TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Treatments for depressive symptoms

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 three systematic reviews that met our inclusion criteria[3-5].

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Treatments for depressive symptoms

- For adjunctive antidepressants compared to placebo or no adjunctive treatment, moderate quality evidence finds a small effect of greater improvement in depressive symptoms with adjunctive antidepressants.
- For antipsychotics compared to placebo, moderate to high quality evidence finds a large effect of greater improvement in depressive symptoms with sulpiride. There were medium-sized improvements with clozapine, amisulpride, and aripiprazole over placebo. There were small improvements with olanzapine, cariprazine, paliperidone, asenapine, quetiapine, risperidone, ziprasidone, lurasidone, haloperidol, and brexpiprazole. There were no improvements over placebo with clopenthixol, sertindole, flupentixol, chlorpromazine, perphenazine, zotepine, zuclopenthixol, thiotixene, loxapine, penfluridol, pimozide, perazine, trifluoperazine, molindone, or levomepromazine.
- Moderate to low quality evidence suggests the antipsychotic clozapine may improve depression symptoms more than any other antipsychotic combined with the antidepressants amitryptiline, mianserin, meclobemide or placebo.

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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

View review abstract online

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.**
Depressive 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.**
Depressive 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

Helfer B, Samara MT, Huhn M, Klupp E, Leucht C, Zhu Y, Engel RR, Leucht S

Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: A systematic review and meta-analysis

American Journal of Psychiatry 2016; 173: 876-86

View review abstract online

Comparison	**Antidepressants vs. placebo or no adjunctive treatment.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, precise, indirect) finds small effects of greater improvement in depressive symptoms with adjunctive antidepressants.**

Depressive symptoms

Small, significant effects of improved depressive symptoms with antidepressants;

42 RCTs, N = 1,849, SMD = -0.25, 95%CI -0.38 to -0.12, *p* = 0.0001, I^2 = 44%, *p* = 0.002

Meta-regressions showed the effect size for depressive symptoms increased with increased mean patient age.

Subgroup analyses found similar effect sizes for individual antidepressants or drug classes, although there were few studies in some of these subgroup analyses and not all analyses were significant.

Risks	Antidepressants were associated with more abdominal pain, constipation, dizziness, and dry mouth.
Consistency in results	Consistent for responder and quality of life only.

Precision in results	Precise
Directness of results	Indirect (mixed drug classes), direct for subgroup analyses of drug classes.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Backers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis

The Lancet 2019; 394: 918

View review abstract online

Comparison	**All antipsychotics vs. placebo for 3-13 weeks.** **Studies with a high risk of bias were excluded.**
Summary of evidence	**Moderate to high quality evidence (large sample, low heterogeneity, mostly precise, indirect) suggests a large effect of greater improvement in depressive symptoms with sulpiride. There were medium-sized improvements with clozapine, amisulpride, and aripiprazole. There were small improvements with olanzapine, cariprazine, paliperidone, asenapine, quetiapine, risperidone, ziprasidone, lurasidone, haloperidol, and brexpiprazole. There were no improvements over placebo with clopenthixol, sertindole, flupentixol, chlorpromazine, perphenazine, zotepine, zuclopenthixol, thiotixene, loxapine, penfluridol, pimozide, perazine, trifluoperazine, molindone, or levomepromazine.** **For side effects (in order of first being best), there was a large effect of less use of antiparkinson drugs with clozapine, and more use of antiparkinson drugs with paliperidone, ziprasidone, risperidone, lurasidone, zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, haloperidol, loxapine, penfluridol, fluphenazine, chlorpromazine, thiotixene and pimozide.** **There was more akathisia with aripiprazole, ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine, sulpiride, molindone, penfluridol,**

