TECHNICAL COMMENTARY

Pharmaceutical treatments for rapid mood cycling

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Introduction

Rapid cycling refers to the presence of four or more discrete mood episodes (mania, hypomania, depression, or mixed) during a one-year period. Studies have suggested that rapid mood cycling is more frequent in women than in men, and has been associated with hypothyroidism and bipolar II disorder (hypomania rather than mania). It is also associated with longer illness duration, greater illness severity, and worse global functioning.

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 two systematic reviews that met our inclusion criteria[3, 4].

- Moderate to low quality evidence suggests the antipsychotics olanzapine, quetiapine, and aripiprazole, and the anticonvulsants divalproex and valproate may be effective for acute clinical response. Anticonvulsant lamotrigine may be more effective than placebo for maintaining stability over time. Antidepressant bupropion may result in a lower risk of switching from depression to mania than antidepressant venlafaxine.
- Moderate quality evidence suggests a small effect of fewer relapses with long-acting injectable risperidone than treatment as usual (various medications).

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Fountoulakis KN, Kontis D, Gonda X, Yatham LN

A systematic review of the evidence on the treatment of rapid cycling bipolar disorder

Bipolar Disorders 2013; 15: 115-37

View review abstract online

Comparison	**All pharmaceutical treatments for rapid mood cycling in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, direct, medium-sized samples) suggests the antipsychotics olanzapine, quetiapine, and aripiprazole, and the anticonvulsants divalproex and valproate may be effective for acute clinical response. Lamotrigine may be more effective than placebo for maintaining stability over time. Antidepressant bupropion may result in a lower risk of switching from depression to mania than antidepressant venlafaxine.** **There were insufficient sample sizes to determine the effects of other medications.**

Acute symptoms

Antipsychotics

Olanzapine vs. placebo

3-4 week RCT (N = 54) found more responsiveness with olanzapine; patients who were more responsive to olanzapine were younger at illness onset, lacked prior substance abuse, and had not previously received antipsychotic treatment.

3 week RCT (N = 43) found greater clinical response (58 vs. 28%), higher trial completion rates, and improved mania symptoms with olanzapine.

1 RCT (N = 90; trial duration not reported, sample also included non-rapid cyclers) found greater clinical response with olanzapine (77 vs. 50%).

3-4 week RCT (N = 253; sample also included non-rapid cyclers) found olanzapine improved cognition.

Quetiapine vs. placebo

8-week RCT (N = 74) found quetiapine improved depression more than placebo.

8-week RCT (N = 108) found quetiapine improved depression and response rates (66.8 vs. 40%) more than placebo.

Aripiprazole vs. placebo

3-week RCT (N = 103) found aripiprazole reduced mania, and resulted in higher rates of responding and remitting than placebo.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Olanzapine vs. anticonvulsant divalproex

47-week RCT (N = 144) found no differences in manic symptoms or global improvement (both groups improved).

Mood stabilisers and anticonvulsants

Anticonvulsant valproate vs. placebo

6-week RCT (N = 54; sample also included non-rapid cyclers) found greater improvement in depression with valproate, but only for those with bipolar I and not bipolar II disorder. Response and remission rates were greater with valproate (38.5 vs. 10.7%; 23.1 vs. 10.7%), but significant only for response rates.

Anticonvulsant lamotrigine vs. mood stabiliser lithium

16-week open-label RCT (N = 68; sample also included non-rapid cyclers) found better global functioning with lamotrigine than lithium, but no differences between groups for depression, mania, or overall symptoms (both groups improved).

Mood stabiliser lithium vs. antidepressant venlafaxine

3-month open-label RCT (N = 27) found venlafaxine reduced depression, and resulted in higher rates of responding and remitting than lithium. There were no differences in rates of mood switching.

Anticonvulsant divalproex vs. antipsychotic olanzapine

47-week RCT (N = 144) found no differences in manic symptoms or global improvement (both groups improved).

Antidepressants

Escitalopram vs. placebo

3-month cross-over RCT (N = 10) of medication-naïve patients found escitalopram reduced depression severity, the percentage of days depressed or high, and the percentage of days impaired more effectively than placebo. There was also a small, but greater reduction of switching to (hypo)mania with escitalopram.

Venlafaxine vs. mood stabiliser lithium

3-month open-label RCT (N = 27) found venlafaxine reduced depression, and resulted in higher rates of responding and remitting than lithium. There were no differences in rates of mood switching.

