TECHNICAL COMMENTARY

Pphmaceutical treatments for dual diagnosis

Pharmaceutical treatments for dual diagnosis

Introduction

Several treatments have been targeted to people with 'dual diagnosis' who have both a psychiatric and substance use disorder. Studies of dual diagnosis may investigate the availability and effectiveness of treatments for either diagnosis, assessing symptom severity, substance use, social functioning, quality of life, and cognition.

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, which describes a preferred way to present a meta-analysis[1]. 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)[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 four systematic reviews that met our inclusion criteria[3-6].

- Moderate to high quality evidence quetiapine significantly improved manic symptoms, but not depression symptoms compared to placebo. There were no effects for mania or depression of mood stabilisers, citicoline, or acamprosate compared to placebo. Lower quality evidence from small trials suggests the anticonvulsants valproate and lamotrigine may also improve mood and reduce substance use.

Azorin JM, Bowden CL, Garay RP, Perugi G, Vieta E, Young AH

Possible new ways in the pharmacological treatment of bipolar disorder and comorbid alcoholism

Neuropsychiatric Disease and Treatment 2010; 6: 37-46

View review abstract online

Comparison	**Pharmaceutical treatments for people with bipolar disorder and alcoholism.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear as to any benefit of pharmaceutical treatments for dual diagnosis.** **Review authors conclude that anticonvulsant valproate may be effective for reducing excessive alcohol consumption.**

Symptoms and alcohol use
Valproate
1, 12-week RCT (N = 27) found less relapse with valproate (0%) than placebo (21%).
1, 24-week open-label trial (N = 20) found alcohol use and mania symptoms reduced by 50% with valproate.
1, 52-week RCT (N = 50) found reduced alcohol use in women, but not in men, with valproate compared to olanzapine.
1, 12-week RCT (N = 30) found no differences in alcohol use with valproate compared to risperidone.
1 RCT (duration not reported, N = 21) found *less* abstinence with valproate alone (43%) than with naltrexone + valproate (71.4%).
Quetiapine
1, 12-week RCT (N = 102) found greater reduction in depression, but not alcohol use, with quetiapine than placebo.
1, 16-week open-label trial (N = 28 with any mood disorder) found 43% of the sample were alcohol free at the end of the trial.
Lamotrigine
1, 24-week open-label trial (N = 28) found a 30-70% reduction in symptoms and alcohol use with lamotrigine.
Naltrexone
1, 16-week open-label trial (N = 34) found improvements in depression scores (28%), mania scores (34%) and alcohol use scores (50%).

Consistency in results[‡]	Unable to assess, no measure of consistency is reported.

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Precision in results§	Unable to assess, CIs not reported.
Directness of results$^\parallel$	Direct

Coles AS, Sasiadek J, George TP

Pharmacotherapies for co-occurring substance use and bipolar disorders: A systematic review

Bipolar Disorders 2019; 21: 595-610

View review abstract online

Comparison	**Pharmaceutical treatments for people with bipolar disorder and substance use.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) is unclear as to any benefit of pharmaceutical treatments for dual diagnosis.** **Review authors conclude that valproate sodium and lamotrigine are preferred pharmacological agents for the treatment of co-occurring psychiatric and substance use outcomes.**

Substance use
Large effects of reduced substance use with; Valproate 4 studies, mean score = 2.49, 95%CI -2.41 to 7.39 Lithium 1 study, mean score = 2.13, 95%CI 2.11 to 2.15 Olanzapine 1 study, mean score = 1.49, 95%CI -0.51 to 3.49 Varenicline 1 study, OR = 8.13, 95%CI 2.03 to 32.5 Bupropion 1 study, mean score = 2.23, 95%CI 0.99 to 3.47 Icariin 1 study, mean score = 1.10, 95%CI 0.7 to 1.5 *Medium-sized effects of reduced substance use with;* Lamotrigine

4 studies, mean score = 0.76, 95%CI -1.22 to 2.74

Small effects of reduced substance use with;

Quetiapine

8 studies, mean score = 0.20, 95%CI -0.8 to 1.2

Aripiprazole

1 study, mean score = 0.20, 95%CI -1.36 to 1.76

Naltrexone

2 studies, mean score = 0.35, 95%CI -1.13 to 1.83

Citicoline

3 studies, mean score = 0.12, 95%CI -0.52 to 0.76

No significant improvements with;

Topiramate

1 study, mean score = -2.66, 95%CI -7.44 to 2.12

Acamprosate

1 study, mean score = -1.01, 95%CI -1.45 to -0.57

Mood

Large effects of improved mood with;

Aripiprazole

1 study, mean score = 1.07, 95%CI 0.41 to 1.73

Olanzapine

1 study, mean score = 3.73, 95%CI 2.97 to 4.49

Bupropion

1 study, mean score = 1.50, 95%CI -2.66 to 5.66

Medium-sized effects of improved mood with;

