TECHNICAL COMMENTARY

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Treatments for dual diagnosis

Introduction

Dual diagnosis is the term used for people with both mental health and substance use disorders. Studies targeting this population often investigate outcomes relating to both diagnoses, such as symptoms, substance use, social function, quality of life, and cognitive outcomes.

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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews 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[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 low quality evidence suggests olanzapine was superior to perphenazine, quetiapine, risperidone, and ziprasidone for overall symptoms in people with a dual diagnosis. Olanzapine was superior to perphenazine, quetiapine, and ziprasidone for positive symptoms. Olanzapine was superior to perphenazine, risperidone, and ziprasidone for negative symptoms.
- The remaining evidence on antipsychotics and other agents (mazindol, lamotrigine, antidepressants, anti-craving agents, or disulfiram) for symptoms or substance use was based on small sample sizes, so no conclusions can be drawn.

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Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutsmiedl K, Leucht S

Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis

European Neuropsychopharmacology 2019; 29: 32-45

View review abstract online

Comparison	**Antipsychotics vs. placebo for people with a dual diagnosis.** **3-12 week outcomes.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, some imprecision, direct) suggests olanzapine was superior to perphenazine, quetiapine, risperidone and ziprasidone for overall symptoms in people with a dual diagnosis. Olanzapine was superior to perphenazine, quetiapine, and ziprasidone for positive symptoms. Olanzapine was superior to perphenazine, risperidone, and ziprasidone for negative symptoms. The remaining evidence for symptoms and substance use was based on small sample sizes, so no conclusions can be drawn.**

Symptoms

Overall symptoms

A significant small effect of more improved overall symptoms with olanzapine than perphenazine;

1 RCT, N = 266, SMD = -0.29, 95%CI -0.53 to -0.05, *p* = 0.02

A significant small effect of more improved overall symptoms with olanzapine than quetiapine;

1 RCT, N = 279, SMD = -0.25, 95%CI -0.48 to -0.01, *p* = 0.04

A significant small effect of more improved overall symptoms with olanzapine than risperidone;

1 RCT, N = 299, SMD = -0.24, 95%CI -0.47 to -0.02, *p* = 0.04

A significant small effect of more improved overall symptoms with olanzapine than ziprasidone;

1 RCT, N = 225, SMD = -0.36, 95%CI -0.63 to -0.09, *p* = 0.01

Positive symptoms

A significant large effect of more improved positive symptoms with risperidone than aripiprazole;

1 RCT, N = 45, SMD = 0.98, 95%CI 0.36 to 1.61, *p* = 0.002

A significant small to medium effect of more improved positive symptoms with olanzapine than perphenazine;

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1 RCT, N = 266, SMD = -0.35, 95%CI -0.59 to -0.10, *p* = 0.005 *A significant small to medium effect of more improved positive symptoms with olanzapine than quetiapine;* 1 RCT, N = 279, SMD = -0.37, 95%CI -0.60 to -0.13, *p* = 0.002 *A significant medium effect of more improved positive symptoms with olanzapine than ziprasidone;* 1 RCT, N = 225, SMD = -0.43, 95%CI -0.71 to -0.16, *p* = 0.002 <u>Negative symptoms</u> *A significant large effect of more improved negative symptoms with clozapine than risperidone;* 1 RCT, N = 36, SMD = -0.77, 95%CI -1.46 to -0.09, *p* = 0.03 *A significant small effect of more improved negative symptoms with olanzapine than perphenazine;* 1 RCT, N = 266, SMD = -0.26, 95%CI -0.50 to -0.02, *p* = 0.03 *A significant small effect of more improved negative symptoms with olanzapine than risperidone;* 1 RCT, N = 299, SMD = -0.23, 95%CI -0.46 to -0.00, *p* = 0.05 *A significant small effect of more improved negative symptoms with olanzapine than ziprasidone;* 1 RCT, N = 225, SMD = -0.27, 95%CI -0.55 to -0.00, *p* = 0.05 There were no other significant differences between antipsychotics.	
Substance use	
A significant large effect of less drug use with clozapine than other antipsychotics; 1 RCT, N = 31, SMD = -1.08, 95%CI -1.84 to -0.32, *p* = 0.005 *A significant large effect of less craving with risperidone than olanzapine;* 1 RCT, N = 41, SMD = 0.82, 95%CI 0.18 to 1.46, *p* = 0.01 There were no other significant differences between haloperidol, olanzapine, clozapine, ziprasidone, or risperidone.	
Risks	There were fewer drop-outs due to adverse events with clozapine than ziprasidone. Risperidone had less weight gain than olanzapine. Clozapine caused more sedation than other antipsychotics.
Consistency in results‡	Unable to assess; all reported outcomes/comparisons are 1 RCT.
Precision in results§	Precise, apart from risperidone vs. aripiprazole for positive symptoms, and clozapine vs. risperidone for negative symptoms.
Directness of results‖	Direct

Sabioni P, Ramos AC, Galduróz JCF

The Effectiveness of Treatments for Cocaine Dependence in Schizophrenic Patients: A Systematic Review

Current Neuropharmacology 2013; 11: 484-490

View review abstract online

Comparison	**Any pharmaceutical treatment for people with schizophrenia who are dependent on cocaine.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear of the benefits of pharmaceutical agents for cocaine dependence.**
Substance use	
2 RCTs compared haloperidol with olanzapine. 1 (N = 24) reporting increased cocaine consumption with haloperidol and decreased cocaine consumption with olanzapine. The other RCT (N = 31) reporting increased cocaine craving with haloperidol and decreased cocaine craving with olanzapine. 1 RCT (N = 28) compared risperidone with olanzapine and reported a small decrease in cocaine consumption with olanzapine. 1 open label trial (N = 18) compared risperidone with chlorpromazine or olanzapine and reported less craving and lower relapse rates with risperidone and a small decrease in cocaine consumption with olanzapine. 2 open label trials (N = 23) assessing the effectiveness of aripiprazole reported decreased cocaine consumption and craving. 1 RCT (N = 24) assessing the effectiveness of mazindol reported no decrease in cocaine consumption or craving.	
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

