TECHNICAL COMMENTARY

Pharmaceutical treatments for mixed bipolar states

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Introduction

Bipolar disorders are a group of disorders characterised by episodes of mania or hypomania and depression. Concurrent 'mixed' episodes of both mania and depression can also be evident. For a mixed episode, the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) states a requirement of at least three manic/hypomanic symptoms (e.g. elevated mood, inflated self-esteem, decreased sleep, increased energy) occurring nearly every day during a major depressive episode. Alternatively, the presence of at least three symptoms of depression (e.g. depressed mood, diminished interest or pleasure, slowed physical and emotional reaction, fatigue or loss of energy, and recurrent thoughts of death) need to occur nearly every day throughout a manic or hypomanic episode.

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 for people with a diagnosis of bipolar or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably 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 three systematic reviews that met our inclusion criteria[3-5].

- High quality evidence suggests a medium-sized effect of improved manic symptoms and a smaller effect of improved depression symptoms with second-generation antipsychotics (with or without adjunctive mood stabilisers) compared to placebo.

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Cuomo A, Nikolova VL, Yalin N, Arnone D, Fagiolini A, Young AH

Pharmacological treatment of mixed states

CNS spectrums 2017; 22: 186-95

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Comparison	**All pharmaceutical treatments for mixed states in bipolar disorder.**
Summary of evidence	**Low quality evidence (unable to assess consistency or precision, direct, mostly small samples) is unable to determine the benefits of pharmaceutical treatments for mixed states.**

Acute symptoms

Antipsychotics

2 RCTs (N = 190 and 113) compared *aripiprazole* with placebo for mixed states and found that aripiprazole significantly decreased manic symptoms. 1 of these RCTs (N = 113) also found a reduction in depressive symptoms.

1 RCT (N = 73) compared *ziprasidone* with placebo in people with a major depressive episode with 2 or 3 manic symptoms found that ziprasidone significantly improved depressive but not manic symptoms. 1 RCT (N = 179) of mixed patients with dysphoric mania found ziprasidone to be significantly superior to placebo for both manic and depressive symptoms.

1 RCT (N = 146) compared *asenapine or olanzapine* with placebo and found a significant effect for olanzapine (vs. placebo) and a trend effect for asenapine (vs. placebo) for improved manic symptoms.

1 RCT (N = 209) compared *lurasidone* with placebo in major depression with mixed features and found that lurasidone significantly improved both depressive and manic symptoms.

1 case series (N = 7) of *clozapine* in people with treatment-resistant bipolar disorder and manic episodes associated with significant depressive symptoms found reductions in affective and psychotic symptoms when treated with clozapine alone or in combination with lithium, an antidepressant, or valproate.

Mood stabilisers

1 RCT (N = 147) compared of *carbamazepine* (extended-release capsules) with placebo in patients with manic or mixed episodes and found carbamazepine significantly improved both manic and depressive symptoms in the subsample of mixed patients.

Combination therapy

3 RCTs (N = 201, 179 and 85) compared *olanzapine* + *valproate* with placebo + valproate or lithium and found all three studies indicated that adjunctive olanzapine treatment is superior for improving both depressive and manic symptoms.

1 RCT (N = 376) compared *olanzapine* + *fluoxetine* with olanzapine alone found no differences between groups.

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1 RCT (N = 55) compared *quetiapine + any other treatment* with placebo + any other treatment and found quetiapine was significantly more effective in improving depressive, but not hypomanic symptoms.
Relapse prevention
Antipsychotics 1 RCT (N = 121) compared *olanzapine* with placebo and found olanzapine significantly improved symptomatic relapse of any kind. Mood stabilisers 1 RCT (N = 247) compared *valproate* with placebo and found no differences between groups. 1 RCT (N = 62) compared *carbamazepine* extended release with placebo and found carbamazepine significantly improved depressive symptoms. Combination therapy 1 RCT (N = 173) compared *aripiprazole + lamotrigine* with placebo + lamotrigine and found time to relapse in the mixed-state group was significantly longer with aripiprazole + lamotrigine. 1 open-label trial (N = 44) investigated the efficacy of *risperidone + mood stabilisers* and found a significant improvement in both manic and depressive symptoms.