Valproate

4 studies, mean score = 1.14, 95%CI -1.26 to 3.54

Lamotrigine

4 studies, mean score = 0.70, 95%CI -0.62 to 2.02

Lithium

1 study, mean score = 0.70, 95%CI 0.38 to 1.02

Small effects of improved mood with;

Quetiapine

8 studies, mean score = 0.41, 95%CI -1.15 to 1.97

Naltrexone

	2 studies, mean score = 0.13, 95%CI -0.77 to 1.03
	Icariin
	1 study, mean score = 0.18, 95%CI -2.28 to 2.64
	No significant differences with;
	Varenicline
	1 study, mean score = 0.06, 95%CI -1.02 to 1.14
	Topiramate
	1 study, mean score = -0.32, 95%CI -0.7 to 0.06
	Acamprosate
	1 study, mean score = -0.20, 95%CI -0.48 to 0.08
	Citicoline
	3 studies, mean score = -0.07, 95%CI -0.85 to 0.71
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, CIs not standardised.
Directness of results	Direct

Salloum IM, Brown ES

Management of comorbid bipolar disorder and substance use disorders

American Journal of Drug & Alcohol Abuse 2017; 43: 366-76

View review abstract online

Comparison	Pharmaceutical treatments vs. placebo.
Summary of evidence	Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear as to any benefit of pharmaceutical treatments for dual diagnosis.
	Review authors conclude that valproate and naltrexone may decrease alcohol use, and citicoline may decrease cocaine use and enhance cognition.
Symptoms and alcohol use	
Valproate	
1 RCT (N = 59) found alcohol use, but not mood symptoms, reduced with valproate.	
Quetiapine	

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1 RCT (N = 115) found greater reduction in depression, but not alcohol use, with quetiapine.

1 RCT (N = 362) found improved clinical global impression, but not other outcomes with quetiapine.

1 RCT (N = 90) found no differences in alcohol use.

Lamotrigine

1 RCT (N = 120) found less reported money spent on cocaine, but no differences in cocaine-positive urine.

Naltrexone

1 RCT (N = 50) found trends toward reductions in alcohol use and improved mood.

Acamprosate

1 RCT (N = 50) found no differences in alcohol use but positive effects on some secondary analyses.

Citicoline

1 RCT (N = 44) found patients receiving citicoline were less likely to have positive urine for cocaine and improved declarative memory.

1 RCT (N = 130) found patients receiving citicoline were less likely to have positive urine for cocaine.

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, CIs not reported.
Directness of results	Direct

Stokes PRA, Jokinen T, Amawi S, Qureshi M, Husain MI, Yatham LN, Strang J, Young AH

Pharmacological Treatment of Mood Disorders and Comorbid Addictions: A Systematic Review and Meta-Analysis

Canadian Journal of Psychiatry 2020; 65: 749-69

View review abstract online

Comparison	Pharmaceutical treatments vs. placebo.
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, mostly precise, direct) quetiapine significantly improved manic symptoms, but not depression symptoms compared to placebo. There were no effects for mania or depression of mood stabilisers, citicoline, or acamprosate compared to placebo.**

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Mania
Quetiapine significantly improved manic symptoms compared to placebo;
4 RCTs, N = 577, SMD = -0.23; 95%CI -0.39 to -0.06, p = 0.008, I^2 = 0%
Mood stabilisers did not significantly improve manic symptoms compared to placebo;
2 RCTs, N = 64, SMD = 0.07, 95%CI -0.54 to 0.40, p = 0.77, I^2 = 0%
Citicoline did not significantly improve manic symptoms compared to placebo;
2 RCTs, N = 187, SMD = 0.04, 95%CI -0.27 to 0.35, p = 0.80, I^2 = 0%
Acamprosate did not significantly improve manic symptoms compared to placebo;
1 RCT, N = 30, SMD = -0.03, 95%CI -0.75 to 0.69, p = 0.93

Depression
There were no significant effects for depression symptoms compared to placebo;
Quetiapine: 4 RCTs, N = 577, SMD = -0.07, 95%CI -0.23 to 0.10, p = 0.42, I^2 = 42%
Mood stabilisers: 3 RCTs, N = 176, SMD = 0.02, 95%CI -0.27 to 0.31, p = 0.63, I^2 = 0%
Citicoline: 3 RCTs, N = 235, SMD = -0.30, 95%CI -0.70 to 0.10, p = 0.14, I^2 = 43%
Acamprosate: 1 RCT, N = 30, SMD = -0.33, 95%CI -1.05 to 0.39, p = 0.37

Consistency in results	Consistent
Precision in results	Precise, apart from acamprosate analysis.
Directness of results	Direct

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, OR = odds ratio, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), RCT = Randomised controlled trial, 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[7].

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† 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[7].

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[8]. 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. I² 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. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[7];

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

§ 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[9].

‖ 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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