

## RECOMENDACIÓN T.9

### BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES

#### Guía de Práctica Clínica Trastorno Bipolar en personas de 15 años y más - 2018

##### A. PREGUNTA CLÍNICA

En personas mayores con trastorno bipolar en fase de mantención ¿Se debe usar antipsicóticos atípicos como monoterapia en comparación a usar otro estabilizador del ánimo como monoterapia?

##### Análisis y definición de los componentes de la pregunta en formato PICO

**Población:** Personas mayores con trastorno bipolar en fase de mantención.

**Intervención:** Antipsicóticos atípicos como monoterapia.

**Comparación:** Otro estabilizador del ánimo como monoterapia.

**Desenlace (outcome):** Impacto clínico.

##### B. BÚSQUEDA DE EVIDENCIA

Se realizó una búsqueda general de revisiones sistemáticas asociadas al tema de “Bipolar affective disorder”. Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; PubMed; LILACS; CINAHL; PsycINFO; EMBASE; EPPI-Centre Evidence Library; 3ie Systematic Reviews and Policy Briefs Campbell Library; Clinical Evidence; SUPPORT Summaries; WHO institutional Repository for information Sharing; NICE public health guidelines and systematic reviews; ACP Journal Club; Evidencias en Pediatría; y The JBI Database of Systematic Reviews and implementation Reports. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un investigador experimentado resolvió cualquier discrepancia entre los distintos revisores. En caso de considerarse necesario, se integraron estudios primarios.

Seleccionadas las revisiones sistemáticas o estudios primarios asociadas a la temática, se clasificaron en función de las potenciales preguntas a las que daban respuesta. Al momento de definir la pregunta la evidencia ya se encontraba previamente clasificada según intervenciones comparadas. Los resultados se encuentran alojados en la plataforma Living Overview of the Evidence (L·OVE), sistema que permite la actualización periódica de la evidencia.

## C. SÍNTESIS DE EVIDENCIA

### Resumen de la evidencia identificada

Se identificaron 13 revisiones sistemáticas que incluyen 105 estudios primarios, de los cuales 104 corresponden a ensayos aleatorizados. Para más detalle ver “*Matriz de evidencia*”<sup>1</sup>, en el siguiente enlace: [Intervenciones para la manía aguda en el trastorno bipolar](#).

Tabla 1: Resumen de la evidencia seleccionada

Revisión Sistemática	13 [1-13]
Estudios primarios	104 [14-117] ensayos aleatorizados y 1 observacional [118]

### Estimador del efecto

Se realizó un análisis de la matriz de evidencia, observando que ninguna de las revisiones o estudios primarios analizan la población de interés (adultos mayores). Además, la pregunta presenta énfasis en los efectos adversos en esta población de mayor vulnerabilidad, por lo cual se consideró inapropiado presentar la evidencia indirecta desde cualquier adulto.

### Metanálisis

No aplica.

### Tabla de Resumen de Resultados (Summary of Findings)

ANTIPSICÓTICOS ATÍPICOS COMPARADO CON OTRO ESTABILIZADOR DEL ÁNIMO PARA TRASTORNO DEL BIPOLAR EN ADULTOS MAYORES			
Desenlaces	Efecto	Certeza de la evidencia (GRADE)	Mensajes clave en términos sencillos
Pacientes	Personas mayores con trastorno bipolar en fase de mantención.		
Intervención	Antipsicóticos atípicos como monoterapia.		
Comparación	Otro estabilizador del ánimo como monoterapia.		
Impacto clínico	No se encontraron estudios comparativos para esta población en específico (adultos mayores).	--	-
GRADE: Grados de evidencia Grading of Recommendations Assessment, Development and Evaluation.			
Fecha de elaboración de la tabla: Noviembre, 2018.			

<sup>1</sup> **Matriz de Evidencia**, tabla dinámica que grafica el conjunto de evidencia existente para una pregunta (en este caso, la pregunta del presente informe). Las filas representan las revisiones sistemáticas y las columnas los estudios primarios que estas revisiones han identificado. Los recuadros en verde corresponden a los estudios incluidos en cada revisión. La matriz se actualiza periódicamente, incorporando nuevas revisiones sistemáticas pertinentes y los respectivos estudios primarios.

