TECHNICAL COMMENTARY

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Beta blockers

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy. Adjunct medications are often prescribed to treat side effects of antipsychotic medications. They may contribute to increasing adherence, which reduces the risk of psychotic relapse.

Beta blockers are adrenergic beta receptor antagonists, inhibiting the action of neurotransmitters adrenaline/epinephrine and noradrenaline/norepinephrine on beta-receptors, ultimately influencing brain regions that control functions such as movement. Beta blockers target extrapyramidal symptoms such as akathisia; a type of restlessness, a common and early-onset side effect of many neuroleptics. Beta blockers have also been used to reduce the physical symptoms of anxiety in schizophrenia (for example, pounding heart, clammy hands, sweating), and have also been suggested to reduce aggression.

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 reporting less than 50% of items 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 six systematic reviews that met our inclusion criteria[3-8].

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Beta blockers

- Moderate quality evidence suggests norepinephrine reuptake inhibitors atomoxetine and reboxetine may reduce depressive symptoms, but not positive or negative symptoms in people with schizophrenia. Reboxetine may result in more weight loss than placebo.
- Moderate quality evidence suggests no benefit of beta blockers for improving relapse or attrition in people with schizophrenia compared to placebo. Lower quality evidence suggests no benefit of beta blockers for improving extrapyramidal symptoms such as akathisia, or for reducing aggression.

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TECHNICAL COMMENTARY

Beta blockers

Barnes TR, Soares-Weiser K, Bacalcthuk J

Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia

Cochrane Database of Systematic Reviews 2004; 4: CD001946

View review abstract online

Comparison	**Central action beta-blockers vs. placebo in people with schizophrenia and neuroleptic-induced akathisia, in addition to treatment as usual.**
Summary of evidence	**Moderate to low quality evidence (very small samples, imprecise, consistent where applicable, direct) suggests no differences in akathisia.**
Remission of akathisia **Measured by the Involuntary Movement and Extrapyramidal Scale**	
Propranol (60-80 mg/day for 48 hours) *No significant difference between groups;* 1 RCT, N = 11, RR = 1.04, 95%CI 0.59 to 1.83, $p = 0.89$	
Akathisia severity **Measured by the Simpson and Angus Scale**	
ICI 118,551 (100 mg/day for 48 hours) *No significant difference between groups;* 1 RCT, N = 10, RR = 0.22, 95%CI 0.03 to 1.45, $p = 0.12$	
Acceptability of treatment	
Beta-blockers (60-100 mg/day for 48 hours) *No significant difference between groups;* 2 RCTs, N = 31, RD = 0.00, 95%CI -0.15 to 0.15, $p > 0.05$, $I^2 = 0\%$	
Risks	No adverse effects occurred in either group.
Consistency in results‡	Consistent for acceptability, N/A for other outcomes (1 RCT)
Precision in results§	Imprecise

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Directness of results‖	Direct

Goedhard LE, Stolker JJ, Heerdink ER, Nijman HLI, Olivier B, Egberts TCG

Pharmacotherapy for the treatment of aggressive behavior in general adult psychiatry: A systematic review

Journal of Clinical Psychiatry 2006; 67(7): 1013-1024

View review abstract online

Comparison	**Beta blockers (nadolol, pindolol, propranolol) plus antipsychotics (unspecified) vs. placebo plus antipsychotics for improving aggressive behaviour.**
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency or precision, direct) is unable to ascertain any benefit of beta-blockers for aggressive behaviour.**
Aggressive behaviour	
2 RCTs, N = 82, reported BPRS-Hostility scores were not significantly different between groups. 2 RCTs, N = 78, reported significant improvements in OAS scores in the adjunctive group, two RCTs, N = 66, reported no difference in OAS scores. One RCT, N = 34, reported improvements in STPI scores in the adjunctive group.	
Risks	Adverse effects included blood pressure drops, bronchial problems. One RCT reported lower rates of extrapyramidal symptoms in the adjunctive group.
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Kishi T, Mukai T, Matsuda Y, Moriwaki M, Iwata N

