Supplementary data

Supplementary data 1A: PRISMA 2020 Checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and Topic**  | **Item #** | **Checklist item**  | **Location where item is reported**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT**  |  |
| Abstract  | 2 | See the PRISMA 2020 for Abstracts checklist. | See table below, supplementary data 1B |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of existing knowledge. | Pages 1-2 |
| Objectives  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 2 |
| **METHODS**  |  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 3 |
| Information sources  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 3 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 3 and supplementary dataset 2 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 3 |
| Data collection process  | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 4 |
| Data items  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 4 and tables 1 and 2, and supplementary data 4.1A-C, 4.2A-C, and 4.5 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | See 10a |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 4, supplementary data 4.4B-E |
| Effect measures  | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Pages 4-5 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Pages 4-5 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Pages 4-5 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Pages 4-5 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Pages 4-5 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Pages 5 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | N/A |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 4 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 4 |
| **RESULTS**  |  |
| Study selection  | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 5 and Figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure 1 |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | Supplementary data 4.1 |
| Risk of bias in studies  | 18 | Present assessments of risk of bias for each included study. | Pages 5-6, supplementary data 4.4B-E |
| Results of individual studies  | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Supplementary data 4.2A-C, 4.5 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Pages 5-6, Tables 1, 2, 3A-B, supplementary data 4.4A |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Pages 6-7, Figures 2A-C, 3A-B |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Pages 6-7, Tables 3A and 3B, Supplementary data 4.3 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | N/A |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Supplementary data 4.4B-E |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Supplementary data 4.4A-E |
| **DISCUSSION**  |  |
| Discussion  | 23a | Provide a general interpretation of the results in the context of other evidence. | Pages 7-9 |
| 23b | Discuss any limitations of the evidence included in the review. | Pages 10-11 |
| 23c | Discuss any limitations of the review processes used. | Pages 10-11 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Page 9 |
| **OTHER INFORMATION** |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 3 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 3  |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Page 11, Supp. data 4.6 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 12 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 12 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | All data and analyses are included in supplementary data.  |

*From:*  Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary data 1B: PRISMA 2020 for Abstract Checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and Topic**  | **Item #** | **Checklist item**  | **Reported (Yes/No)**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | Y |
| **BACKGROUND**  |  |
| Objectives  | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Y |
| **METHODS**  |  |
| Eligibility criteria  | 3 | Specify the inclusion and exclusion criteria for the review. | Y |
| Information sources  | 4 | Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched. | Y |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | Y |
| Synthesis of results  | 6 | Specify the methods used to present and synthesise results. | Y |
| **RESULTS**  |  |
| Included studies  | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | Y |
| Synthesis of results  | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Y – as much as space allowed |
| **DISCUSSION**  |  |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency and imprecision). | N |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Y |
| **OTHER**  |  |
| Funding | 11 | Specify the primary source of funding for the review. | N |
| Registration | 12 | Provide the register name and registration number. | Y |

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary data 2: Search strings used for various search platforms.

Search PubMed

(((((((bipolar disorder\*) OR (bipolar affective disorder\*) OR (manic depressive disorder\*)) AND (lithium)))) NOT ((meta-analysis) OR review))) AND ((((((individual\*) OR people) OR patient\*) OR subject\*) OR participant\*) OR human\*)

Field: Title/Abstract

Search Web of Science

(((((((bipolar disorder\*) OR (bipolar affective disorder\*) OR (manic depressive disorder\*)) AND (lithium)))) NOT ((meta-analysis) OR review))) AND ((((((individual\*) OR people) OR patient\*) OR subject\*) OR participant\*) OR human\*)

Field: Topic (Searches title, abstract, author keywords, and Keywords Plus)

Supplementary data 3: PICOS table (Higgins et al., 2019)

|  |  |
| --- | --- |
| Population  | People with bipolar disorder (any type) |
| Intervention  | Lithium treatment studies |
| Comparison  | Different measures of lithium response (symptom rating scales, clinical scales such as the Alda, time to recurrence/rehospitalisation, etc) |
| Outcome  | Treatment response rates |
| Study design  | RCTs or naturalistic studies |

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons.

Supplementary data 4: Additional data or analyses

Supplementary data 4.1A: Study characteristics RCT

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Continent | Setting | Partici-pants, N | Age mean/ median | Female, % | Intervention | Drug comparison | Study length, months | BD pop-ulation | Diagnostic tool | Current episode | Anxiety comor-bidity | Substance comor-bidity | Psycho-sis comorbidity | Suicide ideation |
|  | 1=North America, 2=Middle America, 3=South America, 4=Europe, 5=Africa, 6=Asia, 7=Australia | 1=out-patient2= in-patient3= com-munity  |  |  |  | Different treatment groups |  |  | 1=BD1 only (or specified as manic)2=BD2 only3=mix of BD4=BD and other psychopathology | 1=DSM, 2=ICD, 3=other | 1=manic/hypomanic, 2=depression, 3=euthymic, 4=other/all | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded |
| T. Suppes et al., 2008 | 1 | 3 | 102 | 36.2 | 57.4 | Lithium; Lamotrigine | Lamotrigine | 4 | 2 | 1 | 2 | 1 | 0 | 0 | 0 |
| Astaneh et al 2012 | 6 | 2 | 60 | n/r | 50 | Lithium control; Lithium + gabapentin | Gabapentin | 1.5 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Pal singh 2008 | 6 | 1, 2 | 50 | 18-50 | 28 | Lithium; Verapamil | Verapamil | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 1 |
| Gao et al., 2018 | 1 | 1 | 42 | 44.7 | 66.6 | Lithium; Quetiapine immediate release | Quetiapine | 4 | 3 | 1 | 4 | 1 | 1 | 1 | 1 |
| Bowden et al., 2003 | 1 | 1 | 302 | 41.9 | 52 | Lithium; Lamotrigine; placebo | Lamotrigine | 19 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| Clark et al., 1997 | 5 | 2 | 40 | 18-65 | nr | Lithium; Clozapine | Clonazepam | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Bowden et al., 2005 | 4, 6 | 2 | 302 | 38.8 | 40.8 | Lithium; Quetiapine; placebo | Quetiapine | 3 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Shafti 2017 | 6 | 2 | 23 | 29.8 | 0 | Lithium; Aripiprazole | Aripiprazole | 1 | 1 | n/r | 1 | 1 | 0 | 1 | 0 |
| Denicoff et al., 1997 | 1 | 1 | 52 | 41.3 | 52 | Lithium; Carbamazepine; Lithium + Carbamazepine | Carbamazepine | 36 | 3 | 1 | 4 | 0 | 0 | 1 | 1 |
| Amsterdam et al., 2008 | 1 | 1 | 83 | 36.3 | 60 | Lithium; Venlafaxine | Venlafaxine | 3 | 2 | 1 | 2 | 1 | 0 | 0 | 1 |
| Weisler et al., 2011 | 1, 2, 3, 4, 6 | 1 | 1172 | 38.4 | 57.4 | Lithium; Quetiapine; placebo | Quetiapine | 30 | 1 | 1 | 4 | 0 | 0 | 1 | 0 |
| Hollander et al., 2005 | 1 | 3 | 40 | 40 | 50 | Lithium; placebo | n/a | 2.5 | 3 | 1 | 4 | 1 | 0 | 0 | 0 |
| Amsterdam et al., 2010 | 1 | 1 | 148 | 36.1 | 53.9 | Lithium; Fluoxetine, placebo | Fluoxetine | 11.5 | 2 | 1 | 3 | 1 | 0 | 0 | 1 |
| Shansis et al., 2016 | 3 | 1 | 68 | 38.85 | 82.35 | Lithium; Valproic acid; Carbamazepine | Carbamazepine; Valproic acid | 2 | 3 | 1, 3 | 4 | 1 | 0 | 1 | 0 |
| Shafti et al., 2018 | 6 | 2 | 50 | 28.64 | 0 | Lithium; Carbamazepine | Extended-release Carbamazepine | 0.75 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| McNamara et al., 2015 | 1 | 2, 3 | 80 | 17.8 | 50 | Lithium; Quetiapine | Quetiapine | 12 | 1 | 1 | 1, 4 | 1 | 0 | 1 | 1 |
| Strakowski et al, 2016 | 1 | 1, 2 | 68 | 18 | 60 | Lithium; Quetiapine; Healthy controls | Quetiapine | 2 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Young et al., 2017 | 1 | 1, 2 | 224 | 67.6 | 50 | Lithium; Divalproex | Divalproex | 2.25 | 1 | 1 | 4 | 1 | 0 | 1 | 0 |
| Singh et al., 2011 | 6 | 2 | 83 | 28.38 | 0 | Lithium one dose daily; Lithium two doses daily  | n/a | 1.38 | 1 | 2 | 1 | 1 | 1 | 1 | 1 |
| Ichim et al., 2000 | 5 | 2 | 3 | 31.9 | 46.67 | Lithium; Lamotrigine | Lamotrigine | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Nierenberg et al., 2013 | 1 | 1 | 283 | 38.7 | 54.6 | Lithium + Optimal treatment; Optimal treatment | n/a | 6 | 3 | 1 | 1, 2 | 1 | 1 | 1 | 0 |
| Greil et al., 1997 | 4 | 1, 2 | 144 | 45 | 50 | Lithium; Carbamazepine | Carbamazepine | 30 | 3 | 1, 2 | 4 | 1 | 0 | 1 | 1 |
| Niufan et al., 2008 | 6 | 1, 2 | 140 | 34 | 49.3 | Lithium; Olanzapine | Olanzapine | 1 | 1 | 1 | 1, 4 | 1 | 1 | 1 | 1 |
| Vestergaard et al., 1998 | 4 | 2 | 91 | 42.13 | 64.83516 | Lithium low dose; Lithium high dose | n/a | 24 | 4 | 1 | 4 | 1 | 1 | 1 | 1 |
| Hartong et al., 2003 | 4 | 1 | 98 | 41.9 | 54.3 | Lithium; Carbamazepine | Carbamazepine | 24 | 3 | 1 | 3 | 1 | 1 | 1 | 1 |
| Li et al., 2008 | 6 | 2 | 154 | 33.6 | 48.1 | Lithium; Quetiapine | Quetiapine | 1 | 1 | 3 | 1 | 1 | 0 | 1 | 1 |
| Segal et al., 1998 | 5 | 2 | 45 | 37.1 | 80 | Lithium; Risperidone, Haloperidol | Risperidone, Haloperidol | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Amsterdam et al 2015 | 1 | 1 | 129 | 43.1 | 47.1 | Lithium; Venlafaxine | Venlafaxine | 9 | 2 | 1 | 2 | 1 | 0 | 0 | 1 |
| Altshuler et al 2017 | 1 | 1 | 142 | 39.5 | 59.2 | Lithium; Sertraline; Lithium + Sertraline | Sertraline | 4 | 2 | 1 | 2 | 1 | 0 | 0 | 1 |
| Simhandl et al 1993 | 4 | 1 | 84 | 42 | 69 | Lithium; Carbamazepine High; Carbamazepine low | Carbamazepine | 24 | 4 | 1 | 1, 2 | 1 | 0 | 1 | 1 |
| Calabrese et al 2003 | 15 countries | 1 | 463 | 43.6 | 60 | Lithium; Lamotrigine 50 mg; Lamotrigine 200 mg; Lamotrigine 400 mg; Placebo | Lamotrigine  | 22 | 1 | 1 | 3 | 0 | 1 | 1 | 0 |
| Gao 2020 | 1 | 1 | 112 | n/r | 59.3 | Lithium; Divalproex | Divalproex | 0.5 | 3 | 1 | 1, 2, 3 | 1 | 0 | 1 | 1 |
| Parker G 2021 | 7 | 1 | 41 | 30.8 | 50 | Lithium; Lamotrigine | Lamotrigine | 5 | 2 | 1 | n/r | 0 | 0 | 0 | 0 |

