TECHNICAL COMMENTARY

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Antidepressants

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy.

Antidepressants have been proposed as an additional therapy to standard antipsychotic treatments to improve functional outcomes and treat symptoms that are not addressed by the antipsychotic medication alone. Antidepressant medications have been studied as treatments for the symptoms of schizophrenia, particularly negative symptoms, as well as for treating people with comorbid schizophrenia and depression.

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 or 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[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 quality evidence finds small effects of greater improvement in overall, negative, positive, and depressive symptoms with adjunctive antidepressants. The effect size was largest for negative

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symptoms and smallest for positive symptoms.

- Moderate to high quality evidence finds a medium-sized effect of more smoking cessation with bupropion than with placebo, which was maintained at 6 months follow-up.
- Moderate quality evidence finds small benefits of adjunctive antidepressants for global cognition and executive functioning, but not memory, attention, processing speed, verbal fluency or visuospatial processing.

Galling B, Vernon JA, Pagsberg AK, Wadhwa A, Grudnikoff E, Seidman AJ, Tsoy-Podosenin M, Poyurovsky M, Kane JM, Correll CU

Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia

Acta Psychiatrica Scandinavica 2018; 137: 187-205

View review abstract online

Comparison	**Antidepressants vs. placebo.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, indirect) finds a small to medium-sized effect of greater improvement in overall and negative symptoms, but not positive or depressive symptoms with adjunctive antidepressants.**

Symptoms

Significant, medium-sized effect of greater reduction in total symptoms with antidepressants;

30 RCTs, N = 1,311, SMD = -0.37, 95%CI -0.57 to -0.17, $p < 0.001$, $I^2 = 66\%$, $p < 0.0001$

Subgroup analyses found only SNRIs and NaSSAs antidepressant classes were significant for total symptoms, and the improvement with NaSSAs was driven by improved positive and not negative symptoms. Only fluoxetine and mirtazapine showed significant improvements in total symptoms, however there were few studies assessing individual drugs.

Meta-regression found increased mean patient age was associated with larger effect sizes for total symptoms.

The effect was significant for negative but not positive or depressive symptoms;

Negative: 34 RCTs, N = 1,413, SMD = -0.28, 95%CI -0.47 to -0.09, $p = 0.003$, $I^2 = 65\%$, $p < 0.0001$

Positive: 30 RCTs, N = 1,193, SMD = -0.11, 95%CI -0.16 to 0.05, $p = 0.190$, $I^2 = 40\%$, $p = 0.013$

Depressive: 25 RCTs, N = 1,129, SMD = -0.13, 95%CI -0.32 to 0.06, $p = 0.185$, $I^2 = 56\%$, $p < 0.0001$

Subgroup analyses found only SNRIs and SSRIs antidepressant classes were significant for negative symptoms and the improvement in negative symptoms was with augmentation with first-generation antipsychotics but not second-generation antipsychotics. Only NaSSAs showed a significant improvement in positive symptoms. Only studies conducted in North America found a significant improvement in depressive symptoms.

Meta-regression found lower risk of study bias was associated with larger effect sizes for negative symptoms.

Risks	There was more dry mouth with antidepressant augmentation.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect (mixed drug classes), direct for subgroup analyses of drug classes.

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 overall, negative, positive, and depressive symptoms with adjunctive antidepressants. The effect size was largest for negative symptoms and smallest for positive symptoms.**

Symptoms

Small, significant effects of improved symptoms and quality of life with antidepressants;

Responder rate: 23 RCTs, N = 933, RR = 1.52, 95%CI 1.29 to 1.78, $p < 0.0001$, $I^2 = 5\%$, $p = 0.39$

Overall symptoms: 47 RCTs, N = 1,858, SMD = -0.24, 95%CI -0.39 to -0.09, $p = 0.002$, $I^2 = 59\%$, $p < 0.00001$

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

Negative: 48 RCTs, N = 1,905, SMD = -0.30, 95%CI -0.44 to -0.16, $p < 0.0001$, $I^2 = 53\%$, $p < 0.0001$

Positive: 42 RCTs, N = 1,658 SMD = -0.17, 95%CI -0.33 to -0.01, $p = 0.04$, $I^2 = 59\%$, $p < 0.00001$

Quality of life: 2 RCTs, N = 235, SMD = -0.32, 95%CI -0.57 to -0.06, $p = 0.02$, $I^2 = 0\%$, $p = 0.97$

Meta-regressions showed the effect size for depressive symptoms increased with increased mean patient age, and the effect size for negative symptoms increased with increased baseline symptom

severity. 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.

