TECHNICAL COMMENTARY

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BIPOLAR DISORDERS LIBRARY

Lithium

Introduction

Since the 1960s, lithium has become a mainstay of treatment for bipolar disorders. It has been recommended for both the treatment of acute mania and for the augmentation of antidepressants in depression, although its effectiveness as an antidepressant when used alone has been disputed. It is also recommended for the prevention of relapses.

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 17 reviews that met our inclusion criteria[3-19].

Symptoms;

- Moderate to high quality evidence suggests medium-sized effects of greater improvement in acute mania symptoms with lithium than with placebo or topiramate, although there was greater improvement in mania symptoms with tamoxefin, risperidone and olanzapine than with lithium. Lithium was more likely than placebo to cause tremor and somnolence.
- Moderate to high quality evidence suggests no benefit of lithium over placebo or quetiapine for depression severity or for response to treatment. There was also no difference between groups in rates of switching to mania.
- Moderate quality evidence finds small to medium-sized effects for the following predictors of lithium response; mania-

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depression sequence (rather than depression-mania sequence), no rapid cycling, having a family history of bipolar disorder, low body mass index, no psychotic symptoms, fewer mood episodes prior to lithium treatment, shorter prelithium illness duration, and later age of onset of bipolar disorder. Having a family history of lithium response and fewer hospitalisations prior to lithium treatment may also predict lithium response.

Relapse;

- Moderate quality evidence finds the recurrence of any mood episode is 39.8%, the recurrence of depressive episodes is 25.6%, and the recurrence of manic/hypomanic or mixed episodes is 18.5% with maintenance lithium treatment.
- Moderate to high quality evidence suggests a small to medium-sized benefit of lithium for preventing relapse to mania when compared to placebo, carbamazepine, lamotrigine or valproate. There may also be some benefit for preventing relapse to depression when lithium is compared to placebo.
- Moderate quality evidence suggests lithium + valproate, lithium + imipramine, or lithium + oxcarbazepine may be effective for any relapse prevention when compared to placebo (small to medium-sized effects). Placebo was better tolerated than lithium or lithium + valproate.
- Moderate quality suggests small to medium-sized effects of fewer relapses with lithium with or without additional valproate or oxcarbazepine, than with imipramine. Lithium + valproate was not as well tolerated as lamotrigine.
- Moderate quality evidence suggests no differences in relapse rates between continued use of lithium and discontinued then reintroduced use of lithium.

Other outcomes;

- Moderate quality evidence finds a small association between increased lithium levels in drinking water and reduced suicide and psychiatric hospitalization rates.
- Moderate to high quality evidence suggests rates of self-harm (but not suicide) may be reduced with lithium treatment when compared to placebo or carbamazepine. There were no differences in rates of self-harm or suicide between lithium and lamotrigine, olanzapine, divalproex, or quetapine.
- Moderate quality evidence suggests lithium is unlikely to elevate prolactin levels, or cause cutaneous adverse reactions, but moderate to low quality evidence suggests serum creatinine may increase slightly.
- Moderate quality evidence finds lithium use during pregnancy was associated with small increased risks of any congenital anomaly, cardiac congenital anomalies, and a medium-sized risk of more spontaneous abortion compared to no lithium use. Note that the findings for cardiac congenital anomalies and spontaneous abortion were not significant when lithium use was compared to no lithium use only in bipolar patients (not general population samples). The finding for any congenital anomaly remained in that comparison. There were no increased risk of preterm birth or low birth weight.
- Moderate quality evidence finds less weight gain with lithium than with antipsychotics or other mood stabilisers. Moderate to high quality evidence finds no differences in weight gain between lithium and placebo. There were no significant changes in weight pre-post treatment with lithium.
- Moderate to high quality evidence finds no increased rates of cancer in people with bipolar disorder taking lithium compared to those not taking lithium.
- Moderate quality evidence finds a non-significant, trend effect of more morningness (more daytime activity) with lithium compared to other medications.

