

Appendix 1. Checklist of PRISMA guideline

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1 title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.3 abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.5-6 Background
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.6 Objective
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.7 Search strategy and inclusion criteria
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.	p.7 Search strategy and inclusion criteria
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p.7 Search strategy and inclusion criteria, Appendix 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.	p.7 Search strategy and inclusion criteria
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.	p.8 Outcome measures and target population
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.	p.8 Outcome measures and target population
	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.	p.8 Outcome measures and target population
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.	p.8 Outcome measures and target population
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.	p.8 Outcome measures and target population
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)).	p.8~9 Data analysis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p.8 Outcome measures and target population
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p.8~9 Data analysis

Section and Topic	Item #	Checklist item	Location where item is reported
	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.	p.8~9 Data analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p.8~9 Data analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p.8~9 Data analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p.8 Outcome measures and target population
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p.8~9 Data analysis
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.	Figure 1 (PRISMA 2020 flow diagram)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix 2
Study characteristics	17	Cite each included study and present its characteristics.	eTable 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	eFigure 2, eFigure 3
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.	p.10 2nd paragraph of Findings Figure 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p.10 1st paragraph of Findings
	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.	p.10 2nd paragraph of Findings
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p.10 2nd paragraph of Findings eFigure 5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	eTable 3, eTable 4 p.10 2nd paragraph of Findings
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	eFigure 2, eFigure 3 p.10 1st paragraph of Findings
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	eTable 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p12 2nd paragraph of Discussion

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	p14 Limitation
	23c	Discuss any limitations of the review processes used.	p14 Limitation
	23d	Discuss implications of the results for practice, policy, and future research.	p15 Clinical implications
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.	Open Science Framework (DOI: 10.17605/OSF.IO/CYPV6)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Open Science Framework (DOI: 10.17605/OSF.IO/CYPV6)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	None
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.	Supplementary and appendix

**Appendix 2.****Database****MEDLINE search strategy**

- 1 "bipolar and related disorders"/ or "bipolar and related disorders".mp. or bipolar disorder/ or "bipolar disorder".mp.(54249)
- 2 (mania or manic).mp.(19561)
- 3 affective psychosis.mp.(1014)
- 4 rapid cycling.mp.(1360)
- 5 (psychos\* or psychotic or anti-psycho\* or antipsycho\*).ti,kf.(107641)
- 6 or/1-5(159894)
- 7 Amisulpride/ or Amisulpride.mp.(1393)
- 8 Blonanserin.mp.(178)
- 9 Risperidone/ or Risperidone.mp.(10808)
- 10 Quetiapine Fumarate/ or Quetiapine Fumarate.mp.(3103)
- 11 Paliperidone Palmitate/ or Paliperidone Palmitate.mp. or Paliperidone.mp.(1643)
- 12 Lumateperone.mp. (45)
- 13 Olanzapine/ or Olanzapine.mp.(10059)
- 14 Lurasidone Hydrochloride/ or Lurasidone Hydrochloride.mp. (332)
- 15 Haloperidol/ or Haloperidol.mp.(22927)
- 16 cariprazine.mp. (330)
- 17 Perospirone.mp. (161)
- 18 asenapine.mp.(467)
- 19 Aripiprazole/ or Aripiprazole.mp.(4815)
- 20 Clozapine/ or Clozapine.mp.(13884)
- 21 Brexpiprazole.mp.(282)
- 22 lloperidone.mp.(224)
- 23 Melperone.mp.(154)
- 24 Pimavanserin.mp.(263)
- 25 Remoxipride/ or Remoxipride.mp. (380)
- 26 Ziprasidone.mp.(2091)
- 27 Antipsychotic Agents/ or Antipsychotic Agents.mp.(58790)
- 28 or/7-27(85330)
- 29 6 and 28(25437)
- 30 randomized controlled trial.pt.(576271)
- 31 randomi\*.ti,ab,kf.(750128)
- 32 (RCT or at random or (random\* adj (assign\* or allocat\* or divid\* or division or number))).ti,ab,kf.(263507)
- 33 trial.ti.(265008)
- 34 clinical trials as topic.sh. (200326)
- 35 placebo.ti,ab,kf. (235339)
- 36 ((singl\* or doubl\* or trebl\* or tripl\*) adj3 (blind\* or mask\* or dummy)).ti,ab,kf.