## Referencias

1. Arbaizar B, Dierssen-Sotos T, Gómez-Acebo I, Llorca J. Aripiprazole in major depression and mania: meta-analyses of randomized placebo-controlled trials. *General hospital psychiatry*. 2009;31(5):478-83.
2. Brown R, Taylor MJ, Geddes J. Aripiprazole alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2013;12(12):CD005000.
3. Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2006;(3):CD004362.
4. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar disorders*. 2010;12(2):116-41.
5. Goikolea JM, Colom F, Torres I, Capapey J, Valentí M, Undurraga J, Grande I, Sanchez-Moreno J, Vieta E. Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol. *Journal of affective disorders*. 2013;144(3):191-8.
6. Jones RM, Thompson C, Bitter I. A systematic review of the efficacy and safety of second generation antipsychotics in the treatment of mania. *European psychiatry : the journal of the Association of European Psychiatrists*. 2006;21(1):1-9.
7. Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. Valproate for acute mood episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*. 2003;(1):CD004052.
8. Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW, Yatham LN. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. *Journal of affective disorders*. 2013;150(2):408-14.
9. Rendell JM, Gijsman HJ, Bauer MS, Goodwin GM, Geddes GR. Risperidone alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2006;(1):CD004043.
10. Rendell JM, Gijsman HJ, Keck P, Goodwin GM, Geddes JR. Olanzapine alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2003;(1):CD004040.
11. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of general psychiatry*. 2007;64(4):442-55.
12. Tamayo JM, Zarate CA, Vieta E, Vázquez G, Tohen M. Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: a systematic review and meta-analysis. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2010;13(6):813-32.
13. Yildiz A, Nikodem M, Vieta E, Correll CU, Baldessarini RJ. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. *Psychological medicine*. 2015;45(2):1-19.
14. 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.
15. Bastrup PC, Alhfors UG, Bjørkenstedt L, Dencker SJ, Fensbo C, Gravem A, Pedersen V, Elgen K, Brekke B, Fredslund-Andersen K. A controlled Nordic multicentre study of zuclopentixol acetate in oil solution, haloperidol and zuclopentixol in the treatment of acute psychosis. *Acta psychiatica Scandinavica*. 1993;87(1):48-58.
16. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *International clinical psychopharmacology*. 1999;14(6):339-43.
17. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *The Journal of clinical psychiatry*. 2007;68(6):843-53.
18. Berwaeerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *Journal of affective disorders*. 2012;136(1-2):e51-60.
19. BOLDER 1. Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, Suppes T. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. *The Journal of clinical psychiatry*. 2008;69(5):769-82.
20. BOLDER 2. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR, BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *Journal of clinical psychopharmacology*. 2006;26(6):600-9.

21. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vågerö M, Svensson K. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *The Journal of clinical psychiatry*. 2005;66(1):111-21.
22. Bowden CL, Janicak PG, Orsulak P, Swann AC, Davis JM, Calabrese JR, Goodnick P, Small JG, Rush AJ, Kimmel SE, Risch SC, Morris DD. Relation of serum valproate concentration to response in mania. *The American journal of psychiatry*. 1996;153(6):765-70.
23. Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA, Abi-Saab W, Saltarelli M, Depakote ER Mania Study Group. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *The Journal of clinical psychiatry*. 2006;67(10):1501-10.
24. Brecher M, Huizar K. Quetiapine monotherapy for acute mania associated with bipolar disorder. 2003;
25. Bristol Myers-Squibb. 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. Registry of Clinical Trials. 2013;
26. Brown D, Silverstone T, Cookson J. Carbamazepine compared to haloperidol in acute mania. *International clinical psychopharmacology*. 1989;4(3):229-38.
27. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *The Journal of clinical psychiatry*. 1999;60(2):79-88.
28. Calabrese JR, Keck Jr. PE, Starace A, Lu K, Ruth A, Laszlovszky I, Nemeth G, Durgam S. Efficacy and safety of low- and high-dose cariprazine in patients with acute mania associated with bipolar I disorder. *European Neuropsychopharmacology*. 2013;23(Suppl 2):S378–S379.
29. Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *The American journal of psychiatry*. 2005;162(7):1351-60.
30. Clothier J, Swann AC, Freeman T. Dysphoric mania. *Journal of Clinical Psychopharmacology*. 1996;12:13-6.
31. CN138-007. El Mallakh RS, Vieta E, Rollin L, Marcus R, Carson WH, McQuade R. A comparison of two fixed doses of aripiprazole with placebo in acutely relapsed, hospitalized patients with bipolar disorder I (manic or mixed) in subpopulations (CN138-007). *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2010;20(11):776-83.
32. Cutler AJ, Datto C, Nordenhem A, Minkwitz M, Acevedo L, Darko D. Extended-release quetiapine as monotherapy for the treatment of adults with acute mania: a randomized, double-blind, 3-week trial. *Clinical therapeutics*. 2011;33(11):1643-58.
33. DelBello MP, Findling RL, Acevedo LD, Stankowski J. Efficacy of quetiapine in children and adolescents with bipolar mania: a 3-week double-blind, randomized, placebo-controlled trial. 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry. 2007;
34. DelBello MP, Findling RL, Kushner S, Wang D, Olson WH, Capece JA, Fazzio L, Rosenthal NR. A pilot controlled trial of topiramate for mania in children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005;44(6):539-47.
35. DelBello MP, Findling RL, Wang PP, Grundapaneni B, Versavel M. Efficacy and safety of ziprasidone in pediatric bipolar disorder. 63rd Annual Meeting of the Society of Biological Psychiatry. 2008;
36. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, Nelson E, Strakowski SM. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006;45(3):305-13.
37. Delbello MP, Schwiers ML, Rosenberg HL, Strakowski SM. A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002;41(10):1216-23.
38. El-Mallakh RS, Marcus R, Baudelet C, McQuade R, Carson WH, Owen R. A 40-week double-blind aripiprazole versus lithium follow-up of a 12-week acute phase study (total 52 weeks) in bipolar I disorder. *Journal of affective disorders*. 2012;136(3):258-66.
39. Fensbo, C. Zuclopentixol acetate, haloperidol, and zuclopentixol in the treatment of acutely psychotic patients: A controlled multicenter study. *Nordisk Psykiatrisk Tidsskrift*. 1990;44(3):295-7.
40. Forest Laboratories. Safety and Efficacy of Cariprazine for Mania. clinicaltrials.gov. 2010;
41. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. *Journal of affective disorders*. 1980;2(4):279-88.

