TECHNICAL COMMENTARY

Lurasidone

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, lurasidone.

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

- Moderate to high quality evidence suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response to treatment with lurasidone adjunctive to mood stabilisers than with placebo. Moderate to low quality evidence also suggests higher rates of remission with adjunctive lurasidone. There were no differences between adjunctive lurasidone and placebo in rates of switching to mania, withdrawal from treatment for any reason, or the number of adverse events.
- Moderate quality evidence suggests greater improvement in depression symptoms, response to treatment and remission with lurasidone monotherapy than with placebo, aripiprazole or ziprasidone monotherapy, with no differences between lurasidone and olanzapine or quetiapine monotherapy. There was less weight gain and somnolence

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with lurasidone than with ziprasidone or quetiapine; less weight gain with lurasidone than with olanzapine; but more switching to mania with lurasidone than with quetiapine.

- Moderate to high quality evidence suggests no differences in depression symptoms between low (20-60 mg) and high (80-120 mg) dose lurasidone monotherapy.

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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 lurasidone monotherapy.**
Summary of evidence	**Moderate to high quality evidence (1 RCT, large sample, precise, direct) suggests no differences in depression symptoms between low (20-60 mg) and high (80-120 mg) dose lurasidone.**
Depression	
No significant differences between groups; Depression scores: 1 x 6 week RCT, N = 323, SMD = 0.000, 95%CI -0.218 to 0.218, $p > 0.05$ Response, 1 x 6 week RCT, N = 323, OR = 1.030, 95%CI 0.836 to 1.271, $p > 0.05$ Remission: 1 x 6 week RCT, N = 323, OR = 1.053, 95%CI 0.811 to 1.366, $p > 0.05$	
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.

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	**Lurasidone vs. placebo or other second-generation**

	antipsychotics.
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistencies, imprecise, direct) finds greater response for acute depression with lurasidone than with placebo. Lower quality evidence (indirect) finds lurasidone was more effective than aripiprazole, cariprazine, and ziprasidone, with no differences when compared to olanzapine or quetiapine.**
Response for acute depression	
A significant, small effect of greater response for acute depression with lurasidone; 1 study, N not reported, OR = 2.50, 95%CI 1.81 to 3.45, $p < 0.05$ Network analysis showed lurasidone was more effective than aripiprazole, cariprazine, and ziprasidone, with no differences when compared to olanzapine or quetiapine.	
Risks	There were no differences in all-cause discontinuation between lurasidone and 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 1	**Lurasidone monotherapy vs. placebo.**
Summary of evidence	**Moderate quality evidence (large sample sizes, consistent, imprecise, some indirectness) suggests greater improvement in depression symptoms, response to treatment, and remission with lurasidone than with placebo. 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 = -0.63, 95%CI -0.90 to -0.37, $p < 0.05$	
Depression symptoms	
Greater improvement in depression symptoms with lurasidone; Network meta-analysis, 14 studies, N = 6,221, MD = -4.70, 95%CI -7.20 to -2.21, $p < 0.05$	
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 = 2.59, 95%CI 1.21 to 3.65, $p < 0.05$	
Remission	
A medium-sized effect of greater odds of remission with lurasidone; Network meta-analysis, 14 studies, N = 6,221, OR = 2.19, 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.
Comparison 2	**Lurasidone monotherapy vs. aripiprazole monotherapy.**
Summary of evidence	**Moderate quality evidence (large sample sizes, 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
Comparison 3	**Lurasidone monotherapy vs. ziprasidone monotherapy.**
Summary of evidence	**Moderate quality evidence (large sample sizes, consistent, imprecise, some indirectness) suggests greater improvement in depression symptoms, response to treatment, and remission with lurasidone than with ziprasidone. There was less weight gain and somnolence with lurasidone.**
Clinical global impression	
Greater improvement in overall symptoms 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	
Greater improvement in depression symptoms 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	
A medium-sized effect of greater odds of response for depression 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 greater odds of remission 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 weight gain and somnolence with lurasidone.
Consistency in results	Authors report that the results are consistent.