(191378)

37 or/30-36 (1348988)

38 29 and 37(4653)

39 exp animals/ not humans.sh. (5042390)

40 38 not 39(4629)

### Cochrane Central Register of Controlled Trials(CENTRAL) search strategy

#1 MeSH descriptor: [Bipolar Disorder] explode all trees (2890)

#2 (bipolar disorder):ti,ab,kw(7150)

#3 MeSH descriptor: [Bipolar and Related Disorders] explode all trees(2891)

#4 (bipolar and related disorders):ti,ab,kw(1658)

#5 MeSH descriptor: [Mania] explode all trees (21)

#6 (mania or manic):ti,ab,kw(3429)

#7 (affective psychosis):ti,ab,kw(927)

#8 (rapid cycling):ti,ab,kw(1921)

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8(10562)

#10 MeSH descriptor: [Risperidone] explode all trees (1443)

#11 (Risperidone):ti,ab,kw(3658)

#12 MeSH descriptor: [Quetiapine Fumarate] explode all trees (749)

#13 (Quetiapine):ti,ab,kw(1998)

#14 MeSH descriptor: [Paliperidone Palmitate] explode all trees(252)

#15 (Paliperidone):ti,ab,kw(655)

#16 MeSH descriptor: [Amisulpride] explode all trees (149)

#17 (Amisulpride):ti,ab,kw(512)

#18 MeSH descriptor: [Olanzapine] explode all trees(1354)

#19 (Olanzapine):ti,ab,kw(3698)

#20 MeSH descriptor: [Haloperidol] explode all trees (1425)

#21 (Haloperidol):ti,ab,kw(3266)

#22 (cariprazine):ti,ab,kw(188)

#23 (asenapine):ti,ab,kw(194)

#24 MeSH descriptor: [Aripiprazole] explode all trees (626)

#25 (Aripiprazole):ti,ab,kw(1704)

#26 MeSH descriptor: [Clozapine] explode all trees(527)

#27 (Clozapine):ti,ab,kw(1559)

#28 (Blonanserin):ti,ab,kw(67)

#29 (Brexipiprazole):ti,ab,kw (174)

#30 (lloperidone):ti,ab,kw(71)

#31 (Lumateperone):ti,ab,kw(50)

#32 MeSH descriptor: [Lurasidone Hydrochloride] explode all trees(119)

#33 (Lurasidone):ti,ab,kw(504)

#34 (Melperone):ti,ab,kw(36)

#35 (Perospirone):ti,ab,kw(38)

#36 (Pimavanserin):ti,ab,kw(113)

#37 MeSH descriptor: [Remoxipride] explode all trees(55)

#38 (Remoxipride):ti,ab,kw(86)

#39 (Ziprasidone):ti,ab,kw(780)

#40 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39(12624)

#41 #9 and #40(2002)

#42 (randomized controlled trial):ti,ab,kw(736915)

#43 #41 and #42(890)

### Embase search strategy

#1. 'bipolar disorder'/exp OR 'bipolar disorder' (85,016)

#2. 'bipolar and related disorders'/exp OR 'bipolar and related disorders' (79,962)

#3. 'mania'/exp OR mania (93,293)

#4. 'affective psychosis'/exp OR 'affective psychosis' (2,814)

#5. 'rapid cycling' (2,087)

#6. 'psychotic'/exp OR psychotic (331,035)

#7. 'risperidone'/exp OR risperidone (39,343)

#8. 'quetiapine'/exp OR quetiapine (25,746)

#9. 'paliperidone'/exp OR paliperidone (5,208)

#10. 'amisulpride'/exp OR amisulpride(6,125)

#11. 'olanzapine'/exp OR olanzapine (36,912)

#12. 'haloperidol'/exp OR haloperidol (62,652)

#13. 'cariprazine'/exp OR cariprazine (732)

#14. 'asenapine'/exp OR asenapine (1,659)

#15. 'aripiprazole'/exp OR aripiprazole (17,284)

#16. 'clozapine'/exp OR clozapine (35,875)

#17. 'blonanserin'/exp OR blonanserin(470)

