TECHNICAL COMMENTARY

Quetiapine

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 quetiapine. Based on its high affinity for dopamine and serotonin receptors, quetiapine 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 13 reviews that met our inclusion criteria[3-15].

Symptoms and functioning

- Moderate to high quality evidence suggests quetiapine was more effective than placebo for symptoms, response, remission, quality of life, sleep and disability in adults, but not in children, with bipolar disorder.
- Moderate to high quality evidence suggests small effects of greater improvement in depression symptoms and greater response to treatment with quetiapine than with paroxetine or risperidone. Moderate quality evidence suggests quetiapine may also be more effective than lithium for depression symptoms.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

- High quality evidence suggests no differences in depression symptoms, response or remission between low (300 mg) and high (600 mg) dose quetiapine.
- Moderate quality evidence suggests small to medium-sized effects of greater improvement in acute mania symptoms with quetiapine than with placebo or topiramate, although there was greater improvement in mania symptoms with tamoxefin than with quetiapine.

Relapses

- Moderate quality evidence suggests a medium-sized effect of fewer relapses with quetiapine than with placebo, and fewer relapses with quetiapine than with lamotrigine or imipramine.

Side effects

- Compared to placebo, moderate quality evidence suggests quetiapine is associated with higher rates of extrapyramidal side effects, somnolence, sedation, dizziness, fatigue, constipation, dry mouth, increased appetite, weight gain, and all-cause discontinuation of treatment. But there may be lower cholesterol and LDL levels, and lower rates of treatment-emergent mania and headache with quetiapine.
- Compared to other medications, there was more somnolence with quetiapine than with paliperidone or lurasidone; more weight gain with quetiapine than with lithium or lurasidone; less switching to mania with quetiapine than with paroxetine, lamotrigine, lurasidone or aripiprazole; more switching to mania with quetiapine than with risperidone; and less adverse events in general with quetiapine than with paroxetine. There was also less all-cause discontinuation of treatment with topiramate than with quetiapine.

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Bartoli F, Dell'Osso B, Crocamo C, Fiorillo A, Ketter TA, Suppes T, Clerici M, Carra G

Benefits and harms of low and high second-generation antipsychotics doses for bipolar depression: A meta-analysis

Journal of Psychiatric Research 2017; 88: 38-46

View review abstract online

Comparison	**High vs. low dose quetiapine.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests no differences in depression symptoms, response or remission between low (300 mg) and high (600 mg) dose quetiapine.**
Depression	
No significant differences between groups; Depression scores: 4 RCTs, N = 1627, SMD = 0.009, 95%CI -0.088 to 0.106, $p > 0.05$, $I^2 = 0\%$ Response: 4 RCTs, N = 1627, OR = 0.995, 95%CI 0.927 to 1.069, $p > 0.05$, $I^2 = 0\%$ Remission: 4 RCTs, N = 1627, N = 430, OR = 0.976, 95%CI 0.907 to 1.051, $p > 0.05$, $I^2 = 0\%$	
Risks	There were no differences between groups for discontinuation for any reason.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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	**Quetiapine vs. placebo or other medications.**

Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests there may be increased somnolence in the short term (<12 weeks) but not in the long term (2 years), with quetiapine compared to placebo. There may also be higher rates of somnolence with quetiapine than with paliperidone.**
Somnolence	
Quetiapine had a significantly higher rate of somnolence than placebo in two trials; 1 x 12 week trial (400-800mg/d immediate release), N = 407, absolute risk increase = 12.2, 95%CI 6.5 to 18.2, $p < 0.05$ 1 x 3 week trial (400-800mg/d extended release), N = 311, absolute risk increase = 12.2, 95%CI 5.5 to 19.3, $p < 0.05$ *No significant differences over the longer term;* 1 x 104 week trial (400-800mg/d immediate release), N = 808, absolute risk increase = 2.5, 95%CI -0.7 to 5.7, $p > 0.05$ *Quetiapine had a significantly higher rate of somnolence than paliperidone;* 1 x 3-12 week trial (3-12 mg/d), N = 386, absolute risk increase = -8.4, 95%CI -15.4 to -1.5, $p < 0.05$ No significant differences were observed between haloperidol and quetiapine.	
Consistency in results	Appears inconsistent for placebo, N/A for 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	**Quetiapine vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, unable to assess precision, direct) suggests greater weight gain with quetiapine than with placebo.**
Weight gain	

