, 95%CI 0.55 to 0.96, *p* = 0.02, I^2 = 3%, *p* = 0.51 Risperidone: 2 RCTs, N = 542, RR = 1.21, 95%CI 0.81 to 1.80, *p* = 0.35, I^2 = 0%, *p* = 0.61 Quetiapine: 2 RCTs, N = 1392, HR = 0.37, 95%CI 0.28 to 0.48, *p* < 0.05, I^2 not reported Aripiprazole: 1 RCT, N = 160, RR = 0.88, 95%CI 0.39 to 2.01, *p* = 0.77	
Risks	Authors report small effects of less discontinuation of treatment for any reason with aripiprazole and risperidone, but not with olanzapine or quetiapine compared to placebo. *There were medium-sized effects of more weight gain with all second-generation antipsychotics than with placebo;* Olanzapine: 4 RCTs, N = 1142, OR = 3.47, 95%CI 2.36 to 5.10, *p* = 0.0001, I^2 = 0%, *p* = 0.65 Risperidone: 2 RCTs, N = 427, OR = 4.58, 95%CI 1.70 to 12.35, *p* = 0.003, I^2 = 0%, *p* = 0.85 Quetiapine: 2 RCTs, N = 1326, OR = 3.39, 95%CI 1.87 to 6.13, *p* = 0.00001, I^2 = 0%, *p* = 0.51 Aripiprazole: 3 RCTs, N = 790, OR = 2.59, 95%CI 1.46 to 4.59, *p* = 0.001, I^2 = 56%, *p* = 0.11 *There were medium-sized effects of more tremor with aripiprazole and risperidone than with placebo (no significant differences for olanzapine and quetiapine);* Risperidone: 2 RCTs, N = 427, OR = 2.40, 95%CI 1.05 to 5.50, *p* = 0.04, I^2 = 0%, *p* = 0.53 Aripiprazole: 2 RCTs, N = 501, OR = 4.15, 95%CI 1.17 to 14.77, *p* = 0.03, I^2 = 0%, *p* = 0.36 *There was a medium-sized effect of more restlessness with aripiprazole than with placebo (no significant differences for*

	risperidone, olanzapine and quetiapine); Aripiprazole: 2 RCTs, N = 501, OR = 2.22, 95%CI 1.06 to 4.64, p = 0.03, I^2 = 0%, p = 0.34 *There were medium-sized effects of more sedation with olanzapine and quetiapine than with placebo (no significant differences for aripiprazole, risperidone or ziprasidone);* Olanzapine: 4 RCTs, N = 1142, OR = 2.80, 95%CI 1.76 to 4.43, p = 0.0001, I^2 = 0%, p = 0.70 Quetiapine: 4 RCTs, N = 2956, OR = 2.61, 95%CI 1.79 to 3.82, p = 0.00001, I^2 = 44%, p = 0.15 *There were medium-sized effects of less insomnia with olanzapine and quetiapine than with placebo (no significant differences for aripiprazole and risperidone);* Olanzapine: 4 RCTs, N = 1142, OR = 0.26, 95%CI 0.15 to 0.45, p < 0.0001, I^2 = 36%, p = 0.19 Quetiapine: 4 RCTs, N = 2956, OR = 0.37, 95%CI 0.29 to 0.49, p = 0.00001, I^2 = 11%, p = 0.34
Consistency in results	Consistent
Precision in results	Precise for any and mania relapse, apart from aripiprazole. Precise for depression relapse, apart from risperidone and aripiprazole. Imprecise for all side effects, apart from insomnia.
Directness of results	Direct
Comparison 2	**Second-generation antipsychotics olanzapine or quetiapine vs. lithium or valproate.** **Authors report some risk of bias in primary studies.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, direct, consistent where applicable, some risk of bias) suggests a small effect of fewer relapses to depression, but not mania, with quetiapine compared to lithium or valproate, with a trend effect for olanzapine for any relapse.**
Any relapse	
Significant, small effect of fewer relapses with quetiapine, but not olanzapine compared to lithium or valproate; Quetiapine: 1 RCT, N = 768, HR = 0.66, 95%CI 0.49 to 0.88, p < 0.05 Olanzapine: 2 RCTs, N = 682, RR = 0.80, 95%CI 0.63 to 1.03, p = 0.09, I^2 = 0%, p = 0.38	

