TECHNICAL COMMENTARY

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.

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[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

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

Results

We found six reviews that met our inclusion criteria[3-8].

Efficacy

- Moderate to high quality evidence finds maintaining antipsychotic or mood stabiliser treatment is associated with fewer relapses than discontinuing antipsychotic or mood stabiliser treatment.
- Moderate quality evidence finds the following medications reduced overall relapse rates more than placebo (in descending order of effectiveness); asenapine, aripiprazole + valproate, lithium + oxcarbazepine, olanzapine, aripiprazole once monthly, lithium + valproate, quetiapine, aripiprazole + lamotrigine, aripiprazole, lithium, valproate, risperidone long-acting injectable, and lamotrigine. Carbamazepine and paliperidone performed no better than placebo.

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- Moderate quality evidence finds a medium-sized reduction in relapse to any mood episode after six months of treatment with second-generation antipsychotics plus mood stabilisers compared to placebo plus mood stabilisers (mostly lithium or valproate). The effect size was similar for relapse to depression or relapse to mania. Aripiprazole + mood stabilisers and quetiapine + mood stabilisers prevented both depression and mania relapses, while lurasidone + mood stabilisers was more effective for preventing relapse to depression, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania.
- Moderate quality evidence suggests fewer relapses 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.
- 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.

Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Mishima K, Iwata N

Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials

Molecular Psychiatry 2021; 26(8): 4146-57

View review abstract online

Comparison 1	**Any medication or combination medications vs. placebo or other medications.** **Mean study duration 70.5 weeks.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, mostly imprecise, indirect) finds the following medications reduced overall relapse rates more than placebo (in descending order of effectiveness); asenapine, aripiprazole + valproate, lithium + oxcarbazepine, olanzapine, aripiprazole once monthly, lithium + valproate, quetiapine, aripiprazole + lamotrigine, aripiprazole, lithium, valproate, risperidone long-acting injectable, and lamotrigine. Carbamazepine and paliperidone performed no better than placebo.** **For mania relapse, all active treatments performed better than placebo, apart from carbamazepine, lamotrigine, aripiprazole + valproate, and lamotrigine + valproate.** **For depression relapse, all active treatments performed better than placebo, apart from aripiprazole + valproate, lamotrigine, lamotrigine + valproate, lithium, olanzapine, and quetiapine.** **For all-cause discontinuation, asenapine, lithium, olanzapine, quetiapine, and valproate performed better than placebo.**

Relapse to any mood episode

42 RCTs, N = 9,821

The following treatments reduced overall relapse rates more than placebo (in descending order of effectiveness);

Asenapine: RR = 0.262, 95%CI 0.133 to 0.517, $p < 0.05$

Aripiprazole + valproate: RR = 0.292, 95%CI 0.114 to 0.748, $p < 0.05$

Lithium + oxcarbazepine: RR = 0.409, 95%CI 0.212 to 0.792, $p < 0.05$

Olanzapine: RR = 0.500, 95%CI 0.400 to 0.625, $p < 0.05$

Aripiprazole once monthly: RR = 0.519, 95%CI 0.335 to 0.803, $p < 0.05$

Lithium + valproate: RR = 0.525, 95%CI 0.363 to 0.760, $p < 0.05$

Quetiapine: RR = 0.526, 95%CI 0.411 to 0.674, $p < 0.05$ Aripiprazole + lamotrigine: RR = 0.530, 95%CI 0.324 to 0.868, $p < 0.05$ Aripiprazole: RR = 0.619, 95%CI 0.383 to 0.999, $p < 0.05$ Lithium: RR = 0.624, 95%CI 0.537 to 0.725, $p < 0.05$ Valproate: RR = 0.634, 95%CI 0.485 to 0.829, $p < 0.05$ Risperidone long-acting injectable: RR = 0.637, 95%CI 0.484 to 0.839, $p < 0.05$ Lamotrigine: RR = 0.764, 95%CI 0.628 to 0.930, $p < 0.05$ Carbamazepine and paliperidone performed no better than placebo. Asenapine outperformed aripiprazole, carbamazepine, lamotrigine, lithium, paliperidone, risperidone long-acting injectable, and valproate. Olanzapine, quetiapine, and aripiprazole + valproate outperformed lamotrigine and paliperidone. For mania relapse, all active treatments performed better than placebo, apart from carbamazepine, lamotrigine, aripiprazole + valproate, and lamotrigine + valproate. For depression relapse, all active treatments performed better than placebo, apart from aripiprazole + valproate, lamotrigine, lamotrigine + valproate, lithium, olanzapine, and quetiapine.	
Risks	Asenapine, lithium, olanzapine, quetiapine, and valproate outperformed placebo for all-cause discontinuation.
Consistency in results‡	Authors report results are reasonably consistent
Precision in results§	Mostly imprecise
Directness of results‖	Indirect (network meta-analysis)
Comparison 2	**Second-generation antipsychotics plus lithium or valproate vs. placebo plus lithium or valproate.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, some imprecision, indirect) finds the following antipsychotics added to lithium or valproate reduced overall relapse rates more than placebo added to lithium or valproate (in descending order of effectiveness); quetiapine, lurasidone, aripiprazole and ziprasidone. Adding olanzapine performed no better than adding placebo.** **For mania relapse, adding aripiprazole or quetiapine outperformed placebo. For depression relapse, adding lurasidone or quetiapine outperformed placebo, aripiprazole, and ziprasidone.** **For all-cause discontinuation, adding lurasidone or quetiapine outperformed placebo.**
Relapse to any mood episode	