Quetiapine had a significantly greater rate of weight gain than placebo in four trials; 1 x 12 week trial (400-800 mg/d), N = not reported, MD = +2.7, $p < 0.05$ 1 x 12 week trial (400-800 mg/d), N = 203, MD = +2.1, $p < 0.05$ 1 x 12 week trial (400-800 mg/d), N = 407, MD = +2.7, $p < 0.05$ 1 x 3 week trial (400-800 mg/d), N = 311, MD = +1.2, $p < 0.05$	
Consistency in results	Appears consistent.
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	**Quetiapine 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 quetiapine and haloperidol.**
Switch to depression	
No significant differences between groups; 1 RCT, N = 199, RR = 0.36, 95%CI 0.10 to 1.33, $p > 0.05$	
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Kishi T, Ikuta T, Sakuma K, Matsuda Y, Iwata N

Comparison of quetiapine immediate- and extended-release formulations for bipolar depression: A systematic review and network meta-analysis of double-blind, randomized placebo-controlled trials

Journal of Psychiatric Research 2019; 115: 121-8

View review abstract online

Comparison 1	**Quetiapine extended-release 300mg/day, quetiapine immediate-release 300mg/day, or quetiapine immediate-release 600mg/day vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, direct) finds improved depression, response and remission in people taking quetiapine. However, there was more extrapyramidal symptoms, dry mouth, somnolence, constipation, dizziness, blood glucose levels, and increase in body weight with quetiapine.**
Depression **Montgomery Asberg Depression Rating Scale scores, response and remission**	
All quetiapine formulations were superior to placebo; Quetiapine extended-release 300mg/d vs. placebo Scores: 3 RCTs, N = 905, MD = -3.63, 95%CI -5.52 to -1.74, $p = 0.0002$, $I^2 = 58\%$, $p = 0.09$ Response: 3 RCTs, N = 905, RR = 0.69, 95%CI 0.52 to 0.91, $p = 0.009$, $I^2 = 75\%$, $p = 0.02$ Remission: 3 RCTs, N = 905, RR = 0.76, 95%CI 0.64 to 0.90, $p = 0.001$, $I^2 = 48\%$, $p = 0.15$ Quetiapine immediate-release 300mg/d vs. placebo Scores: 4 RCTs, N = 1,391, MD = -4.65, 95%CI -6.04 to -3.26, $p < 0.00001$, $I^2 = 0\%$, $p = 0.50$ Response: 4 RCTs, N = 1,391, RR = 0.70, 95%CI 0.62 to 0.79, $p < 0.00001$, $I^2 = 0\%$, $p = 0.95$ Remission: 4 RCTs, N = 1,391, RR = 0.72, 95%CI 0.64 to 0.80, $p < 0.00001$, $I^2 = 0\%$, $p = 0.55$ Quetiapine immediate-release 600mg/d vs. placebo Scores: 4 RCTs, N = 1,396, MD = -4.70, 95%CI -6.10 to -3.31, $p < 0.00001$, $I^2 = 0\%$, $p = 0.49$ Response: 4 RCTs, N = 1,396, RR = 0.69, 95%CI 0.62 to 0.78, $p < 0.05$, $p < 0.00001$, $I^2 = 0\%$, $p = 0.85$ Remission: 4 RCTs, N = 1,396, RR = 0.69, 95%CI 0.62 to 0.78, $p < 0.00001$, $I^2 = 0\%$, $p = 0.74$	
Comparison 2	**Quetiapine immediate-release 300mg/day vs. quetiapine immediate-release 600mg/day.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, direct) finds no differences in depression,**

