TECHNICAL COMMENTARY

Catecholamines

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Introduction

Catecholamines are a group of neurotransmitters that includes dopamine and noradrenaline. The dopamine hypothesis of schizophrenia suggests that some symptoms of the illness may be caused by increased levels of dopamine in certain brain areas. To this end, most antipsychotic medications typically have dopamine-blocking actions. However, these medications do not treat all of the symptoms of schizophrenia, and it is thought that some of the remaining symptoms may be affected by the low levels of dopamine. Consequently, the effects of medications that increase dopamine levels, in addition to ongoing antipsychotic medications, have been investigated as a treatment for general symptoms of schizophrenia, as well as for the alleviation of some antipsychotic side effects such as tardive dyskinesia (abnormal, involuntary movements).

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 a medium-sized benefit of L-DOPA over placebo for improving overall symptom severity. There may also be a benefit for tardive dyskinesia with dopaminergic

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medications, with no differences in acceptability.

- Moderate to low quality evidence suggests large benefits of mirtazapine or mianserin for improving total and negative symptoms, but not general or positive symptoms. Review authors report that the treatment was well tolerated.
- Moderate to low quality evidence suggests some benefit of noradrenergic reuptake inhibitors over placebo for general symptoms in the short-term (2-12 weeks) and negative symptoms in the medium-term (13-26 weeks). There may also be some improvements in quality of life, with no differences between groups in nausea.

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El-Sayeh HG, Rathbone J, Soares-Weiser K, Bergman H

Non-antipsychotic catecholaminergic drugs for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 1: CD000458

View review abstract online

Comparison 1	**Noradrenergic medications (celiprolol or alpha-methyldopa) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (very small sample, consistent, imprecise, direct) finds no differences between noradrenergic medications and placebo for tardive dyskinesia.**
Tardive dyskinesia	
No significant differences between groups; 2 RCTs, N = 55, RR = 0.91, 95%CI 0.65 to 1.27, p = 0.57, I^2 = 0%, p = 0.52	
Risks	No significant differences in acceptability.
Consistency in results‡	Consistent
Precision in results§	Imprecise
Directness of results‖	Direct
Comparison 2	**Dopaminergic medications (reserpine, carbidopa/levodopa or L-DOPA) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (very small sample, consistent, imprecise, direct) finds a trend effect of greater improvement in tardive dyskinesia with dopaminergic medications compared to placebo.**
Tardive dyskinesia	
A small, trend effect of greater improvement with dopaminergic medications; 3 RCTs, N = 57, RR = 0.60, 95%CI 0.35 to 1.03, p = 0.06, I^2 = 0%, p = 0.90 There were no significant differences in levels of deterioration (tardive dyskinesia or mental state).	

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Risks	No significant differences in acceptability.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Dopaminergic medication plus antipsychotics vs. noradrenergic medications plus antipsychotics.**
Summary of evidence	**Low quality evidence (one very small RCT) is unclear as to any benefit of dopaminergic over noradrenergic medication.**
Tardive dyskinesia	
No significant differences between groups; 1 RCT, N = 20, RR = 0.60, 95%CI 0.19 to 1.86, *p* = 0.38	
Risks	Not reported
Consistency in results	Not applicable.
Precision in results	Imprecise
Directness of results	Direct

Hecht EM, Landy DC

Alpha-2 receptor antagonist add-on therapy in the treatment of schizophrenia; a meta-analysis

Schizophrenia Research 2012; 134: 202-206

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Comparison	**Mirtazapine (30 mg/day) or mianserin (15 or 30 mg/day) for 4-8 weeks plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, some inconsistency and imprecision, direct) suggests a benefit of mirtazapine or mianserin for improving total and negative symptoms, but not general or positive symptoms.**

Symptom severity	
Large effect of improved total symptoms with alpha-2 antagonists; 8 RCTs, N = 244, *d* = 0.80, 95%CI 0.15 to 1.46, *p* < 0.05, Q = 33.1, *p* < 0.01 *Large effect of improved negative symptoms with alpha-2 antagonists;* 8 RCTs, N = 244, *d* = 0.84, 95%CI 0.17 to 1.51, *p* < 0.05, Q = 37.4, *p* < 0.01 *No differences between groups in general symptoms;* 6 RCTs, N = 196, *d* = 0.28, 95%CI -0.08 to 0.64, *p* > 0.05, Q = 7.6, *p* = 0.18 *No differences between groups in positive symptoms;* 8 RCTs, N = 244, *d* = 0.16, 95%CI -0.30 to 0.62, *p* > 0.05, Q = 19.9, *p* < 0.01	
Risks	Authors report that the combination treatment of antipsychotics and alpha-2 antagonists were well tolerated, with no serious adverse events reported.
Consistency in results	Inconsistent, apart from general symptoms.
Precision in results	Imprecise, apart from general and positive symptoms.
Directness of results	Direct