5 RCTs, N = 2,399 *The following treatments reduced overall relapse rates more than placebo (in descending order of effectiveness);* Quetiapine + lithium or valproate: RR = 0.383, 95%CI 0.322 to 0.456, $p < 0.05$ Lurasidone + lithium or valproate: RR = 0.402, 95%CI 0.306 to 0.528, $p < 0.05$ Aripiprazole + lithium or valproate: RR = 0.595, 95%CI 0.396 to 0.894, $p < 0.05$ Ziprasidone + lithium or valproate: RR = 0.607, 95%CI 0.390 to 0.944, $p < 0.05$ Olanzapine + lithium or valproate performed no better than placebo. Lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed olanzapine + lithium or valproate. For mania relapse, aripiprazole + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate. For depression relapse, lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate, aripiprazole + lithium or valproate, and ziprasidone + lithium or valproate.	
Risks	Lurasidone + lithium or valproate and quetiapine + lithium or valproate outperformed placebo + lithium or valproate for all-cause discontinuation. Quetiapine + lithium or valproate was associated with a higher incidence of somnolence compared with placebo + lithium or valproate. Olanzapine + lithium or valproate and quetiapine + lithium or valproate were associated with a lower incidence of insomnia compared with placebo + lithium or valproate. Olanzapine + lithium or valproate and quetiapine + lithium or valproate were associated with a higher incidence of increased weight compared with placebo + lithium or valproate and Aripiprazole + lithium or valproate.
Consistency in results	Authors report results are reasonably consistent.
Precision in results	Precise for quetiapine and lurasidone analyses only.
Directness of results	Indirect (network meta-analysis)

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Kishi T, Matsuda Y, Sakuma K, Okuya M, Mishima K, Iwata N

Recurrence rates in stable bipolar disorder patients after drug discontinuation v. drug maintenance: a systematic review and meta-analysis

Psychological medicine 2020; 51(15: 2721-2729

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Comparison	**Recurrence rates following antipsychotic/mood stabiliser discontinuation vs. antipsychotic/mood stabiliser maintenance.** **Mean study duration was 64.50 ± 69.35 weeks of discontinuation or maintenance of aripiprazole, asenapine, divalproex, long-acting injectable aripiprazole, long-acting injectable risperidone, lamotrigine, lithium, olanzapine, paliperidone, or quetiapine.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds maintaining antipsychotic/mood stabiliser treatment is associated with fewer relapses than discontinuing antipsychotic/mood stabiliser treatment. Maintaining treatment was also associated with less all-cause discontinuation.**
Relapse to any mood episode	
The maintenance group demonstrated lower recurrence rates of any mood episode at 6 months; Any relapse: 20 RCTs, N = 4,178, RR = 0.61, 95%CI 0.54 to 0.70, $p < 0.05$, $I^2 = 75\%$ Depressive relapse: 18 RCTs, N = 3,770, RR = 0.72, 95%CI 0.60 to 0.87, $p < 0.05$, $I^2 = 73\%$ Mania/hypomania/mixed relapse: 17 RCTs, N = 3,717, RR = 0.45, 95%CI 0.36 to 0.57, $p < 0.05$, $I^2 = 72\%$	
Risks	The maintenance group demonstrated reduced all-cause discontinuation in the study.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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).

Kishi T, Sakuma K, Okuya M, Matsuda Y, Esumi S, Hashimoto Y, Hatano M, Miyake N, Miura I, Mishima K, Iwata N

Effects of a conventional mood stabilizer alone or in combination with second-generation antipsychotics on recurrence rate and discontinuation

rate in bipolar I disorder in the maintenance phase: A systematic review and meta-analysis of randomized, placebo-controlled trials

Bipolar Disorders: 2021; doi: 10.1111/bdi.13053

View review abstract online

Comparison	**Second-generation antipsychotics (aripiprazole, lurasidone, olanzapine, quetiapine, or ziprasidone) + mood stabilisers (lithium, valproate, lamotrigine, or divalproex) vs. placebo + mood stabilisers.** **Mean study duration = 58.25 ± 33.63 weeks**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) finds a medium-sized reduction in relapse to any mood episode after 6 months of treatment with second-generation antipsychotics plus mood stabilisers compared to placebo plus mood stabilisers. The effect size was similar for relapse to depression or relapse to mania. Aripiprazole + mood stabilisers and quetiapine + mood stabilisers prevented both depression and mania relapses, while lurasidone + mood stabilisers was more effective for preventing relapse to depression, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania.**
Relapse to any mood episode	
A medium-sized effect showed second-generation antipsychotics plus mood stabilisers showed lower rates of any relapse by 6 months than placebo plus mood stabilisers; 8 RCTs, N = 2,850, RR = 0.51, 95%CI 0.39 to 0.86, $p < 0.05$, $I^2 = 73\%$ Subgroup analysis showed similar effect sizes for relapse to mania (RR = 0.42) and depression (RR = 0.39). Results were similar to the overall results for aripiprazole + mood stabilisers and quetiapine + mood stabilisers, while lurasidone + mood stabilisers was more effective for preventing relapse to depression than mania, and ziprasidone + mood stabilisers was more effective for preventing relapse to mania than depression.	
Risks	There was less all-cause discontinuation with second-generation antipsychotics + mood stabilisers.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

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 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 Mood stabilisers/anticonvulsants 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 Antipsychotics 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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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[9].

† 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[9].

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[10]. 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[9];

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

§ 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[11].

‖ 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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