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Anmella G, Fico G, Lotfaliany M, Hidalgo-Mazzei D, Soto-Angona O, Gimenez-Palomo A, Amoretti S, Murru A, Radua J, Solanes A, Pacchiarotti I, Verdolini N, Cowdery S, Dodd S, Williams LJ, Mohebbi M, Carvalho AF, Kessing LV, Vieta E, Berk M

Risk of cancer in bipolar disorder and the potential role of lithium: International collaborative systematic review and meta-analyses

Neuroscience and Biobehavioral Reviews 2021; 126: 529-41

View review abstract online

Comparison	**Rates of cancer in people with bipolar disorder vs. people without bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds no increased rates of cancer in people taking lithium.**
Cancer	
Bipolar disorder patients on lithium showed no increased risk of cancer; 5 studies, N = 2,606,187, RR = 0.94, 95%CI 0.72 to 1.22, p = 0.66, I^2 = 59%	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Cipriani A, Hawton K, Stockton S, Geddes JR

Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

BMJ 2013; 346: f3646

View review abstract online

Comparison 1	**Lithium vs. placebo in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant differences in rates of suicide or all-cause death between lithium**

	and placebo, although self-harm may be reduced with lithium.
Deliberate self-harm, suicide and all-cause death	
A trend, medium-sized effect of less self-harm with lithium, and no significant differences between groups for suicide or all-cause death; Deliberate self-harm: 2 RCTs, N = 1,064, OR = 0.35, 95%CI 0.11 to 1.10, $p = 0.07$, $I^2 = 0\%$, $p = 0.62$ Suicide: 1 RCT, N = 205, OR = 0.14, 95%CI 0.00 to 7.02, $p = 0.32$ All-cause death: 2 RCTs, N = 254, OR = 0.73, 95%CI 0.16 to 3.33, $p = 0.69$, $I^2 = 0\%$, $p = 0.70$	
Comparison 2	**Lithium vs. carbamazepine in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, direct, imprecise) suggests no significant differences in rates of suicide or all-cause death between lithium and carbamazepine, although self-harm may be reduced with lithium.**
Deliberate self-harm, suicide and all-cause death	
A significant, large effect of less self-harm with lithium, and no significant differences between groups for suicide or all-cause death; Deliberate self-harm: 2 RCTs, N = 285, OR = 0.14, 95%CI 0.02 to 0.83, $p = 0.03$, $I^2 = 0\%$, $p = 0.99$ Suicide: 2 RCTs, N = 285, OR = 0.37, 95%CI 0.09 to 1.51, $p = 0.17$, $I^2 = 0\%$, $p = 0.37$ All-cause death: 2 RCTs, N = 285, OR = 0.37, 95%CI 0.09 to 1.51, $p = 0.17$, $I^2 = 0\%$, $p = 0.37$	
Comparison 3	**Lithium vs. lamotrigine in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant differences in rates of suicide, all-cause death or self-harm between lithium and lamotrigine.**
Deliberate self-harm, suicide and all-cause death	
No significant differences between groups; Deliberate self-harm: 2 RCTs, N = 260, OR = 0.15, 95%CI 0.01 to 2.46, $p = 0.18$, $I^2 = 0\%$, $p = 0.94$ Suicide: 2 RCTs, N = 497, OR = 1.37, 95%CI 0.08 to 23.23, $p = 0.83$, $I^2 = 34\%$, $p = 0.22$ All-cause death: 2 RCTs, N = 497, OR = 1.37, 95%CI 0.08 to 23.23, $p = 0.83$, $I^2 = 34\%$, $p = 0.22$	
Comparison 4	**Lithium vs. olanzapine in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, 1 RCT, direct, imprecise) suggests no significant differences in rates of**

	suicide, all-cause death or self-harm between lithium and olanzapine.
Deliberate self-harm, suicide and all-cause death	
No significant differences between groups; Deliberate self-harm: 1 RCT, N = 431, OR = 0.30, 95%CI 0.05 to 1.76, *p* = 0.18 Suicide: 1 RCT, N = 431, OR = 7.49, 95%CI 0.15 to 377.68, *p* = 0.31 All-cause death: 1 RCT, N = 431, OR = 7.53, 95%CI 0.47 to 120.76, *p* = 0.15	
Comparison 5	**Lithium vs. divalproex in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, direct, imprecise) suggests no significant differences in rates of self-harm between lithium and divalproex. Moderate quality evidence (1 RCT) also suggests no differences in all-cause death.**
Deliberate self-harm and all-cause death	
No significant differences between groups; Deliberate self-harm: 2 RCTs, N = 318, OR = 0.64, 95%CI 0.30 to 1.36, *p* = 0.24, I^2 = 0%, *p* = 0.52 All-cause death: 1 RCT, N = 220, OR = 0.67, 95%CI 0.11 to 3.90, *p* = 0.65	
Comparison 6	**Lithium vs. quetiapine in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, 1 RCT, direct, imprecise) suggests no significant differences in rates of self-harm between lithium and quetiapine.**
Deliberate self-harm	
No significant differences between groups; Deliberate self-harm: 1 RCT, N = 822, OR = 0.97, 95%CI 0.19 to 4.81, *p* = 0.97	
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise
Directness of results	Direct