Supplementary data 4.1B: Study characteristics NRT 2 arm studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Continent | Setting | Participants, N | Age mean/ median | Female, % | Treatment groups | Drug comparison | Study length, months | BD population | Diagnostic tool | Current episode | Anxiety | Substance | Psychosis | Suicide ideation |
|  | 1=North America, 2=Middle America, 3=South America, 4=Europe, 5=Africa, 6=Asia, 7=Australia | 1=out-patient2= in-patient3= com-munity  |  |  |  | Different treatment groups |  |  | 1=BD1 only (or specified as manic), 2=BD2 only, 3=mix of BD, 4=BD and other psychopathology | 1=DSM, 2=ICD, 3=other | 1=manic/hypomanic, 2=depression, 3=euthymic, 4=other/all | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded |
| Kessing et al., 2012 | 4 | 1, 2 | 4248 | n/r | 58 | Lithium; Lamotrigine | Lamotrigine | n/r | 3 | 2 | 4 | 1 | 1 | 1 | 1 |
| Dalkilic et al., 2000 | 1 | 2 | 47 | 35.9 | 25 | Lithium; Divalproex | Divalproex | 0.33 | 3 | 1 | 4 | 1 | 1 | 1 | 1 |
| Pae et al., 2008 | 6 | n/r | 45 | 32.7 | 55.6 | Lithium; Valproate; Carbamazepine | Valproate; Carbamazepine | 1.2 | 1 | 1 | n/r | 1 | 1 | 1 | 1 |
| Silverstone et al., 2005 | 1 | n/r | 10 | 30.2 | 80 | Lithium depressed group; Lithium euthymic group | n/a | 0.5 | 3 | 1 | 2, 3  | 0 | 0 | 0 | 1 |
| Hayes et al., 2016 | 4 | 1 | 5089 | 44.9 | 57.1 | Lithium; Valproate; Quetiapine; Olanzapine | Valproate; Olanzapine; Quetiapine | 4.2 | 3 | 2 | 4 | 1 | 1 | 0 | 1 |
| Maj et al., 2002 | 4 | 1 | 116 | 34.1 | 55.17 | Lithium psychosis group; Lithium no psychosis group | n/a | 60 | 3 | 1 | 4 | 1 | 1 | 1 | 1 |
| Altamura et al., 2008 | 4 | 1 | 232 | 51.3 | 55 | Lithium; Valproate; Lamotrigine; Quetiapine | Quetiapine; Valproate; Lamotrigine | 48 | 3 | 1 | 3 | 1 | 1 | 0 | 1 |
| Rucci et al 2002 | 1 | 1 | 175 | 35.1 | 56 | Lithium; Divalproex; Carbamazepine | n/a | 24 | 1 | 3 | 1, 2 | 1 | 0 | 1 | 1 |
| Kessing et al., 2011 | 4 | 1, 2 | 4268 | 49 | 58 | Lithium; Valproate | Valproate | 144 | 3 | 2 | 4 | 1 | 1 | 1 | 1 |
| Kessing et al 2014 | 4 | 1, 2 | 4714 | 48.7 | 57.4 | Early intervention Lithium; late intervention Lithium | n/a | 120 | 3 | 2 | 4 | 1 | 1 | 0 | 1 |
| Bohlken 2020 | 4 | 1 | 4990 | 50.6 | 50.3 | Lithium; Valproate; Quetiapine; Olanzapine; Venlafaxine; Citalopram | Valproate; Quetiapine; Olanzapine; Venlafaxine; Citalopram | 24 | 3 | 2 | 4 | 1 | 1 | 1 | 1 |
| Barbuti, 2021 | 4 | 1 ,2 | 70 | 37.88 | 62.9 | Lithium | n/a | 12 | 3 | 1 | 1, 2, 3, 4 | 1 | 1 | 1 | 1 |
| Burton 2021 | 1 | 1, 2 | 48 | 70.9 | 4 | Lithium; SGA (second generation antipsychotic) | Aripiprazole; Quetiapine; Risperidone; Olanzapine; Lurasidone | 37.1 | 3 | n/r | n/r | 1 | 1 | 0 | 1 |