Jaskiw GE, Popli AP

A meta-analysis of the response to chronic L-dopa in patients with schizophrenia: therapeutic and heuristic implications

Psychopharmacology 2004; 171(4): 365-74

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Comparison	**Dopaminergic medication (L-DOPA, 300-5 000 mg/day) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, inconsistent, unable to assess precision, direct) suggests a benefit of L-DOPA for reducing symptom severity.**
Symptom severity	

Significant, medium-sized effect of improved symptoms severity with L-DOPA; 5 RCTs, N = 163, *d* = 0.71, 95%CI not reported, *p* < 0.001, Q = 24.411, *p* < 0.001	
Risks	Not reported
Consistency in results	Inconsistent
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Matthews PRL, Horder J, Pearce M

Selective noradrenaline reuptake inhibitors for schizophrenia

Cochrane Database of Systematic Reviews 2018; 1: CD010219

View review abstract online

Comparison	**Noradrenergic reuptake inhibitors (reboxetine, atomoxetine or viloxazine) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, mostly inconsistent, unable to assess precision, direct) suggests some benefit of noradrenergic reuptake inhibitors for general symptoms in the short-term (2-12 weeks) and negative symptoms in the medium-term (13-26 weeks). There may also be some improvements in quality of life.**
Symptom severity	
Short-term (2-12 weeks) *A medium-sized effect of greater improvement in general symptoms with noradrenergic medications;* PANSS general: 5 RCTs, N = 294, MD = -2.17, 95%CI -3.93 to -0.40, *p* = 0.01, I^2 = 44%, *p* = 0.13 PANSS total: 4 RCTs, N = 308, MD = -2.84, 95%CI -5.28 to 0.40, *p* = 0.02, I^2 = 72%, *p* = 0.01 *No significant differences between groups;* PANSS negative: 6 RCTs, N = 359, MD = -0.99, 95%CI -2.53 to 0.56, *p* = 0.21, I^2 = 71%, *p* = 0.004 PANSS positive: 5 RCTs, N = 294, MD = -0.16, 95%CI -0.96 to 0.63, *p* = 0.68, I^2 = 0%, *p* = 0.85 Medium-term (13-26 weeks)	

A medium-sized effect of greater improvement in negative symptoms with noradrenergic medications; PANSS negative: 3 RCTs, N = 219, MD = -3.25, 95%CI -4.04 to -2.47, $p < 0.00001$, $I^2 = 0\%$, $p = 0.78$ *No significant differences between groups;* PANSS general: 2 RCTs, N = 154, MD = -2.90, 95%CI -7.57 to 1.77, $p = 0.22$, $I^2 = 69\%$, $p = 0.07$ PANSS total: 3 RCTs, N = 219, MD = -3.67, 95%CI -10.07 to 2.72, $p = 0.26$, $I^2 = 94\%$, $p < 0.00001$ PANSS positive: 2 RCTs, N = 154, MD = -0.14, 95%CI -1.30 to 1.01, $p = 0.81$, $I^2 = 0\%$, $p = 0.80$	
Quality of life, global state and cognition	
A medium-sized effect of greater improvement in quality of life with noradrenergic medications; 1 RCT, N = 114, MD = 9.36, 95%CI 7.89 to 10.83, $p < 0.05$ *No significant differences in global state or cognition;* Global state: 1 RCT, N = 28, RR = 0.99, 95%CI 0.45 to 2.20, $p < 0.05$ Cognition: 4 RCTs, N = 180, SMD = 0.04, 95%CI -0.28 to 0.36, $p = 0.79$, $I^2 = 8\%$, $p = 0.35$	
Risks	There were no differences in all-cause withdrawal or nausea.
Consistency in results	Mostly inconsistent
Precision in results	Precise for cognition, unable to assess MDs (not standardised).
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* standardised mean differences, 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), RR = risk ratio, 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].

† 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.

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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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