Temmingh HS, Williams T, Siegfried N, Stein DJ

Risperidone versus other antipsychotics for people with severe mental

illness and co-occurring substance misuse

Cochrane Database of Systematic Reviews 2018; 1: CD011057

View review abstract online

Comparison	**Risperidone vs. other antipsychotics for people with a dual diagnosis.** **All studies included people with schizophrenia or schizoaffective disorder.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, mostly imprecise, consistent where applicable, direct) is unable to determine differences between risperidone and other antipsychotics for symptoms, study retention or substance use.**

Symptoms and study retention

There were no significant differences between;

Risperidone vs. clozapine for;

Positive symptoms: 1 RCT, N = 36, MD = 0.90, 95%CI −2.21 to 4.01, $p > 0.05$

Leaving the study early: 2 RCTs, N = 45, RR = 0.49, 95%CI 0.10 to 2.51, $p > 0.05$, $I^2 = 34\%$

Risperidone vs. olanzapine for;

Positive symptoms: 1 RCT, N = 37, MD = -1.50, 95%CI −3.82 to 0.82, $p > 0.05$

Leaving the study early: 2 RCTs, N = 77, RR = 0.68, 95%CI 0.34 to 1.35, $p > 0.05$, $I^2 = 0\%$

Risperidone vs. perphenazine for;

Leaving the study early: 1 RCT, N = 281, RR = 1.05, 95%CI 0.92 to 1.20, $p > 0.05$

Risperidone vs. quetiapine for;

Leaving the study early: 1 RCT, N = 294, RR = 0.96, 95%CI 0.86 to 1.07, $p > 0.05$

Risperidone vs. ziprasidone for;

Leaving the study early: 1 RCT, N = 240, RR = 0.96, 95%CI 0.85 to 1.10, $p > 0.05$

Substance use

Clozapine was associated with lower levels of craving for cannabis than risperidone;

1 RCT, N = 28, MD = 7.00, 95%CI 2.37 to 11.63, $p < 0.05$

There were no significant differences between;

Risperidone vs. clozapine for;

Reduction in cannabis use: 1 RCT, N = 14, RR = 1.00, 95%CI 0.30 to 3.35, *p* > 0.05 Risperidone vs. olanzapine for; Reduction in cannabis use: 1 RCT, N = 41, MD = 0.40, 95%CI -4.72 to 5.52, *p* > 0.05 Craving for cannabis: 1 RCT, N = 41, MD = 5.00, 95%CI -4.86 to 14.86, *p* > 0.05	
Risks	There were no differences in adverse effects.
Consistency in results	Consistent where applicable (>2 RCTs).
Precision in results	Mostly imprecise
Directness of results	Direct

Wobrock T, Soyka M

Pharmacotherapy of schizophrenia and comorbid substance use disorder – Reviewing the evidence and clinical recommendations

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2008; 32: 1375-1385

View review abstract online

Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear of the benefits of pharmaceutical agents for substance use disorders.**
Comparison 1	**Anticonvulsant (lamotrigine, dose unspecified) plus clozapine (dose unspecified) for alcohol-dependence.**
Substance use	
One case series (N = 3) reported significant reduction in alcohol use and alcohol craving in treatment-resistant patients receiving clozapine augmented with lamotrigine (statistics not reported).	
Comparison 2	**Antidepressant (desipramine, imipramine), dose range 100-250mg/day plus clozapine (dose unspecified) vs. placebo plus clozapine.**
Substance use	

Four trials (N = 164) compared adjunctive antidepressants with placebo for clozapine augmentation; One trial (N = 27) reported better study retention in the desipramine group, fewer positive urine tests and fewer relapses by the end of 12 week treatment. One trial (N = 80) reported fewer positive urine tests in the desipramine group by the end of 12 week treatment, but no difference in study retention. One trial (N = 46) reported lower levels of post-psychotic depression in the imipramine group following 6 week treatment, and no exacerbation of psychotic symptoms. One trial (N = 11) reported better CGI scores in the imipramine group, but no difference in depression scores after 9 weeks. Cocaine cravings were reportedly reduced, but not cannabis cravings. At 6 month follow up, imipramine group had more relapses than placebo.	
Comparison 3	**Anti-craving medication (naltrexone, dose 50mg/day) plus antipsychotics (unspecified) vs. various comparisons.**
Substance use	
Three trials (N = 122) investigated anti-craving agents for reducing substance dependence; Two open trials (N = 91) reported significant reductions in substance use following naltrexone over 8 weeks, and one trial reported improvements in PANSS scores. One RCT (N = 31) reported significant reduction of alcohol use and craving in patients receiving naltrexone compared to placebo, but no difference in psychopathology scores over 12 weeks.	
Comparison 4	**Disulfiram, dose 250mg/day plus antipsychotics (unspecified) vs. various comparisons.**
Substance use	
One retrospective open trial (N = 32) reported high study attrition, but the remaining patients showed reduction in hospital treatment days following adjunctive disulfiram. A second open trial (N = 33) reported significantly reduced alcohol or drug use and number of days in hospital, but no effect on psychopathology following adjunctive disulfiram.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
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), MD = mean difference, 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, 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[7].

† 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

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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 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[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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