TECHNICAL COMMENTARY

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Olanzapine

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, olanzapine.

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 ten reviews that met our inclusion criteria[3-12].

Symptoms

- Moderate to high quality evidence suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response to treatment with olanzapine than with placebo. Olanzapine + fluoxetine resulted in greater improvement in depression symptoms and response than olanzapine alone.
- Moderate quality evidence suggests small to medium-sized effects of greater improvement in acute mania symptoms with olanzapine than with placebo, lithium, topiramate or lamotrigine, although there was greater improvement in mania symptoms with tamoxefin than with olanzapine.
- People with more severe mania symptoms at the start of treatment showed the greatest improvements with olanzapine over placebo.

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Olanzapine

- Moderate to low quality evidence suggests intramuscular olanzapine was more effective at reducing agitation than placebo or lorazepam.

Relapse

- Moderate to high quality evidence suggests a medium-sized effect of fewer relapses with olanzapine than with placebo. There were small effects of fewer relapses (any) with olanzapine compared to lamotrigine, paliperidone and imipramine.

Side effects

- Moderate quality evidence suggests more weight gain with olanzapine than with lurasidone.
- Moderate quality evidence suggests olanzapine may be more likely to elevate prolactin levels than placebo. Moderate to low quality evidence suggests olanzapine may be more likely to elevate prolactin levels than risperidone, and be less likely to elevate prolactin levels than valproate.
- Moderate quality evidence suggests less all-cause discontinuation with olanzapine than with placebo, cariprazine, lithium, carbamazepine, asenapine, verapamil, lamotrigine, licarbazepine and topiramate.
- There were no differences between olanzapine and placebo in rates of switching to mania.

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Dundar Y, Greenhalgh J, Richardson M, Dwan K

Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: A systematic review and meta-analysis

Human Psychopharmacology 2016; 31: 268-85

View review abstract online

Comparison	**Efficacy of olanzapine for reducing agitation compared to placebo or another pharmaceutical treatment.**
Summary of evidence	**Moderate to low quality evidence (large sample, 1 RCT, unable to assess precision, direct) suggests intramuscular olanzapine (10mg x 2 doses, + 5mg x 1 dose) is more effective at reducing agitation in people with bipolar disorder than placebo or lorazepam.**
Agitation **Change measured on the Positive and Negative Syndrome Scale Excited Component**	
1 RCT (N = 201) found that at two hours after the first injection, bipolar patients treated with olanzapine (10mg x 2 doses, 5mg x 1 dose) showed a significantly greater reduction in agitation compared with bipolar patients treated with either placebo or lorazepam (2mg x 2 doses, 1mg x 1 dose) .	
Consistency in results‡	Not applicable; 1 RCT.
Precision in results§	No measure of precision is reported (no CIs).
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	**Olanzapine monotherapy or add-on vs. haloperidol**

	monotherapy or add-on.
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, 1 RCT, imprecise, direct) suggests no significant differences in rates of switching to depression between haloperidol and olanzapine.**
Switch to depression	
No significant differences between groups; 1 RCT, N = 259, RR = 0.56, 95%CI 0.29 to 1.08, *p* = 0.08	
Consistency in results	No applicable (1 RCT).
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	**Olanzapine 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 olanzapine than with placebo. Lower quality evidence (indirect) finds no differences in acute depression when olanzapine was compared to lurasidone, ziprasidone, aripiprazole, cariprazine, or quetiapine. There were lower levels of all-cause discontinuation with olanzapine than with placebo.**
Response for acute depression	
A significant, small effect of greater response for acute depression with olanzapine; 3 studies, N not reported, OR = 1.58, 95%CI 1.15 to 2.17, *p* < 0.05 Network analysis showed no differences when olanzapine was compared to lurasidone,	

ziprasidone, aripiprazole, cariprazine, or quetiapine.	
Risks	There were lower levels of all-cause discontinuation with olanzapine than with placebo.
Consistency in results	Authors report some inconsistencies.
Precision in results	Imprecise
Directness of results	Direct for pairwise comparison with placebo only.