Consistency‡	Unable to assess; no measure of consistency is reported.
Precision§	Unable to assess; no measure of precision is reported.
Directness‖	Direct

Fornaro M, Stubbs B, De Berardis D, Perna G, Valchera A, Veronese N, Solmi M, Gananca L

Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials

International Journal of Molecular Sciences 2016; 17: 241

View review abstract online

Comparison	**Assessment of second-generation antipsychotics (ziprasidone, olanzapine, lurasidone, quetiapine or asenapine for an average of 6.5 weeks) vs. placebo in people with acute depression and mania features.**
Summary of evidence	**Moderate quality evidence (large sample, direct, precise, inconsistent, possible measurement biases), suggests a large**

	effect of improved depression symptoms with second-generation antipsychotics over placebo. **Moderate to low quality evidence (imprecise) also suggests improved mania symptoms after adjustment for possible publication bias.**
Symptoms	
A large, significant effect of improved depression symptoms with second-generation antipsychotics; 4 studies, N = 1,657, SMD = -1.08, 95%CI -1.35 to -0.81, $p < 0.05$, $I^2 = 68\%$, $p < 0.001$ *No significant differences between groups for mania symptoms;* 3 studies, N = 1,559, SMD = -0.40, 95%CI -0.90 to 0.11, $p = 0.12$, $I^2 = 91\%$, $p < 0.001$ *This effect was significant after adjusting for publication bias;* SMD = -0.74, 95%CI -1.20 to -0.28, $p = 0.12$ Authors report possible measurement biases in the included studies.	
Consistency	Inconsistent
Precision	Precise for depression symptoms only.
Directness	Direct

Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW, Yatham LN

Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials

Journal of Affective Disorders 2013; 150: 408-14

View review abstract online

Comparison	**Assessment of monotherapy or adjunctive second-generation antipsychotics (aripiprazole, paliperidone, risperidone, ziprasidone, olanzapine, lurasidone, or asenapine for an average 3-6 weeks) vs. placebo in people with acute mixed episodes.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a medium-sized effect of improved manic symptoms and a smaller effect of improved depression symptoms with second-generation antipsychotics with or without adjunctive mood stabilisers compared with placebo.**
Symptoms	

A medium-sized, significant effect of improved manic symptoms with second-generation antipsychotics alone or in combination with mood stabilisers compared to placebo; 9 RCTs, N = 1,289, SMD = -0.41, 95%CI -0.53 to -0.30, $p < 0.00001$, $I^2 = 0\%$, $p = 0.66$ The results are similar in subgroup analyses of 6 monotherapy trials of second-generation antipsychotics (N = 888, SMD = -0.35), and 4 adjunctive trials of second-generation antipsychotics + mood stabilisers (N = 402, SMD = -0.55). *A smaller, significant effect of improved depression symptoms with second-generation antipsychotics alone or in combination with mood stabilisers compared to placebo;* 2 RCTs, N = 561, SMD = -0.30, 95%CI -0.47 to -0.13, $p < 0.001$, $I^2 = 0\%$, $p = 0.74$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct, particularly for monotherapy trials.

Explanation of acronyms

CI = confidence interval, DSM = American Psychiatric Association's Diagnostic and Statistical Manual, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = probability of rejecting a null hypothesis of no differences between groups, 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[6].

† 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).

Weighted 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. Standardsed mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that 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. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[6].

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[7]. 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

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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[6];

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

§ 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[8].

‖ 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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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Cuomo A, Nikolova VL, Yalin N, Arnone D, Fagiolini A, Young AH (2017): Pharmacological treatment of mixed states. *Cns Spectrums* 22: 186-95.
4. Fornaro M, Stubbs B, De Berardis D, Perna G, Valchera A, Veronese N*, et al.* (2016): Atypical Antipsychotics in the Treatment of Acute Bipolar Depression with Mixed Features: A Systematic Review and Exploratory Meta-Analysis of Placebo-Controlled Clinical Trials. *International Journal of Molecular Sciences* 17: 241.
5. Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW*, et al.* (2013): Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *Journal of Affective Disorders* 150: 408-14.
6. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
7. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
8. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.