#18. 'brexpiprazole'/exp OR brexpiprazole (628)

#19. 'iloperidone'/exp OR iloperidone (895)

#20. 'lumateperone'/exp OR lumateperone(129)

#21. 'lurasidone'/exp OR lurasidone (1,982)

#22. 'melperone'/exp OR melperone(952)

#23. 'perospirone'/exp OR perospirone(510)

#24. 'pimavanserin'/exp OR pimavanserin(644)

#25. 'remoxipride'/exp OR remoxipride(1,037)

#26. 'ziprasidone'/exp OR ziprasidone (9,535)

#27. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (392,373)

#28. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 (134,246)

#29. #27 AND #28 (134,246)

#30. #29 AND 'randomized controlled trial'/de (3,987)

**PsycINFO search strategy**

S1 bipolar disorder OR (bipolar and related disorders)(44,887)  
 S2 mania OR manic (25,051)  
 S3 affective psychosis(1,906)  
 S4 rapid cycling (1,096)  
 S5 psychotic (107,242)  
 S6 S1 OR S2 OR S3 OR S4 OR S5 (150,936)  
 S7 risperidone(7,854)  
 S8 quetiapineorseroquel (4,104)  
 S9 paliperidone (879)  
 S10 Amisulpride(848)  
 S11 Olanzapine(6,762)  
 S12 haloperidol (10,033)  
 S13 cariprazine (152)  
 S14 asenapine(251)  
 S15 aripiprazole(3,212)  
 S16 clozapine(8,849)  
 S17 Blonanserin(102)  
 S18 brexpiprazole(132)  
 S19 iloperidone(106)  
 S20 lumateperone(13)  
 S21 lurasidone(297)  
 S22 Melperone(66)  
 S23 Perospirone(101)  
 S24 Pimavanserin(81)  
 S25 Remoxipride(178)  
 S26 ziprasidone(1,388)  
 S27 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR  
 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26(29,614)  
 S28 S6 and S27(10,526)  
 S29 S28 AND randomized controlled trial(1,025)

**ClinicalTrials.gov (<https://clinicaltrials.gov/>)**

Olanzapine | Bipolar Disorder, Manic(26)  
 Risperdal | Bipolar Disorder, Manic (6)  
 Quetiapine | Bipolar Disorder, Manic (29)  
 Paliperidone | Bipolar Disorder, Manic (5)  
 Amisulpride | Bipolar Disorder, Manic (1)  
 Haloperidol | Bipolar Disorder, Manic (6)  
 Cariprazine | Bipolar Disorder, Manic (3)  
 Asenapine | Bipolar Disorder, Manic (11)  
 Aripiprazole | Bipolar Disorder, Manic (18)  
 Clozapine | Bipolar Disorder, Manic (1)

Blonanserin | Bipolar Disorder, Manic (0)  
Iloperidone | Bipolar Disorder, Manic (0)  
Lumateperone | Bipolar Disorder, Manic (0)  
Lurasidone | Bipolar Disorder, Manic (1)  
Melperone | Bipolar Disorder, Manic (0)  
Perospirone | Bipolar Disorder, Manic (0)  
Pimavanserin | Bipolar Disorder, Manic (0)  
Remoxipride | Bipolar Disorder, Manic (0)  
Ziprasidone | Bipolar Disorder, Manic (15)

**World Health Organization (ICTRP)(<https://trialsearch.who.int/AdvSearch.aspx>)**

(Bipolar Disorder or Mania) AND Risperidone (8)  
(Bipolar Disorder or Mania) AND Quetiapine (23)  
(Bipolar Disorder or Mania) AND Paliperidone (3)  
(Bipolar Disorder or Mania) AND Olanzapine (13)  
(Bipolar Disorder or Mania) AND Haloperidol (1)  
(Bipolar Disorder or Mania) AND Cariprazine (5)  
(Bipolar Disorder or Mania) AND Asenapine (8)  
(Bipolar Disorder or Mania) AND Aripiprazole (21)  
(Bipolar Disorder or Mania) AND Clozapine (0)  
(Bipolar Disorder or Mania) AND Blonanserin (0)  
(Bipolar Disorder or Mania) AND Brexpiprazole (6)  
(Bipolar Disorder or Mania) AND Iloperidone (1)  
(Bipolar Disorder or Mania) AND Lumateperone (2)  
(Bipolar Disorder or Mania) AND Lurasidone (5)  
(Bipolar Disorder or Mania) AND Melperone (0)  
(Bipolar Disorder or Mania) AND Perospirone (0)  
(Bipolar Disorder or Mania) AND Pimavanserin (0)  
(Bipolar Disorder or Mania) AND Remoxipride (0)  
(Bipolar Disorder or Mania) AND Ziprasidone (15)

