TECHNICAL COMMENTARY

Serotonin modulators

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Introduction

Atypical antipsychotics are thought to have some affinity for serotonin 5-HT receptors, for example clozapine, quetiapine, and olanzapine among others. This suggests a potential for the use of serotonin-specific medications in the treatment of schizophrenia.

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 five systematic reviews that met inclusion criteria[3-7].

- Moderate to low quality evidence finds a large effect of greater improvement in overall symptoms with adjunctive buspirone compared to placebo, with no differences in adverse effects apart from fewer extrapyramidal symptoms with buspirone. However, there were no significant effects in the subgroup analyses of positive, negative, general symptoms or for cognition. There were no benefits of tandospirone.
- Moderate to low quality evidence suggests a large benefit for overall and negative symptoms with adjunctive granisetron, ondansetron, or tropisetron compared to placebo.

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Bennett AC, Vila TM

The Role of Ondansetron in the Treatment of Schizophrenia

Drug Information Rounds 2010; 44: 1301-1306

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Comparison	**Ondansetron (4-16mg/day) plus antipsychotic medication (varying) vs. placebo or antipsychotic medication alone.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) suggests adjunctive ondansetron in combination with antipsychotics may improve general psychopathology, particularly negative symptoms.**

Mental state

Measured by PANSS, BPRS, CGI

8 mg ondansetron daily + haloperidol (4–30 mg daily) or risperidone (4–6 mg daily) for 12 weeks vs. haloperidol or risperidone alone

Statistically significant improvement in;

Total PANSS: 2 RCTs, N = 151, $p \leq 0.05$

Negative PANSS: 2 RCTs, N = 151, $p \leq 0.05$

PANSS general psychopathology: 2 RCTs, N = 151, $p \leq 0.05$

Cognition: 2 RCTs, N = 121, $p \leq 0.05$

Clinical response rates: 2 RCTs, N = 121, $p \leq 0.05$

No significant differences were reported in;

Positive symptom or CGI severity scores: 2 RCTs, N = 121, $p > 0.05$

7 days ondansetron (8mg/day) + clozapine (mean 360 mg/day), followed by 7 days placebo + clozapine, cross-over trial

No significant changes reported in PANSS or CGI scores, but significantly greater improvement with ondansetron than with placebo on Rey-Osterich Complex Figure Test;

1 trial, N = 21, $p < 0.002$

12 weeks 8mg ondansetron – pre- post treatment

Significant improvements in;

PANSS total score: 1 trial, N = 20, $p < 0.0002$

PANSS positive: 1 trial, N = 20, $p < 0.002$

PANSS negative: 1 trial, N = 20, $p < 0.003$ PANSS general psychopathology: 1 trial, N = 20, $p < 0.001$ CGI severity: 1 trial, N = 20, $p < 0.01$ 4 weeks 4-8mg ondansetron– pre- post treatment *Significant improvements in;* PANSS total score: 1 trial, N = 10, $p < 0.001$ PANSS positive: 1 trial, N = 10, $p < 0.002$ PANSS negative: 1 trial, N = 10, $p < 0.002$ PANSS general psychopathology: 1 trial, N = 10, $p < 0.01$ CGI severity: 1 trial, N = 10, $p < 0.003$	
Risks	Two open-label trials (N = 30) reported reduced severity and mean total scores on the Abnormal Involuntary Movement Scale ($p < 0.002$). 1 crossover trial reported no changes on the Extrapyramidal Symptom Rating Scale. Review authors state that in all studies, ondansetron was well tolerated, with no severe adverse reactions reported.
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct

Choi K, Wykes T, Kurtz M

Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy

The British Journal of Psychiatry 2013; 203: 172-178

View review abstract online

Comparison	**Adjunctive serotonergic agonists plus antipsychotics (various) vs. antipsychotics plus placebo.**
Summary of evidence	**Moderate to high quality evidence (small or unclear samples, consistent, precise, direct) suggests a small effect of adjunctive serotonergic agonists for improving positive symptoms, with no benefit for other symptoms or cognitive functioning.**

Symptoms	
Small effect of improved positive symptoms in those taking adjunctive serotonergic agonists; Positive symptoms: 5 RCTs, N unclear, *d* = 0.33, 95%CI 0.00 to 0.66, *p* = 0.048, Q_W = 0.17, *p* = 1.00 Negative symptoms: 4 RCTs, N unclear, *d* = -0.31, 95%CI -0.74 to 0.11, *p* = 0.148, Q_W = 1.38, *p* = 0.71 Overall symptoms: 5 RCTs, N unclear, *d* = 0.12, 95%CI -0.21 to 0.44, *p* = 0.484, Q_W = 0.90, *p* = 0.92	
Cognition	
No differences between groups; Overall function: 6 RCTs, N = 182, *d* = 0.07, 95%CI -0.22 to 0.37 *p* = 0.625 Q_W = 2.73, *p* = 0.74 Verbal learning and memory: 4 RCTs, N unclear, *d* = 0.14, 95%CI -0.22 to 0.49, *p* = 0.455, Q_W = 2.54, *p* = 0.47 Reasoning/problem-solving: 5 RCTs, N unclear, *d* = 0.09, 95%CI -0.22 to 0.41, *p* = 0.565, Q_W = 2.11, *p* = 0.72	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kishi T, Mukai H, Matsuda Y, Iwata N

Selective serotonin 3 receptor antagonist treatment for schizophrenia: Meta-analysis and systematic review