Tsoi DT, Porwal M, Webster AC

Interventions for smoking cessation and reduction in individuals with schizophrenia

Cochrane Database of Systematic Reviews 2013; 2: Art. No.: CD007253

View review abstract online

Comparison	**Bupropion with or without NRT vs. placebo with or without NRT.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, imprecise, direct) finds a medium-sized effect of more smoking cessation with bupropion than placebo, which was maintained at 6 months follow-up.**
Smoking cessation	
A medium-sized, significant effect of more smoking cessation with bupropion; End of treatment: 7 RCTs, N = 340, RR = 3.03, 95%CI 1.69 to 5.42, $p = 0.0002$, $I^2 = 0\%$, $p = 0.71$ 6 months follow-up: 5 RCTs, N = 214, RR = 2.78, 95%CI 1.02 to 7.58, $p = 0.045$, $I^2 = 0\%$, $p = 0.90$	
Risks	There were no reports of major adverse events such as seizures with bupropion.
Consistency in results	Consistent

Precision in results	Imprecise
Directness of results	Direct

Vernon JA, Grudnikoff E, Seidman AJ, Frazier TW, Vemulapalli MS, Pareek P, Goldberg TE, Kane JM, Correll CU

Antidepressants for cognitive impairment in schizophrenia – A systematic review and meta-analysis

Schizophrenia Research 2014; 159: 385-394

View review abstract online

Comparison	**Antidepressants vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, precise, indirect) suggests small benefits of antidepressants for global cognition and executive functioning only.**
Global cognition	
Small, significant effect of greater improvement in the antidepressant group; 11 RCTs, N = 501, *g* = 0.09, 95%CI 0.02 to 0.17, *p* = 0.012, I^2 = 45%	
Executive functioning	
Small, significant effect of greater improvement in the antidepressant group; 8 RCTs, N = 259, *g* = 0.17, 95%CI 0.02 to 0.31, *p* = 0.02, I^2 = 47%	
Memory	
No significant differences between groups; Global memory: 9 RCTs, N = 432, *g* = 0.077, 95%CI -0.038 to 0.19, *p* = 0.19, I^2 = 46% Auditory verbal long-term memory: 4 RCTs, N = 110, *g* = 0.06, 95%CI -0.20 to 0.31, *p* = 0.66, I^2 = 41% Visuospatial long-term memory: 4 RCTs, N = 141, *g* = 0.07, 95%CI -0.45 to 0.59, *p* = 0.79, I^2 = 66% Long-term memory: 7 RCTs, N = 214, *g* = 0.11, 95%CI -0.18 to 0.40, *p* = 0.45, I^2 = 45%	

Auditory verbal working memory: 4 RCTs, N = 288, *g* = 0.11, 95%CI -0.12 to 0.34, *p* = 0.34, I^2 = 0%	
Visuospatial working memory: 4 RCTs, N = 123, *g* = 0.06, 95%CI -0.18 to 0.31, *p* = 0.61, I^2 = 7%	
Working memory: 8 RCTs, N = 412, *g* = 0.07, 95%CI -0.087 to 0.24, *p* = 0.37, I^2 = 0%	
Auditory verbal memory: 5 RCTs, N = 308, *g* = 0.08, 95%CI -0.081 to 0.25, *p* = 0.32, I^2 = 20%	
Visuospatial memory: 5 RCTs, N = 160, *g* = 0.06, 95%CI -0.16 to 0.29, *p* = 0.57, I^2 = 0%	
Attention	
No significant differences between groups; 5 RCTs, N = 321, *g* = 0.02, 95%CI -0.19 to 0.23, *p* = 0.84, I^2 = 0%	
Processing speed	
No significant differences between groups; 6 RCTs, N = 344, *g* = 0.09, 95%CI -0.031 to 0.21, *p* = 0.15, I^2 = 16%	
Visuospatial processing	
No significant differences between groups; 3 RCTs, N = 94, *g* = 0.14, 95%CI -0.73 to 1.00, *p* = 0.76, I^2 = 78%	
Verbal fluency	
No significant differences between groups; 5 RCTs, N = 327, *g* = 0.019, 95%CI -0.14 to 0.18, *p* = 0.81, I^2 = 0%	
Risks	No differences between groups for any adverse event, apart from sedation which was higher in the antidepressant group (RR 2.91, 95%CI 1.03 to 8.17, *p* = 0.04, I^2 = 0%).
Consistency in results	Inconsistent for visuospatial long-term memory and processing, general psychopathology, negative and positive symptoms, and depressive symptoms scale scores.
Precision in results	Imprecise for visuospatial processing.
Directness of results	Indirect (mixed drug classes).

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NASSA = noradrenergic and specific serotonergic antidepressant**,** NRT = nicotine replacement therapy, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRIs = selective serotonin reuptake inhibitor, 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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