McKnight RF, de La Motte de Broons de Vauvert SJGN, Chesney E, Amit BH, Geddes J, Cipriani A

Lithium for acute mania

Cochrane Database of Systematic Reviews 2019 (6)

View review abstract online

Comparison	**Olanzapine vs. lithium for mania in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, consistent, imprecise, direct) suggests better response with olanzapine than with lithium.**
Mania	
Olanzapine was more effective than lithium; 2 studies, N = 180, OR = 0.44, 95%CI 0.20 to 0.94, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Imprecise
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	**Olanzapine monotherapy or add-on vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, some indirectness) suggests a medium-sized effect of less relapses, particularly to mania with olanzapine. Placebo was significantly better tolerated than olanzapine.**
Any relapse	
A significant, medium-sized effect of lower risk of any relapse with olanzapine; N = 573, RR = 0.50, 95%CI 0.39 to 0.63, $p < 0.05$	
Mania relapse	
A significant, medium-sized effect of lower risk of mania relapse with olanzapine; N = 573, RR = 0.35, 95%CI 0.25 to 0.50, $p < 0.05$	
Depression relapse	
No significant differences between groups; N = 573, RR = 0.80, 95%CI 0.57 to 1.12, $p > 0.05$	
Comparison 2	**Olanzapine monotherapy or add-on vs. other pharmaceutical treatments.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, some indirectness) suggests small effects of fewer relapses with olanzapine compared to lamotrigine, paliperidone and imipramine.**
Any relapse	
Significant, small effects of olanzapine preventing relapse compared to; Lamotrigine: RR = 0.66, 95%CI 0.48 to 0.89, $p < 0.05$ Paliperidone: RR = 0.60, 95%CI 0.37 to 0.94, $p < 0.05$ Imipramine: RR = 0.53, 95%CI 0.34 to 0.80, $p < 0.05$ There were no other differences between olanzapine and any other medication.	
Risks	Placebo was significantly better tolerated than olanzapine. There

	were no differences in tolerability in any other comparison.
Consistency in results	Authors state that the data were consistent.
Precision in results	Precise for placebo comparisons for any relapse and mania relapse only.
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	**Olanzapine monotherapy vs. lurasidone 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 more weight gain with olanzapine.**
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

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	**Olanzapine vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large samples, appears consistent, direct, unable to assess precision) suggests olanzapine may be more likely to elevate prolactin levels than placebo. Moderate to low quality evidence (1 RCT each comparison) suggests olanzapine may be more likely to elevate prolactin levels than risperidone, and be less likely to elevate prolactin levels than valproate.**
Hyperprolactemia	
1 x 3 week RCT (N = 161) found olanzapine was more likely to cause elevated prolactin levels than placebo. 1 x 12 week RCT (N = 421) found olanzapine was more likely to cause elevated prolactin levels than placebo or valproate. 1 x 3 week RCT (N = 329) found olanzapine was less likely to cause elevated prolactin levels than risperidone.	
Consistency in results	Appears consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Samara MT, Goldberg Y, Levine SZ, Furukawa TA, Geddes JR, Cipriani A, Davis J M, Leucht S

Initial symptom severity of bipolar I disorder and the efficacy of olanzapine: a meta-analysis of individual participant data from five placebo-controlled studies