de Vries C, van Bergen A, Regeer EJ, Benthem E, Kupka RW, Boks MP

The effectiveness of restarted lithium treatment after discontinuation:

reviewing the evidence for discontinuation-induced refractoriness **Bipolar Disorders 2015; 15: 645-9** View review abstract online	
Comparison	**Continuous use of lithium vs. discontinued use then reintroduction of lithium.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, imprecise, direct) suggests no differences in relapse prevention between continued use and discontinued/reintroduced use of lithium.**
Relapse	
No significant differences between groups; 5 RCTs, N = 212, OR = 1.40, 95%CI 0.85 to 2.31, *p* = 0.19	
Consistency in results	Authors report results were inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Eyre-Watt B, Mahendran E, Suetani S, Firth J, Kisely S, Siskind D

The association between lithium in drinking water and neuropsychiatric outcomes: A systematic review and meta-analysis from across 2678 regions containing 113 million people

Australian and New Zealand Journal of Psychiatry 2021; 55: 139-52

View review abstract online

Comparison	**Relationship between the level of lithium in drinking water and suicide and hospitalizations.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, some imprecision, direct) finds a small association between increased lithium levels in drinking water and reduced suicide and psychiatric hospitalization rates.**
Suicide and psychiatric hospitalizations	

A small association between higher lithium concentrations and reduced suicide rates; 14 studies, 94 million, r = -0.191, 95%CI -0.287 to -0.090, $p < 0.001$, I^2 = 81% *A medium association between higher lithium concentrations and reduced psychiatric hospital admissions;* 2 studies, 5 million, r = -0.413, 95%CI -0.689 to -0.031, p = 0.035 Authors report possible publication bias.

Consistency in results	Inconsistent
Precision in results	Precise for suicide, imprecise for hospitalizations
Directness of results	Direct

Fornaro M, Maritan E, Ferranti R, Zaninotto L, Miola A, Anastasia A, Murru A, Solé E, Stubbs B, Carvalho A, Serretti A, Vieta E, Fusar-Poli P, McGuire P, Young AH, Dazzan P, Vigod S, Correll CU, Solmi M

Lithium exposure during pregnancy and the postpartum period: A systematic review and meta-analysis of safety and efficacy outcomes

The American Journal of Psychiatry 2020; 177: 76-92

View review abstract online

Comparison	**Lithium during pregnancy vs. no lithium use during pregnancy for fetal outcomes.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) finds lithium use during pregnancy was associated with small increased risks of any congenital anomaly, cardiac congenital anomalies, and a medium-sized risk of more spontaneous abortion compared to no lithium use. Note that the findings for cardiac congenital anomalies and spontaneous abortion were not significant when lithium use was compared to no lithium use only in bipolar patients (not general population samples). The finding for any congenital anomaly remained in that comparison. There were no increased risk of preterm birth or low birth weight.**
Fetal outcomes	
Lithium use during pregnancy was associated with increased risk of; Any congenital anomaly: 4 studies, N = 23,046, OR = 1.75, 95%CI 1.23 to 2.48, I^2 = 26%	

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Cardiac congenital anomalies: 4 studies, N = 1,348,475, OR = 1.86, 95%CI 1.16 to 2.96, I^2 = 40% Spontaneous abortion: 2 studies, N = 1,289, OR = 3.77, 95%CI 1.15 to 12.39, I^2 = 86% The findings for cardiac congenital anomalies and spontaneous abortion were not significant when compared to only bipolar patients not on lithium (not general population samples). The finding for any congenital anomaly remained. *Lithium was not associated with increased risk of;* Preterm birth (<37weeks): 6 studies, N = 23,695, OR = 1.42, 95%CI 0.98 to 2.06, I^2 = 60% Low birth weight: 3 studies, N = 23,238, OR = 0.99, 95%CI 0.84 to 1.19, I^2 = 0%
Relapse post-pregnancy
Lithium decreased risk of relapse post-pregnancy (4 weeks to 2 years) vs. no treatment; 2 studies, N = 48, OR = 0.16, 95%CI 0.03 to 0.89, I^2 = 53%