	response and remission.
Depression	
There were no significant differences between groups; Quetiapine immediate-release 300mg/d vs. 600mg/d Scores: 4 RCTs, N = 1,627, MD = -0.10, 95%CI -1.43 to 1.23, p = 0.88, I^2 = 0%, p = 0.85 Response: 4 RCTs, N = 1,627, RR = 0.99, 95%CI 0.87 to 1.13, p = 0.93, I^2 = 0%, p = 0.98 Remission: 4 RCTs, N = 1,627, RR = 0.97, 95%CI 0.68 to 1.09, p = 0.58, I^2 = 0%, p = 0.91	
Risks	There was more extrapyramidal symptoms, dry mouth, somnolence, constipation, and increase in body weight with quetiapine than placebo. Both immediate release groups had higher incidences of dizziness than placebo. The immediate-release 300mg/d group had higher blood HbA1c levels than the placebo group. The immediate-release 600mg/d group had a higher discontinuation rate due to adverse events than placebo. The extended-release 300mg/d group had a higher incidence of fatigue than the immediate-release 300mg/d and placebo groups.
Consistency in results	Mostly consistent
Precision in results	Precise
Directness of results	Direct

Maneeton B, Putthisri S, Maneeton N, Woottiluk P, Suttajit S, Charnsil C, Srisurapanont M

Quetiapine monotherapy versus placebo in the treatment of children and adolescents with bipolar depression: A systematic review and meta-analysis

Neuropsychiatric Disease and Treatment 2017; 13: 1023-32

View review abstract online

Comparison	**Quetiapine vs. placebo for children and adolescents with bipolar depression. Treatment duration = 8 weeks.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, unable to assess precision, consistent, direct) suggests no differences in the effects of quetiapine and placebo for depression symptoms and no differences in discontinuation due to adverse events.**

Depression symptoms Children's Depression Rating Scale–Revised (CDRS-R)	
No significant differences in depression scores between quetiapine and placebo; 2 RCTs, N = 224, WMD = -1.82, 95%CI -5.98 to 2.34, $p = 0.39$, $I^2 = 0\%$, $p = 0.58$ Response and remission rates were also not different between groups.	
Risks	There were no differences in discontinuation due to adverse events.
Consistency in results	Consistent
Precision in results	Unable to assess; standardised CIs not reported.
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

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Comparison 1	**Quetiapine vs. placebo.**
Summary of evidence	**Moderate quality evidence (consistent, precise, some indirectness) suggests a medium-sized effect of fewer relapses with quetiapine than with placebo. There were no significant differences in discontinuation due to adverse events.**
Any relapse	
A significant, medium-sized effect of fewer relapses with quetiapine; RR = 0.52, 95%CI 0.40 to 0.68, $p < 0.05$	
Risks	No significant differences in discontinuation due to adverse events between quetiapine and placebo.
Consistency in results	Authors state that the data were consistent.
Precision in results	Precise

Directness of results	Some indirectness
Comparison 2	**Quetiapine vs. other pharmaceutical treatments.**
Summary of evidence	**Moderate to low quality evidence (consistent, imprecise, some indirectness) suggests medium-sized effects of fewer relapses with quetiapine than with lamotrigine or imipramine. There were no significant differences in relapses between quetiapine and any other medication. There were no differences in discontinuation due to adverse events.**
Any relapse	
Medium-sized, significant effects of fewer relapses with quetiapine than with lamotrigine or imipramine; Quetiapine vs. lamotrigine: RR = 0.69, 95%CI 0.50 to 0.96, $p < 0.05$ Quetiapine vs. imipramine: RR = 0.55, 95%CI 0.36 to 0.86, $p < 0.05$ Authors report no significant differences between quetiapine and any other medication.	
Risks	No significant differences in discontinuation due to adverse events between quetiapine and any other medication.
Consistency in results	Authors state that the data were consistent.
Precision in results	Imprecise
Directness of results	Some indirectness

