TECHNICAL COMMENTARY

Aripiprazole

Introduction

The treatment of bipolar disorder is complex due to the presence of varying configurations of symptoms in patients. The primary treatments for bipolar disorder are pharmacological, and often involve second generation antipsychotic drugs, such as aripiprazole. Aripiprazole is is a partial agonist of dopamine D2 and serotonin 5-HT1A receptors and an antagonist of 5-HT2A receptors. It has a distinct receptor-binding profile compared to other second generation antipsychotic drugs.

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, the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items 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 seven reviews that met our inclusion criteria[3-9].

Symptoms

- Moderate quality evidence suggests a small effect of greater improvement in mania and psychotic symptoms and greater response to treatment with aripiprazole compared to placebo. This effect is large in pediatric patients. Moderate to low quality evidence suggests no significant differences in mania symptoms between aripiprazole and other medications.
- Moderate to high quality evidence suggests no significant differences between

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aripiprazole monotherapy and placebo for depression symptoms, or response to treatment. Moderate quality evidence suggests greater improvement in depression symptoms, response to treatment, and remission with lurasidone monotherapy than with aripiprazole monotherapy.

- Moderate quality evidence suggests greater overall improvement in symptoms with aripiprazole than with haloperidol or lithium, with no differences in acute depression or response for mania between these medications.

Relapse

- Moderate quality evidence suggests medium-sized effects of fewer relapses with aripiprazole + valproate or aripiprazole + lamotrigine than with placebo.
- Moderate quality evidence suggests medium-sized effects of fewer relapses with aripiprazole + valproate than with paliperidone or imipramine.

Switching to mania or depression

- Moderate to low quality suggests a large, significant effect of more switching to mania with aripiprazole than with quetiapine or ziprasidone. Moderate to high quality evidence suggests no significant differences in switching to mania between aripiprazole and placebo.
- Moderate quality evidence suggests no significant differences in switching to depression between aripiprazole and haloperidol.

Side effects

- Moderate quality evidence suggests more high-density lipoprotein, sedation, extrapyramidal symptoms, constipation, nausea, vomiting, anxiety, salivation, fatigue, insomnia, and pain in the extremities with aripiprazole than with placebo. However, there was less hyperprolactinemia, less elevated fasting glucose, less increased appetite, and less total cholesterol with aripiprazole than with placebo.
- Moderate to low quality evidence more activation symptoms with aripiprazole than other antimanic medications.

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Goikolea JM, Colom F, Torres I, Capapey J, Valenti M, Undurraga J, Grande I, Sanchez-Moreno J, Vieta E

Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol

Journal of Affective Disorders 2013; 144: 191-8

View review abstract online

Comparison	**Aripiprazole monotherapy or add-on vs. haloperidol monotherapy or add-on.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests no significant differences in rates of switching to depression between aripiprazole and haloperidol.**
Switch to depression	
No significant differences between groups; 2 RCTs, N = 669, RR = 0.93, 95%CI 0.60 to 1.45, $p > 0.05$, $I^2 = 84\%$, $p = 0.01$	
Consistency in results‡	Inconsistent
Precision in results§	Imprecise
Directness of results‖	Direct

Kadakia A, Dembek C, Heller V, Singh R, Uyei J, Hagi K, Nosaka T, Loebel A

Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis

BMC Psychiatry 2021; 21: 249

View review abstract online

Comparison	**Aripiprazole vs. placebo or other second-generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistencies, direct) finds no benefit of aripiprazole over placebo for acute depression. Lower quality evidence (indirect)**

	finds aripiprazole was less efficacious than olanzapine and quetiapine, and there were no differences when aripiprazole was compared to lurasidone, ziprasidone, and cariprazine.
Response for acute depression	
No significant differences between aripiprazole and placebo; 2 studies, N not reported, MD = -1.07, 95%CI -3.03 to 0.89, $p > 0.05$ Network analysis showed aripiprazole was less efficacious than olanzapine and quetiapine.	
Risks	There was more all-cause discontinutation with aripiprazole than with placebo.
Consistency in results	Authors report some inconsistencies.
Precision in results	Unable to assess; MDs are not standardised.
Directness of results	Direct for pairwise comparison with placebo only.