Consistency in results	Mostly inconsistent
Precision in results	Imprecise
Directness of results	Direct

Gomes-da-Costa S, Marx W, Corponi F, Anmella G, Murru A, Pons-Cabrera MT, Gimenez-Palomo A, Gutierrez-Arango F, Llach CD, Fico G, Kotzalidis GD, Verdolini N, Valenti M, Berk M, Vieta E, Pacchiarotti I

Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2021; doi: 10.1016/j.neubiorev.2021.07.011

View review abstract online

Comparison	**Weight change with lithium medication.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, unclear precision, direct) finds no differences in weight gain between lithium and placebo. Moderate quality evidence (large samples, inconsistent or indirect) finds less weight gain with lithium than with antipsychotics or other mood stabilisers. There were no significant changes in weight pre-post treatment with lithium.**
Weight gain	

There was less weight gain with lithium than with antipsychotics or other mood stabilisers; 5 studies, N = 1,282, MD = -1.446, 95%CI -2.489 to -0.404, p = 0.007, I^2 = 0% *There were no significant differences in weight gain with lithium compared to placebo;* 3 studies, N = 437, MD = -0.354, 95%CI -1.011 to 0.303, p = 0.291, I^2 = 0% *There were no significant increases in weight gain pre-post treatment;* 9 studies, N = 991, weight increase = 0.462kg, 95%CI 0.179 to 1.103, p = 0.158, I^2 = 89% A shorter duration of treatment was significantly associated with more weight gain (<12 weeks).

Consistency in results	Consistent, apart from the pre-post treatment analysis.
Precision in results	Unable to assess; MD not standardised
Directness of results	Direct, apart from active comparison analysis.

Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, Hayes JF

A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder

Acta Psychiatrica Scandinavica 2019; 140: 94-115

View review abstract online

Comparison	**Clinical predictors of lithium response.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent and/or imprecise, direct) finds small to medium-sized effects that predictors of lithium response are; mania-depression sequence (rather than depression-mania sequence), no rapid cycling, having a family history of bipolar disorder, low body mass index, no psychotic symptoms, fewer mood episodes prior to lithium treatment, shorter prelithium illness duration, and later age of onset of bipolar disorder. Having a family history of lithium response and fewer hospitalisations prior to lithium treatment may also predict lithium response.**

Relapse
Significant predictors of good response were (ordered from medium to small effects); Mania-depression sequence vs. depression-mania sequence: 6 studies, N = 340, OR = 4.27, 95%CI 2.61 to 6.97, p < 0.001, I^2 = 0%, p = 0.680 Absence of rapid cycling: 9 studies, N = 1,442, OR = 0.30, 95%CI 0.17 to 0.53, p < 0.001, I^2 = 38%,

	$p = 0.119$ Family history of bipolar disorder: 10 studies, N = 1,454, OR = 1.61, 95%CI 1.03 to 2.52, $p = 0.036$, $I^2 = 44\%$, $p = 0.068$ Lower body mass index: 2 studies, N = 336, SMD = -0.61, 95%CI -0.90 to -0.32, $p < 0.001$, $I^2 = 0\%$, $p = 0.111$ Absence of psychotic symptoms: 8 studies, N = 1,066, OR = 0.52, 95%CI 0.34 to 0.79, $p = 0.002$, $I^2 = 43\%$, $p = 0.093$ Fewer episodes prior to lithium treatment: 7 studies, N = 824, SMD = -0.42, 95%CI -0.84 to -0.01, $p = 0.046$, $I^2 = 86\%$, $p < 0.001$ Shorter prelithium illness duration: 5 studies, N = 931, SMD = -0.26, 95%CI -0.41 to -0.12, $p < 0.001$, $I^2 = 0\%$, $p = 0.70$ Later age of onset: 14 studies, N = 2,063, SMD = 0.17, 95%CI 0.02 to 0.36, $p = 0.029$, $I^2 = 58\%$, $p = 0.003$ *Trend effects for;* Family history of lithium response; 2 studies, N = 79, OR = 10.28, 95%CI 0.66 to 161.26, $p = 0.097$, $I^2 = 63\%$, $p = 0.102$ Fewer hospitalisations prior to lithium treatment: 4 studies, N = 673, SMD = -0.40, 95%CI -0.81 to 0.01, $p = 0.055$, $I^2 = 83\%$, $p < 0.001$ *No significant effects for;* Bipolar I vs. bipolar II disorder: 11 studies, N = 1,556, OR = 1.01, 95%CI 0.58 to 1.76, $p = 0.971$, $I^2 = 71\%$, $p < 0.001$ Continuous cycling: 7 studies, N = 804, OR = 0.65, 95%CI 0.34 to 1.26, $p = 0.204$, $I^2 = 47\%$, $p = 0.076$ Irregular sequence: studies/N not reported, OR = 1.13, 95%CI 0.70 to 1.83, $p = 0.628$, $I^2 = 0\%$, $p = 0.496$ Polarity of index episode: 6 studies, N not reported, OR = 1.12, 95%CI 0.56 to 2.21, $p = 0.753$, $I^2 = 74\%$, $p = 0.002$ Predominant polarity: 3 studies, N = 280, OR = 1.07, 95%CI 0.07 to 15.74, $p = 0.959$, $I^2 = 94\%$, $p < 0.001$ Family history of any affective disorder: OR = 1.13, 95%CI 0.75 to 1.69, $p = 0.560$, $I^2 = 0\%$, $p = 0.786$ Substance use: 3 studies, N = 540, OR = 0.55, 95%CI 0.23 to 1.34, $p = 0.189$, $I^2 = 55\%$, $p = 0.111$ Sex: 17 studies, N = 1,729, OR = 0.89, 95%CI 0.68 to 1.15, $p = 0.356$, $I^2 = 23\%$, $p = 0.191$
Consistency in results	Mostly inconsistent.
Precision in results	Imprecise or ORs, SMDs are precise.
Directness of results	Direct