42. GlaxoSmithKline. A 3 Week Multicenter, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of LAMICTAL (lamotrigine) Compared to Placebo in the Treatment of An Acute Manic or Mixed Episode in Patients who have Bipolar Disorder (GSK Study ID: SCAA2008). GSK Study Register. 1999;
43. Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM. Lamotrigine: a review of its use in bipolar disorder. *Drugs.* 2003;63(19):2029-50.
44. Gopal S, Steffens D, Kramer ML, Olsen MK. Mania remission rates in a randomized controlled trial of risperidone. Fifth International Conference on Bipolar Disorders. 2003;
45. Gopal S, Steffens DC, Kramer ML, Olsen MK. Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy. *The Journal of clinical psychiatry.* 2005;66(8):1016-20.
46. Haas M, Delbello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, Quiroz J, Kusumakar V. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. *Bipolar disorders.* 2009;11(7):687-700.
47. HGEH Trial, 1999. Tohen M, Sanger TM, McElroy SL, Tollefson GD, Chengappa KN, Daniel DG, Petty F, Centorrino F, Wang R, Grundy SL, Greaney MG, Jacobs TG, David SR, Toma V. Olanzapine versus placebo in the treatment of acute mania. Olanzapine HGEH Study Group. *The American journal of psychiatry.* 1999;156(5):702-9.
48. HGFU Trial 2002. Tohen M, Chengappa KN, Suppes T, Zarate CA, Calabrese JR, Bowden CL, Sachs GS, Kupfer DJ, Baker RW, Risser RC, Keeter EL, Feldman PD, Tollefson GD, Breier A. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Archives of general psychiatry.* 2002;59(1):62-9.
49. HGGW Trial 2000. Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, Sanger T, Risser R, Zhang F, Toma V, Francis J, Tollefson GD, Breier A. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group. *Archives of general psychiatry.* 2000;57(9):841-9.
50. HGHD Trial 2002. Tohen M, Zhang F, Feldman PD, Evans AR, Breier AF. Olanzapine versus haloperidol treatment of acute mania. Annual Meeting of the American Psychiatric Association, New Orleans. 2001;
51. HGHQ Trial 2002. Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, Milton DR, Risser R, Gilmore JA, Breier A, Tollefson GA. Olanzapine versus divalproex in the treatment of acute mania. *The American journal of psychiatry.* 2002;159(6):1011-7.
52. Hirschfeld RM, Allen MH, McEvoy JP, Keck PE, Russell JM. Safety and tolerability of oral loading divalproex sodium in acutely manic bipolar patients. *The Journal of clinical psychiatry.* 1999;60(12):815-8.
53. Hirschfeld RM, Bowden CL, Vigna NV, Wozniak P, Collins M. A randomized, placebo-controlled, multicenter study of divalproex sodium extended-release in the acute treatment of mania. *The Journal of clinical psychiatry.* 2010;71(4):426-32.
54. Hirschfeld RM, Keck PE, Kramer M, Karcher K, Canuso C, Eerdeken M, Grossman F. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *The American journal of psychiatry.* 2004;161(6):1057-65.
55. Houston JP, Tohen M, Degenhardt EK, Jamal HH, Liu LL, Ketter TA. Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes: a double-blind, placebo-controlled study. *The Journal of clinical psychiatry.* 2009;70(11):1540-7.
56. Janicak PG, Sharma RP, Pandey G, Davis JM. Verapamil for the treatment of acute mania: a double-blind, placebo-controlled trial. *The American journal of psychiatry.* 1998;155(7):972-3.
57. Kakkar AK, Rehan HS, Unni KE, Gupta NK, Chopra D, Kataria D. Comparative efficacy and safety of oxcarbazepine versus divalproex sodium in the treatment of acute mania: a pilot study. *European psychiatry : the journal of the Association of European Psychiatrists.* 2009;24(3):178-82.
58. Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. Efficacy and safety of olanzapine in the treatment of Japanese patients with bipolar I disorder in a current manic or mixed episode: a randomized, double-blind, placebo- and haloperidol-controlled study. *Journal of affective disorders.* 2012;136(3):476-84.
59. Keck PE, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, Ingenito G, Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *The American journal of psychiatry.* 2003;160(9):1651-8.
60. Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K, Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *The American journal of psychiatry.* 2003;160(4):741-8.

61. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekkens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *The British journal of psychiatry : the journal of mental science.* 2005;187:229-34.
62. Knesevich M, Papadakis K, Bose A, Andor G, Laszlovszky I. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *European Neuropsychopharmacology.* 2009;19(suppl 3):S469.
63. Kowatch RA, Findling RL, Scheffer RE, Stanford K. Pediatric bipolar collaborative mood stabilizer trial. 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry. 2007;
64. Kudo Y, Ichimaru S, Kawakita Y, Saito M, et al.. Comparison of therapeutic effect on mania of sultopride hydrochloride with haloperidol using double-blind technique. 1987;
65. Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar disorders.* 2006;8(1):15-27.
66. Lenox RH, Newhouse PA, Creelman WL, Whitaker TM. Adjunctive treatment of manic agitation with lorazepam versus haloperidol: a double-blind study. *The Journal of clinical psychiatry.* 1992;53(2):47-52.
67. Li H, Ma C, Wang G, Zhu X, Peng M, Gu N. Response and remission rates in Chinese patients with bipolar mania treated for 4 weeks with either quetiapine or lithium: a randomized and double-blind study. *Current medical research and opinion.* 2008;24(1):1-10.
68. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *Journal of clinical psychopharmacology.* 2008;28(2):156-65.
69. McElroy SL, Keck PE, Stanton SP, Tugrul KC, Bennett JA, Strakowski SM. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. *The Journal of clinical psychiatry.* 1996;57(4):142-6.
70. McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J. Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology.* 2005;15(5):573-85.
71. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar disorders.* 2009;11(7):673-86.
72. McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of affective disorders.* 2010;122(1-2):27-38.
73. McQuade RD, Marcus R, Sanchez R. Aripiprazole vs placebo in acute mania: safety and tolerability pooled analysis. 5th International Conference on Bipolar Disorder. 2003;
74. Müller-Oerlinghausen B, Retzow A, Henn FA, Giedke H, Walden J. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. European Valproate Mania Study Group. *Journal of clinical psychopharmacology.* 2000;20(2):195-203.
75. Niufan G, Tohen M, Qiuqing A, Fude Y, Pope E, McElroy H, Ming L, Gaohua W, Xinbao Z, Huichun L, Liang S. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *Journal of affective disorders.* 2008;105(1-3):101-8.
76. Novartis. Randomized, double-blind, placebo-controlled multicenter study to evaluate efficacy and tolerability of licabazepine 1000-2000 mg/d in the treatment of manic episodes of bipolar I disorder over 3 weeks. Study ID Number: CLIC477D2301. Novartis Clinical Trial Results Database. 2007;
77. Pal Singh G. A double-blind comparative study of clinical efficacy of verapamil versus lithium in acute mania. *International journal of psychiatry in clinical practice.* 2008;12(4):303-8.
78. Perlis RH, Baker RW, Zarate CA, Brown EB, Schuh LM, Jamal HH, Tohen M. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. *The Journal of clinical psychiatry.* 2006;67(11):1747-53.
79. Pope HG, McElroy SL, Keck PE, Hudson JI. Valproate in the treatment of acute mania. A placebo-controlled study. *Archives of general psychiatry.* 1991;48(1):62-8.
80. Potkin SG, Keck PE, Segal S, Ice K, English P. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *Journal of clinical psychopharmacology.* 2005;25(4):301-10.

