TECHNICAL COMMENTARY

Pharmaceutical treatments for medication resistance

Introduction

Bipolar disorder is a persistent, episodic and debilitating condition associated with recurring episodes of mania, hypomania, depression, and mixed manic-depressive states. These symptoms can lead to severe functional impairment, substance abuse, and suicidal behaviour. Treatment guidelines advocate the use of individual medications, with multiple medications indicated when a patient relapses on maintenance treatment. Unsatisfactory response to therapies is common in bipolar disorder, particularly during depression episodes. Hence, there is a need to study medications that specifically target people with treatment resistance[1].

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, only the most recent version 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, which describes a preferred way to present a meta-analysis[2]. Reviews rated as having 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 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)[3]. 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 one systematic review that met inclusion criteria[1].

- Moderate to low quality evidence suggests clozapine and triiodothyronine may be effective for people with treatment-resistant bipolar disorder, although possible side effects of clozapine require careful monitoring.
- The remainder of the samples were too small (< 100 patients) to draw definitive conclusions for other medications, however review authors suggest there are encouraging findings for adjunctive aripiprazole, bupropion, ketamine, memantine, pramipexole, and pregabalin.

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Poon SH, Sim K, Baldessarini RJ

Pharmacological Approaches for Treatment-resistant Bipolar Disorder

Current Neuropharmacology 2015; 13: 592-604

View review abstract online

Comparison	**All pharmaceutical treatments for people with treatment-resistant bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, direct, unable to assess consistency or precision) suggests clozapine and triiodothyronine may be effective for people with treatment-resistant bipolar disorder, although possible side effects of clozapine require careful monitoring.** **The remainder of the samples were too small (< 100 patients) to draw definitive conclusions for other medications, however review authors suggest there are encouraging findings for adjunctive aripiprazole, bupropion, ketamine, memantine, pramipexole, and pregabalin.**

Symptoms

Second-generation antipsychotics

Clozapine

3 open-label trials and 2 chart reviews (total N = 182 with bipolar disorder) found efficacy for symptoms, particularly mania, and functioning when given alone or adjunctively with lithium or an anticonvulsant. There were risks of agranulocytosis, carditis, ileus, and seizures.

Aripiprazole

3 open-label trials (total N = 43 with bipolar disorder) found efficacy for symptoms and functioning, without greater risk of adverse effects apart from restlessness, with adjunctive aripiprazole (added to various medications).

Olanzapine

2 open-label trials (total N = 41 with bipolar disorder) found efficacy for refractory mania, including reduction in relapses, with or without adjunctive moodstabilising treatments.

Quetiapine

1 open-label trial (total N = 38 with bipolar disorder) found quetiapine plus anticonvulsant lamotrigine showed improvements in overall symptoms (Clinical Global Improvement scores), however, there was excessive sedation in some cases.

Anticonvulsants

Eslicarbazepine

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1 case report found improvements in refractory mania with adjunctive eslicarbazepine.

Pregabalin

1 open-label trial and 1 case report (total N = 59 with bipolar disorder) found better response to treatment with adjunctive pregabalin (added to various medications). Authors report there may be some benefit for dual diagnosis.

Topiramate

1 open-label trial (total N = 34 with bipolar disorder) found adjunctive topiramate had no sustained effect.

Antidepressants

Bupropion

1 open-label trial (total N = 7 with bipolar disorder) found adjunctive bupropion improved depression symptoms with no mania switch.

Glutamatergic agents

Ketamine

2 RCTs and 2 case series (total N = 49 with bipolar disorder) found improved depression symptoms with adjunctive intravenous, intramuscular or sublingual ketamine.

Memantine

3 open-label trials and one case report (total N = 89 with bipolar disorder) found marked improvements in mood, with many reaching remission, with adjunctive memantine.

Anticholinesterases

Donepezil

1 RCT and 1 chart review (total N = 22 with bipolar disorder) found poor response rates and increased risk of emotional destabilisation with adjunctive donepezil.

Dopamine agonists

Pramipexole

1 RCT, 1 open-label trial and 2 chart reviews (total N = 41 with bipolar disorder) found more than half the sample responded with adjunctive pramipexole, and the drug was quite well tolerated, with a reported risk of mood-switching in less than 5% or the sample. However, authors report that dopamine agonists may carry particular risks of emotional destabilisation following their discontinuation.

Ropinirole

1 chart review (total N = 18 with bipolar II disorder) found nearly half the sample responded with adjunctive ropinirole.

Psychostimulants

Modafinil

1 chart review and 1 case series (total N = 90 with bipolar disorder) found adjunctive modafinil was better tolerated than pramipexole, although only about a third of the sample showed improved symptoms.

Calcium channel antagonists

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Diltiazem 1 open-label trial (total N = 8 with bipolar disorder) found adjunctive diltiazem to lithium showed some improvements in mood. <u>Opioids</u> *Oxycodone* 1 case study (N = 1 with bipolar disorder) found improved and sustained symtoms with adjunctive oxycodone, but their risks of dependency and withdrawal reactions, as well as other adverse effects, limit their use. <u>Thyroid hormones</u> *Triiodothyronine* 1 chart review (total N = 159 with bipolar disorder) found 85% of the sample improved, and 33% achieved remission with adjunctive triiodothyronine. *Thyroxine* 1 RCT and 1 open-label trial (total N = 75 with bipolar disorder) found inconsistent results; the RCT found minor differences with placebo and the open-label trial reported 71% of the sample improved with adjunctive thyroxine.	
Consistency in results‡	Unable to assess; no measure of consistence is reported.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Explanation of acronyms

N = number of participants, RCT = randomised controlled trial, 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[4].

† 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. 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[4].

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[5]. 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[4];

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

§ 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[6].

‖ 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, which 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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