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Kishi T, Sakuma K, Okuya M, Matsuda Y, Esumi S, Hashimoto Y, Hatano M, Miyake N, Miura I, Miyahara K, Fujita K, Kawashima K, Mishima K, Iwata N

Recurrence of Mania or Depression among Adult Bipolar Patients Who Continued Using Lithium: A Single-group Summary Meta-Analysis of Randomized Trials

Journal of Clinical Psychopharmacology 2020; 40: 468-74

View review abstract online

Comparison	**Rates of relapse with continuous use of lithium.** **Mean study duration was 78.40 ± 32.10 weeks.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) finds the recurrence of any mood episode is 39.8%, the recurrence of depressive episodes is 25.6% and the recurrence of manic/hypomanic or mixed episodes is 18.5%.**
Relapse	
21 RCTs, N = 1,415 Recurrence of any mood episode: 39.8%, 95%CI 32.8% to 47.1% Recurrence of depressive episodes: 25.6%, 95%CI 18.8% to 34.0% Recurrence of manic/hypomanic/mixed episodes: 18.5%, 95%CI 13.7% to 24.7%	
Risks	Discontinuation rate due to adverse events was 8.7%.
Consistency in results	Authors report results were inconsistent.
Precision in results	Unable to assess; not standardised.
Directness of results	Direct

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

Lithium for acute mania

Cochrane Database of Systematic Reviews 2019 (6)

View review abstract online

Comparison 1	**Lithium vs. placebo for mania in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests better response and remission of mania symptoms with lithium than placebo, although lithium was more likely to cause tremor and somnolence.**
Mania	
Lithium was more effective than placebo; Response: 6 studies, N = 1,707, OR = 2.13, 95%CI 1.73 to 2.63, $p < 0.05$, $I^2 = 16\%$ Remission: 5 studies, N = 1,597, OR = 2.16, 95%CI 1.73 to 2.69, $p < 0.05$, $I^2 = 21\%$	
Risks	Lithium was more likely to cause tremor and somnolence.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Lithium vs. other medications for mania in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, mostly inconsistent, imprecise, direct) suggests better response with lithium than with topiramate, but poorer response with lithium than with risperidone or olanzapine.**
Mania	
Lithium was more effective than; Topiramate: 1 study, N = 660, OR = 2.28, 95%CI 1.63 to 3.20 *Lithium was less effective than;* Risperidone: 3 studies, n = 241, MD = 7.28, 95%CI 5.22 to 9.34, $I^2 = 49\%$ Olanzapine: 2 studies, N = 180, OR = 0.44, 95%CI 0.20 to 0.94, $I^2 = 0\%$ *No differences between lithium and*; Valproate: 5 studies, N = 607, OR = 1.22, 95%CI 0.87 to 1.70, $I^2 = 22\%$ Lamotrigine: 3 studies, N = 304, MD = -0.35, 95%CI -1.24 to 0.53, $p = 0.43$, $I^2 = 83\%$ Carbamazepine: 3 studies, N = 102, SMD = 0.21, 95%CI -0.18 to 0.60, $I^2 = 0\%$ Quetiapine: 2 studies, N = 335, OR = 0.66, 95%CI 0.28 to 1.55, $I^2 = 71\%$ Haloperidol: 3 studies, N = 80, MD = -2.40, 95%CI -6.31 to 1.50, $I^2 = 95\%$	

