TECHNICAL COMMENTARY

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BIPOLAR DISORDERS LIBRARY

Ziprasidone

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 antipsychotic drugs such as the second-generation antipsychotic, ziprasidone.

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 small to medium-sized effects of better improvement in acute mania symptoms with ziprasidone than with placebo or topiramate, although there was better improvement in mania symptoms with tamoxefin than with ziprasidone.
- Moderate to low quality evidence finds no differences in acute depression between ziprasidone and placebo.
- Moderate quality evidence suggests greater improvement in clinical global impression, depression symptoms, response to treatment, and remission with lurasidone than with ziprasidone.
- Moderate quality evidence suggests no differences in depression symptoms, response or remission between low (40-80

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mg) and high (120-160 mg) dose ziprasidone.

Side effects

- Compared to placebo, moderate quality evidence suggests an increased risk of more prolactin, hyperkinesia, akathisia, muscle weakness, somnolance and sedation with ziprasidone, with no differences between ziprasidone and placebo in insomnia, agitation or weight gain.
- Moderate to low quality evidence suggests lower risk of switching to mania with ziprasidone than with aripiprazole or lamotrigine. There are no differences in rates of switching to depression between ziprasidone and haloperidol.
- Moderate quality evidence suggests more somnolence with ziprasidone than with lurasidone.

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Bartoli F, Dell'Osso B, Crocamo C, Fiorillo A, Ketter TA, Suppes T, Clerici M, Carra G

Benefits and harms of low and high second-generation antipsychotics doses for bipolar depression: A meta-analysis

Journal of Psychiatric Research 2017; 88: 38-46

View review abstract online

Comparison	**High vs. low dose ziprasidone.**
Summary of evidence	**Moderate to low quality evidence (1 RCT, medium-sized sample, some imprecision, direct) suggests no differences in depression symptoms, response or remission between low (40-80 mg) and high (120-160 mg) dose ziprasidone.**
Depression	
No significant differences between groups; Depression scores: 1 x 6 week RCT, N = 324, SMD = -0.080, 95%CI -0.298 to 0.138, $p > 0.05$ Response: 1 x 6 week RCT, N = 324, RR = 1.147, 95%CI 0.919 to 1.433, $p > 0.05$ Remission: 1 x 6 week RCT, N = 324, RR = 1.036, 95%CI 0.814 to 1.320, $p > 0.05$	
Risks	There were no differences between groups for discontinuation for any reason.
Consistency in results	Not applicable; 1 RCT.
Precision in results	Precise for depression, imprecise for response and remission.
Directness of results	Direct.

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	**Ziprasidone vs. haloperidol.**
Summary of evidence	**Moderate to low quality evidence (1 RCT, medium-sized sample, imprecise, direct) suggests no significant differences in rates of switching to depression between haloperidol and ziprasidone.**
Switch to depression	
No significant differences between groups; 1 RCT, N = 369, RR = 0.51, 95%CI 0.22 to 1.18, *p* = 0.12	
Consistency in results	No applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct

Harrington CA, English C

Adverse drug events related to ziprasidone: A meta-analysis of randomized, placebo-controlled trials

Pharmacotherapy 2011: 31: 840-9

View review abstract online

Comparison	**Ziprasidone vs. placebo.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent and imprecise, direct) suggests an increased risk of hyperkinesia, akathisia, muscle weakness, somnolance and sedation with ziprasidone compared to placebo, with no differences in insomnia, agitation or weight gain.**
Movement effects	
Increased risk of hyperkinesia or akathisia with ziprasidone; 5 RCTs, N = 1631, RD = 6, 95%CI 2 to 9, *p* < 0.05 *Increased risk of muscle weakness;* 4 RCTs, N = 1365, RD = 4, 95%CI 0 to 8, *p* > 0.05	
Somnolence, sedation and insomnia	

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Increased risk of somnolance or sedation ; 6 RCTs, N = 2135, RD = 14, 95%CI 2 to 27, $p < 0.05$ *No differences in insomnia;* 5 RCTs, N = 1903, RD = 1, 95%CI -2 to 3, $p > 0.05$
Agitation
No significant differences between groups; 2 RCTs, N = 837, RD = 1, 95%CI -2 to 10, $p > 0.05$
Weight gain > 7%
No significant differences between groups; 3 RCTs, N = 689, RD = 3, 95%CI -1 to 8, $p > 0.05$

Consistency in results	Inconsistent, apart from weight gain and insomnia.
Precision in results	Appears imprecise, apart from insomnia.
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

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Comparison	**Ziprasidone vs. placebo or other second-generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistencies, imprecise, direct) finds no differences in acute depression between ziprasidone and placebo. Lower quality evidence (indirect) finds ziprasidone performed worse than lurasidone and quetiapine, with no differences when compared to aripiprazole, cariprazione, olanzapine.**
Response for acute depression	

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There were no significant differences in response for acute depression between ziprasidone and placebo; 6 studies, N not reported, OR = 1.06, 95%CI 0.81 to 1.38, $p > 0.05$ Network analysis showed ziprasidone performed worse than lurasidone and quetiapine, with no differences when compared to aripiprazole, cariprazione, olanzapine.

Risks	There was more all-cause discontinuation with ziprasidone than with placebo.
Consistency in results	Authors report some inconsistencies.
Precision in results	Imprecise
Directness of results	Direct for pairwise comparison with placebo only.