Supplementary data 4.1C: Study characteristics NRT 1 arm studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Continent | Setting | Participants, N | Age mean/ median | Female, % | Treatment groups | Drug comparison | Study length, months | BD population | Diagnostic tool | Current episode | Anxiety | Substance | Psychosis | Suicide ideation |
|  | 1=North America, 2=Middle America, 3=South America, 4=Europe, 5=Africa, 6=Asia, 7=Australia | 1=out-patient2= in-patient3= com-munity  |  |  |  | Different treatment groups |  |  | 1=BD1 only (or specified as manic), 2=BD2 only, 3=mix of BD, 4=BD and other psychopathology | 1=DSM, 2=ICD, 3=other | 1=manic/hypomanic, 2=depression, 3=euthymic, 4=other/all | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded | 0=Comorbidity excluded1=comorbidity not excluded |
| Licht et al 2001 | 4 | 1 | 148 | 45 | 62 | Lithium | n/a | 24 | 3 | 2 | 4 | 1 | 1 | 1 | 1 |
| Selek et al 2013 | 1 | 1, 2 | 41 | 31.8 | nr | Lithium; Healthy control | n/a | 1 | 1 | 1 | 4 | 0 | 0 | 0 | 1 |
| Machado-Vieira et al., 2015 | 3 | 1 | 24 | 28.9 | 70.8 | Lithium | n/a | 1.5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| Moore et al., 2009 | 1 | 1, 3 | 28 | 33 | 46 | Lithium | n/a | 1 | 3 | 1 | 2, 3 | 0 | 0 | 0 | 1 |
| Keck et al., 2001 | 1 | 2 | 15 | 32 | 53 | Lithium | n/a | 0.33 | 1 | 1 | 4 | 1 | 1 | 1 | 1 |
| Machado-Vieira et al., 2016 | 3 | 1 | 23 | 28.2 | 78.3 | Lithium | n/a | 1.5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| Tondo et al., 1997 | 4 | 1 | 86 | 35.4 | 65.1 | Lithium | n/a | 4.5 | 3 | 1 | 1, 2 | 1 | 0 | 1 | 1 |
| Serretti et al., 2004 | 4 | 2 | 83 | 45.6 | 66.3 | Lithium; Lithium plus additional treatment | n/a | 36 | 3 | 1 | n/r | 1 | 0 | 1 | 1 |
| Machado-Vieira et al., 2017 | 3 | 1 | 26 | 28.8 | 80 | Lithium; Healthy control | n/a | 1.5 | 3 | 1 | 2 | 1 | 0 | 1 | 1 |
| Teixeira et al., 2015 | 3 | 1 | 56 | 28.4 | 72.41 | Lithium; Healthy control | n/a | 1.5 | 3 | 1 | 2 | 1 | 0 | 1 | 1 |
| Lowthert et al., 2012 | 1 | n/r | 26 | 38.25 | 70 | Lithium; Healthy control | n/a | 2 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| Soeiro-de-Souza et al., 2014 | 3 | n/r | 48 | 28.5 | 76 | Lithium; Healthy control | n/a | 1.5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| Machado-Vieira et al., 2014 | 3 | 1 | 31 | 28.4 | 72.4 | Higher (Li >0.5 mEq/L) and lower (Li <0.5 mEq/L) blood lithium levels | n/a | 1.5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| De Sousa et al., 2015 | 3 | 1 | 49 | 28.4 | 74.1 | Lithium; Healthy control | n/a | 1.5 | 3 | 1 | 2 | 1 | 0 | 1 | 1 |
| Altinay et al., 2017 | 1 | 1, 3 | 41 | 33 | 54 | Lithium; Healthy control | n/a | 2 | 3 | 1 | 1, 2 | 0 | 0 | 0 | 0 |
| Spielberg et al., 2018 | 1 | 1, 3 | 42 | 34.5 | 53.8 | Lithium; Healthy control | n/a | 2 | 3 | 1 | 1, 2 | 0 | 0 | 0 | 0 |
| Breen et al., 2016 | 1 | 1 | 125 | 48.06 | 0 | Lithium | n/a | 3 | 3 | 1 | n/r | 0 | 0 | 0 | 0 |
| Tandon et al., 1981 | 6 | 1, 2 | 50 | 16-65 | 12 | Lithium unipolar; Lithium bipolar | n/a | 1 | 4 | n/r | 1, 2 | 1 | 1 | 1 | 1 |
| Maj et al., 1998 | 4 | 1 | 402 | 40.7 | 55.2 | Lithium | n/a | 60 | 1 | 3 | n/r | 1 | 1 | 1 | 1 |
| Serretti et al., 2000a | 4 | 1 | 61 | 46.7 | 57.4 | Lithium | n/a | 53.5 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| De Sousa et al., 2013 | 3 | 1 | 57 | 28.4 | 72.4 | Lithium; Control | n/a | 1.5 | 3 | 1 | 2 | 0 | 0 | 1 | 1 |
| Ananth et al., 2020 | 1 | n/r | 27 | 34 | 47.4 | Lithium | n/a | 2 | n/r | 1 | 2 | 0 | 0 | 0 | 0 |
| Moore et al., 1999 | 1 | 2 | 12 | 36.3 | 58.3 | Lithium | n/a | 1 | 3 | 1 | 2 | 0 | 0 | 0 | 1 |
| Mallinger et al 2008 | 1 | 1, 2 | 45 | 36 | n/r | Lithium | n/a | 0.75 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Machado-Vieira et al., 2016 | 3 | 1 | 26 | 28.8 | 80 | Lithium; Healthy control | n/a | 1.5 | 3 | 1 | 2 | 1 | 0 | 1 | 1 |

Supplementary data 4.2A: Lithium treatment, RCT

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | N (baseline, whole study) | N (baseline, lithium group) | Duration (month) | Dose | Lithium levels | Lithium efficacy response type | Results | Tolerability (Measure / value) | Acceptability (measure / value) |
| T. Suppes et al., 2008 | 102 | 54 | 4 | 900mg | 0.6–1.2 mEq/L | Depression response | 55.1% | Mean/SD AE/TEAE per participant | mean 9.2 | % Discontinuation from lithium group | 61% |
| Astaneh et al 2012 | 60 | 30 | 1.5 | nr | nr | Change YMRS | -37 points | nr | n/r | N/R | nr |
| Pal singh 2008 | 50 | 25 | 1 | 900mg | 0.8 - 1.2 meq/l | Change YMRSChange BMRS | -20.84 points-19.36 points | Mean/SD AE/TEAE per participant | 0.8 | % Discontinuation from lithium group | 0 |
| Gao et al., 2018 | 42 | 18 | 4 | 600 mg/day | 0.5 mmol/L | Time to discontinuationChange MADRSChange YMRSChange HAM-AChange CGI-S-BP | 7.7 weeks-11.76-6.54-5.73-2.14 | % discontinuing due to tolerability / AEs | 33.00% | % Discontinuation from lithium group | 77.80% |
| Bowden et al., 2003 | 175 | 46 | 19 | n/r | 0.8-1.1 mEq/L | No response/new episode/eventTime to interventionChange MRSChange HAM-DChange Global assessment scaleChange CGI | 39%292 days-0.04+2.68 (bad)-3.85+0.44 (bad) | % discontinuing due to tolerability / AEs | 24% | % Discontinuation from lithium group | 98% |
| Clark et al., 1997 | 40 | 15 | 1 | 750-1800mg | 0.6-1.2 mmol/L | Change CGIChange MRSChange GAF ImprovementChange BPRS | -2.66-20.2+17.67 (good)-11.66 | N/R | n/r | % Discontinuation from lithium group | 0 |
| Bowden et al., 2005 | 302 | 98 | 3 | 900 mg/day | 0.8 mEq/L, median at endpoint | Mania responseMania remissionChange YMRS | 75.5%72.4%-20.76 | % any AE/TEAE | 6.10% | % Discontinuation from lithium group | 31.60% |
| Shafti 2017 | 23 | 11 | 1 | 300mg | nr | Change MSRS-IChange MSRS-FChange CGIChange BRMS | -39.06-27.16-1.36-13.67 | N/R | NR | % Discontinuation from lithium group | 36% |
| Denicoff et al., 1997 | 52 | 50 | 36 | 0.5-1.2mmol/l | 0.84 mmol/L | Mixed scale response | 33.3% | % discontinuing due to tolerability / AEs | 3.80% | % Discontinuation from lithium group | 42% |
| Amsterdam et al., 2008 | 83 | 40 | 3 | 966.24mg | 0.64mmol/l | Depression responseDepression remissionChange HAM-DChange YMRS | 20%15%-14-0.33 | % discontinuing due to tolerability / AEs | 12.50% | % Discontinuation from lithium group | 62.50% |
| Weisler et al., 2011 | 1172 | 364 | 30 | 0.63 mEq/l | 0.6-1.2 meql | No response/no new episode/event | 40% | % discontinuing due to tolerability / AEs | 5.5% | % Discontinuation from lithium group | 51.60% |
| Hollander et al., 2005 | 40 | 18 | 2.5 | 1150 mg (mean) | 0.87 meq/l | Change Mania scaleChange HAM-D | -6.58-6.67 | % discontinuing due to tolerability / AEs | 0 | % Discontinuation from lithium group | 33.30% |
| Amsterdam et al., 2010 | 148 | 26 | 11.5 | 1027 mg/day | 0.69 mmol/l | Relapse rate | 57.7% | Mean/SD AE/TEAE per participant | 1.58 | % Discontinuation from lithium group | 23.10% |
| Shansis et al., 2016 | 68 |  | 2 | 900-1200 mg/day | 0.8-1.2 mEq/L | Mixed scale response | 20.60%23.50%23.5% | n/r | n/r | n/r | n/r |
| Shafti et al., 2018 | 50 | 25 | 0.75 | 965.8 mg/day | 0.74 mEq/L | Change MSRS-FChange MSRS-IChange CGI-SChange CGI-I | -19.69-10.75-0.65-0.96 | N/R | nr | % Discontinuation from lithium group | 24.00% |
| McNamara et al., 2015 | 80 |  | 12 | 600-1800 mg/day | 0.8-1.2 meq/l | Change YMRS (week 8)Change YMRS (52 weeks) | -17-17.5 | n/r | n/r | n/r | n/r |
| Strakowski et al, 2016 | 68 |  | 2 | N/R | 0.8-1.2 meq/l | Mixed scale remissionResponse NOS | 50%58% | N/R | N/R | % Discontinuation (whole study) | 38% |
| Young et al., 2017 | 224 | 112 | 2.25 | 300 mg/day | 0.80–0.99mEq/L | Mania responseMania remissionChange YMRS | 78.6%69.6%-3.9 | % discontinuing due to tolerability / AEs | 22% | % Discontinuation from lithium group | 46.70% |
| Singh et al., 2011 | 83 | 83 | 1.38 | 1149.2 | 0.86 meq/l | Change BRMRS | -27.1 | Side effects tool | n/r | % Discontinuation from lithium group | 25.30% |
| Ichim et al., 2000 | 30 | 15 | 1 | 800mg | 0.743mmol/L | Mixed scale responseMania response | 27%60%27% | % any SAE | 6.67% | % Discontinuation from lithium group | 20% |
| Nierenberg et al., 2013 | 283 | 141 | 6 | 600 mg/day  | 0.47 mEq/L  | Mixed scale remissionChange CGI-BP-SChange MADRSChange YMRS | 26.5%-1.22-8.2-6.35 | N/R | N/R | % Discontinuation from lithium group | 17.70% |
| Greil et al., 1997 | 144 | 74 | 30 | 27 mmol/day | 0.63 mmol/L | Other response / No intervention requiredOther remission / no new episodes | 82%77% | % any AE/TEAE | 61% | % Discontinuation from lithium group | 18.92% |
| Niufan et al., 2008 | 140 | 71 | 1 | 1110mg (mean) | nr | Mania responseMania remissionChange CGI-BP-SChange CGI-BP maniaChange CGI-BP depressionChange YMRSChange BPRSChange MADRS | 73.2%70.4%-2.22-2.33+0.12 (bad)-20.15-9.04-2.51 | % any AE/TEAE | 42.3 | % Discontinuation from lithium group | 21.1 |
| Vestergaard et al., 1998 | 91 | 91 | 24 | 22-28meqv/day | 0.64-0.80 mmol/l | Other response / no intervention requiredOther remission / no new episodes | 34%80% | % discontinuing due to tolerability / AEs | 7.69% | % Discontinuation from lithium group | 66.6% |
| Hartong et al., 2003 | 98 | 44 | 24 | nr | 0.75 mmol/L | Other remission /  | 72.7% | % discontinuing due to tolerability / AEs | 11.40% | % Discontinuation from lithium group | 36.30% |
| Li et al., 2008 | 154 | 77 | 1 | 1444.8mg mean | 0.8 mmol/l | Mania responseMania remissionMixed scale remission | 59.7%48.1%32.5%48.1% | Mean/SD AE/TEAE per participant | 1.2 | % Discontinuation from lithium group | 19.5% |
| Segal et al., 1998 | 45 | 15 | 1 | 800-1200mg | 0.6-1.2 mmol/L | Change MRSChange BPRSChange CGI-SChange GAF | -12.7-8.3-1.3+22 (good) | Simpson Angus Scale | 0.66 | % Discontinuation from lithium group | 6.70% |
| Amsterdam et al 2015 | 129 | 64 | 9 | 1090 mg/day | 0.72 mEq/L | Depression responseNo response / New mood episode/event | 34.4%26.7% | N/R | n/r | % Discontinuation from lithium group | 11.76% |
| Altshuler et al 2017 | 142 | 49 | 4 | 900 mg/day (minimum) | 0.63 mEq/L | Depression response | 67.4% | % discontinuing due to tolerability / AEs | 29.60% | % Discontinuation from lithium group | 55.10% |
| Simhandl et al 1993 | 84 | 26 | 24 | 450 mg/day | 0.66 mmol/L | Change in hospitalisationsChange duration of episodesDuration of symptom free interval | -9.4 hospitalisations-12.1 weeks+11 weeks (good) | % any AE/TEAE | 69.30% | % Discontinuation from lithium group | 19.23% |
| Calabrese et al 2003 | 463 | 121 | 22 | 900mg (mean) | 0.8 mEq/L | Other response / no intervention requiredTime to intervention | 17%86%46%170 days | % discontinuing due to tolerability / AEs | 16% | % Discontinuation from lithium group | 37% |
| Gao 2020 | 112 | 53 | 0.5 | n/r | 0.61 mEq/L.  | Mixed scale responseNo response / switch/change in medication for responseChange BISSChange CGI-SChange CGI-S depressionChange CGI-S maniaChange Q.o.L. | 5.7%15.1%-20-1.28-1.11-0.69+6.04 (good) | Mean/SD AE/TEAE per participant | 0.603774 | % Discontinuation from lithium group | 43% |
| Parker G 2021 | 41 | 20 | 5 | 1070 mg | 0.78 mEq/L | Change HAM-DChange YMRSChange CGI-BD Change CGI-BD maniaChange CGI-BD depression | -10.2-13-0.8-0.9+0.3 (bad) | % discontinuing due to tolerability / AEs | 11.76% | % Discontinuation from lithium group | 29.41% |