Moteshafi H, Stip E

Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: a meta-analysis

Expert Opinion on Drug Safety 2012; 11: 713-32

View review abstract online

Comparison	**Quetiapine vs. placebo.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests significant decreases in cholesterol and LDL levels with quetiapine compared to placebo.**
Metabolic measures	

Significant decrease in cholesterol levels with quetiapine than with placebo; 7 RCTs, N = 2433, MD = -2.765, 95%CI -4.604 to -0.927, $p < 0.05$ *Significant decrease in LDL levels with quetiapine than with placebo;* 7 RCTs, N = 2433, MD = -2.762, 95%CI -4.415 to -1.109, $p < 0.05$	
Consistency in results	Authors report that the results are inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A

Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis

World Journal of Biological Psychiatry 2017; 1-11

View review abstract online

Comparison	**Quetiapine vs. lurasidone.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, imprecise, some indirectness) suggests no differences between groups in depression symptoms, response to treatment, and remission between quetiapine and lurasidone. There was more weight gain and somnolence with quetiapine than with lurasidone.**
Clinical global impression	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = -0.09, 95%CI -0.39 to 0.21, $p > 0.05$	
Depression symptoms	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, MD = 0.10, 95%CI -2.68 to 2.84, $p > 0.05$	
Response for depression	
No significant differences between groups;	

Network meta-analysis, 14 studies, N = 6,221, OR = 1.29, 95%CI 0.78 to 2.01, $p > 0.05$	
Remission	
No significant differences between groups; Network meta-analysis, 14 studies, N = 6,221, OR = 1.11, 95%CI 0.66 to 1.77, $p > 0.05$	
Risks	There was more weight gain and somnolence with quetiapine.
Consistency in results	Authors report that the results are consistent.
Precision in results	Imprecise
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 quality evidence (medium to large samples, appears consistent, direct, unable to assess precision) suggests no differences in prolactin levels between quetiapine and placebo.**
Hyperprolactemia	
1 x 12 week RCT (N = 204) found no significant differences between quetapine and placebo or lithium. Pooled analysis of 2 x 12 week RCTs (N = 407) found no significant differences between quetapine and placebo.	
Consistency in results	Appears consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Suttajit S, Srisurapanont M, Maneeton N, Maneeton B

Quetiapine for acute bipolar depression: a systematic review and meta-analysis

Drug design, development & therapy 2014; 8: 827-38

View review abstract online

Comparison 1	**Quetiapine vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests quetiapine is more effective than placebo for symptoms, response, remission, quality of life, sleep and disability. However, quetiapine may result in higher rates of extrapyramidal side effects, sedation, somnolence, dizziness, fatigue, constipation, dry mouth, increased appetite, and weight gain, but lower rates of treatment-emergent mania and headache.**

Depression and anxiety symptoms, and clinical global impression

Significant effects of greater improvement in depression and anxiety symptoms and clinical global impression with quetiapine;

Depression symptoms: 11 RCTs, N = 3,488, MD = -4.66, 95%CI -5.59 to -3.73, $p < 0.05$

Anxiety symptoms: 11 RCTs, N = 3,488, MD = -2.44, 95%CI -3.34 to -1.55, $p < 0.05$

Clinical global impression: 11 RCTs, N = 3,488, MD = -0.45, 95%CI -0.56 to -0.34, $p < 0.05$

The effect sizes were similar in studies using 300 or 600mg/d dose.

Response and remission

Small, significant effect of greater response to treatment and rates of remission with quetiapine;

Response: 11 RCTs, N = 3,488, RR = 1.31, 95%CI 1.23 to 1.40, $p < 0.05$

Remission: 11 RCTs, N = 3,488, RR = 1.36, 95%CI 1.24 to 1.49, $p < 0.05$

The effect sizes were similar in studies using 300 or 600mg/d dose.