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Consistency in results	Consistent for olanzapine, valproate and carbamazepine only.
Precision in results	Imprecise
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 1	**Lithium vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, precise, some indirectness) suggests a small effect of lithium for preventing relapses, particularly to mania. Moderate quality evidence (imprecise) suggests lithium + valproate, lithium + imipramine, or lithium + oxcarbazepine may also be effective for relapse prevention (small to medium-sized effects). Placebo was significantly better tolerated than lithium or lithium + valproate.**

Any relapse

Lithium with or without valproate, imipramine or oxcarbazepine had significantly lower risks of any relapse than placebo (small to medium-sized effects);

Lithium: N = 1,364, RR = 0.62, 95%CI 0.53 to 0.72, $p < 0.05$

Lithium + valproate: N = 110, RR = 0.52, 95%CI 0.35 to 0.77, $p < 0.05$

Lithium + imipramine: N = 79, RR = 0.62, 95%CI 0.40 to 0.96, $p < 0.05$

Lithium + oxcarbazepine: N not reported, RR = 0.40, 95%CI 0.21 to 0.79, $p < 0.05$

Mania relapse

Lithium and lithium + valproate had a significantly lower risk of mania relapse than placebo (small to medium-sized effects);

Lithium: N = 1,364, RR = 0.58, 95%CI 0.45 to 0.76, $p < 0.05$

Lithium + valproate: N = 110, RR = 0.42, 95%CI 0.23 to 0.76, $p < 0.05$

Lithium + imipramine: N = 79, RR = 0.78, 95%CI 0.39 to 1.54, $p > 0.05$	
Depression relapse	
Lithium alone had a significantly lower risk of depression relapse than placebo (small effect); Lithium: N = 368, RR = 0.76, 95%CI 0.61 to 0.93, $p < 0.05$ Lithium + valproate: N = 110, RR = 0.70, 95%CI 0.41 to 1.17, $p > 0.05$ Lithium + imipramine: N = 79, RR = 0.54, 95%CI 0.27 to 1.07, $p > 0.05$	
Comparison 2	**Lithium vs. other pharmaceutical treatments.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, some indirectness) suggests small to medium-sized effects of fewer relapses with lithium, with or without valproate or oxcarbazepine than with imipramine. Lamotrigine was significantly better tolerated than lithium + valproate.**
Any relapse	
Lithium, with or without valproate or oxcarbazepine had a significantly lower risk of relapse than imipramine (small to medium-sized effects); Lithium vs. imipramine: RR = 0.65, 95%CI 0.46 to 0.92, $p < 0.05$ Lithium + valproate vs. imipramine: RR = 0.52, 95%CI 0.35 to 0.77, $p < 0.05$ Lithium + oxcarbazepine vs. imipramine: RR = 0.43, 95%CI 0.20 to 0.89, $p < 0.05$	
Risks	Placebo and lamotrigine were significantly better tolerated than lithium and lithium + valproate.
Consistency in results	Authors state that the data were consistent.
Precision in results	Precise for lithium vs. placebo, imprecise for other comparisons.
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

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Comparison	**Lithium vs. placebo or other medications.**

Summary of evidence	**Moderate quality evidence (several large sample, appears consistent, direct, unable to assess precision) suggests lithium is unlikely to elevate prolactin levels.**
Hyperprolactemia	
1 x 12 week RCT (N = 302) found no differences in prolactin levels between lithium, quetiapine or placebo. 1 x 8 week RCT (N = 279) found lithium was associated with lower prolactin levels compared to risperidone. 1 study (N = 150) found prolactin levels were higher patients compared to controls for those on lithium for less than 2 years, but not for patients on lithium for over 2 years. 1 study (N = 50) found prolactin levels were similar in patients on lithium for under 6 months, and lower in patients on lithium for over 6 months. 1 study (N = 28) found prolactin levels were lower in patients on lithium than patients who were on citalopram. 1 x 12 week RCT (N = 40) found prolactin levels were lower with aripiprazole than with lithium.	
Consistency in results	Appears consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Paul R, Minay J, Cardwell C, Fogarty D, Kelly C