Supplementary data 4.2B: Lithium treatment, NRT 2 arms

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | N (baseline, whole study) | N (baseline, lithium group) | Duration (month) | Dose | Lithium levels | Lithium efficacy response type | Results | Tolerability (Measure / value) | Acceptability (measure / value) |
| Kessing et al., 2012 | 4248 | 3518 | n/r | n/r | n/r | No response / hospitalisation  | 57% | n/r | n/r | % Discontinuation from lithium group | 6.30% |
| Dalkilic et al., 2000 | 47 | 20 | 0.33 | 1,140mg ±471 | 0.64 mEq/L  | Length of hospital stay after treatment start | 10.3 days | N/R | n/r | N/R | n/r |
| Pae et al., 2008 | 45 | 30 | 1.2 | 1066.7 mg | N/R | Change YMRSChange CGI | -27.8-1.5 | N/R | N/R | N/R | N/R |
| Silverstone et al., 2005 | 10 | 10 | 0.5 | NR | NR | Change HAM-D (depressed group) | -4.4 | N/R | N/R | % Discontinuation from lithium group | 0% |
| Hayes et al., 2016 | 5089 | 1505 | 4.2 | NR | NR | No response / new mood episode/eventTime to treatment failure (75% group) | 75%2.05 years | n/r | n/r | N/R | n/r |
| Maj et al., 2002 | 116 | 116 | 60 | NR | 0.5-1 mmol/L | Response NOSOther remission / no new episodes | 56.6%56.7%23.3% | N/R | N/R | % Discontinuation from lithium group | 32.70% |
| Altamura et al., 2008 | 232 | 39 | 48 | nr | 0.7 mEq/l | No response / New mood episode/eventOther remission / no new episodesEuthymia duration | 53.8%46.2%33.1 months | N/R | N/R | % Discontinuation from lithium group | 43.6 |
| Rucci et al 2002 | 175 | 166 | 24 | n/r | 0.83 meq/l | Change suicide attempt rate | -94.3 % | % discontinuing due to tolerability / AEs | 9.10% | % Discontinuation (whole study) | 38.30% |
| Kessing et al., 2011 | 4268 | 3549 | 144 | n/r | n/r | No response / Hospitalisation  | 54% | N/R | n/r | % Discontinuation from lithium group | 6% |
| Kessing et al 2014 | 4714 | 4714 | 120 | nr | n/r | Other response / No intervention required | 13.3%13.2%6.3%6.7%8.7%10.1%4%4.2% | N/R | n/r | N/R | n/r |
| Bohlken 2020 | 4990 | 1098 | 24 | NR | n/r | Response NOS | 23.7%32.9% | N/R | n/r | N/R | n/r |
| Barbuti, 2021 | 70 | 70 | 12 | Baseline 15 mmol/day, endpoint 22 mmol/day | 0.63 mEq/L | Change FASTChange CGI-BD (prolonged release group)Change CGI-BD (immediate release group) | -15.81-1.61-1.56 | Mean/SD AE/TEAE per participant | 0.878788 | % Discontinuation from lithium group | 53% |
| Burton 2021 | 48 | 24 | 37.1 | 560 mg | n/r | No response / Hospitalisation Time to discontinuation of treatment (mean) | 14%1128.7 days | % discontinuing due to tolerability / AEs | 42% | % Discontinuation from lithium group | 100 |

