TECHNICAL COMMENTARY

Risperidone

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Introduction

The treatment of bipolar disorder is complex due to the presence of varying configurations of symptoms in patients. The primary treatments for bipolar disorder are pharmacological, and often involve second generation antipsychotic drugs, such as risperidone. Based on its affinity for dopamine and serotonin receptors, risperidone has been proposed as a treatment for bipolar disorder.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review 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 that 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 eight reviews that met our inclusion criteria[3-10].

Symptoms

- Moderate quality evidence suggests small to medium-sized effects of greater improvement in acute mania symptoms with risperidone than with placebo, aripiprazole, lithium, valporate, lamotrigine, licarbazepine, or topiramate, although there was greater improvement with tamoxefin than with risperidone.
- Moderate to high quality evidence suggests small to medium-sized effects of greater improvement in depression symptoms and better response to treatment with quetiapine than with risperidone.

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Relapse

- Moderate quality evidence suggests a small effect of fewer relapses (any) with risperidone than with placebo.

Side effects

- Moderate to low quality evidence suggests greater increases in prolactin levels with risperidone than with lithium or valproate.
- Moderate quality evidence suggests more somnolence and all cause treatment discontinuation with risperidone than with placebo. There was also less all-cause discontinuation with topiramate than with risperidone and more switching to mania with quetiapine than with risperidone
- Moderate to low quality evidence suggests no significant differences in rates of switching to depression between risperidone and haloperidol, or switching to mania between risperidone and quetiapine.

Fang F, Sun H, Wang Z, Ren M, Calabrese JR, Gao K

Antipsychotic Drug-Induced Somnolence: Incidence, Mechanisms, and Management

CNS Drugs 2016; 30: 845-67

View review abstract online

Comparison	**Risperidone vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large sample, 1 RCT, imprecise, direct) suggests increased somnolence with risperidone compared to placebo.**
Somnolence	
Risperidone had a significantly higher rate of somnolence than placebo; 1 x 3 week RCTs, N = 553, absolute risk incidence = 11.5, 95%CI 6.6 to 16.5, $p < 0.05$ There were no significant differences between risperidone and haloperidol.	
Consistency in results	N/A - 1 RCT.
Precision in results	Appears imprecise.
Directness of results	Direct

Fang F, Wang Z, Wu R, Calabrese JR, Gao K

Is there a 'weight neutral' second-generation antipsychotic for bipolar disorder?

Expert Review of Neurotherapeutics 2017; 17: 407-18

View review abstract online

Comparison	**Risperidone vs. placebo.**
Summary of evidence	**Low quality evidence (unclear sample size, inconsistent, unable to assess precision, direct) is unable to determine differences in weight gain between risperidone and placebo.**
Weight gain	

Risperidone had a significantly greater rate of weight gain than placebo in one of three trials; 1 x 3 week trial (4.1mg/d), N = not reported, MD = +1.85kg, $p < 0.05$ 1 x 3 week trial (1-6 mg/d), N = not reported, MD = -0.01, $p > 0.05$ 1 x 3 week trial (dose not reported), N = not reported, MD = +0.3, $p > 0.05$

Consistency in results	Appears inconsistent.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Goikolea JM, Colom F, Torres I, Capapey J, Valenti M, Undurraga J, Grande, I, Sanchez-Moreno J, Vieta E

Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol

Journal of Affective Disorders 2013; 144: 191-8

View review abstract online

Comparison	**Risperidone vs. haloperidol.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, unable to assess consistency, imprecise, direct) suggests no significant differences in rates of switching to depression between risperidone and haloperidol.**

Switch to depression
No significant differences between groups; 1 RCT, N = 298, RR = 0.82, 95%CI 0.30 to 2.20, $p > 0.05$

Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

McKnight RF, de La Motte de Broons de Vauvert SJGN, Chesney E, Amit BH, Geddes J, Cipriani A

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Lithium for acute mania

Cochrane Database of Systematic Reviews 2019 (6)

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Comparison 1	**Risperidone vs. lithium for mania in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, uable to assess precision, direct) suggests better response with risperidone than lithium.**
Mania	
Risperidone was more effective than lithium; 3 studies, n = 241, MD = 7.28, 95%CI 5.22 to 9.34, I^2 = 49%	
Consistency in results	Inconsistent
Precision in results	Unable to assess; MDs not standardised.
Directness of results	Direct

Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, Salanti G, Motomura K, Shimano-Katsuki S, Leucht S, Cipriani A, Geddes JR, Kanba S

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: A systematic review and network meta-analysis

The Lancet Psychiatry 2014; 1: 351-9

View review abstract online

Comparison	**Risperidone long-acting injection vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (consistent, precise, some indirectness) suggests a small effect of fewer relapses with risperidone than with placebo. There were no significant differences in discontinuation due to adverse events.**
Any relapse	