	pimozide, fluphenazine, flupentixol, and zuclopenthixol. **There was more weight gain with haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine.** **There was less prolactin elevation with aripiprazole, clozapine, and zotepine, and more prolactin elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone.** **There was more sedation with aripiprazole, lurasidone, haloperidol, risperidone, asenapine, loxapine, olanzapine, chlorpromazine, thioridazine, thiotixene, ziprasidone, perazine, clozapine, clopenthixol, quetiapine, sulpiride, zotepine, and zuclopenthixol.** **There was more QTc prolongation with quetiapine, olanzapine, risperidone, iloperidone, ziprasidone, amisulpride, and sertindole.** **There was more anticholinergic side-effects haloperidol, olanzapine, clozapine, chlorpromazine, zotepine, iloperidone, thioridazine, and quetiapine.**
Depressive symptoms	
Large effect of more improvement in depressive symptoms with; Sulpiride N = 4,875, SMD = -0.90, 95%CrI -1.46 to -0.44, $p < 0.05$ *Medium-sized effects of more improvement in depressive symptoms with (in descending order of effect);* Clozapine N = 4,931, SMD = -0.52, 95%CrI -0.82 to -0.23, $p < 0.05$ Amisulpride N = 5,486, SMD = -0.44, 95%CrI -0.60 to -0.28, $p < 0.05$ Aripiprazole N = 4,973, SMD = -0.40, 95%CrI -0.69 to -0.10, $p < 0.05$ *Small effects of more improvement in depressive symptoms with (in descending order of effect);* Olanzapine N = 7,576, SMD = -0.37, 95%CrI -0.46 to -0.29, $p < 0.05$ Cariprazine	

	N = 5,128, SMD = -0.36, 95%CrI -0.63 to -0.09, $p < 0.05$ Paliperidone N = 6,090, SMD = -0.33, 95%CrI -0.44 to -0.21, $p < 0.05$ Asenapine N = 5,499, SMD = -0.32, 95%CrI -0.47 to -0.17, $p < 0.05$ Quetiapine N = 6,819, SMD = -0.24, 95%CrI -0.34 to -0.13, $p < 0.05$ Risperidone N = 6,389, SMD = -0.23, 95%CrI -0.34 to -0.11, $p < 0.05$ Ziprasidone N = 5,390, SMD = -0.21, 95%CrI -0.36 to -0.06, $p < 0.05$ Lurasidone N = 6,070, SMD = -0.20, 95%CrI -0.32 to -0.09, $p < 0.05$ Haloperidol N = 6,745, SMD = -0.17, 95%CrI -0.26 to -0.08, $p < 0.05$ Brexpiprazole N = 5,913, SMD = -0.16, 95%CrI -0.29 to -0.03, $p < 0.05$ *There were no significant effects for clopenthixol, sertindole, flupentixol, chlorpromazine, perphenazine, zotepine, zuclopenthixol, thiotixene, loxapine, penfluridol, pimozide, perazine, trifluoperazine, molindone, and levomepromazine.*
Risks	*The following antipsychotics were significantly associated with;* More use of antiparkinson drugs Small effects: paliperidone, ziprasidone, risperidone, and lurasidone Medium-sized effects: zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, loxapine, penfluridol, haloperidol, fluphenazine, and chlorpromazine Large effects: thiotixene and pimozide. There was a large effect of less use of antiparkinson drugs with clozapine. Akathisia Small effects: aripiprazole Medium-sized effects: ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine, and sulpiride, Large effects: molindone, penfluridol, pimozide, fluphenazine, flupentixol, and zuclopenthixol

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	Weight gain In order of increasing effect (measured in kg): haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine Prolactin elevation Less elevation with aripiprazole, clozapine, and zotepine More elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone Sedation Small effects: aripiprazole, lurasidone, and haloperidol Medium-sized effects: risperidone, thioridazine, asenapine, loxapine, olanzapine, thiotixene, ziprasidone, quetiapine, perazine, chlorpromazine, sulpiride, clopenthixol, and clozapine Large effects: zotepine and zuclopenthixol QTc prolongation Medium-sized effects: quetiapine, olanzapine, and risperidone Large effects: iloperidone, ziprasidone, amisulpride, and sertindole Anticholinergic side-effects Small effects: haloperidol and olanzapine Medium-sized effects: clozapine, iloperidone, chlorpromazine, zotepine, thioridazine, and quetiapine
Consistency in results	Authors state that overall heterogeneity was low to moderate
Precision in results	Mostly precise
Directness of results	Some indirectness; network meta-analysis

Explanation of acronyms

CI = Confidence Interval, CPRS = Comprehensive Psychopathological Rating 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), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RCT = randomised controlled trial, 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[6].

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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) 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[6].

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[7]. 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[6];

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

§ 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[8].

‖ 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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