Mania symptoms	
No significant differences between groups; Quetiapine: 1 RCT, N = 768, HR = 0.78, 95%CI 0.53 to 1.15, $p > 0.05$ Olanzapine: 2 RCTs, N = 682, RR = 0.67, 95%CI 0.39 to 1.15, $p = 0.14$, $I^2 = 16\%$, $p = 0.27$	
Depression symptoms	
Significant, small effect of fewer relapses to depression with quetiapine, but not olanzapine compared to lithium or valproate; Quetiapine: 1 RCT, N = 768, HR = 0.54, 95%CI 0.35 to 0.84, $p < 0.05$ Olanzapine: 2 RCTs, N = 682, RR = 1.44, 95%CI 0.92 to 2.24, $p = 0.11$, $I^2 = 0\%$, $p = 0.89$	
Consistency in results	Consistent for olanzapine, not applicable for quetiapine (1 RCT).
Precision in results	Precise for any relapse, imprecise for mania and depression data.
Directness of results	Direct
Comparison 3	**Second-generation antipsychotics aripiprazole, olanzapine, quetiapine, risperidone or ziprazidone + lithium or valproate vs. placebo + lithium or valproate.** **Authors report some risk of bias in primary studies.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, direct, consistent, some risk of bias) suggests significant, small effects of fewer relapses to mania or depression with quetiapine + lithium or valproate.** **Moderate to low quality evidence (imprecise and/or 1 RCT) suggests significant, small effects of fewer relapses to mania with aripiprazole or risperidone + lithium or valproate, and fewer (any) relapse with olanzapine or ziprazidone + lithium or valproate.**
Any relapse	
Significant, small effects of fewer relapses with olanzapine, risperidone, quetiapine, aripiprazole or ziprazidone + lithium or valproate; Quetiapine: 2 RCTs, N = 1326, RR = 0.38, 95%CI 0.32 to 0.46, $p < 0.00001$, $I^2 = 0\%$, $p = 0.84$ Aripiprazole: 2 RCTs, N = 688, RR = 0.65, 95%CI 0.50 to 0.85, $p = 0.001$, $I^2 = 0\%$, $p = 0.57$ Olanzapine: 1 RCT, N = 99, RR = 0.49, 95%CI 0.27 to 0.91, $p = 0.02$ Risperidone: 1 RCT, N = 124, RR = 0.50, 95%CI 0.30 to 0.85, $p = 0.01$ Ziprazidone: 1 RCT, N = 240, RR = 0.62, 95%CI 0.40 to 0.96, $p = 0.01$	

Mania symptoms	
Significant, medium-sized effects of fewer relapses to mania with risperidone, quetiapine or aripiprazole + lithium or valproate, but not olanzapine + lithium or valproate; Quetiapine: 2 RCTs, N = 1326, RR = 0.39, 95%CI 0.30 to 0.52, $p < 0.00001$, $I^2 = 0\%$, $p = 0.69$ Aripiprazole: 2 RCTs, N = 688, RR = 0.46, 95%CI 0.26 to 0.80, $p = 0.006$, $I^2 = 29\%$, $p = 0.23$ Risperidone: 1 RCT, N = 124, RR = 0.38, 95%CI 0.14 to 1.01, $p = 0.05$ Olanzapine: 1 RCT, N = 99, RR = 0.51, 95%CI 0.21 to 1.28, $p = 0.15$	
Depression symptoms	
Significant, medium-sized effect of fewer relapses to depression with quetiapine + lithium or valproate, but not risperidone, olanzapine or aripiprazole + lithium or valproate; Quetiapine: 2 RCTs, N = 1326, RR = 0.38, 95%CI 0.29 to 0.49, $p < 0.00001$, $I^2 = 0\%$, $p = 0.50$ Risperidone: 1 RCT, N = 124, RR = 0.66, 95%CI 0.29 to 1.53, $p = 0.33$ Olanzapine: 1 RCT, N = 99, RR = 0.44, 95%CI 0.20 to 0.98, $p = 0.15$ Aripiprazole: 2 RCTs, N = 688, RR = 0.76, 95%CI 0.54 to 1.16, $p = 0.23$, $I^2 = 0\%$, $p = 0.93$	
Consistency in results	Consistent where applicable (>1 RCT).
Precision in results	Precise for any relapse quetiapine and aripiprazole, mania relapse quetiapine, and depression relapse quetiapine.
Directness of results	Direct

Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A, Geddes JR, Kanba S

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis

The Lancet Psychiatry 2014; 1: 351-9

View review abstract online

Comparison 1	**Pharmaceutical treatments (antipsychotics, mood stabilisers/anticonvulsants and antidepressants) vs. placebo.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, some imprecision, and indirectness) suggests small to medium-sized effects of lithium, lithium + imipramine (but not for bipolar I disorder), lithium + oxcarbazepine, lithium + valproate,**

	lamotrigine, lamotrigine + aripiprazole, valproate, valproate + aripiprazole, olanzapine, quetiapine, and risperidone long-acting injections for preventing mood relapses over placebo. Placebo was significantly better tolerated than carbamazepine, lithium, and lithium + valproate (medium-sized effects).
Any relapse	
The following pharmaceutical treatments had a significantly lower risk of relapse than placebo (all small to medium-sized effects); 33 RCTs, N = 6,846 <u>Mood stabilisers/anticonvulsants</u> Lithium: RR = 0.62, 95%CI 0.53 to 0.72 Lithium + imipramine: RR = 0.62, 95%CI 0.40 to 0.96 (This effect was not significant when patients with bipolar I disorder were analysed separately) Lithium + oxcarbazepine: RR = 0.40, 95%CI 0.21 to 0.79 Lithium + valproate: RR = 0.52, 95%CI 0.35 to 0.77 Lamotrigine: RR = 0.76, 95%CI 0.62 to 0.94 Lamotrigine + aripiprazole: RR = 0.53, 95%CI 0.32 to 0.88 Valproate: RR = 0.63, 95%CI 0.47 to 0.83 Valproate + aripiprazole: RR = 0.29, 95%CI 0.22 to 0.76 <u>Antipsychotics</u> Olanzapine: RR = 0.50, 95%CI 0.39 to 0.63 Quetiapine: RR = 0.52, 95%CI 0.40 to 0.68 Risperidone long-acting injection: RR = 0.64, 95%CI 0.48 to 0.85 Aripiprazole + lamotrigine: RR = 0.53, 95%CI 0.32 to 0.88 Aripiprazole + valproate: RR = 0.29, 95%CI 0.22 to 0.76	
Risks	Placebo was significantly better tolerated than carbamazepine, lithium, and lithium + valproate (medium-sized effects).
Consistency in results	Consistent
Precision in results	Some imprecision
Directness of results	Some indirectness
Comparison 2	**Pharmaceutical treatments (antipsychotics, mood stabilisers/anticonvulsants and antidepressants) vs. other pharmaceutical treatments.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, some imprecision and indirectness) suggests small to medium-sized**

	effects of fewer relapses with olanzapine than imipramine, paliperidone, or lamotrigine. Fewer relapses with quetiapine than with imipramine or lamotrigine. Fewer relapses with lithium or lithium + valproate than imipramine. Fewer relapses with aripiprazole + valproate than imipramine or paliperidone. Lamotrigine was significantly better tolerated than carbamazepine, lithium, and lithium + valproate (medium to large effects).
Any relapse	
The following pharmaceutical treatments had a significantly lower risk of relapse over other pharmaceutical treatments (small to medium-sized effects); 33 RCTs, N = 6,846 Olanzapine over imipramine: RR = 0.53, 95%CI 0.34 to 0.80 Olanzapine over paliperidone: RR = 0.60, 95%CI 0.37 to 0.94 Olanzapine over lamotrigine: RR = 0.66, 95%CI 0.48 to 0.89 Quetiapine over imipramine: RR = 0.55, 95%CI 0.36 to 0.86 Quetiapine over lamotrigine: RR = 0.69, 95%CI 0.50 to 0.96 Lithium over imipramine: RR = 0.55, 95%CI 0.33 to 0.90 Lithium + valproate over imipramine: RR = 0.52, 95%CI 0.35 to 0.77 Lithium + oxcarbazepine over imipramine: RR = 0.43, 95%CI 0.20 to 0.89 Aripiprazole + valproate over imipramine: RR = 0.30, 95%CI 0.11 to 0.84 Aripiprazole + valproate over paliperidone: RR = 0.34, 95%CI 0.12 to 0.99	
Risks	Lamotrigine was significantly better tolerated than carbamazepine, lithium, and lithium + valproate (medium to large effects).
Consistency in results	Consistent
Precision in results	Some imprecision
Directness of results	Some indirectness

Explanation of acronyms

CI = Confidence Interval, HR = hazard ratio, 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), RCT = randomised controlled trial, RR = relative risk, vs. = versus, WMD = weighted mean difference

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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[6].

† 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).

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[6].

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

Correlation coefficients (eg, r) indicate the strength of association or relationship

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

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

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

§ 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[8].

‖ 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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