81. Sachs G, Chengappa KN, Suppes T, Mullen JA, Brecher M, Devine NA, Sweitzer DE. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. *Bipolar disorders*. 2004;6(3):213-23.
82. Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Impellizzeri C, Kaplita S, Rollin L, Iwamoto T, Aripiprazole Study Group. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *Journal of psychopharmacology (Oxford, England)*. 2006;20(4):536-46.
83. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *The American journal of psychiatry*. 2002;159(7):1146-54.
84. Sanchez R, Bourin M, Auby P, Swanik R, Marcus R, McQuade RD, et al.. Fifth International Conference on Bipolar Disorder. 2003;3509
85. SCA40910. Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, Monaghan ET, Leadbetter RA. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar disorders*. 2008;10(2):323-33.
86. SCAA2010. Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, Monaghan ET, Leadbetter RA. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar disorders*. 2008;10(2):323-33.
87. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clinical neuropharmacology*. 1998;21(3):176-80.
88. Shafti SS. Olanzapine vs. lithium in management of acute mania. *Journal of affective disorders*. 2010;122(3):273-6.
89. Shopsin B, Gershon S, Thompson H, Collins P. Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine, and haloperidol. *Archives of general psychiatry*. 1975;32(1):34-42.
90. Small JG, Klapper MH, Marhenke JD, Milstein V, Woodham GC, Kellams JJ. Lithium combined with carbamazepine or haloperidol in the treatment of mania. *Psychopharmacology bulletin*. 1995;31(2):265-72.
91. Small JG, Klapper MH, Milstein V, Kellams JJ, Miller MJ, Marhenke JD, Small IF. Carbamazepine compared with lithium in the treatment of mania. *Archives of general psychiatry*. 1991;48(10):915-21.
92. Smulevich AB, Khanna S, Eerdekkens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2005;15(1):75-84.
93. Suppes T, Eudicone J, McQuade R, Pikalov A, Carlson B. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. *Journal of affective disorders*. 2008;107(1-3):145-54.
94. Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, Carson WH, Marcus RN, Owen R. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *Journal of clinical psychopharmacology*. 2008;28(1):13-20.
95. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, Azorin JM, Vieta E, Hardy-Bayle MC, Lawson WB, Emsley RA, Zhang F, Baker RW, Risser RC, Namjoshi MA, Evans AR, Breier A. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Archives of general psychiatry*. 2003;60(12):1218-26.
96. Tohen M, Kryzhanovskaya L, Carlson G, Delbello M, Wozniak J, Kowatch R, Wagner K, Findling R, Lin D, Robertson-Plouch C, Xu W, Dittmann RW, Biederman J. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *The American journal of psychiatry*. 2007;164(10):1547-56.
97. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tolleson GD, Breier A. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of general psychiatry*. 2003;60(11):1079-88.
98. Tohen M, Vieta E, Goodwin GM, Sun B, Amsterdam JD, Banov M, Shekhar A, Aaronson ST, Bardenstein L, Grecu-Gabos I, Tochilov V, Prelipceanu D, Oliff HS, Kryzhanovskaya L, Bowden C. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *The Journal of clinical psychiatry*. 2008;69(11):1776-89.
99. Tramontina S, Zeni CP, Ketzer CR, Pheula GF, Narvaez J, Rohde LA. Aripiprazole in children and adolescents with bipolar disorder comorbid with attention-deficit/hyperactivity disorder: a pilot randomized clinical trial. *The Journal of clinical psychiatry*. 2009;70(5):756-64.
100. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology*. 2000;150(1):15-23.