CENTRAL: Cochrane Central Register of Controlled Trials



**Conference abstract (n = 9)**

1. Adewuya AO, Makanjuola ROA. A double blind randomised controlled trial of haloperidol vs. carbamazepine vs. valproate monotherapy in acute manic episodes. *World psychiatry*. 2009;8(Suppl 1):187.
2. Bose A, Starace A, Wang Q, Diaz E, Goodman J, Ruth A, et al. Cariprazine in the treatment of acute mania in bipolar disorder: a double-blind, placebo-controlled, phase III trial. *International journal of neuropsychopharmacology*. 2012;15:111-2.
3. Buckley PF, Paulsson B, Brecher M. Treatment of agitation and aggression in bipolar mania: efficacy of quetiapine. *Journal of affective disorders*. 2007;100 Suppl 1:S33-43.
4. Calabrese J, Lu K, Laszlovszky I, DeBelle M, Earley W, Durgam S. Efficacy of cariprazine in patients with acute manic or mixed episodes associated with bipolar I disorder: results from 2 phase III, placebo-controlled trials. *Bipolar disorders*. 2014;16:93.
5. Fricchione Parise V, Addeo L, Laezza R, Di Benedetto R, De Vivo E, Bianco P. Lithium versus quetiapine and aripiprazole: Real-world comparative effectiveness on bipolar disorder patients. *European Neuropsychopharmacology*. 2019;29:S336-S7.
6. Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. *Journal of affective disorders*. 2007;100 Suppl 1:S45-53.
7. Laszlovszky I, Bose A, Andor G, Nemeth G, Werner P. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *International clinical psychopharmacology*. 2011;26:e15.
8. Madera J, Jin N, Amatniek J, Johnson B, Baker RA, Such P. Remission and recovery in patients with bipolar I disorder (BP-I) treated with aripiprazole once-monthly (AOM 400). *Neuropsychopharmacology*. 2017;43:S528.
9. McIntyre RS, Konarski JZ, Jones M, Paulsson B. Quetiapine in the treatment of acute bipolar mania: efficacy across a broad range of symptoms. *Journal of affective disorders*. 2007;100 Suppl 1:S5-14.

**Not double-blinded randomized clinical trials (n=12)**

1. Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E. Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study. *Journal of affective disorders*. 2003;76(1-3):267-71.
2. Azorin JM, Luquiens A, Aubrun E, Reed C, Gasquet I, Lukasiewicz M. Management of patients with acute manic or mixed episodes and outcome at three months. *Encephale*. 2010;36(3):226-35.
3. Bahk W-M, Yoon B-H, Lee K-U, Chae J-H. Combination of mood stabilizers with quetiapine for treatment of acute bipolar disorder: an open label study. *Human psychopharmacology*. 2004;19(3):181-5.
4. Buoli M, Esposito CM, Godio M, Caldiroli A, Serati M, Altamura AC. Have antipsychotics a different speed of action in the acute treatment of mania? A single-blind comparative study. *Journal of psychopharmacology (Oxford, England)*. 2017;31(12):1537-43.
5. Chen J, Muzina DJ, Kemp DE, Conroy C, Chan P, Serrano MB, et al. Safety and efficacy of olanzapine monotherapy in treatment-resistant bipolar mania: a 12-week open-label study. *Human psychopharmacology*. 2011;26(8):588-95.
6. Forsthoff A, Grunze H, Seemuller F, Stampfer R, Dittmann S, Amann B, et al. Risperidone monotherapy in manic inpatients: an open label, multicentre trial. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 2007;8(4):256-61.
7. Novick D, Reed C, Haro JM, Gonzalez-Pinto A, Perrin E, Aguado J, et al. Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *International clinical psychopharmacology*. 2010;25(5):257-63.
8. Pae C-U, Masand PS, Mandel FS, O'Gorman C. Achieving and sustaining remission in bipolar I disorder with ziprasidone : a post hoc analysis of a 24-week, double-blind, placebo-controlled study. *Clinical drug investigation*. 2012;32(11):747-54.
9. Pae CU, Masand PS, Mandel FS, O'Gorman C. Achieving and sustaining remission in bipolar I disorder with ziprasidone : a post hoc analysis of a 24-week, double-blind, placebo-controlled study. *Clinical drug investigation*. 2012;32(11):747-54.
10. Sekhar S, Kalra B, Mendhekar DN, Tekur U. Efficacy of sodium valproate and haloperidol in the management of acute mania: a randomized open-label comparative study. *Journal of clinical pharmacology*. 2010;50(6):688-92.