Combination therapy

Anticonvulsant lamotrigine + mood stabiliser lithium or anticonvulsant valproate vs. placebo + lithium or valproate

16-week open-label RCT (N = 36; sample included people with a substance use disorder) found no differences in symptoms between groups (both groups improved).

Antidepressant bupropion + mood stabilisers vs. antidepressant sertraline + mood stabilisers vs.

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antidepressant venlafaxine + mood stabilisers

10-week RCT (N = 174; sample also included non-rapid cyclers) found bupropion had a lower risk than venlafaxine of risk of switching from depression to mania, with no differences between sertraline and bupropion or venlafaxine.

Mood stabiliser + omega-3 fatty acid ethyl-eicosapentanoate vs. mood stabiliser + placebo

4-month RCT (N = 59) found no differences between groups in symptoms or mood switching.

Relapse prevention

Antipsychotics

Aripiprazole vs. placebo

100-week RCT (N = 28), found that time to relapse was significantly longer with aripiprazole.

Olanzapine vs. placebo

RCT (N = 90; trial duration not reported, sample also included non-rapid cyclers) found non-rapid cyclers had a better long-term outcomes (remission, especially depression, suicide attempts) than rapid cyclers.

Quetiapine vs. anticonvulsant valproate

12-month open-label RCT (N = 38), found fewer moderate to severe depressive days with quetiapine, although there were no differences for number of days with mania symptoms, response rates, overall symptom severity, or mood swings.

Mood stabilisers and anticonvulsants

Anticonvulsant lamotrigine vs. placebo

RCT (N = 177) found patients taking lamotrigine were 1.8 times more likely than those taking placebo to achieve euthymia at least once per week in 6 months.

6-month RCT (N = 177) found lamotrigine was associated with higher stabilisation rates (41 vs. 26%), longer time to premature treatment discontinuation, less relapse for patients with bipolar II disorder but not bipolar I disorder, with no differences between groups in time to additional pharmacotherapy for emerging symptoms.

Anticonvulsant lamotrigine vs. lithium

1-year open-label RCT (N = 14), found fewer mood episodes with lamotrigine (43 vs. 86%).

Mood stabiliser lithium vs. anticonvulsant divalproex

20-month RCT (N = 60), found no differences in relapse rates (56 vs. 50%).

Combination therapy

Anticonvulsant carbamazepine vs. mood stabiliser lithium vs. carbamazepine + lithium

1-year crossover RCT (N = 31), found better response to treatment with carbamazepine + lithium than either carbamazepine or lithium.

Mood stabiliser lithium vs. lithium + anticonvulsant divalproex

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6-month RCT (N = 31 with substance abuse or dependence), found no differences in relapse rates (56% vs. 53%). *Mood stabilisers + antidepressant continuation vs. mood stabilisers + antidepressant discontinuation* 1-year to 3-year open-label RCT (N = 35; sample also included non-rapid cyclers) found 3 times *more* depressive episodes with antidepressant continuation vs. discontinuation. Rapid cyclers had more depressive episodes, shorter episode latency, and fewer weeks in remission, independently of treatment.	
Consistency‡	Unable to assess; no measure of consistency is reported.
Precision§	Unable to assess; no measure of precision is reported.
Directness‖	Direct

Kishi T, Oya K, Iwata N

Long-acting injectable antipsychotics for prevention of relapse in bipolar disorder: A systematic review and meta-analyses of randomized controlled trials

International Journal of Neuropsychopharmacology 2016; 19: 1-10

View review abstract online

Comparison	**Long-acting injectable risperidone + treatment as usual vs. treatment as usual (1 RCT) or placebo + treatment as usual (1 RCT).** **Treatment duration ranged from 6 to 24 months. Treatment as usual involved a mix of medications, or no medications.**
Summary of evidence	**Moderate quality evidence (consistent, precise, indirect, medium-sized sample) suggests a small effect of fewer relapses with long-acting injectable risperidone vs. treatment as usual (mixed medications).**
Relapse	
A small, significant effect of fewer relapses with long-acting injectable risperidone; 2 RCTs, N = 169, RR = 0.58, 95%CI 0.43 to 0.79, $p = 0.0004$, $I^2 = 0\%$, $p > 0.05$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Indirect comparison (mixed treatment as usual).

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = relative risk, vs. = versus

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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[5].

† 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[5].

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[6]. 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[5];

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

§ 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[7].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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