Quality of life, sleep and disability

Significant effects of greater improvement in quality of life, quality of sleep and disability with quetiapine;

Quality of life: 3 RCTs, N = 1,620, MD = 2.95, 95%CI 1.70 to 4.20, $p < 0.05$

Quality of sleep: 1 RCT, N = 542, MD = -2.31, 95%CI -2.95 to -1.66, $p < 0.05$

Disability: 3 RCTs, N = 1,675, MD = -1.42, 95%CI -2.32 to -0.53, $p < 0.05$ The effect sizes were similar in studies using 300 or 600mg/d dose.	
Risks	Drop-outs due to adverse events were higher with quetiapine, which had higher rates of extrapyramidal side effects, sedation, somnolence, dizziness, fatigue, constipation, dry mouth, increased appetite, and weight gain, but lower risks of treatment-emergent mania and headache.
Consistency in results	Authors report that the results are consistent, apart from anxiety symptoms and treatment-emergent mania. Excluding one outlier with a sample of children and adolescents resulted in consistent results for both of these outcomes.
Precision in results	Precise for response and remission, mostly imprecise for other outcomes.
Directness of results	Direct.
Comparison 2	**Quetiapine vs. other medications.**
Summary of evidence	**Moderate quality evidence (large samples, 1 RCT, unable to assess precision, direct) suggests quetiapine may be more effective than paroxetine or lithium for depression symptoms, and may result in more weight gain than with lithium and less adverse events than paroxetine.**
Depression symptoms	
Quetiapine was more effective than the following medications; Paroxetine: 1 RCT, N = 611, found both 300 mg/d and 600 mg/d quetiapine was superior to 20mg/d paroxetine. Authors report that the efficacy of paroxetine might be higher at a higher dose. Lithium: 1 RCT, N = 669, found 600 mg/d but not 300 mg/d quetiapine was superior to lithium. *No significant differences were found between;* Quetiapine + mood stabilisers and sertraline + mood stabilisers Quetiapine and quetiapine plus lithium	
Sedation	
Quetiapine immediate release vs. quetiapine extended release: 1 RCT, N = 139, found between 1 and 3 hours after administration, 50mg quetiapine extended release had a significantly lower sedative effect than quetiapine immediate release. This effect was not significant at 4 to 14 hours.	
Risks	Quetiapine vs. paroxetine: more serious adverse events with paroxetine.

	Quetiapine vs. lithium or vs. quetiapine + lithium: more clinically relevant weight gain with quetiapine or quetiapine + lithium. Quetiapine immediate release vs. quetiapine extended release: more adverse events with quetiapine immediate release.
Consistency in results	Not applicable (all 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 1	**Quetiapine vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests significant, small effects of greater improvement in depression symptoms and better response to treatment with quetiapine than with placebo. There were no differences between groups in rates of switching to mania or withdrawal from treatment (for any reason).**
Depression symptoms	
Significant, small effect of greater improvement in depression symptoms with quetiapine; 4 RCTs, N = 2614, SMD = -0.29, 95%CI -0.43 to -0.15, $p < 0.05$	
Response	
Significant, small effect of better treatment response with quetiapine; 4 RCTs, N = 2614, OR = 1.85, 95%CI 1.53 to 2.23, $p < 0.05$	
Switch to mania	
No significant differences between groups; 4 RCTs, N = 2614, OR = 0.59, 95%CI 0.32 to 1.11, $p > 0.05$	