Supplementary data 4.2C: Lithium treatment, NRT 1 arm

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | N (baseline, whole study) | N (baseline, lithium group) | Duration (month) | Dose | Lithium levels | Lithium efficacy response type | Results | Tolerability (Measure / value) | Acceptability (measure / value) |
| Licht et al 2001 | 148 | 132 | 24 | nr | 0.63 +/- 0.18 mmol/ | No response / hospitalisationOther response / No intervention required | 21.6%30.4% | % any AE/TEAE | 72% | % Discontinuation from lithium group | 48.00% |
| Selek et al 2013 | 41 | 30 | 1 | nr | 0.67 mEq/L | Mixed scale responseMixed scale remission | 50%25% | N/R | n/r | % Discontinuation from lithium group | 20% |
| Machado-Vieira et al., 2015 | 24 | 24 | 1.5 | 712 mg/day, max | 0.49 mEq/L | Depression responseDepression remission | 91%71% | N/R | n/r | N/R | n/r |
| Moore et al., 2009 | 28 | 28 | 1 | nr | 0.9 meq/l | Depression response | 39.3% | N/R | n/r | % Discontinuation from lithium group | 0 |
| Keck et al., 2001 | 15 | 15 | 0.33 | 1380 mg/day | 1.0 mEq/L +/- 0.2  | Mania responseChange HAM-D-24Change YMRS | 60%-11.2-16.6 | Mean/SD AE/TEAE per participant | 0.933333 | % Discontinuation from lithium group | 20% |
| Machado-Vieira et al., 2016 | 23 | 23 | 1.5 | 710.05 mg/day, mean | 0.49 mEq/L, endpoint mean | Depression responseDepression remissionMixed scale remissionChange HAM-D | 85%65.2%60%-15.2 | N/R | n/r | N/R | NR |
| Tondo et al., 1997 | 86 | 86 | 4.5 | nr | 0.62 meq/l | Change episodes per yearChange hospitalisations per yearChange time spent ill | -1.48 episodes-0.48-32.5% | N/R | n/r | N/R | n/r |
| Serretti et al., 2004 | 83 | 83 | 36 | mean 1173 mg/die | 0.65–0.75mMol/l | Response NOS | 56.6% | N/R | N/R |  | n/r |
| Machado-Vieira et al., 2017 | 26 | 26 | 1.5 | 671.1mg | 0.48 mmL | Depression responseMixed scale responseChange HAM-DChange CGI | 85%60%-14.5-1.85 | n/r | n/r | % Discontinuation from lithium group | 23.10% |
| Teixeira et al., 2015 | 56 | 29 | 1.5 | 450 mg/day | 0.49 mEq/L | Depression responseMixed scale remission | 82.8%62.1% | N/R | n/r | N/R | N/R |
| Lowthert et al., 2012 | 26 | 26 | 2 | 0.6-1.2 mEq/L | 0.64 mmol/L | Depression response | 50% | N/R | N/R | % Discontinuation from lithium group | 23.10% |
| Soeiro-de-Souza et al., 2014 | 48 | 25 | 1.5 | 450 mg/day | 0.49 mEq/L | Depression responseDepression remission | 84%64% | Side effects tool | 28% weight gain | % Discontinuation from lithium group | 0% |
| Machado-Vieira et al., 2014 | 31 | 31 | 1.5 | 450-900 mg/day | 0.49 mEq/L | Depression responseDepression remission | 86.2%62% | Side effects tool | polydipsia/polyuria (62.1%), cognitive complaints (41.4%), nausea (31.0%), increased oniric activity (31.0%) and sedation (31.0%). | % Discontinuation from lithium group | 6.50% |
| De Sousa et al., 2015 | 49 | 27 | 1.5 | 450 mg/day start | 0.49 mEq/L | Depression responseMixed scale remission | 85%63% | N/R | N/R | % Discontinuation from lithium group | 0% |
| Altinay et al., 2017 | 41 | 29 | 2 | 600 mg/day | 0.67 | Change HAM-D (depressed group)Change HAM-D (hypomanic group)Change YMRS (depressed group)Change YMRS (hypomanic group)Change CGI-S (depressed group)Change CGI-S (hypomanic group) | -11+3 (bad)0-12.5-1.3-0.9 | Side effects tool | headache, increased appetite, dry mouth, blurred vision, dizziness, muscle twitching, bad taste after the drug was taken, heart palpitations, fatigue, nervousness and | % Discontinuation from lithium group | 17.20% |
| Spielberg et al., 2018 | 42 | 29 | 2 | 600 mg/day | 0.7 mEq/L | Change HAM-D (depressed group)Change HAM-D (manic group)Change YMRS (depressed group)Change YMRS (manic group) | -7.7-0.3-1.7-10.2 | N/R | N/R | % Discontinuation from lithium group | 10.30% |
| Breen et al., 2016 | 125 | 125 | 3 | NR | n/r | Response NOS | 50% | N/R | N/R | % Discontinuation from lithium group | 87.20% |
| Tandon et al., 1981 | 50 | 50 | 1 | 600-1500 mg/day | 0.32-1.23 mEq/L | Mania responseChange HAM-DChange Beigel’s rating scale | 26%52%-20.8-13.3 | N/R | N/R | N/R | N/R |
| Maj et al., 1998 | 402 | 402 | 60 | NR | 0.5-1 mmol/L | Response NOSOther remission / no new episodes | 61%85%23% | % discontinuing due to tolerability / AEs | 6.72 | % Discontinuation from lithium group | 38.60% |
| Serretti et al., 2000a | 61 | 61 | 53.5 | nr | 0.4-0.7 meq/l | Other remission / no new episodes | 21.3%54.1% | N/R | n/r |  | n/r |
| De Sousa et al., 2013 | 57 | 29 | 1.5 | nr | 0.49 mmol | Depression responseMixed scale remissionChange HAM-DChange YMRS | 86.2%62.1%-15.3-2.3 | N/R | n/r | % Discontinuation from lithium group | 3.40% |
| Ananth et al., 2020 | 27 | 27 | 2 | nr | 0.8–1.2 mEq/l | Depression remissionChange HAM-D | 26.3%-11.8 | N/R | n/r | % Discontinuation from lithium group | 29.63% |
| Moore et al., 1999 | 12 | 12 | 1 | nr | 0.8-1.2 meq/l | Change HAM-D | -6.75 | % discontinuing due to tolerability / AEs | 0 | % Discontinuation from lithium group | 0 |
| Mallinger et al 2008 | 45 | 45 | 0.75 | 900-1200 mg/day | 0.8-1.4 mmol/l | Mania response | 58% | N/R | n/r | % Discontinuation from lithium group | 2.22% |
| Machado-Vieira et al., 2016 | 26 | 26 | 1.5 | 671mg | 0.48 mmol/L | Depression responseDepression remissionMixed scale remissionChange HAM-D | 85%62.5%60%-15.2 | N/R | n/r | % Discontinuation from lithium group | 23.10% |

Supplementary data 4.3: Meta-analysis of primary outcome, only low and moderate risk of bias studies

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Depression | Mania | Global impression |
| Subgroup | k | N | ES | SE | 95% CI | I2 | k  | N | ES | SE | 95% CI | I2 | k  | N | ES | SE | 95% CI | I2 |
| All | 13 |  439 | 1.38 | 0.20 | 0.99-1.77 | 90% | 18 |  739 | 1.78 | 0.22 | 1.34-2.22 | 95% | 12 |  421 | 0.98 | 0.14 | 0.69-1.26 | 89% |
| RCT vs non-RCTRCTNRT | 58 |  295144 | 0.572.05 | 0.100.35 | 0.38-0.761.36-2.74 | 56%82% | 144 | 64693  | 1.553.47 | 0.221.45 | 1.12-1.990.63-6.32 | 95%67% | 93 |  387105 | 0.951.16 | 0.140.57 | 0.68-1.210.05-2.27 | 84%96% |
| Baseline affective sateDepressedManicMixed | 67 | 125314 | 2.050.68 | 0.430.13 | 1.21-2.880.43-0.93 | 86%68% | 88 | 426421 | 3.041.13 | 0.540.22 | 1.99-4.090.69-1.56 | 96%91% |  |  |  |  |  |  |

Supplementary data 4.4A: Overall Risk of Bias results

|  |
| --- |
| TOTAL RoB |
| High | N = 16 (22.5%) |
| Moderate | N = 38 (53.5%) |
| Low | N = 17 (23.9%) |
| **RCT** |
| High | N = 7 (21.2%) |
| Moderate | N = 13 (39.4%) |
| Low | N = 13 (39.4%) |
| **Non-RCT, 2 arm** |
| High | N = 4 (30.8%) |
| Moderate | N = 6 (46.2%) |
| Low | N = 3 (23.1%) |
| **Non-RCT, 1 arm** |
| High | N = 5 (20%) |
| Moderate | N = 19 (76%) |
| Low | N = 1 (4%) |

Supplementary data 4.4B: Risk of bias scoring key

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Random allocation | Allocation concealment | Blinding  | Rater blinding | Equal treatment | Balanced groups | Appropriate outcomes | ITT | Deviations |
| Were the participants randomised to treatment in a truly random fashion? | Were participants/raters unable to determine what intervention a participant would get until they were assigned? | Were participants and those delivering intervention blinded to assigned intervention? | Were outcome assessors blind to intervention? If not, could this knowledge influence ratings? | Did groups receive the same treatment, including monitoring, follow up type/length etc. | Did treatment groups have similar characteristics? If not, could this confound effect of intervention? | 1) Were groups assessed using different measures? 2) Were several analyses used for same outcome? | Was *everyone* assigned to Li analysed, regardless of whether they completed or adhered? | Did study deviate from plans in design, treatment, or analysis? |
| 1 = yes 0 = no 0.5=for unclear/unstated or method controlled by humansNon-RCT = N/A | 1 = yes0 = no0.5 = unclear, or if it just described as "randomised".Non-RCT = N/A | 1 = yes to both0 = no0.5 = if only one part was blinded. Non-RCT = N/A | 1 = yes0 = no0.5 = if blinded but <5% reported to have been unblinded. Non-RCT = N/A | 1 = yes, no evidence of different methods in study design between groups. 0 = no0.5 = minor differencesN/A for one arm trials | 1 = yes0 = no0.5 = minor differencesN/A for one arm trials | 1 = no to both0 = yes to both0.5 = yes to either/both but justification provided.  | 1 = yes, everyone was analysed. 0 = no0.5 = <5% of patients were excluded (not taking intervention or lack of outcome) and no correction for bias potential in analyses.  | 1 = no0 = yes, evidence of deviation that may have influenced efficacy outcomes0.5 = no evidence of pre-specified methods or outcomes |