Precision in results	Imprecise
Directness of results	Some indirectness
Comparison 4	**Lurasidone monotherapy vs. olanzapine monotherapy.**
Summary of evidence	**Moderate quality evidence (large sample sizes, consistent, imprecise, some indirectness) suggests no differences in depression symptoms, response to treatment, or remission with lurasidone compared to olanzapine. There was less weight gain with lurasidone.**
Clinical global impression	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = -0.31, 95%CI -0.65 to 0.03, $p > 0.05$	
Depression symptoms	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = -0.15, 95%CI -3.12 to 2.74, $p > 0.05$	
Response for depression	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, OR = 1.68, 95%CI 0.99 to 2.69, $p > 0.05$	
Remission	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, OR = 1.54, 95%CI 0.87 to 2.53, $p > 0.05$	
Risks	There was significantly less weight gain with lurasidone, and no differences between groups in rates of somnolence.
Consistency in results	Authors report that the results are consistent.
Precision in results	Imprecise
Directness of results	Some indirectness
Comparison 5	**Lurasidone monotherapy vs. quetiapine monotherapy.**
Summary of evidence	**Moderate quality evidence (large sample sizes, consistent, imprecise, some indirectness) suggests no differences in depression symptoms, response to treatment, or remission with lurasidone compared to quetiapine. There was less weight gain and somnolence with lurasidone.**

Clinical global impression
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = -0.09, 95%CI -0.39 to 0.21, $p > 0.05$
Depression symptoms
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = 0.10, 95%CI -2.68 to 2.84, $p > 0.05$
Response for depression
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, OR = 1.29, 95%CI 0.78 to 2.01, $p > 0.05$
Remission
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, OR = 1.11, 95%CI 0.66 to 1.77, $p > 0.05$

Risks	There was significantly less weight gain and somnolence with lurasidone.
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	**Lurasidone vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large samples, appears consistent, direct, unable to assess precision) suggests lurasidone is unlikely to elevate prolactin levels.**

Hyperprolactemia	
2 x 6 week RCTs (N = 619 and 348) found no clinically meaningful changes in prolactin levels with lurasidone).	
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

View review abstract online

Comparison 1	**Lurasidone vs. placebo.** **Most participants were also taking mood stabilisers.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, some imprecision, direct) suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response to treatment with lurasidone than with placebo. There were no differences between groups in rates of switching to mania or withdrawal from treatment (for any reason).**
Depression symptoms	
Significant, small to medium-sized effect of greater improvement in depression symptoms with lurasidone; 2 RCTs, N = 853, SMD = -0.36, 95%CI -0.51 to -0.22, $p < 0.05$	
Response	
Significant, small effect of better treatment response with lurasidone; 2 RCTs, N = 853, OR = 2.60, 95%CI 1.94 to 3.48, $p < 0.05$	
Switch to mania	

No significant differences between groups; 2 RCTs, N = 853, OR = 0.61, 95%CI 0.12 to 3.03, $p > 0.05$	
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	**Lurasidone vs. quetiapine.** **Most participants were also taking mood stabilisers.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, consistent, imprecise, indirect) suggests more switching to mania with lurasidone than with quetiapine.**
Switch to mania	
The network (indirect) meta-analysis found more switching to mania with lurasidone than with quetiapine; OR = 4.69, 95%CI 1.02 to 13.90, $p < 0.05$	
Consistency in results	Authors report data are consistent.
Precision in results	Imprecise
Directness of results	Indirect

Wang H, Xiao L, Wang HL, Wang GH

Efficacy and safety of lurasidone versus placebo as adjunctive to mood stabilizers in bipolar I depression: A meta-analysis

Journal of Affective Disorders 2020; 264: 227-33

View review abstract online

Comparison	**Lurasidone (20-120mg/day for 6 weeks) plus lithium or valproate vs. placebo plus lithium or valproate.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent and imprecise, direct) suggests greater improvement in**

	depression, better response to treatment, and more remission with adjunctive lurasidone, with no differences in adverse events.
Depression symptoms	
Significant effect of greater improvement in depression symptoms with adjunctive lurasidone; Montgomery Asberg Depression Rating Scale total: 4 RCTs, N = 1,177, MD = -4.31, 95%CI -6.93 to -1.70, p = 0.001, I^2 = 95% Clinical Global Impressions scale total: 4 RCTs, N = 1,532, MD = -0.37, 95%CI -0.59 to -0.15, p = 0.0008, I^2 = 92%	
Response and remission	
Significant, small effects of better treatment response and remission with lurasidone; Response: 7 RCTs, N = 2,152, RR = 1.73, 95%CI 1.46 to 2.05, p < 0.00001, I^2 = 53% Remission: 7 RCTs, N = 2,221, RR = 1.57, 95%CI 1.38 to 1.79, p < 0.00001, I^2 = 15%	
Risks	There were no differences in rates of adverse events.
Consistency in results	Consistent for remission rates only.
Precision in results	Precise for remission rates only.
Directness of results	Direct

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, RR = relative risk, 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[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 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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