TECHNICAL COMMENTARY

Depression

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Introduction

Depression is characterised by a depressed mood or a loss of interest or pleasure in activities. Symptoms of depression may include changes in appetite, weight, sleep or psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty concentrating or making decisions, and thoughts of death or suicide. Depression may also be associated with increased hopelessness, which is the absence of positive future orientation.

Depressive symptoms are common in people with schizophrenia during the acute phase of the illness and less prevalent during remission. There is an overlap in symptoms between the negative symptoms of schizophrenia and depression, including sleep disturbances, lack of appetite, concentration difficulties, decreased motor activity, anhedonia, which is the inability to experience pleasure, apathy, decreased initiative, blunted affect and social withdrawal.

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 given priority for inclusion.

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 rated as having < 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 five systematic reviews that met our inclusion criteria[3-7].

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- Moderate to high quality evidence suggests the prevalence of a depressive disorder in people with first-episode schizophrenia is around 26%. This prevalence was higher when using cut-off scale scores (around 45%) than diagnostic criteria for depression. The prevalence of depressive disorders in people at high risk for psychosis is around 41%.
- Moderate to high quality evidence finds a medium to large improvement in global state with adjunctive antidepressants compared to adjunctive placebo, with no additional benefit for reducing specific symptoms.
- Moderate to low quality evidence suggests patients receiving the antipsychotic sulpride may show greater improvement in depressive symptoms than patients receiving the antipsychotic chlorpromazine. Patients receiving the antipsychotic clozapine may show greater improvement in depressive symptoms than patients receiving any other antipsychotic combined with the antidepressants amitryptiline, mianserin, meclobemide or with placebo. No differences in improvement were found between people taking the antipsychotics quetiapine or haloperidol.

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Furtado VA, Srihari V, and Kumar A

Atypical antipsychotics for people with both schizophrenia and depression

Cochrane Database of Systematic Reviews 2008; 1: CD005377

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Comparison	**Second generation antipsychotics (sulpride and quetiapine) vs. first-generation antipsychotics (haloperidol and chlorpromazine).**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) suggests sulpride may improve depressive symptoms more than chlorpromazine. No differences were found between quetiapine and haloperidol.**
Depression symptoms	
Patients receiving sulpride had significantly lower depression scores on the CPRS compared to those receiving chlorpromazine. 1 RCT, N = 36, WMD = -0.70, 95%CI -1.20 to -0.20, *p* = 0.0058 *No significant differences between quetiapine and haloperidol in:* *PANSS depression scores:* 1 RCT, N = 180, WMD = -0.57, 95%CI -1.40 to 0.30, *p* = 0.20 *Or in overall symptom improvement:* 1 RCT, N =180, RR 0.91, 95%CI 0.91 to 1.00, *p* = 0.14	
Consistency in results‡	1 study – not applicable
Precision in results§	Unable to assess for non-standardised measures (WMD).
Directness of results‖	Direct
Comparison 2	**Second generation antipsychotic clozapine vs. first generation antipsychotics plus antidepressants (mianserin, meclobemide, amitryptiline) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) suggests that clozapine may improve depression symptoms more than any other antipsychotic combined with amitryptiline, mianserin, meclobemide or placebo.**
Depression symptoms	

Patients receiving clozapine showed significantly lower depression scores on the HRDS compared to those receiving antipsychotics combined with: Amitryptiline: 1 RCT, N = 30, WMD = -3.61, 95%CI -6.58 to -0.64, *p* = 0.017 Mianserin: 1 RCT, N = 29, WMD = -5.53, 95%CI -8.23 to -2.8, *p* = 0.000061 Meclobemide: 1 RCT, N = 32, WMD = -4.35, 95%CI -6.7 to -2.03, *p* = 0.00024 Placebo: 1 RCT, N = 33, WMD = -6.35, 95%CI -8.6 to -4.1, *p* = 0.00001

Consistency in results	Not applicable; 1 RCT for each comparison.
Precision in results	Unable to assess for non-standardised measures (WMD).
Directness of results	Direct

Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK

Comorbid Depressive and Anxiety Disorders in 509 Individuals With an At-Risk Mental State: Impact on Psychopathology and Transition to Psychosis

Schizophrenia Bulletin 2014; 40(1): 120–131

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Comparison	**Proportion of people at high clinical risk of psychosis with depressive disorders.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests the prevalence of a depressive disorder in people at high clinical risk for psychosis is around 41%.**
Prevalence of depressive disorders	
10 studies, N = 1,683, prevalence = 40.7%, 95%CI 32.5% to 49.4%	
Consistency in results	Authors state that study results were inconsistent.
Precision in results	Appears precise.
Directness of results	Direct