Supplementary data 4.4C: Risk of bias results, RCT

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Authors | Random allocation | Allocation concealment | Blinding (participant & intervention) | Rater blinding | Equal treatment | Balanced groups | Appropriate outcomes | ITT | Deviations | ROB score |
| T. Suppes et al., 2008 | 0.5 | 0 | 0 | 1 | 0.5 | 1 | 1 | 0 | 1 | High |
| Astaneh et al 2012 | 0.5 | 0.5 | 0 | 0 | 0.5 | 1 | 1 | 1 | 1 | High |
| Pal singh 2008 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Gao et al., 2018 | 0.5 | 0.5 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Bowden et al., 2003 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Clark et al., 1997 | 0.5 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Bowden et al., 2005 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Shafti 2017 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Denicoff et al., 1997 | 0.5 | 0.5 | 1 | 0.5 | 1 | 1 | 1 | 0 | 1 | Moderate |
| Amsterdam et al., 2008 | 0.5 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Weisler et al., 2011 | 1 | 1 | 1 | NR | 1 | 1 | 1 | 1 | 1 | Low |
| Hollander et al., 2005 | 0.5 | 0.5 | 1 | NR | 1 | 1 | 1 | 0 | 1 | Moderate |
| Amsterdam et al., 2010 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Shansis et al., 2016 | 0.5 | 0.5 | 0 | 0 | 1 | NR | 1 | 1 | 1 | High |
| Shafti et al., 2018 | 0.5 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | Moderate |
| McNamara et al., 2015 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | High |
| Strakowski et al, 2016 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | High |
| Young et al., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Singh et al., 2011 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Ichim et al., 2000 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Nierenberg et al., 2013 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Greil et al., 1997 | 0.5 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Niufan et al., 2008 | 0.5 | 0.5 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Vestergaard et al., 1998 | 1 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Hartong et al., 2003 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | Low |
| Li et al., 2008 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Segal et al., 1998 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Amsterdam et al 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | Moderate |
| Altshuler et al 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Simhandl et al 1993 | 0.5 | 0.5 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | High |
| Calabrese et al 2003 | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Gao 2020 | 0.5 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate |
| Parker G 2021 | 0.5 | 0.5 | 0 | 0.5 | 1 | 1 | 1 | 0 | 0 | High |

|  |
| --- |
| Low risk = <1 criteria rated high RoB and <4 unclear RoB |
| High risk = >4 criteria rated high or unclear RoB |
| Moderate risk if not meeting criteria for high or low risk of bias. |

Supplementary data 4.4D: Risk of bias results, NRT 2 arm studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Authors | Random allocation | Allocation concealment | Blinding (participant & intervention) | Rater blinding | Equal treatment | Balanced groups | Appropriate outcomes | ITT | Deviations | ROB score |
| Kessing et al., 2012 | n/a | n/a | n/a | n/a | 0.5 | 0.5 | 1 | 1 | 1 | High |
| Dalkilic et al., 2000 | n/a | n/a | n/a | n/a | 1 | 1 | 1 | 1 | 1 | Low |
| Pae et al., 2008 | n/a | n/a | n/a | n/a | 1 | 1 | 1 | 1 | 1 | Low |
| Silverstone et al., 2005 | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | 1 | 1 | Moderate |
| Hayes et al., 2016 | n/a | n/a | n/a | n/a | 0 | 0.5 | 1 | 1 | 1 | High |
| Maj et al., 2002 | ? | n/a | n/a | n/a | 1 | 1 | 1 | 0.5 | 1 | Moderate |
| Altamura et al., 2008 | n/a | n/a | n/a | n/a | 1 | 0 | 1 | 0 | 1 | High |
| Rucci et al 2002 | n/a | n/a | n/a | n/a | 1 | n/r | 1 | 1 | 1 | Moderate |
| Kessing et al., 2011 | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | 1 | 1 | Moderate |
| Kessing et al 2014 | n/a | n/a | n/a | n/a | 0 | 0.5 | 1 | 1 | 1 | High |
| Bohlken 2020 | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | 1 | 1 | Moderate |
| Barbuti, 2021 | n/a | n/a | n/a | n/a | 1 | 1 | 1 | 0 | 1 | Moderate |
| Burton 2021 | n/a | n/a | n/a | n/a | 1 | 1 | 1 | 1 | 1 | Low |

|  |
| --- |
| Low risk = <1 criteria rated high RoB and <5 unclear RoB |
| High risk = >5 criteria rated high or unclear RoB |
| Moderate risk if not meeting criteria for high or low risk of bias. |

Supplementary data 4.4E: Risk of bias results, NRT 1 arm studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Authors | Random allocation | Allocation concealment | Blinding (participant & intervention) | Rater blinding | Equal treatment | Balanced groups | Appropriate outcomes | ITT | Deviations | ROB score |
| Licht et al 2001 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Selek et al 2013 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Machado-Vieira et al., 2015 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Moore et al., 2009 | n/a | n/a | 0.5 | 1 | n/a | n/a | 1 | 1 | 1 | Low |
| Keck et al., 2001 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Machado-Vieira et al., 2016 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Tondo et al., 1997 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Serretti et al., 2004 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Machado-Vieira et al., 2017 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Teixeira et al., 2015 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Lowthert et al., 2012 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Soeiro-de-Souza et al., 2014 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Machado-Vieira et al., 2014 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| De Sousa et al., 2015 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Altinay et al., 2017 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | High |
| Spielberg et al., 2018 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | High |
| Breen et al., 2016 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 0 | 1 | High |
| Tandon et al., 1981 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Maj et al., 1998 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 0 | 1 | High |
| Serretti et al., 2000a | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| De Sousa et al., 2013 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Ananth et al., 2020 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Moore et al., 1999 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Mallinger et al 2008 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 1 | 1 | Moderate |
| Machado-Vieira et al., 2016 | n/a | n/a | n/a | n/a | n/a | n/a | 1 | 0.5 | 1 | High |

|  |
| --- |
| Low risk = <1 criteria rated high RoB and <6 unclear RoB |
| High risk = >6 criteria rated high or unclear RoB |
| Moderate risk if not meeting criteria for high or low risk of bias. |