Li DJ, Tseng PT, Stubbs B, Chu CS, Chang HY, Vieta E, Fornaro M, Carvalho AF, Solmi M, Veronese N, Chen TY, Chen YW, Lin PY, Chow PC

Efficacy, safety and tolerability of aripiprazole in bipolar disorder: An updated systematic review and meta-analysis of randomized controlled trials

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2017; 79: 289-301

View review abstract online

Comparison 1	**Aripiprazole monotherapy or add-on vs. placebo for acute bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, some imprecision, direct) suggests small effects of greater improvement on rating scales for mania symptoms with aripiprazole, and larger effects for remission and response rates for mania.** **Moderate to high quality evidence (large samples, consistent, precise, direct) suggests small effects of greater improvement on rating scales for psychosis symptoms with aripiprazole, and no effect for depression symptoms.** **Aripiprazole was associated with more constipation, nausea,**

	vomiting, extrapyramidal symptoms, anxiety, salivation, fatigue, insomnia, over-sedation, and pain in the extremities. Aripiprazole was associated with a lower rates of elevated fasting glucose, increased appetite, and total cholesterol. **There were no significant differences in BMI, body weight, high density lipoprotein, triglycerides, diarrhea, indigestion, dizziness, agitation, headache or light headedness.**
Acute mania symptoms	
Small, significant improvements in mania symptoms; 5 RCTs, N = 1,332, *g* = -0.299, 95%CI -0.476 to -0.123, *p* = 0.001, I^2 = 66%, *p* = 0.008 Meta-regression showed older sample age was correlated with increased effect size. There were no moderating effects of sex, dose, ethnicity or type of disorder (percentage of manic mood state, rapid-cycling, or mixed episodes).	
Remission and response for mania	
A medium to large effect of increased remission rates with aripiprazole than placebo; 3 RCTs, N = 824, OR = 4.893, 95%CI 1.373 to 17.432, *p* = 0.014, I^2 = 88%, *p* < 0.001 *A small to medium effect of increased response rates with aripiprazole than placebo;* 5 RCTs, N = 1,497, OR = 2.054, 95%CI 1.366 to 3.089, *p* = 0.001, I^2 = 72%, *p* = 0.002	
Psychotic symptoms	
Small, significant improvements in psychotic symptoms; 4 RCTs, N = 1,330, *g* = -0.296, 95%CI -0.411 to -0.181, *p* < 0.001, I^2 = 0%, *p* = 0.992	
Acute depression symptoms	
No significant differences in depression symptoms; 4 RCTs, N = 931, *g* = -0.127, 95%CI -0.257 to 0.002, *p* = 0.054, I^2 = 9%, *p* =0.353 Meta-regressions showed no moderating effects of age, sex, dose, ethnicity or study quality.	
Clinical global impression	
A small to medium effect of greater improvement with aripiprazole than placebo; 9 RCTs, N = 2,450, *g* = -0.322, 95%CI -0.418 to -0.225, *p* < 0.001, I^2 = 40%, *p* = 0.082	
Risks	Aripiprazole was associated with higher rates of discontinuation than placebo due to side effects. These side effects included constipation, nausea, vomiting, extrapyramidal symptoms, anxiety, salivation, fatigue, insomnia, over-sedation, and pain in the extremities.

	Aripiprazole was associated with a lower risk of elevated fasting glucose, increased appetite, and total cholesterol. There were no significant differences in BMI, body weight, high density lipoprotein, triglycerides, diarrhea, indigestion, dizziness, agitation, headache or light headedness.
Consistency in results	Consistent for all outcomes apart from mania.
Precision in results	Precise for all outcomes apart from remission and response for mania.
Directness of results	Direct
Comparison 2	**Aripiprazole monotherapy or add-on vs. placebo for maintenance of bipolar disorder (non-acute).**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests greater overall improvement in symptoms with aripiprazole than with placebo.** **Aripiprazole was associated with higher rates of discontinuation than placebo due to side effects. These side effects included diarrhea, dry mouth, akathisia, and increased high-density lipoprotein.** **There were no significant differences in the rates of headache, upper respiratory-tract infection, fasting glucose, body weight, total cholesterol, or triglycerides.**
Clinical global impression	
A medium-sized effect of greater improvement with aripiprazole than placebo; 2 RCTs, N = 333, g = -0.483, 95%CI -0.674 to -0.292, $p < 0.001$, $I^2 = 0\%$, $p = 0.488$	
Risks	Aripiprazole was associated with higher rates of discontinuation than placebo due to side effects. These side effects included diarrhea, dry mouth, akathisia, and increased high-density lipoprotein. There were no significant differences in the rates of headache, upper respiratory-tract infection, fasting glucose, body weight, total cholesterol, or triglycerides.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 3	**Aripiprazole + other medications (lamotrigine, psychostimulant,**