Herniman SE, Allott K, Phillips LJ, Wood SJ, Uren J, Mallawaarachchi SR, Cotton SM

Depressive psychopathology in first-episode schizophrenia spectrum disorders: A systematic review, meta-analysis and meta-regression

Psychological Medicine 2019; 49: 2463-74

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Comparison	**Prevalence of depressive disorder in people with first-episode schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests the prevalence of a depressive disorder in people with first-episode schizophrenia is around 26%. The prevalence is higher when using cut-off scale scores (around 45%).**
Prevalence of depressive disorder diagnosis	
7 studies, N = 855, prevalence = 26.0%, 95%CI 22.1% to 30.3%, I^2 = 31%, p = 0.194	
Prevalence of depressive disorder according to a cut-off scale score	
11 studies, N = 1,312, prevalence = 43.9%, 95%CI 30.3% to 58.4%, I^2 = 95%, p < 0.001	
Consistency in results	Consistent for diagnosis only.
Precision in results	Appears precise.
Directness of results	Direct

Whitehead C, Moss S, Cardno A, Lewis G

Antidepressants for people with both schizophrenia and depression

Cochrane Database of Systematic Reviews 2002; 2: CD002305

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Depression

Comparison	**Any antidepressant plus any antipsychotic vs. placebo plus any antipsychotic.**
Summary of evidence	**Moderate to high quality evidence (small to medium sized sample, consistent, precise, direct) finds a medium to large improvement in global state with antidepressant use compared to placebo, with no differences in attrition or side effects.** **Moderate to low quality evidence (small samples, inconsistent, unable to assess precision, direct) suggests no benefit for overall mental state or depression symptoms.**
Global State	
Medium to large effect size shows a significant, clinically important improvement in the antidepressant group compared to placebo; 5 RCTs, N = 209, RD = -0.26, 95%CI -0.39 to -0.13, *p* = 0.000057 Q = 5.36, *p* = 0.25, I^2 = 25%	
Leaving the study early	
No significant difference was reported between groups for risk of leaving the study early; *Before 12 weeks:* 10 RCTs, N = 426, RD = 0.04, 95%CI 0.02 to 0.10, *p* = 0.23 Q = 12.21, *p* = 0.20, I^2 = 26% *After 12 weeks:* 1 RCT, N = 40, RD = -0.10, 95%CI -0.41 to 0.21, *p* = 0.53	
Mental State	
No differences in mental state; HAM-D Endpoint score: 3 RCTs, N = 132, MD = -1.18, 95%CI -3.06 to -0.70, *p* = 0.22, I^2 = 0%, *p* = 0.54 HAM-D Change score: 1 RCT, N = 52, MD = -0.53, 95%CI -5.55 to 4.49, *p* = 0.84 BPRS Endpoint score: 4 RCTs, N = 176, MD = 0.60, 95%CI -3.11 to 4.31, *p* = 0.75, I^2 = 80%, *p* = 0.03 BPRS Change score: 1 RCT, N = 51, MD = 2.92, 95%CI -4.04 to 9.88, *p* = 0.41	
Risks	No significant difference was reported for risk of any side effect; 2 RCTs, N = 110, RD = 0.11, 95%CI -0.03 to 0.25, *p* = 0.12, I^2 = 87%, *p* = 0.01.
Consistency in results	Consistent for global state, inconsistent for all other relevant outcomes. N/A for outcomes with 1 RCT.

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Precision in results	Precise where applicable. Unable to assess MD.
Directness of results	Direct for overall antidepressants vs. placebo.

Wilson RS, Yung AR, Morrison AP

Comorbidity rates of depression and anxiety in first episode psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; Nov: doi: 10.1016/j.schres.2019.11.035

View review abstract online

Comparison	**Prevalence of depression symptoms in people with first-episode psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence of depression symptoms in people with first-episode psychosis is around 23%.**
Prevalence of depression symptoms	
3 studies, N = 653, prevalence = 23%, range 14% to 34%, I^2 = 84%	
Consistency in results	Inconsistent
Precision in results	Appears imprecise.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, CI = Confidence Interval, CPRS = Comprehensive Psychopathological Rating Scale, HAM-D = Hamilton Depression Scale, HRDS = Hamilton Rating Scale for Depression, 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), PANSS = Positive and Negative Syndrome Scale, Q = test for heterogeneity, *r* = correlation coefficient, RCT = randomised controlled trial, RD = risk difference, RR = risk ratio, vs. = versus, WMD = weighted mean difference

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[8].

† 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) 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[8].

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[9]. 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[8];

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

§ 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[10].

‖ 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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