Supplementary Appendix 1.

There was only one study on divalproex, so we did not perform a subgroup analysis for this drug. Only 1 or 2 studies on each SGA were included in the meta-analysis, so we did not compare individual SGA drugs to placebo. Therefore, we classified SGA trials into subgroups according to drug formulation (i.e., LAI-SGAs vs. OSGAs). Five studies (Bowden et al., 2000; Bowden et al., 2003; Calabrese et al., 2003; Vieta et al., 2012; Weisler et al., 2011) examined two drug that could not be classified in the same subgroup (e.g., LAI-SGA and OSGAs). We did not perform subgroup analysis versus the placebo group because there were few studies classified into LAI-SGAs, lithium, and lamotrigine subgroups ($\leq$ 2 studies, see Supplementary Table 4). Although there were 15 enrichment studies in total, there were only two enrichment studies on lithium, which otherwise was the subject of the largest number of studies. All SGA studies other than one olanzapine study (Vieta et al., 2012) and all lamotrigine studies used an enriched design. Therefore, we also did not perform subgroup analysis stratified by study design (enrichment vs. without enrichment).

Bowden, C.L., Calabrese, J.R., McElroy, S.L., Gyulai, L., Wassef, A., Petty, F., Pope, H.G., Jr., Chou, J.C., Keck, P.E., Jr., Rhodes, L.J., Swann, A.C., Hirschfeld, R.M., Wozniak, P.J., 2000. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry 57, 481-489.

Bowden, C.L., Calabrese, J.R., Sachs, G., Yatham, L.N., Asghar, S.A., Hompland, M., Montgomery, P., Earl, N., Smoot, T.M., DeVeaugh-Geiss, J., Lamictal 606 Study, G., 2003. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 60, 392-400.

Calabrese, J.R., Bowden, C.L., Sachs, G., Yatham, L.N., Behnke, K., Mehtonen, O.P., Montgomery, P., Ascher, J., Paska, W., Earl, N., DeVeaugh-Geiss, J., Lamictal 605 Study, G., 2003. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 64, 1013-1024.

Vieta, E., Montgomery, S., Sulaiman, A.H., Cordoba, R., Huberlant, B., Martinez, L., Schreiner, A., 2012. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Neuropsychopharmacol 22, 825-835.

Weisler, R.H., Nolen, W.A., Neijber, A., Hellqvist, A., Paulsson, B., Trial 144 Study, I., 2011. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). J Clin Psychiatry 72, 1452-1464.

Supplementary Figure 1. Flow diagram of the literature search

The authors searched Embase, PubMed, and the Cochrane Central Register of Controlled Trials for studies published prior to May 22, 2020. The search terms were (bipolar disorder OR mania OR manic OR hypomania OR hypo-mania OR rapid cycle OR rapid-cycle OR bipolar depression OR affective) AND (randomized OR random OR randomly) AND (depot OR decanoate OR enanthate OR long-acting injectable OR microsphere OR once monthly OR palmitate OR pamoate OR valproic acid OR valproate OR divalproate OR divalproex OR carbamazepine OR oxcarbazepine OR risperidone OR olanzapine OR aripiprazole OR quetiapine OR perospirone OR ziprasidone OR clozapine OR amisulpride OR asenapine OR blonanserin OR clothiapine OR iloperidone OR lurasidone OR mosapramine OR paliperidone OR remoxipride OR sertindole OR sulpiride OR tiapride OR chlorpromazine OR thioridazine OR mesoridazine OR loxapine OR molindone OR perphenazine OR thiothixene OR trifluoperazine OR haloperidol OR fluphenazine OR droperidol OR zuclopenthixol OR pimozide OR flupenthixol OR prochlorperazine OR lithium OR lamotrigine) AND (placebo).