	or valproate) vs. placebo for maintenance of bipolar disorder.
Summary of evidence	**Moderate quality evidence (medium-large sample, consistent, imprecise, indirect) suggests fewer relapses to mania with aripiprazole combination therapy than with placebo.**
Relapse rates for mania	
A medium-sized effect of fewer relapses to mania with aripiprazole combination therapy; 3 RCTs, N = 494, OR = 0.522, 95%CI 0.291 to 0.937, p = 0.029, I^2 = 0%, p = 0.534	
Risks	Aripiprazole was associated with increased total cholesterol, with no differences in fasting glucose, triglycerides, or headaches.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Indirect (various combination medications)
Comparison 4	**Aripiprazole vs. other medications (lithium or haloperidol) for acute or maintenance of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, some imprecision, indirect) suggests greater overall improvement in symptoms with aripiprazole than with haloperidol or lithium, with no differences in acute depression or response for mania.** **There were no significant differences in discontinuation due to side effects, akathisia, extrapyramidal symptoms, headache or tremor.**
Clinical global impression	
A small effect of greater improvement with aripiprazole than haloperidol or lithium; 3 RCTs, N = 994, g = -0.191, 95%CI -0.315 to -0.067, p = 0.003, I^2 = 0%, p = 0.439	
Acute depression symptoms	
No significant differences between groups; 3 RCTs, N = 994, g = -0.039, 95%CI -0.193 to 0.115, p = 0.620, I^2 = 35%, p = 0.214	
Response for mania	
No significant differences between groups; 3 RCTs, N = 1,031, OR = 1.271, 95%CI 0.647 to 2.496, p = 0.486, I^2 not reported	

Risks	No significant differences in discontinuation due to side effects, akathisia, extrapyramidal symptoms, headache or tremor.
Consistency in results	Consistent for clincal global impression and depression. Unable to assess response for mania (not reported).
Precision in results	Precise for clincal global impression and depression, imprecise for response for mania.
Directness of results	Indirect (various combination medications)

Meduri M, Gregoraci G, Baglivo V, Balestrieri M, Isola M, Brambilla P

A meta-analysis of efficacy and safety of aripiprazole in adult and pediatric bipolar disorder in randomized controlled trials and observational studies

Journal of Affective Disorders 2016; 191: 187-208

View review abstract online

Comparison 1	**Aripiprazole with or without antimanic medications vs. placebo.** **Samples included people with bipolar disorder or schizoaffective disorder who had a manic or mixed episode with or without psychotic symptoms.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, indirect) suggests a small effect of greater improvement in mania symptoms with aripiprazole. This effect was large in the subgroup analysis of pediatric patients. Rates of sedation and extrapyramidal side effects were higher with aripiprazole, and rates of hyperprolactinemia were lower with aripiprazole. Drop-out rate differences were inconclusive.**

Mania symptoms

Small, significant effects of greater improvement in mania symptoms with aripiprazole;

By 3 weeks: 6 studies, N = 1,781, SMD = -0.31, 95%CI -0.46 to -0.16, $p < 0.05$, $I^2 = 58.2\%$, $p = 0.035$

By 12 weeks: 6 studies, N = 1,773, SMD = -0.48, 95%CI -0.78 to -0.18, $p < 0.05$, $I^2 = 88.6\%$, $p < 0.0001$

There was a large effect in the subgroup analysis of pediatric patients, favouring aripiprazole;

By 12 weeks: 2 studies, N = 339, SMD = -1.08, 95%CI -1.32 to -0.85, $p < 0.05$, $I^2 = 0\%$, $p = 0.566$

Authors report no evidence of publication bias.