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 depression symptoms only.
Directness of results	Direct (pairwise comparisons).
Comparison 2	**Quetiapine vs. other medications.**
Summary of evidence	**Moderate to high quality evidence (large sample, 1 RCT, some imprecision, direct) suggests small effects of greater improvement in depression symptoms and greater response to treatment with quetiapine than with paroxetine or risperidone. There was less switching to mania with quetiapine than with paroxetine, and more switching to mania with quetiapine than with risperidone. There were no differences on any outcome when quetiapine was compared to lithium.** **Moderate to low quality evidence (unclear sample size, consistent, imprecise, indirect) suggests less switching to mania with quetiapine than with lamotrigine lurasidone or aripiprazole.**
Depression symptoms	
A significant, small effect of greater improvement in depression symptoms with quetiapine than with paroxetine; 1 RCT, N = 613, SMD = -0.22, 95%CI -0.42 to -0.01, $p < 0.05$ *A significant, small effect of greater improvement in depression symptoms with quetiapine than with risperidone;* 1 RCT, N = 613, SMD = 0.22, 95%CI 0.01 to 0.42, $p < 0.05$ *No significant differences between quetiapine and lithium;* 1 RCT, N = 669, SMD = -0.15, 95%CI -0.34 to 0.04, $p > 0.05$	
Response	
A significant, small effect of better response rates with quetiapine than with paroxetine; 1 RCT, N = 613, OR = 1.51, 95%CI 1.03 to 2.29, $p < 0.05$ *A significant, small effect of better response rates with quetiapine than with risperidone;* 1 RCT, N = 613, OR = 0.65, 95%CI 0.44 to 0.97, $p < 0.05$ *No significant differences between quetiapine and lithium;*	

1 RCT, N = 669, OR = 1.23, 95%CI 0.83 to 1.82, *p* > 0.05
Switch to mania
A significant, medium-sized effect of less switching to mania with quetiapine than with paroxetine; 1 RCT, N = 613, OR = 0.26, 95%CI 0.12 to 0.57, *p* < 0.05 *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 *No significant differences between quetiapine and lithium;* 1 RCT, N = 669, OR = 1.31, 95%CI 0.38 to 4.55, *p* > 0.05 *The network (indirect) meta-analysis found less switching to mania with quetiapine than with lamotrigine lurasidone or aripiprazole;* Lamotrigine: OR = 4.66, 95%CI 1.21 to 12.20, *p* < 0.05 Lurasidone: OR = 4.69, 95%CI 1.02 to 13.90, *p* < 0.05 Aripiprazole: OR = 5.35, 95%CI 1.29 to 14.30, *p* < 0.05

Consistency in results	Authors report data are consistent in the network meta-analysis.
Precision in results	Precise for depression symptoms only.
Directness of results	Direct, apart from the network meta-analysis results.

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

Psychological Medicine 2015; 45: 299-317

View review abstract online

Comparison	**Quetiapine vs. placebo or other medications.**
Summary of evidence	**Moderate quality evidence (large sample size, consistent, some imprecision and indirectness) suggests small to medium-sized effects of greater improvement in acute mania symptoms with quetiapine than placebo or topiramate, although there was greater improvement with tamoxefin than with quetiapine. There was less all-cause discontinuation with placebo and topiramate than with quetiapine.**

Quetiapine

Acute mania symptoms	
A significant, small effect of greater improvement with quetiapine than with placebo; Network meta-analysis; 57 studies, N = 14,256, SMD = 0.35, 95%CrI 0.14 to 0.56, $p < 0.05$ *A significant, medium-sized effect of greater improvement with quetiapine than with topiramate;* Network meta-analysis; 57 studies, N = 14,256, SMD = 0.42, 95%CrI 0.12 to 0.71, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with quetiapine;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.57, 95%CrI 1.99 to 3.17, $p < 0.05$ Authors report no other significant differences between quetiapine and other medications.	
Risks	There was less all-cause discontinuation with placebo and topiramate than with quetiapine.
Consistency in results	Authors report data are consistent.
Precision in results	Precise for placebo and topiramate comparison, imprecise for tamoxefin comparison.
Directness of results	Some indirectness.

Explanation of acronyms

CI = confidence interval, 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, OR = odds ratio, 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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[16].

† 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[16].

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[17]. 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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[16];

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

§ 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[18].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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