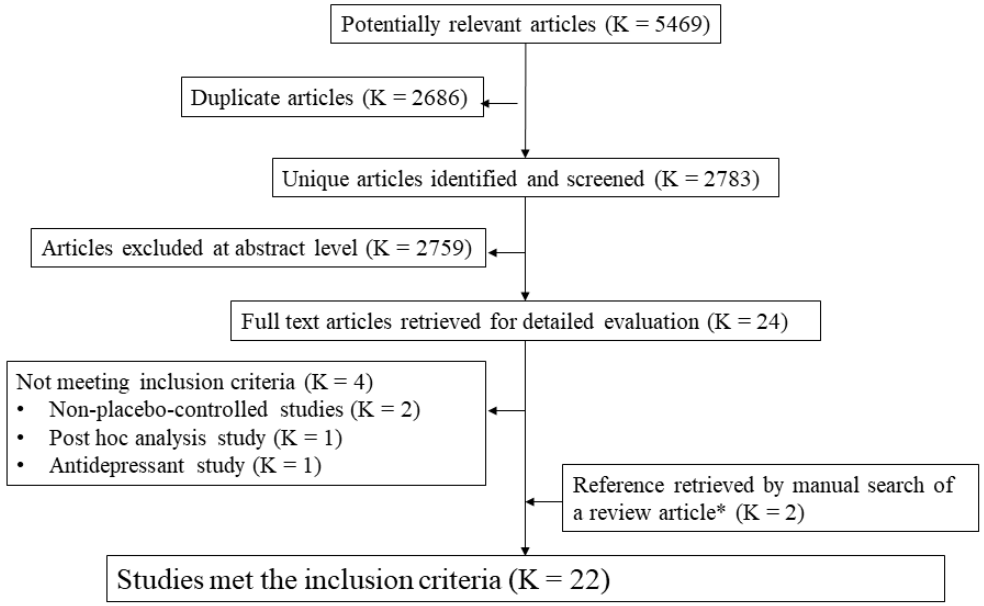
<u>Not meet inclusion criteria (K = 4)</u>

Altamura, A. C., Russo, M., Vismara, S. & Mundo, E. (2004). Comparative evaluation of olanzapine efficacy in the maintenance treatment of bipolar disorder. J Clin Psychopharmacol 24, 454-6. (non-placebo-controlled study)

Amsterdam JD, & Shults J. (2005) Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study.
Int Clin Psychopharmacol. Sep;20(5):257-64. (antidepressant study)

Amsterdam, J. D., Lorenzo-Luaces, L., Soeller, I., Li, S. Q., Mao, J. J. & DeRubeis, R. J. (2015). Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. J Affect Disord 185, 31-7. (non-placebo-controlled study)

McIntyre, R. S., Cohen, M., Zhao, J., Alphs, L., Macek, T. A. & Panagides, J. (2010). Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord 126, 358-65. (post hoc study)



Reference retrieved by manual search of a review article * (K = 2)

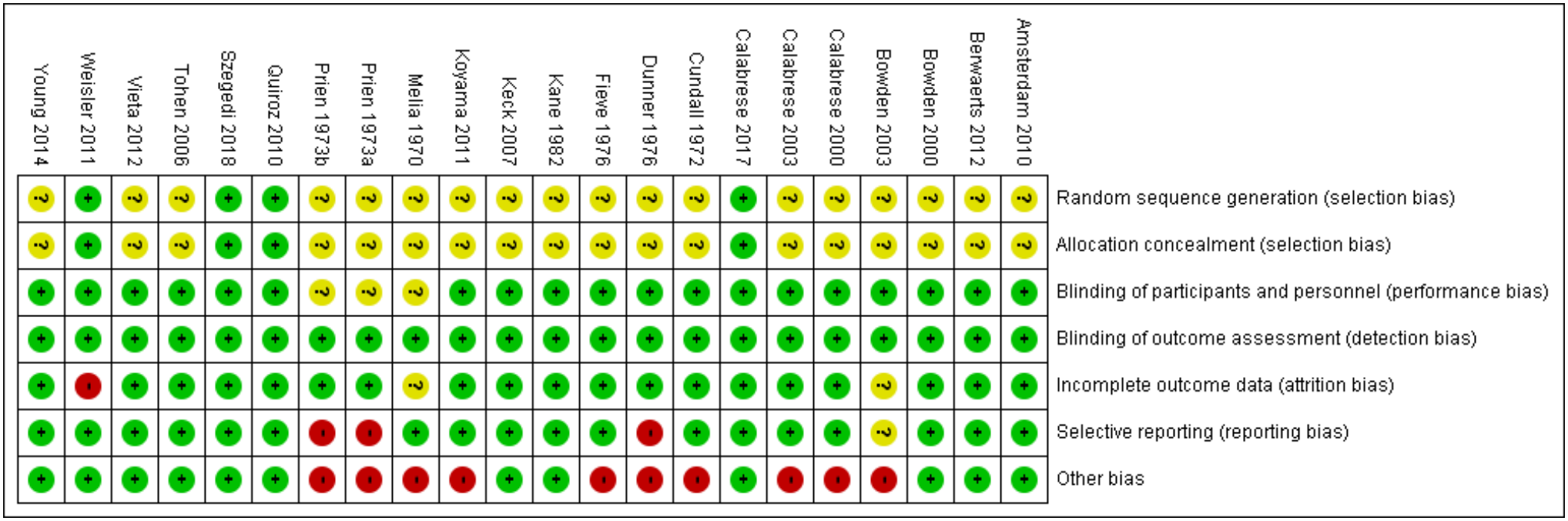
Cundall, R. L., Brooks, P. W. & Murray, L. G. (1972). A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med 2, 308-11.