101. Vieta E, Bourin M, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, Abou-Gharbia N, Swanink R, Iwamoto T, Aripiprazole Study Group. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *The British journal of psychiatry : the journal of mental science*. 2005;187:235-42.
102. Vieta E, Nuamah IF, Lim P, Yuen EC, Palumbo JM, Hough DW, Berwaerts J. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar disorders*. 2010;12(3):230-43.
103. Vieta E, Ramey T, Keller D, English PA, Loebel AD, Miceli J. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. *Journal of psychopharmacology (Oxford, England)*. 2010;24(4):547-58.
104. Vieta E, T'joen C, McQuade RD, Carson WH, Marcus RN, Sanchez R, Owen R, Nameche L. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *The American journal of psychiatry*. 2008;165(10):1316-25.
105. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, D'Souza J, Wamil A, Lehman RB, Berv D, Linden D. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *The American journal of psychiatry*. 2006;163(7):1179-86.
106. Wagner KD, Redden L, Kowatch RA, Wilens TE, Segal S, Chang K, Wozniak P, Vigna NV, Abi-Saab W, Saltarelli M. A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009;48(5):519-32.
107. Weisler RH, Dunn J, English P. Ziprasidone in adjunctive treatment of acute bipolar mania: a randomized, placebo-controlled trial. *16th Congress of the European College of Neuropsychopharmacology*. 2003;
108. Weisler RH, Kalali AH, Ketter TA, SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *The Journal of clinical psychiatry*. 2004;65(4):478-84.
109. Weisler RH, Keck PE, Swann AC, Cutler AJ, Ketter TA, Kalali AH, SPD417 Study Group. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry*. 2005;66(3):323-30.
110. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. *The British journal of psychiatry : the journal of mental science*. 2003;182:141-7.
111. Yatham LN, Paulsson B, Mullen J, Vågerö AM. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. *Journal of clinical psychopharmacology*. 2004;24(6):599-606.
112. Yildiz A, Guleryuz S, Ankerst DP, Ongür D, Renshaw PF. Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Archives of general psychiatry*. 2008;65(3):255-63.
113. Young AH, Oren DA, Lowy A, McQuade RD, Marcus RN, Carson WH, Spiller NH, Torbevens AF, Sanchez R. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *The British journal of psychiatry : the journal of mental science*. 2009;194(1):40-8.
114. Youngstrom E, Zhao J, Mankoski R, Forbes RA, Marcus RM, Carson W, McQuade R, Findling RL. Clinical significance of treatment effects with aripiprazole versus placebo in a study of manic or mixed episodes associated with pediatric bipolar I disorder. *Journal of child and adolescent psychopharmacology*. 2013;23(2):72-9.
115. Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *The Journal of clinical psychiatry*. 2002;63(12):1148-55.
116. Zajecka JM, Weisler, Swann A. Divalproex sodium vs. olanzapine for the treatment of mania in bipolar disorder. *39th ACNP Annual Meeting*, San Juan, Puerto Rico. 2000;
117. Zarate CA, Singh JB, Carlson PJ, Quiroz J, Jolkovsky L, Luckenbaugh DA, Manji HK. Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar disorders*. 2007;9(6):561-70.
118. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, Emslie GJ, Weinberg WA, Rush AJ. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000;39(6):713-20.