The Lancet Psychiatry 2017; 4: 859-67

View review abstract online

Comparison	**Olanzapine monotherapy vs. placebo in people with acute mania associated with bipolar I disorder.**
Summary of evidence	**Moderate to high quality evidence (large samples, appears consistent, precise, direct) suggests small to medium-sized effects of greater improvement in acute mania symptoms with olanzapine than with placebo. People with more severe mania symptoms at the start of treatment showing the greatest improvements with olanzapine.**
Mania symptoms	
Small to medium-sized effects of greater improvements with olanzapine than placebo at 3 weeks; Baseline mania scores 20-25: 5 RCTs, N = 939, *d* = 0.35, 95%CI 0.11 to 0.60, *p* = 0.003 Baseline mania scores 25-35: 5 RCTs, N = 939, *d* = 0.58, 95%CI 0.34 to 0.86, *p* = 0.001 Baseline mania scores 35-50: 5 RCTs, N = 939, *d* = 0.70, 95%CI 0.31 to 1.23, *p* = 0.002 *Greater the baseline severity was associated with greater the magnitude of the differences;* 5 RCTs, N = 939, β = 0.22, 95%CI 0.05 to 0.39, *p* = 0.013	
Consistency in results	Appears consistent.
Precision in results	Precise
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	**Olanzapine monotherapy vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response with olanzapine than placebo. There was less withdrawal from treatment for any reason with olanzapine, and no differences between groups in rates of switching to mania.**
Depression symptoms	
A significant, medium-sized effect of greater improvement in depression symptoms with olanzapine; 3 RCTs, N = 1329, SMD = -0.51, 95%CI -0.87 to -0.17, $p < 0.05$	
Response	
A significant, small effect of better response with olanzapine; 3 RCTs, N = 1329, OR = 1.58, 95%CI 1.15 to 2.26, $p < 0.05$	
Switch to mania	
No significant differences between groups; 3 RCTs, N = 1329, OR = 0.79, 95%CI 0.43 to 1.45, $p > 0.05$	
Risks	There was less withdrawal from treatment for any reason with olanzapine.
Consistency in results	Authors report data are consistent.
Precision in results	Imprecise
Directness of results	Direct (pairwise comparisons).
Comparison 2	**Olanzapine monotherapy vs. other medications.**
Summary of evidence	**Moderate to high quality evidence (1 RCT, large samples, consistent, precise, direct) suggests significant, small to medium-sized effects of greater improvement in depression symptoms and better response with olanzapine + fluoxetine than with olanzapine alone. There were no differences between groups in rates of withdrawal from treatment (any reason).**
Depression symptoms	

A significant, small effect of greater improvement with olanzapine + fluoxetine than olanzapine alone; 1 RCT, N = 456, SMD = 0.27, 95%CI 0.03 to 0.51, $p < 0.05$ There were no other significant differences between olanzapine and other medications.
Response
A significant, medium-sized effect of better response with olanzapine + fluoxetine than olanzapine alone; 1 RCT, N = 456, SMD = 0.51, 95%CI 0.32 to 0.82, $p < 0.05$ There were no other significant differences between olanzapine and other medications.
Switch to mania
There were no significant differences between olanzapine and other medications.

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.
Directness of results	Direct (pairwise comparisons).

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	**Olanzapine 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 olanzapine than with placebo, topiramate or lamotrigine, although there was greater improvement with tamoxefin than with olanzapine. There was less all-cause discontinuation with olanzapine than with placebo, cariprazine, lithium, carbamazepine, asenapine, verapamil, lamotrigine,**

	licarbazepine and topiramate.
Acute mania symptoms	
A significant, medium-sized effect of greater improvement with olanzapine than with placebo; Network meta-analysis; 57 studies, N = 14,256, MD = 0.48, 95%CrI 0.34 to 0.62, $p < 0.05$ *A significant, medium-sized effect of greater improvement with olanzapine than with topiramate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.55, 95%CrI 0.29 to 0.79, $p < 0.05$ *A significant, small effect of greater improvement with olanzapine than with lamotrigine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.35, 95%CrI 0.02 to 0.66, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with olanzapine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.44, 95%CrI 1.88 to 3.02, $p < 0.05$ Authors report no other significant differences between olanzapine and other medications.	
Risks	There was less all-cause discontinuation with olanzapine than with placebo, cariprazine, lithium, carbamazepine, asenapine, verapamil, lamotrigine, licarbazepine and topiramate.
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, *d* = Cohen's *d*, standardised mean difference, 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[13].

† 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[13].

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[14]. 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.

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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[13];

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

§ 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[15].

‖ 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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