Meta-analysis of the effects of lithium usage on serum creatinine levels

Journal of Psychopharmacology 2010; 24: 1425-31

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Comparison	**Lithium vs. no lithium.**
Summary of evidence	**Moderate to low quality evidence (large samples, inconsistent, appears imprecise, direct) suggests serum creatinine may increase with lithium use, although this effect may not be clinically significant.**
Serum creatinine	
Significantly increased creatinine in patients on lithium vs. patients not on lithium; 9 cross-sectional studies, N = 1,243, MD = 5.7µmol/L, 95%CI 1.7 to 9.9, p = 0.005, I^2 = 59%, p =	

0.013 *Significantly increased creatinine in patients on lithium;* 8 prospective studies (mean 64 months), N = 675, MD = 7.0μmol/L, 95%CI 0.2 to 13.8, $p = 0.045$, $I^2 = 75\%$, $p \leq 0.001$ *No significant differences in pre-post studies;* 6 pre-post studies (mean 86 months), N = 407, MD = 2.9μmol/L, 95%CI -1.4 to 7.4, $p > 0.10$, $I^2 = 68\%$, $p = 0.008$ Authors report that any lithium-associated increase in serum creatinine is quantitatively small and of questionable clinical significance. However, routine renal function monitoring of patients on lithium is essential.	
Consistency in results	Inconsistent.
Precision in results	Appears imprecise (wide CIs).
Directness of results	Direct

Pinna M, Manchia M, Puddu S, Minnai G, Tondo L, Salis P

Cutaneous adverse reaction during lithium treatment: a case report and updated systematic review with meta-analysis

International Journal of Bipolar Disorders 2017; 5 (1)

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Comparison	**Rates of cutaneous adverse reaction with lithium vs. placebo, lamotrigine, risperidone or valproic acid.**
Summary of evidence	**Moderate to high quality evidence (large samples, direct, consistent, imprecise) suggests no significant differences in cutaneous adverse reaction between lithium and placebo. Moderate quality evidence (indirect) also suggests no differences between lithium and lamotrigine, risperidone or valproic acid.**
Cutaneous adverse reactions	
No significant differences between groups; Lithium vs. placebo: 2 RCTs, N = 438, OR = 1.14, 95%CI 0.44 to 2.94, $p > 0.05$ Lithium vs. lamotrigine, risperidone or valproic acid: 2 RCTs, N = 726, OR = 0.61, 95%CI 0.34 to 1.11, $p > 0.05$	

Consistency in results	Authors report data are consistent.
Precision in results	Imprecise
Directness of results	Direct for placebo comparison only.

Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR

Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis

International Journal of Bipolar Disorders 2014; 2: 15

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Comparison 1	**Lithium vs. placebo.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a small to medium-sized effect of less relapses to mania with lithium than with placebo. There may also be some benefit of lithium for reducing relapses to depression.**
Any relapse	
A small, significant effect for lithium being more effective than placebo; 7 RCTs, N = 1,580, RR = 0.66, 95%CI 0.53 to 0.82, $p < 0.001$, $I^2 = 68\%$, $p = 0.0046$	
Mania relapse	
A small to medium-sized, significant effect for lithium being more effective than placebo; 6 RCTs, N = 1,375, RR = 0.52, 95%CI 0.38 to 0.71, $p < 0.001$, $I^2 = 24.6\%$, $p = 0.2495$	
Depression relapse	
A trend effect for lithium being more effective than placebo; 6 RCTs, N = 1,375, RR = 0.78, 95% CI 0.59 to 1.03, $p = 0.08$, $I^2 = 43.4\%$, $p = 0.1156$ *This result became significant using a fixed effects model;* 6 RCTs, N = 1,375, RR 0.73, 95%CI 0.60 to 0.88, $p < 0.001$, $I^2 = 43.4\%$, $p = 0.1156$	
Comparison 2	**Lithium vs. anticonvulsants (carbamazepine, lamotrigine or valproate).**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests lithium may be more effective than**