Melia, P. I. (1970). Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry 116, 621-4.

*Review article

Miura, T., Noma, H., Furukawa, T. A., Mitsuyasu, H., Tanaka, S., Stockton, S., Salanti, G., Motomura, K., Shimano-Katsuki, S., Leucht, S., Cipriani, A., Geddes, J. R. & Kanba, S. (2014). Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 1, 351-9.

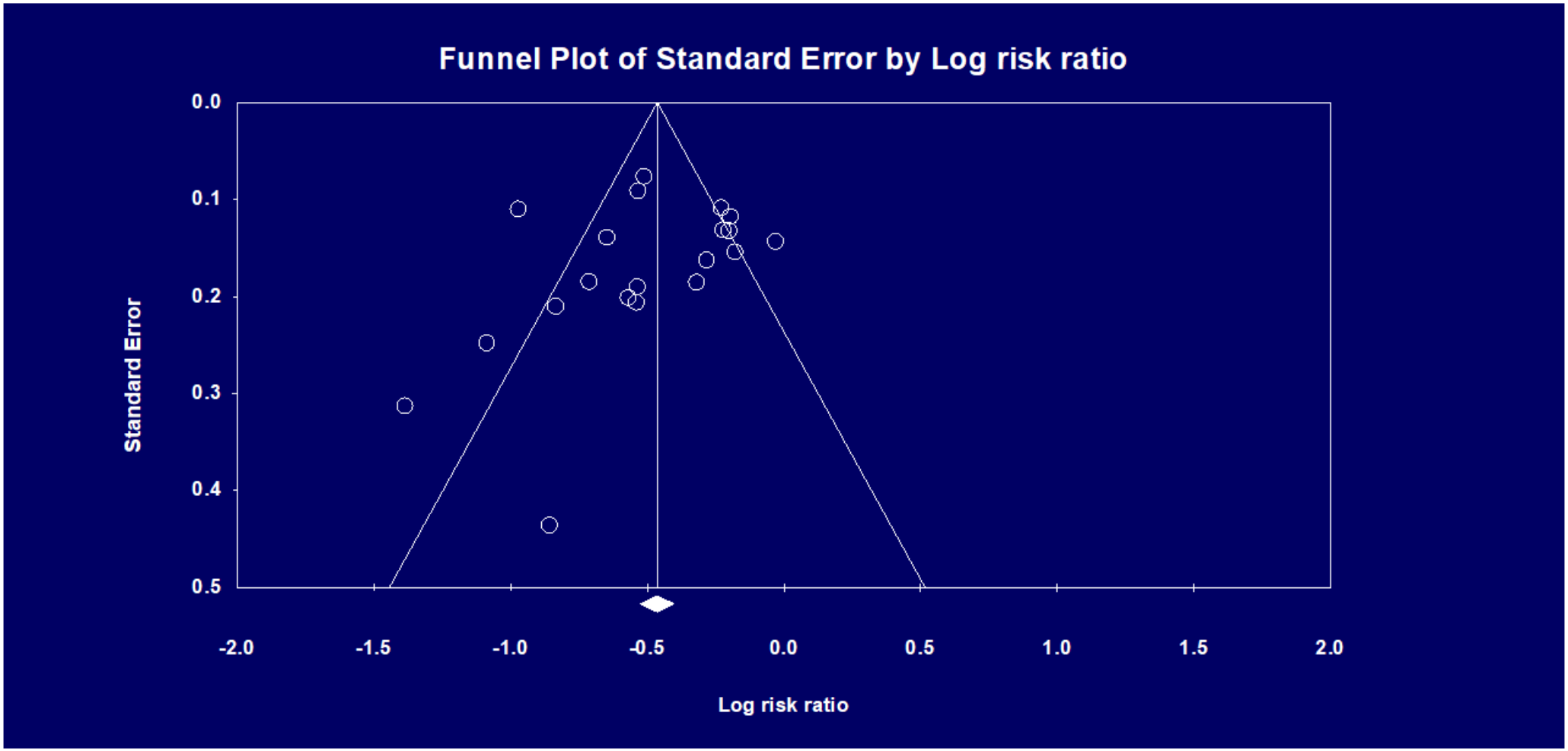
Supplementary Figure 2. Risk of bias summary