Supplementary data 4.5: Lithium efficacy of binary data

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Lithium response type | Reference | Depression baseline | Mania baseline | N analysed | Measurement | Outcome description | Result |
| Depression response | Suppes et al 2008 | HAM-D-17 21.2; MADRS 30.2 | YMRS 6.71 | 49 | HAM-D 17 | Response: 50% or higher decrease in score from baseline to endpoint | 55.10% |
|  | Machado-vieira 2015 | HAM-D 21.7 | YMRS 4.7 | 24 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 91% |
|  | Moore et al 2009 | HAM-D 17.6 | NR | 28 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 39.30% |
|  | Amsterdam et al., 2008 | HAM-D 28.8 | YMRS 1.2 | 40 | HAM-D 28 | Response: 50% or higher decrease in score from baseline to endpoint | 20% |
|  | Machado-Vieira et al., 2017 | HAM-D 22.4 | N/A | 20 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 85% |
|  | Teixeira et al., 2015 | NR | N/R | 29 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 82.80% |
|  | Lowthert et al., 2012 | HAM-D 27.65 | 6.1 | 20 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 50% |
|  | Soeiro-de-Souza et al., 2014 | NR | NR | 25 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 84% |
|  | Machado-Vieira et al., 2014 | HAM-D 22.5 | YMRS 6.1 | 29 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 86.20% |
|  | De Sousa et al., 2015 | HAM-D 22.2 | YMRS 5.6 | 27 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 85% |
|  | De Sousa et al., 2013 | HAM-D 22.5 | YMRS 6.1 | 29 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 86.20% |
|  | Amsterdam et al 2015 | HAM-D 18.8  | YMRS 0.6 | 64 | HAM-D + CGI-S | 50% or more HRSD decrease from baseline to week 12 + final CGI-S score of 3 or less | 34.40% |
|  | Altshuler et al 2017 | Depressive symptomatology-clinician-rated score 35.2 | YMRS 5.6 | 49 | IDS-C (Inventory of Depressive symptomatology - Clinician rated) + CGI | Response: 50% or higher decrease of score of IDS-C, OR a 2 point or higher decrease in CGI from baseline, for at least two consecutive visits spanning at least a 2 week period | 67.40% |
|  | Machado-Vieira et al., 2016 | HAM-D 22.4 | NR | 20 | HAM-D | Response: 50% or higher decrease in score from baseline to endpoint | 85% |
|  |  |  |  | *Total N = 453* |  |  | *Mean = 68.0%* |
| Depression remission | Machado-vieira 2015 | HAM-D 21.7 | YMRS 4.7 | 24 | HAM-D | Remission: Score of 8 or less | 71% |
|  | Machado-Vieira et al., 2016 | 22.6 HAMD | NR | 23 | HAM-D | Remission: Score of 8 or less | 65.20% |
|  | Amsterdam et al., 2008 | 28.6 HAMD | YMRS 1.2 | 40 | HAM-D 17 | Remission: Score of 8 or less | 15.00% |
|  | Soeiro-de-Souza et al., 2014 | NR | NR | 25 | HAM-D | Remission: Score of 8 or less | 64% |
|  | Machado-Vieira et al., 2014 | HAM-D 22.5 | YMRS 6.1 | 29 | HAM-D | Remission: Score of 8 or less | 62% |
|  | Ananth et al., 2020 | HAM-D 27.3 | NR | 19 | HAM-D | <10 HDRS-24 and >=50% reduction in HDRS-24 from pre to post treatment | 26.30% |
|  |  |  |  | *Total N = 160* |  |  | *Mean = 50.55%* |
| Mania response | Keck et al 2001 | 20.0 HAMD mean | 28.3 mean YMRS | 15 | YMRS | Response: 50% or higher decrease in score from baseline to endpoint | 60% |
|  | Bowden et al., 2005 | 6.3 MADRS | 33.3, YMRS | 98 | YMRS | Response: 50% or higher decrease in score from baseline to endpoint | 75.50% |
|  | Young et al., 2017 | N/A | 26.3 YMRS | 112 | YMRS | Response: 50% or higher decrease in score from baseline to endpoint | 78.60% |
|  | Ichim et al., 2000 | n/r | MRS mean 31.6 | 15 | MRS | Response: 50% or higher decrease in score from baseline to endpoint | 60% |
|  | Ichim et al., 2000 | n/r | MRS mean 31.6 | 15 | BPRS | Response: 50% or higher decrease in score from baseline to endpoint | 27% |
|  | Tandon et al., 1981 | HAM-D 19.9 | mean Beigel's Rating scale for mania 14.36  | 50 | Beigels rating scale | Response: 90% or higher decrease in score from baseline to endpoint | 26% |
|  | Tandon et al., 1981 | HAM-D 19.9 | mean Beigel's Rating scale for mania 14.36  | 50 | Beigels rating scale | Response: 70-90% decrease in score from baseline to endpoint | 52% |
|  | Niufan et al., 2008 | 5.0 (MADRS) | 32.4 (YMRS) | 71 | YMRS | Response: 50% or higher decrease in score from baseline to endpoint | 73.20% |
|  | Li et al., 2008 | 4.8 MADRS | 29.8, YMRS | 77 | YMRS | Response: 50% or higher decrease in score from baseline to endpoint | 59.70% |
|  | Mallinger et al 2008 | nr | nr | 45 | BRMS | Response: less than or 7 on RSMS AND less than or 15 on BRMS after minimum 3 weeks of lithium treatment | 58% |
|  |  |  |  | *Total N =548* |  |  | *Mean = 57%* |
| Mania remission | Bowden et al., 2005 | 6.3 MADRS | 33.3, YMRS | 98 | YMRS | Total score of 12 or less at endpoint | 72.40% |
|  | Young et al., 2017 | N/A | 26.3 YMRS | 112 | YMRS | Total score of 9 or less at endpoint | 69.60% |
|  | Niufan et al., 2008 | 5.0 (MADRS) | 32.4 (YMRS) | 71 | YMRS | Total score of 12 or less at endpoint | 70.40% |
|  | Li et al., 2008 | 4.8 MADRS | 29.8, YMRS | 77 | YMRS | Total score of 12 or less at endpoint | 48.10% |
|  | Li et al., 2008 | 4.8 MADRS | 29.8, YMRS | 77 | YMRS | Total score of 8 or less at endpoint | 32.50% |
|  |  |  |  | *Total N = 435* |  |  | *Mean = 58.6%* |
| Mixed scale response | Selek et al 2013 | HAMD 13.52 | YMRS 7.76 | 24 | HAM-D + YMRS | 50% or higher decrease in score from baseline to endpoint | 50% |
|  | Denicoff et al., 1997 | 7.1 HAMD | 3.3 YMRS | 42 | CGI | % with good response to lithium (marked or mod improv) | 33.30% |
|  | Shansis 2016  | 19.20 (HAMD-21) | 10.04 for YMRS, 7.04 for BRMS, 12.06 for CARS-M.  | 68 | HAM-D + YMRS | 50% of higher reduction in symptoms | 22.10% |
|  | Shansis 2016  | 19.20 (HAMD-21) | 10.04 for YMRS, 7.04 for BRMS, 12.06 for CARS-M.  | 68 | HAM-D + BRMS | 50% of higher reduction in symptoms | 20.60% |
|  | Shansis 2016  | 19.20 (HAMD-21) | 10.04 for YMRS, 7.04 for BRMS, 12.06 for CARS-M.  | 68 | HAM-D + CARS-M | 50% of higher reduction in symptoms | 23.50% |
|  | Ichim et al., 2000 | n/r | MRS mean 31.6 | 15 | CGI | Response: score of 1 or 2 | 27% |
|  | Gao 2020 | 4.09, CGI-S depression | 2.69, CGI-S mania | 53 | CGI | <3 after 2 weeks | 5.66% |
|  |  |  |  | *Total N = 338* |  |  | *Mean = 26%* |
| Mixed scale remission | Selek et al 2013 | HAMD 13.52 | YMRS 7.76 | 24 | HAM-D + YMRS | HAM-D score 7 or less + YMRS score 12 or less | 25% |
|  | Strakowski et al, 2016 | HDRS 14 | YMRS 25 | 19 | HAM-D + YMRS | HAM-D + YMRS score 10 or less | 50% |
|  | Machado-Vieira et al., 2017 | HDRS 22.4 | N/A | 20 | HAM-D + YMRS | HAM-D + YMRS score 8 or less | 60% |
|  | Teixeira et al., 2015 | n/r | N/R | 29 | HAM-D + YMRS | HAM-D + YMRS score 8 or less | 62.10% |
|  | De Sousa et al., 2015 | HAM-D 22.2 | YMRS 5.6 | 27 | HAM-D + YMRS | HAM-D + YMRS score 8 or less | 63% |
|  | Nierenberg et al., 2013 | MADRS 22.4 | YMRS 13 | 141 | CGI-BP-S | Score of 2 or less for 2 months | 26.50% |
|  | De Sousa et al., 2013 | 22.5, HAM-D | 6.1, YMRS | 29 | HAM-D + YMRS | HAM-D + YMRS score 8 or less | 62.10% |
|  | Li et al., 2008 | 4.8 MADRS | 29.8, YMRS | 77 | MADRS + YMRS  | MADRS score 8 or less + YMRS score 12 or less | 48.10% |
|  | Machado-Vieira et al., 2016 | 22.4 HAMD | nr | 20 | HAM-D + YMRS | HAM-D + YMRS score 8 or less | 60% |
|  |  |  |  | *Total N = 386* |  |  | *Mean = 51%* |
| Negative response / switch or change in medication for response | Kessing et al., 2012 | nr | nr | 1547 | Switch to/add on of another psychotropic drug | During study period | 72% |
|  | Kessing et al., 2011 | nr | n/r | 1555 | Switch to/add on of another psychotropic drug | During study period | 72% |
|  | Gao 2020 | 4.09, CGI-S depression | 2.69, CGI-S mania | 53 | Switched | Intolerant to Lithium, switched to Divalproex (other study arm) | 15.09% |
|  |  |  |  | Total N = 3155 |  |  | Mean = 53.03% |
| Negative response resulting in hospitalisation | Licht et al 2001 | n/r | n/r | 148 | Recurrence hospitalization | % with BD related hospitalisation in study period | 21.60% |
|  | Kessing et al., 2012 | nr | nr | 3518 | Recurrence hospitalization | % with BD related hospitalisation in study period | 57% |
|  | Kessing et al., 2011 | nr | n/r | 3549 | Recurrence hospitalization | % with BD related hospitalisation in study period | 54% |
|  | Burton 2021 | nr | n/r | 24 | Recurrence hospitalization | % with BD related hospitalisation in study period | 14% |
|  |  |  |  | *Total N = 7239* |  |  | *Mean = 36.7%* |
| Negative response / new mood episode/events | Weisler et al., 2011 | 3.3 (MADRS) | 3.7 YMRS | 364 | Any mood event by end of study | At least 1: initiation of medication to treat a mood event; hospitalisation for a mood event, YMRS or MADRS score of 20 or higher at 2 consecutive assessments, or discontinuation from the study if due to mood event | 40% |
|  | Altamura et al., 2008 | nr | n/r | 39 | Major mood episode recurrence | 4 year follow up | 53.80% |
|  | Amsterdam et al 2015 | 18.8 (HAMD) | 0.6, YMRS | 15 | Relapse (major depressive episode), HRSD + CGI-S | HRSD 14 or more + CGI-S score of 4 or more for minimum 14 days | 26.70% |
|  | Bowden et al., 2003 | HAMD-17 6.7 | 22.3, Mania rating scale | 46 | Intervention for any mood episode | New medication, ECT | 39% |
|  | Hayes et al., 2016 | nr | n/r | 1505 | Treatment failure after 2.05 years | Stop medication, add-on of another mood stabilizer, antipsychotic, antidepressant or benzodiazepine | 75% |
|  |  |  |  | *Total N = 1969* |  |  | *Mean = 47%* |
| Other response / no new intervention required  | Kessing et al 2014 | nr | n/r | 715 | Response, early intervention (lithium at first contact) | After 5 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 13.30% |
|  | Kessing et al 2014 | nr | n/r | 410 | Response, early intervention (lithium after single episode diagnosis) | After 5 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 13.20% |
|  | Kessing et al 2014 | nr | n/r | 3999 | Response, late intervention (lithium at later contact) | After 5 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 6.30% |
|  | Kessing et al 2014 | nr | n/r | 4304 | Response, late intervention (lithium at BD diagnosis) | After 5 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 6.70% |
|  | Kessing et al 2014 | nr | n/r | 715 | Response, early intervention (lithium at first contact) | After 10 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 8.70% |
|  | Kessing et al 2014 | nr | n/r | 410 | Response, early intervention (lithium after single episode diagnosis) | After 10 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 10.10% |
|  | Kessing et al 2014 | nr | n/r | 3999 | Response, late intervention (lithium at later contact) | After 10 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 4.00% |
|  | Kessing et al 2014 | nr | n/r | 4304 | Response, late intervention (lithium at BD diagnosis) | After 10 years: after 6 months of index purchase of lithium, no polypharmacy and no admission to psychiatric ward/hospital | 4.20% |
|  | Licht et al 2001 | n/r | n/r | 148 | No rehospitalization | % who were not rehospitalised in 2 years | 30.40% |
|  | Greil et al., 1997 | n/r | NR | 74 | No hospitalisation | During study | 82% |
|  | Vestergaard et al., 1998 | nr | n/r | 91 | No recurrence or readmission to hospital | During 2 years follow up | 34.00% |
|  | Calabrese et al 2003 | 5.6 (HAMD) | 2.0 MRS | 121 | Completed study without intervention | n/a | 17% |
|  | Calabrese et al 2003 | 5.6 (HAMD) | 2.0 MRS | 120 | No intervention, mania | % of those going 1 year without intervention | 86% |
|  | Calabrese et al 2003 | 5.6 (HAMD) | 2.0 MRS | 120 | No intervention, depression | % of those going 1 year without intervention | 46% |
|  |  |  |  | *Total N = 19530* |  |  | *Mean = 26%* |
| Response NOS | Strakowski et al, 2016 | HDRS 14 | YMRS 25 | 19 | Response | How many showed response, not otherwise specified  | 58% |
|  | Serretti et al., 2004 | N/R | N/R | NR | Response | Response is if lithium is needed only and they continue to take it for 3 years without a new episode (and continue to show up for the study) | 56.60% |
|  | Breen et al., 2016 | NR | NR | 16 | Response | Reaching the end of the maintenance phase of the study without relapse = lithium responders | 50% |
|  | Maj et al., 1998 | n/r | NR | 402 | Still taking prophylactic lithium | At follow up, 5 years  | 61% |
|  | Maj et al., 2002 | nr | n/r | 53 | Still taking prophylactic lithium | At follow up, 5 years  | 56.60% |
|  | Maj et al., 1998 | nr | n/r | 402 | hospital time | a 50% reduction in mean annual time spent in the hospital compared to a reference pretreatmentperiod | 85% |
|  | Maj et al., 2002 | nr | n/r | 30 | Reduced time in hospital | a 50% reduction in mean annual time spent in the hospital compared to a reference pre-treatmentperiod | 56.70% |
|  | Bohlken 2020 | nr | n/r | 1098 | No treatment failure | Within 24 months, no discontinuation of treatment or add-on of either mood stabilizer, antipsychotic, antidepressant drug or benzodiazepine | 23.70% |
|  | Bohlken 2020 | nr | n/r | 1098 | No treatment failure | Within 12 months, no discontinuation of treatment or add-on of either mood stabilizer, antipsychotic, antidepressant drug or benzodiazepine | 32.90% |
|  |  |  |  | *Total N = 3118* |  |  | *Mean = 53%* |
| Other remission / no new episodes | Maj et al., 1998 | nr | n/r | 247 | Illness recurrence | No affective episode during treatment period | 23% |
|  | Maj et al., 2002 | nr | n/r | 30 | No new episodes | No new manic or depressive episodes  | 23.30% |
|  | Serretti et al 2000 | n/r | nr | 61 | mood episode prevention | % having no episodes during FU | 21.31% |
|  | Serretti et al 2000 | nr | n/r | 61 | mood episode prevention | % having reduced mood ep frequency during FU | 54.10% |
|  | Vestergaard et al., 1998 | nr | n/r | 91 | No recurrence of affective disorder episode | During 2 years follow up | 80.00% |
|  | Hartong et al., 2003 | 5.23, Bech Rafaelsen Melancholia scale | 1.8, Bech Rafaelsen Mania scale | 44 | mood episode prevention | % completing 2 years without episode | 72.70% |
|  | Altamura et al., 2008 | nr | n/r | 39 | Euthymia / remission | 4 year follow up | 46.20% |
|  | Greil et al., 1997 | nr | n/r | 74 | No recurrence of symptoms | During study | 77% |
|  |  |  |  | *Total N = 647* |  |  | *Mean = 50%* |