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	**Ziprasidone vs. lurasidone.**
Summary of evidence	**Moderate quality evidence (large sample sizes, consistent, imprecise, some indirectness) suggests greater improvement in clinical global impression, depression symptoms, response to treatment, and remission with lurasidone compared to ziprasidone. There was more somnolence with ziprasidone.**
Clinical global impression	
Significantly better clinical global impression scores with lurasidone; Network meta-analysis, **14 studies, N = 6,221,** MD = -0.59, 95%CI -0.94 to -0.24, $p < 0.05$	
Depression symptoms	
Significantly better depression scores with lurasidone; Network meta-analysis, 14 studies, N = 6,221, MD = -3.38, 95%CI -6.68 to -0.11, $p < 0.05$	
Response for depression	

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A medium-sized effect of significantly better response rates with lurasidone; Network meta-analysis, 14 studies, N = 6,221, OR = 2.45, 95%CI 1.38 to 4.05, $p < 0.05$
Remission
A medium-sized effect of significantly better remission rates with lurasidone; Network meta-analysis, 14 studies, N = 6,221, OR = 2.18, 95%CI 1.21 to 3.65, $p < 0.05$

Risks	There was significantly less somnolence with lurasidone, and no differences between groups in weight gain.
Consistency in results	Authors report that the results are consistent.
Precision in results	Imprecise
Directness of results	Some indirectness.

Pacchiarotti I, Murru A, Kotzalidis GD, Bonnin CM, Mazzarini L, Colom F, Vieta E

Hyperprolactinemia and medications for bipolar disorder: systematic review of a neglected issue in clinical practice

European Neuropsychopharmacology 2015; 25: 1045-59

View review abstract online

Comparison	**Ziprasidone vs. placebo.**
Summary of evidence	**Moderate quality evidence (large samples, appears consistent, direct, unable to assess precision) suggests ziprasidone may be more likely to elevate prolactin levels than placebo.**
Hyperprolactemia	
1 x 6 month RCT (N = 240) found ziprasidone was more likely to cause elevated prolactin levels than placebo. 1 x 3 week RCT (N = 656) found both low and high dose ziprasidone was more likely to cause elevated prolactin levels.	
Consistency in results	Appears consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

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Comparison 1	**Ziprasidone vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, some imprecision, direct) suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response with olanzapine than placebo. There were no differences between groups in rates of switching to mania or withdrawal from treatment (any reason).**
Depression symptoms	
No significant differences between groups; 1 RCT, N = 198, SMD = -0.02, 95%CI -0.25 to 0.21, $p > 0.05$	
Response	
No significant differences between groups; 1 RCT, N = 198, OR = 0.99, 95%CI 0.63 to 1.58, $p > 0.05$	
Switch to mania	
No significant differences between groups; 1 RCT, N = 198, OR = 0.20, 95%CI 0.01 to 4.26, $p > 0.05$	
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	Precise for depression symptoms only.
Directness of results	Direct (pairwise comparisons).
Comparison 2	**Ziprasidone vs. other medications.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, consistent, imprecise, indirect) suggests large, lower risks of**

	switching to mania with ziprasidone than with aripiprazole or lamotrigine.
Depression symptoms	
There were no significant differences between ziprasidone and any other medication.	
Response	
There were no significant differences between ziprasidone and any other medication.	
Switch to mania	
There were large, significant effects of lower risk of switch to mania with ziprasidone than with; Aripiprazole: Network meta-analysis, OR = 11.40, 95%CI 1.16 to 47.20, $p < 0.05$ Lamotrigine: Network meta-analysis, OR = 9.99, 95%CI 1.04 to 40.70, $p < 0.05$ There were no other differences between ziprasidone and other medications.	
Consistency in results	Authors report data are consistent.
Precision in results	Imprecise.
Directness of results	Indirect (network meta-analysis).

Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ

A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania

Psychological Medicine 2015; 45: 299-317

View review abstract online

Comparison	**Ziprasidone vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large sample size, consistent, some imprecision and indirectness) suggests small to medium-sized effects of greater improvement in acute mania symptoms with ziprasidone than with placebo or topiramate, although there was greater improvement with tamoxefin than with ziprasidone. There were no differences in all-cause discontinuation between ziprasidone and placebo or any other medication.**
Acute mania symptoms	

Ziprasidone

A significant, small to medium-sized effect of greater improvement with ziprasidone than with placebo; Network meta-analysis; 57 studies, N = 14,256, SMD = 0.33, 95%CrI 0.08 to 0.59, $p < 0.05$ *A significant, small to medium-sized effect of greater improvement with ziprasidone than with topiramate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.40, 95%CrI 0.07 to 0.73, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with ziprasidone;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.58, 95%CrI 1.99 to 3.20, $p < 0.05$ Authors report no other significant differences between ziprasidone and other medications.	
Risks	There were no differences all-cause discontinuation between ziprasidone and placebo or any other medication.
Consistency in results	Authors report data are consistent.
Precision in results	Precise apart from tamoxefin comparison.
Directness of results	Some indirectness.

Explanation of acronyms

CI = confidence interval, CrI = credible interval, 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, RD = risk difference, RR = risk ratio, SMD = standardised mean difference, vs. = versus

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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[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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