	anticonvulsants for prevention of relapse to mania, but not to depression.
Any relapse	
No significant differences between groups; 7 RCTs, N = 1,305, RR = 0.89, 95%CI 0.79 to 1.01, p = 0.07, I^2 = 0%, p = 0.5523	
Mania relapse	
A small, significant effect for lithium being more effective than anticonvulsants; 5 RCTs, N = 941, RR = 0.66, 95%CI 0.44 to 1.00, p = 0.05, I^2 = 40.9%, p = 0.1488	
Depression relapse	
No significant differences between groups; 5 RCTs, N = 941, RR = 1.15, 95%CI 0.92 to 1.43, p = 0.23, I^2 = 0%, p = 0.7617	
Risks	There was more discontinuation with lithium than placebo for reasons other than a mood episode. There no differences between lithium and anticonvulsants.
Consistency in results	Consistent for all comparisons, apart from lithium vs. placebo; any relapse outcome.
Precision in results	Precise for all comparisons, apart from lithium vs. anticonvulsants; mania and depression outcomes.
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

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Comparison 1	**Lithium vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, some imprecision, direct) suggests no benefit of lithium over placebo for depression severity or response to treatment. There were also no differences between groups in rates of switching to**

	mania.
Depression scores and response	
No significant differences between groups; Depression scores: 1 RCT, N = 269, SMD = -0.14, 95%CI -0.38 to 0.10, $p > 0.05$ Response to treatment: 1 RCT, N = 269, OR = 1.41, 95%CI 0.87 to 2.30, $p > 0.05$	
Switch to mania	
No significant differences between groups; 1 RCT, N = 269, OR = 2.93, 95%CI 0.30 to 28.60, $p > 0.05$	
Comparison 2	**Lithium vs. quetiapine.**
Summary of evidence	**Moderate to high quality evidence (large samples, some imprecision, direct) suggests no benefit of lithium over quetiapine for depression severity or response to treatment. There were also no differences between groups in rates of switching to mania.**
Depression scores and response	
No significant differences between groups; Depression scores: 1 RCT, N = 669, SMD = 0.15, 95%CI -0.04 to 0.34, $p > 0.05$ Response to treatment: 1 RCT, N = 669, OR = 0.81, 95%CI 0.55 to 1.21, $p > 0.05$	
Switch to mania	
No significant differences between groups; 1 RCT, N = 669, OR = 0.77, 95%CI 0.22 to 2.65, $p > 0.05$	
Risks	There were no differences between groups in rates of withdrawal from treatment (any reason).
Consistency in results	Not applicable (1 RCT).
Precision in results	Precise for depression scores only.
Directness of results	Direct

Xu N, Shinohara K, Saunders KEA, Geddes JR, Cipriani A

Effect of lithium on circadian rhythm in bipolar disorder: A systematic

review and meta-analysis **Bipolar Disorders 2021; 23: 445-53** View review abstract online	
Comparison	**Lithium vs. other medications.**
Summary of evidence	**Moderate quality evidence (large sample size, inconsistent, precise, indirect) finds a non-significant, trend effect of more morningness with lithium compared to other medications.**
Morningness	
Non-significant, trend effect of more morningness with lithium; 5 studies, N = 697, SMD = 0.42, 95%CI -0.05 to 0.90, p = 0.08, I^2 = 74%	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect; mixed comparison group.

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	**Lithium vs. placebo or other medications.**
Summary of evidence	**Moderate to high quality evidence (large sample size, consistent, mostly precise, some indirectness) suggests medium-sized effects of greater improvement in acute mania symptoms with lithium than placebo or topiramate, although there was greater improvement with tamoxefin than with lithium.**
Acute mania symptoms	
A significant, medium-sized effect of greater improvement with lithium than with placebo; Network meta-analysis; 57 studies, N = 14,256, SMD = 0.45, 95%CrI 0.30 to 0.61, $p < 0.05$ *A significant, medium-sized effect of greater improvement with lithium than with topiramate;*	

Network meta-analysis; 57 studies, N = 14,256, SMD = 0.52, 95%CrI 0.29 to 0.75, $p < 0.05$ *A significant, large effect of greater improvement with tamoxefin than with lithium;* Network meta-analysis; 57 studies, N = 14,256, SMD = 2.46, 95%CrI 1.91 to 3.05, $p < 0.05$ Authors report no other significant differences between lithium and other medications.	
Risks	More discontinuation with lithium than with olanzapine.
Consistency in results	Authors report data are consistent.
Precision in results	Precise, apart from tamoxefin comparison.
Directness of results	Some indirectness.

Explanation of acronyms

CI = confidence interval, CrI = credible 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, *r* = correlation coefficient, 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[20].

† 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[20].

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[21]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[20];

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

§ 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[22].

‖ 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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