Response	
Small, significant effects of greater response to treatment with aripiprazole; By 3 weeks: 6 studies, N = 1,781, RR = 1.41, 95%CI 1.25 to 1.58, $p < 0.05$, $I^2 = 40.6\%$, $p = 0.135$ By 12 weeks: 6 studies, N = 1,797, RR = 1.28, 95%CI 1.09 to 1.50, $p < 0.05$, $I^2 = 58.8\%$, $p = 0.024$ *There was a large effect in the subgroup analysis of pediatric patients, favouring aripiprazole;* By 12 weeks: 2 studies, N = 332, RR = 1.92, 95%CI 1.44 to 2.56, $p < 0.05$, $I^2 = 0\%$, $p = 0.560$ Subgroup/regression analyses found no modulating effects of dose, study design, and whether aripiprazole was administered alone or as an adjunctive treatment.	
Treatment drop outs	
A small, significant effect of fewer drop-outs with aripiprazole; By 3 weeks: 6 studies, N = 1,883, RR = 0.90, 95%CI 0.82 to 0.98, $p < 0.05$, $I^2 = 32.5\%$, $p > 0.05$ *A small, significant effect of more drop-outs with aripiprazole;* By 12 weeks: 6 studies, N = 1,865, RR = 1.22, 95%CI 1.04 to 1.43, $p < 0.05$, $I^2 = 13.9\%$, $p > 0.05$	
Risks	Sedation and extrapyramidal side effects were more frequent with aripiprazole, with no significant differences between groups in weight gain, gastroenteric disturbances, or activation symptoms. There was a lower risk of hyperprolactinemia with aripiprazole than with placebo.
Consistency in results	Inconsistent for mania symptoms and response rates by 12 weeks. Consistent for compliance.
Precision in results	Precise
Directness of results	Indirect (mixed comparisons).
Comparison 2	**Aripiprazole with or without antimanic medications vs. antimanic medications.**
Summary of evidence	**Moderate to low quality evidence (large samples, some inconsistency and imprecision, indirect) suggests no differences in symptoms, response or treatment drop-out between aripiprazole and other antimanic medications. There may be an increased risk of activation symptoms with aripiprazole.**
Mania symptoms	
No significant differences between groups;	

By 3 weeks: 3 studies, N = 974, SMD = 0.01, 95%CI -0.12 to 0.13, $p > 0.05$, $I^2 = 0\%$, $p = 0.682$ By 4-12 weeks: 3 studies, N = 689, SMD = -0.14, 95%CI -0.29 to 1.01, $p > 0.05$, $I^2 = 0\%$, $p = 0.852$	
Response	
No significant differences between groups; By 3 weeks: 3 studies, N = 974, RR = 1.16, 95%CI 0.84 to 1.61, $p > 0.05$, $I^2 = 78.3\%$, $p = 0.010$ By 12 weeks: 5 studies, N = 1,047, RR = 1.13, 95%CI 0.92 to 1.39, $p > 0.05$, $I^2 = 74.9\%$, $p = 0.003$ Subgroup/regression analyses found no differences in the effect size according to study design and whether aripiprazole was administered alone or as an adjunctive agent.	
Treatment drop outs	
No significant differences between groups; By 3 weeks: 6 studies, N = 994, RR = 0.80, 95%CI 0.52 to 1.23, $p > 0.05$, $I^2 = 84.4\%$, $p < 0.05$ *No significant differences between groups;* By 4-12 weeks: 5 studies, N = 1,067, RR = 0.92, 95%CI 0.70 to 1.21, $p > 0.05$, $I^2 = 75.2\%$, $p < 0.05$	
Risk	Activation symptoms were higher with aripiprazole use.
Consistency in results	Consistent for mania symptoms, inconsistent for response and compliance.
Precision in results	Precise for mania symptoms at 3 weeks only.
Directness of results	Indirect (mixed comparisons).

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	**Aripiprazole vs. placebo.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, some indirectness) suggests medium-sized effects of fewer relapses with aripiprazole + valproate or aripiprazole + lamotrigine than**

	with placebo. There were no significant differences between aripiprazole alone and placebo, and not differences in adverse events.
Any relapse	
No significant differences between groups for aripirazole alone compared to placebo, but there were fewer relapses with aripirazole + valproate or aripirazole + lamotrigine vs. placebo; Aripiprazole: RR = 0.62, 95%CI 0.38 to 1.03, $p > 0.05$ Aripiprazole + valproate: RR = 0.29, 95%CI 0.11 to 0.76, $p < 0.05$ Aripiprazole + lamotrigine: RR = 0.53, 95%CI 0.32 to 0.88, $p < 0.05$	
Risks	No significant differences in discontinuation due to adverse events.
Consistency in results	Authors state that the data were consistent.
Precision in results	Imprecise
Directness of results	Some indirectness
Comparison 2	**Aripiprazole vs. other pharmaceutical treatments.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, some indirectness) suggests medium-sized effects of fewer relapses with aripiprazole + valproate than with paliperidone or imipramine. There were no significant differences between aripiprazole with or without other medications, and any other medication. There were no differences in adverse events.**
Any relapse	
Medium-sized, significant effects of fewer relapses with aripirazole + valproate compared to paliperidone or imipramine; Aripiprazole + valproate vs. paliperidone: RR = 0.34, 95%CI 0.12 to 0.99, $p < 0.05$ Aripiprazole + valproate vs. imipramine: RR = 0.30, 95%CI 0.11 to 0.84, $p < 0.05$ Authors report no significant differences were found between aripiprazole alone, aripiprazole + valproate or aripiprazole +lamotrigine and any other medication.	
Risks	No significant differences in discontinuation due to adverse events.
Consistency in results	Authors state that the data were consistent.
Precision in results	Imprecise.
Directness of results	Some indirectness

Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A

Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis

World Journal of Biological Psychiatry 2017; 1-11

View review abstract online

Comparison	**Aripiprazole monotherapy vs. lurasidone monotherapy.**
Summary of evidence	**Moderate quality evidence (large sample, consistent, imprecise, some indirectness) suggests greater improvement in depression symptoms, response to treatment, and remission with lurasidone than with aripiprazole. There were no differences between groups in weight gain or somnolence.**
Clinical global impression	
Greater improvement in overall symptoms with lurasidone; Network meta-analysis, 14 studies, N = 6,221, MD = -0.42, 95%CI -0.78 to -0.07, $p < 0.05$	
Depression symptoms	
Greater improvement in depression symptoms with lurasidone; Network meta-analysis, 14 studies, N = 6,221, MD = -3.62, 95%CI -7.04 to -0.20, $p < 0.05$	
Response for depression	
A medium-sized effect of greater odds of response for depression with lurasidone; Network meta-analysis, 14 studies, N = 6,221, OR = 2.40, 95%CI 1.36 to 3.96, $p < 0.05$	
Remission	
A medium-sized effect of greater odds of remission with lurasidone; Network meta-analysis, 14 studies, N = 6,221, OR = 2.28, 95%CI 1.22 to 3.90, $p < 0.05$	
Risks	There were no significant differences in weight gain or somnolence.
Consistency in results	Authors report that the results are consistent.
Precision in results	Imprecise
Directness of results	Some indirectness

Taylor DM, Cornelius V, Smith L, Young AH

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

Acta Psychiatrica Scandinavica 2014; 130: 452-69

View review abstract online

Comparison 1	**Aripiprazole monotherapy or add-on vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests no significant differences between aripiprazole and placebo for depression, response to treatment or switching to mania. There were no differences between groups in rates of withdrawal from treatment (any reason).**
Depression symptoms	
No significant differences between groups; 2 RCTs, N = 749, SMD = -0.10, 95%CI -0.25 to 0.05, $p > 0.05$	
Response	
No significant differences between groups; 2 RCTs, N = 749, OR = 1.04, 95%CI 0.77 to 1.39, $p > 0.05$	
Switch to mania	
No significant differences between groups; 2 RCTs, N = 749, OR = 1.68, 95%CI 0.60 to 4.68, $p > 0.05$	
Risks	There were no differences between groups in rates of withdrawal from treatment (any reason).
Consistency in results	Authors report data are consistent.
Precision in results	Imprecise for response and switch to mania.
Directness of results	Direct (pairwise comparisons).
Comparison 2	**Aripiprazole vs. other medications.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, consistent, imprecise, indirect) suggests no significant**

	differences in depression symptoms between aripiprazole and any other medication. There were large, significant effects of more switching to mania with aripiprazole than with quetiapine or ziprasidone.
Depression symptoms	
No significant differences between groups between aripiprazole and any other medication; Network meta-analysis SMD ranged from -0.14 to 0.46, all $p > 0.05$	
Switch to mania	
Large, significant effects of more switching to mania with aripiprazole than with quetiapine or ziprasidone; Aripiprazole vs. quetiapine: network meta-analysis OR = 5.39, 95%CI 1.29 to 14.30, $p < 0.05$ Aripiprazole vs. ziprasidone: network meta-analysis OR = 11.40, 95%CI 1.16 to 47.20, $p < 0.05$ There were no other significant differences between aripiprazole and other medications.	
Consistency in results	Authors report data are consistent.
Precision in results	All analyses were imprecise.
Directness of results	Indirect (network meta-analysis).

Explanation of acronyms

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

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

† 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[10].

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[11]. 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[10];

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

§ 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[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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