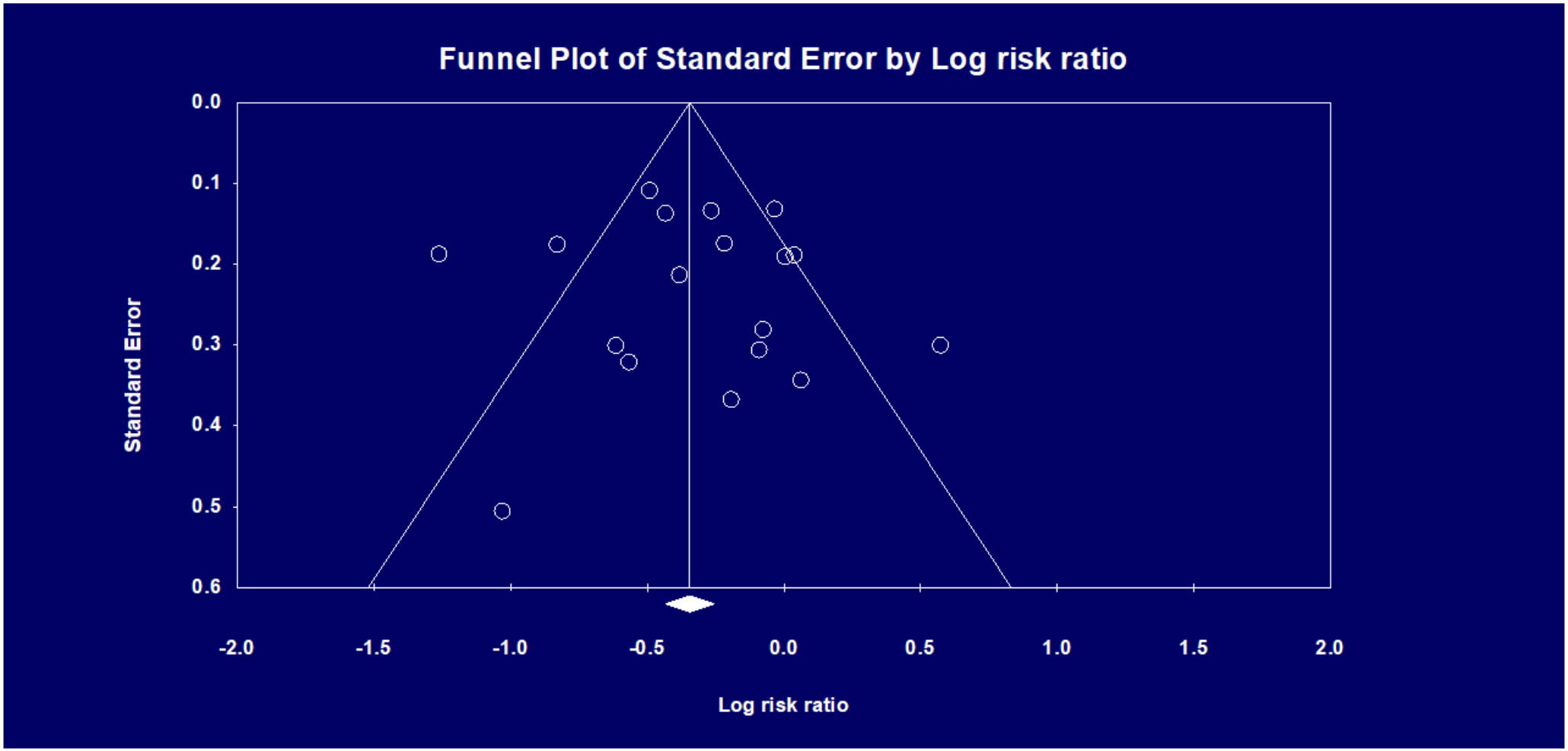
Other bias: insufficient assessment of recurrent of mood episode