Efficacy and safety of noradrenalin reuptake inhibitor augmentation therapy for schizophrenia: A meta-analysis of double-blind randomized

placebo-controlled trials	
Journal of Psychiatric Research 2013: 47; 1557-1563 View review abstract online	
Comparison	**Noradrenalin reuptake inhibitors (atomoxetine and reboxetine) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, mostly consistent and precise, direct) suggests NRIs atomoxetine and reboxetine may reduce depressive symptoms, but not positive or negative symptoms.**
Symptoms	
A significant, large effect for reduced depressive symptoms in the NRI group compared to placebo; 5 RCTs, N = 168, SMD = -1.08, 95%CI -2.71 to 0.01, p = 0.05, I^2 = 89% *Excluding 1 RCT of reboxetine-betahistine reduced heterogeneity and the effect size to medium;* 4 RCTs, N = 128, SMD = -0.50, 95%CI -0.85 to -0.14, p = 0.007, I^2 = 0% *No differences for positive or negative symptoms;* Overall: 3 RCTs, N = 76, SMD = -0.03, 95%CI -0.45 to 0.45, p = 0.90, I^2 = 10% Positive 7 RCTs, N = 218, SMD = -0.03, 95%CI -0.30 to 0.24, p = 0.81, I^2 = 0% Negative: 7 RCTs, N = 218, SMD = 0.02, 95%CI -0.29 to 0.25, p = 0.89, I^2 = 0%	
Risks	Pulse was significantly higher with NRIs (3 RCTs, N = 86, SMD 0.70, 95%CI 0.13 to 1.28, p = 0.02, I^2 = 35%), and reboxetine caused less weight gain (3 RCTs, N = 111, SMD -0.78, 95%CI -1.17 to -0.38, p = 0.0001, I^2 = 0%). No differences were reported for drop-out due to all-cause, inefficacy, adverse events, nausea, insomnia, parkinsonism, extrapyramidal symptoms, use of anticholinergic drugs, sedation/fatigue, and use of benzodiazepines.
Consistency in results	Mostly consistent
Precision in results	Mostly precise
Directness of results	Direct

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Beta blockers

Shek E, Barhan S, Cheine MV, Ahonen J, Wahlbeck K

Beta-blocker supplementation of standard drug treatment for schizophrenia

Cochrane Database of Systematic Reviews 2010; (3): CD000234

View review abstract online

Comparison	**Central action beta-blockers (propranolol, nadolol or oxprenolol) vs. placebo in people with schizophrenia, in addition to treatment as usual, treatment duration up to four months.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, imprecise, direct) suggests no significant benefit of beta blockers for improving relapse or attrition compared to placebo.**
Treatment acceptability (attrition)	
No significant difference between groups for study attrition, though there was a trend to higher attrition in the beta-blocker group; 6 weeks: 8 RCTs, N = 274, RR = 1.62, 95%CI 0.92 to 2.83, *p* = 0.093, Q = 7.00, *p* = 0.43, I^2 = 0%	
Relapse	
No significant difference between groups for relapse (as defined by individual studies); 2 RCTs, N = 68, RR = 3.12, 95%CI 0.34 to 28.36, *p* = 0.31, Q = 0.00, *p* = 0.97, I^2 = 0%	
Risks	No increased risk of death was reported in beta blockers compared to placebo in the short term (9 RCT, N = 282, risk difference = 0.00, 95%CI -0.04 to 0.04, *p* = 1.0, I^2 = 0%) or in the medium term (1 RCT, N = 20, risk difference = 0.0, 95%CI -0.17 to 0.17, *p* = 1.0). No significant differences in *cardiovascular effects* were reported in the short term (8 RCT, N = 274, RR = 1.63, 95%CI 0.70 to 3.84, *p* = 0.26, I^2 = 0%), including collapse (2 RCT, N = 68, RR = 4.14, 95%CI 0.49 to 34.94, *p* = 0.19, I^2 = 0%); dizziness (1 RCT, N = 41, RR = 0.32, 95%CI 0.01 to 7.38, *p* = 0.48); hypotension (3 RCT, N = 80, RR = 0.74, 95%CI 0.16 to 3.53, *p* = 0.71, I^2 = 0%); increased creatine phosphokinase (1 RCT, N = 25, RR = 0.31, 95%CI 0.01 to 6.94, *p* = 0.46); palpitations (1 RCT, N = 60, RR = 11.00, 95%CI 0.64 to 190.53, *p* = 0.099).