11. Shi L, Juarez R, Hackworth J, Edgell ET, Haro JM, Vieta E, et al. Open-label olanzapine treatment in bipolar I disorder: clinical and work functional outcomes. *Current medical research and opinion*. 2006;22(5):961-6.
12. Shi L, Namjoshi MA, Zhang F, Gandhi G, Edgell ET, Tohen M, et al. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *International clinical psychopharmacology*. 2002;17(5):227-37.

**No outcome of interest (n=116)**

1. Azorin JM, Sapin C, Weiller E. Effect of asenapine on manic and depressive symptoms in bipolar I patients with mixed episodes: results from post hoc analyses. *Journal of affective disorders*. 2013;145(1):62-9.
2. Bahk W-M, Shin Y-C, Woo J-M, Yoon B-H, Lee J-S, Jon D-I, et al. Topiramate and divalproex in combination with risperidone for acute mania: a randomized open-label study. *Progress in neuro-psychopharmacology & biological psychiatry*. 2005;29(1):115-21.
3. Barekatin M, Fatemi A, Bashardoost N, Darougheh A, Salehi M, Asadollahi GH. Valproate-risperidone valproate-lithium combination in acute mania. *Journal of Research in Medical Sciences*. 2005;10(5):274-80.
4. Bersudsky Y, Applebaum J, Gaiduk Y, Sharony L, Mishory A, Podberezsky A, et al. Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial. *Bipolar disorders*. 2010;12(4):376-82.
5. Berwaerts J, Lane R, Nuamah IF, Lim P, Remmerie B, Hough DW. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *Journal of affective disorders*. 2011;129(1-3):252-60.
6. Berwaerts J, Melkote R, Nuamah I, Lim P. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. *Journal of affective disorders*. 2012;138(3):247-58.
7. Bobo WV, Reilly-Harrington NA, Ketter TA, Brody BD, Kinrys G, Kemp DE, et al. Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: results from the Bipolar CHOICE trial. *Journal of affective disorders*. 2014;161:30-5.

8. Bowden C, Karayal O, Gundapaneni B, O'Gorman C, Pappadopulos E, Schwartz J. Treatment outcomes based on disease severity for subjects with bipolar I disorder treated with ziprasidone plus a mood stabilizer. *Bipolar disorders*. 2010;12:10.
9. Bowden CL, Myers JE, Grossman F, Xie Y. Risperidone in combination with mood stabilizers: a 10-week continuation phase study in bipolar I disorder. *The Journal of clinical psychiatry*. 2004;65(5):707-14.
10. Brown D, Silverstone T, Cookson J. Carbamazepine compared to haloperidol in acute mania. *International clinical psychopharmacology*. 1989;4(3):229-38.
11. Calabrese JR, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Findling RL. New data on the use of lithium, divalproate, and lamotrigine in rapid cycling bipolar disorder. *European psychiatry : the journal of the Association of European Psychiatrists*. 2005;20(2):92-5.
12. Carlson BX, Ketter TA, Sun W, Timko K, McQuade RD, Sanchez R, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). *Bipolar disorders*. 2012;14(1):41-53.
13. Carta MG, Zairo F, Mellino G, Hardoy MC, Vieta E. An open label follow-up study on amisulpride in the add-on treatment of bipolar I patients. *Clinical practice and epidemiology in mental health : CP & EMH*. 2006;2:19.
14. Chan HY, Jou SH, Juang YY, Chang CJ, Chen JJ, Chen CH, et al. A single-blind, comparative study of zotepine versus haloperidol in combination with a mood stabilizer for patients with moderate-to-severe mania. *Psychiatry and Clinical Neurosciences*. 2010;64(2):162-9.
15. Chou JC, Czobor P, Charles O, Tuma I, Winsberg B, Allen MH, et al. Acute mania: haloperidol dose and augmentation with lithium or lorazepam. *Journal of clinical psychopharmacology*. 1999;19(6):500-5.
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**Unpublished clinical trials, which did not meet our inclusion criteria (n=12)**