Supplementary data 4.6: Changes from protocol

|  |  |
| --- | --- |
| **Element changed** | **Details of change** |
| Title | Changed to accurately reflect inclusion of meta-analysis |
| Anticipated completion date | Changed to accurately reflect inclusion of meta-analysis |
| Inclusion of studies with participants under 18 years of age | We included 3 studies which had a minority of participants under the age of 18 in order to provide a more comprehensive picture of literature on the topic. |
| Inclusion of additional study designs | We included more study designs not mentioned in the protocol, such as Open label lithium studies and register studies in order to provide a more comprehensive picture of literature on the topic. |
| Removal of one Risk of Bias criterion | We did not assess if study question in the included studies were clear and appropriate as we found no variation between studies meaning this data was not informative |
| Removal of several data categories | We did not report ethnicity, previous number of bipolar episodes, illness duration prior to treatment or type of monitoring in the included studies, as this data was not available. |
| Use of Cochrane Risk of Bias tool for all included studies | We used the Cochrane Risk of bias tool for RCT for all studies instead of splitting up RCT from NRT in order to give an appropriate risk of bias rating to non-randomised studies when compared to randomised |
| Did not follow the SWIM method | In the interest of brevity and prioritisation of meta-analytic results, we didn’t fully follow the SWIM method, including doing subanalysis of the binary data. |

Supplementary data 5: Included publications for systematic review and meta-analysis

Altamura, A. C., Mundo, E., Dell’Osso, B., Tacchini, G., Buoli, M., & Calabrese, J. R. (2008). Quetiapine and classical mood stabilizers in the long-term treatment of Bipolar Disorder: A 4-year follow-up naturalistic study. *Journal of Affective Disorders*, *110*(1–2), 135–141. https://doi.org/10.1016/j.jad.2008.01.017

Altinay, M., Karne, H., & Anand, A. (2018). Lithium monotherapy associated clinical improvement effects on amygdala-ventromedial prefrontal cortex resting state connectivity in bipolar disorder. *Journal of Affective Disorders*, *225*, 4–12. https://doi.org/10.1016/j.jad.2017.06.047

Altshuler, L. L., Sugar, C. A., McElroy, S. L., Calimlim, B., Gitlin, M., Keck, P. E., Aquino-Elias, A., Martens, B. E., Fischer, E. G., English, T. L., Roach, J., & Suppes, T. (2017). Switch Rates During Acute Treatment for Bipolar II Depression With Lithium, Sertraline, or the Two Combined: A Randomized Double-Blind Comparison. *The American Journal of Psychiatry*, *174*(3), 266–276. https://doi.org/10.1176/appi.ajp.2016.15040558

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