A significant, small effect of fewer relapses with risperidone; RR = 0.64, 95%CI 0.48 to 0.85, $p < 0.05$ There were no significant differences between risperidone and any other medication.	
Risks	No significant differences in discontinuation due to adverse events between risperidone and placebo or any other medication.
Consistency in results	Authors state that the data were consistent.
Precision in results	Precise
Directness of results	Some indirectness

Pacchiarotti I, Murru A, Kotzalidis GD, Bonnin CM, Mazzarini L, Colom F, Vieta E

Hyperprolactinemia and medications for bipolar disorder: systematic review of a neglected issue in clinical practice

European Neuropsychopharmacology 2015; 25: 1045-59

View review abstract online

Comparison	**Quetiapine vs. placebo or other medications.**
Summary of evidence	**Moderate to low quality evidence (medium to large sample, 1 RCT, direct, unable to assess precision) suggests greater increase in prolactin levels with risperidone than with lithium or valproate.**
Hyperprolactemia	
1 x 8 week RCT (N = 279) found increased prolactin levels with risperidone compared to lithium and valproate.	
Consistency in results	N/A; 1 RCT.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Taylor DM, Cornelius V, Smith L, Young AH

Comparative efficacy and acceptability of drug treatments for bipolar

depression: a multiple-treatments meta-analysis

Acta Psychiatrica Scandinavica 2014; 130: 452-69

View review abstract online

Comparison	**Risperidone vs. placebo or other medications.**
Summary of evidence	**Moderate to high quality evidence (large sample, 1 RCT, mostly precise, direct) suggests small to medium-sized effects of greater improvement in depression symptoms, and better response to treatment with quetiapine than with risperidone. However, there was a medium-sized effect of more switching to mania with quetiapine.**
Depression symptoms and response to treatment	
A significant, small to medium-sized effects of greater improvement in depression symptoms and better response to treatment with quetiapine than with risperidone; Symptoms: 1 RCT, N = 613, SMD = 0.22, 95%CI 0.01 to 0.42, $p < 0.05$ Response: 1 RCT, N = 613, SMD = 0.65, 95%CI 0.44 to 0.97, $p < 0.05$ There were no significant differences between risperidone and placebo.	
Switch to mania	
A significant, medium-sized effect of more switching to mania with quetiapine than with risperidone; 1 RCT, N = 613, OR = 3.80, 95%CI 1.76 to 8.20, $p < 0.05$ There were no significant differences between risperidone and placebo.	
Risks	There were no differences between groups in rates of withdrawal from treatment (any reason).
Consistency in results	Authors report data are consistent.
Precision in results	Precise for symptoms and response only.
Directness of results	Direct (pairwise comparisons).

Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ

A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania

Risperidone

Psychological Medicine 2015; 45: 299-317

View review abstract online

Comparison	**Risperidone vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large sample size, consistent, mostly precise, some indirectness) suggests small to medium-sized effects of greater improvement in acute mania symptoms with risperidone than with placebo, aripiprazole, valporate, lamotrigine, licarbazepine, or topiramate, although there was greater improvement with tamoxefin than with risperidone. There was less all-cause discontinuation with placebo and topiramate than with risperidone.**
Acute mania symptoms	
A significant, medium-size to large effect of greater improvement with risperidone than with aripiprazole; Network meta-analysis; 57 studies, N = 14,256, = 0.27, 95%CrI 0.01 to 0.54, $p < 0.05$ *A significant, medium-sized effect of greater improvement with risperidone than with valproate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.33, 95%CrI 0.06 to 0.58, $p < 0.05$ *A significant, small to medium-sized effect of greater improvement with risperidone than with lamotrigine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.51, 95%CrI 0.14 to 0.87, $p < 0.05$ *A significant, small to medium-sized effect of greater improvement with risperidone than with licarbazepine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.56, 95%CrI 0.07 to 1.04, $p < 0.05$ *A significant, small effect of greater improvement with risperidone than with placebo;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.65, 95%CrI 0.44 to 0.85, $p < 0.05$ *A significant, small effect of greater improvement with risperidone than with topiramate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.71, 95%CrI 0.41 to 1.00, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with risperidone;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.54, 95%CrI 1.98 to 3.14, $p < 0.05$ Authors report no other significant differences between risperidone and other medications.	
Risks	There was less all-cause discontinuation with placebo and topiramate than with risperidone.
Consistency in results	Authors report data are consistent.
Precision in results	Precise for all comparisons apart from tamoxefin.

Directness of results	Some indirectness.

Explanation of acronyms

CI = confidence interval, MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, 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[11].

† 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).

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[11].

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[12]. 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.

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[11];

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

§ 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[13].

‖ 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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