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Wahlbeck K, Cheine MV, Gilbody S, Ahonen J

Efficacy of β-blocker supplementation for schizophrenia: a systematic review of randomized trials

Schizophrenia Research 2000; 41: 341-347

View review abstract online

Comparison	**Central action beta-blockers (propranolol, nadolol or oxprenolol) vs. placebo, in addition to treatment as usual.**
Summary of evidence	**Moderate quality evidence (small samples, consistent, imprecise, direct) suggests no significant benefit of beta blockers for study attrition or relapse compared to placebo, although some benefit was reported for extrapyramidal symptoms.**
Treatment acceptability (attrition)	
No significant difference between groups for study attrition; 5 RCT, N = 117, OR = 2.1, 95%CI 0.50 to 7.90, *p* = > 0.05, Q = 0.49, *p* = 0.49	
Relapse	
No significant difference between groups for relapse; 1 RCT, N = 20, OR = 8.3, 95%CI 0.50 to 142.0, *p* = 0.31	
Mental state	
From five trials, authors report no significant difference between beta blockers and placebo for symptom scores. Two trials (N = 55) rated behavioural change (using nurse observation scales) and authors report significant behavioural improvements in the beta blocker group.	
Risks	Two studies reported improved extrapyramidal symptoms in the beta

	blocker group compared to placebo, but one trial reported no difference in symptoms of parkinsonism. No apparent difference between groups in risk of death, blood pressure change, or collapse.
Consistency in results	Consistent for acceptability, N/A for other outcomes.
Precision in results	Imprecise
Directness of results	Direct

Zheng W, Li XB, Shi ZM, Yang XH, Cai DB, Ng CH, Ungvari GS, Liu WJ, Wu YJ, Wang YY, Ning YP, Xiang YT

Adjunctive Reboxetine for Schizophrenia: Meta-analysis of Randomized Double-blind, Placebo-controlled Trials

Pharmacopsychiatry 2020; 53: 5-13

View review abstract online

Comparison	**Reboxetine plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, some inconsistency and imprecision, direct) suggests no benefit of reboxetine over placebo for symptoms, although there may be more weight loss with reboxetine.**
Symptoms	
No significant differences between groups; Overall psychopathology: 6 RCTs, N = 473, SMD = -0.50, 95%CI -1.05 to 0.06, $p = 0.08$, $I^2 = 88\%$ Positive symptoms: 9 RCTs, N = 602, SMD -0.00, 95%CI -0.16 to 0.16, $p = 0.98$, $I^2 = 0\%$ Negative symptoms: 8 RCTs, N = 492, SMD = -0.36, 95%CI -0.77 to 0.05, $p = 0.09$, $I^2 = 79\%$	
Risks	Reboxetine outperformed placebo in reducing weight and body mass index, although reboxetine caused more dry mouth.
Consistency in results	Consistent for positive symptoms only.
Precision in results	Precise for positive and negative symptoms only.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression Scale, CI = Confidence Interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OAS = Overt Aggression Scale, *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, RD = risk difference, SMD = standardized mean difference, STPI = State-Trait Personality Inventory, 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[9].

† 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[9].

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[10]. 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[9];

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

§ 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[11].

‖ 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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