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4. Quetiapine Fumarate (Seroquel) as Mono-Therapy or Adjunct to Lithium in the Treatment of Patients with Acute Mania in Bipolar Disorder. <https://clinicaltrials.gov/show/NCT00672490> => **no dose reported**
5. Naturalistic Study, Comparison of Divalproex Extended Release (ER) and Quetiapine for Adults with Acute Mania or Mixed Episodes.  
<https://clinicaltrials.gov/show/NCT00397020> => **no dose reported**
6. Adult Bipolar Mania. <https://clinicaltrials.gov/show/NCT00931723> => **Duplicated database**
7. Quetiapine Sr as Adjunctive Treatment In Mixed States of Bipolar Disorder. <https://clinicaltrials.gov/show/NCT01195363> => **no dose reported**
8. Week Trial to Study the Safety of Asenapine When Added to Lithium or Valproate in the Treatment of Bipolar Disorder (A7501009)(P05786). <https://clinicaltrials.gov/show/NCT00145509> => **no outcome of interest**
9. Study to Evaluate the Efficacy and Safety of Aripiprazole Administered With Lithium or Valproate Over 12 Weeks in the Treatment of Mania in Bipolar I Disorder. <https://clinicaltrials.gov/show/NCT00665366> => **no outcome of interest**

10. A Multicenter, Investigative Study of the Safety and Efficacy of Extended Administration of Aripiprazole in Combination With Mood Stabilizer for the Treatment of Patients With Bipolar Disorder Experiencing a Manic or Mixed Episode. <https://clinicaltrials.gov/show/NCT00606320>=> **no outcome of interest**
11. Multicenter Investigative Study of the Safety and Efficacy of Long-term Administration of Aripiprazole in Combination With Mood Stabilizer for the Treatment of Patients With Bipolar Disorder Experiencing a Manic or Mixed Episode. <https://clinicaltrials.gov/show/NCT00606229>=> **no outcome of interest**
12. 3-week Study to Evaluate Efficacy and Safety of Ziprasidone with Either Lithium or Divalproex in Acutely Manic Subjects. <https://clinicaltrials.gov/show/NCT00312494>=> **no outcome of interest**

**Appendix 3.** Formula of Efficacy-adjusted weighted mean dose method for antipsychotic dose equivalence

Formula

$$\text{Log}((\text{WMD}_A/\text{WMD}_B)*W)=\text{SMD}_{\text{Drug A-Drug B}}$$

$$\text{Eq}=1/W$$

$\text{WMD}_A$  : weighted mean dose of drug A

$\text{WMD}_B$  : weighted mean dose of drug B

$\text{SMD}_{\text{Drug A-Drug B}}$ : the difference of drug A versus drug (positive value indicates that A is superior to B)

W: coefficient

Eq: the dose equivalence of drug A to drug B

Example: Haloperidol equivalent to 1 mg olanzapine (without significantly different efficacy)

$\text{Log}((10.15/14.89)*W)=0$  (because these two drug did not significantly differ in SMD, we set this value as zero)

$\text{Eq}=1/W=0.68$  (0.68 mg of haloperidol is equivalent to 1 mg of olanzapine)

Example: Risperidone equivalent to 1 mg olanzapine (without efficacy-adjusted)

$\text{Log}((4.72/14.89)*W)=0$  (without efficacy-adjusted)

$\text{Eq}=0.32$

$\text{Log}((4.72/14.89)*W)=0.22$  (with efficacy-adjusted; see League table (Figure 1))

$\text{Eq}=0.19$