NeuroMolecular Medicine (2014). 16: 61-69

View review abstract online

Comparison	**Granisetron plus risperidone, ondansetron plus risperidone, ondansetron plus haloperidol, or tropisetron plus risperidone vs. antipsychotics plus placebo.**

Summary of evidence	**Moderate to low quality evidence (medium sample size, inconsistent, imprecise, direct) suggests a large effect for overall and negative symptoms in those receiving adjunctive granisetron, ondansetron, or tropisetron compared to placebo.**
Psychiatric symptoms	
Large effect of improved overall and negative symptoms those taking adjunctive 5-HT3 antagonists compared to placebo; PANSS total: 5 RCTs, N = 261, *d* = -1.03, 95%CI -1.70 to -0.36, *p* = 0.003, I^2 = 85% PANSS general: 5 RCTs, N = 261, *d* = -0.70, 95%CI -1.23 to -0.17, *p* = 0.01, I^2 = 73% Negative symptoms: 5 RCTs, N = 261, *d* = -1.10, 95%CI -1.82 to -0.39, *p* = 0.002, I^2 = 84% *No differences in positive symptoms;* Positive symptoms: 5 RCTs, N = 261, *d* = -0.12, *p* = 0.33, I^2 not reported	
Risks	Dropout due to all cause (RR = 0.80, *p* = 0.50), inefficacy (RR = 0.76, *p* = 0.65), or adverse events (RR = 0.84, p = 0.75) was similar in both groups. Constipation occurred significantly more often with 5HT3 agonists than placebo (RR = 2.05, 95%CI 1.07 to 3.91, *p* = 0.03, NNH = 11, *p* = 0.02).
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Zheng W, Li XH, Cai DB, Yang XH, Ungvari GS, Ng CH, Ning YP, Xiang YT

Adjunctive azapirone for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials

European Neuropsychopharmacology 2018; 28: 149-58

View review abstract online

Comparison	**Buspirone (6-24 weeks; 21.6-60mg/d) or tandospirone (6 weeks; 30mg/d) plus antipsychotics (various) vs. antipsychotics plus placebo.**

Summary of evidence	**Moderate to low quality evidence (small to medium samples, inconsistent, imprecise, direct) suggests a large effect of greater improvement in overall symptoms with adjunctive buspirone than placebo, with no differences in adverse effects apart from fewer extrapyramidal symptoms with buspirone. There were no effects of tandospirone compared to placebo.**
Psychiatric symptoms **PANSS and BPRS**	
A large, significant effect of greater improvement in overall symptoms with adjunctive buspirone; 6 RCTs, N = 327, SMD = -1.03, 95%CI -1.91 to -0.15, p = 0.02, I^2 = 92%, p < 0.0001 However, after removing two outliers, this effect became non-significant, and there were no significant effects in the subgroup analyses of positive, negative, general symptoms or cognition. In meta-regression analyses, older age and worse baseline symptoms predicted greater effects of adjunctive buspirone. There were no moderating effects of dose or illness duration. *There were no significant differences between tandospirone and placebo;* 1 RCT, N = 26, SMD = -0.02, 95%CI -0.80 to 0.76, p = 0.96	
Risks	There were no significant differences in all-cause discontinuation or adverse effects, apart from fewer extrapyramidal symptoms with buspirone.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Zheng W, Cai D-B, Zhang Q-E, He J, Zhong L-Y, Sim K, Ungvari GS, Ning Y-P, Xiang Y-T

Adjunctive ondansetron for schizophrenia: A systematic review and meta-analysis of randomized controlled trials

Journal of Psychiatric Research 2019; 113: 27-33

View review abstract online

Comparison	**Ondansetron (4-8 mg/day) plus antipsychotics (various) vs. antipsychotics plus placebo.**

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Summary of evidence	**Moderate quality evidence (medium-sized samples, inconsistent, imprecise, direct) suggests large improvements in total, negative and general symptoms with adjunctive ondansetron. There may also be some benefit for positive symptoms.**
Psychiatric symptoms **PANSS and BPRS**	
Significant, large effects of improved total, negative and general symptoms with ondansetron; PANSS total: 3 RCTs, N = 171, SMD = -1.06, 95%CI -2.10 to -0.02, *p* = 0.04, I^2 = 85% Heterogeneity for total symptoms was reduced to 0% after exclusion of one outlier. Lower study quality was associated with larger effect sizes. Negative symptoms: 4 RCTs, N = 209, SMD = -0.96, 95%CI -1.71 to -0.22, *p* = 0.01, I^2 = 80% General psychopathology: 3 RCTs, N = 171, SMD = -0.97, 95%CI -1.91 to -0.02, *p* = 0.04, I^2 = 82% *A trend effect was found for;* Positive symptoms: 4 RCTs, N = 209, SMD = -0.27, 95%CI -0.55 to 0.00, *p* = 0.05, I^2 = 0% *No significant differences in;* Depressive symptoms: 2 RCTs, N = 68, SMD = -0.03, 95%CI -0.54 to 0.48, *p* = 0.91, I^2 = 12%	
Risks	Ondansetron was superior than placebo for improving extrapyramidal symptoms. No group differences were found in discontinuation rate or adverse drug reactions.
Consistency in results	Inconsistent, apart from positive and depressive symptoms.
Precision in results	Imprecise, apart from positive and depressive symptoms.
Directness of results	Direct

Explanation of acronyms

BPRS = brief psychiatric rating scale, CGI = clinical global impression scale, *d* = standardised mean difference, 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* = significance level, PANSS = positive and negative syndrome scale, RR = relative risk, SMD = standardised mean difference, 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 [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) 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[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, 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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