Supplementary Figure 3. Funnel plot and Egger's regression test

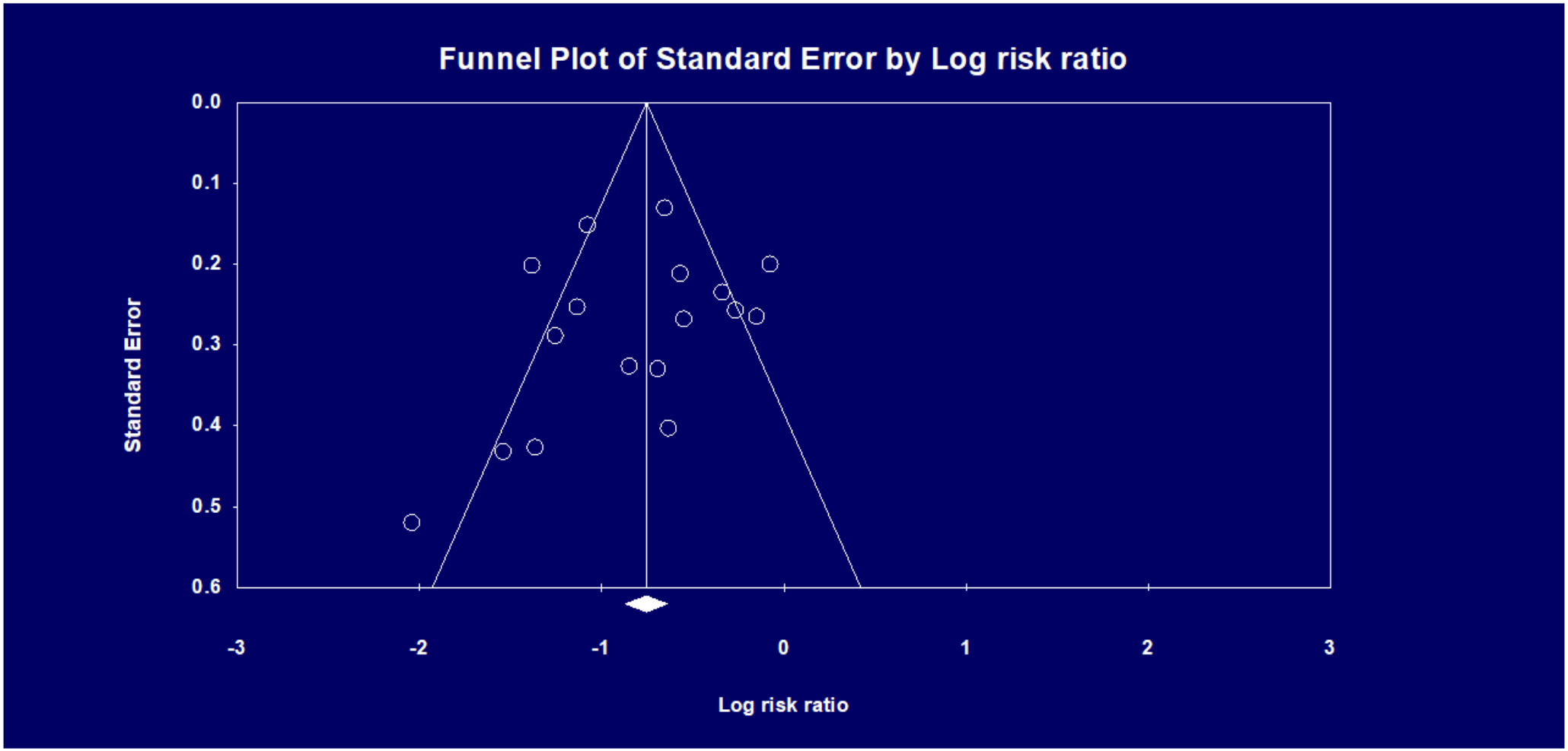
Recurrence of any mood episode at 6 months (Egger's regression: p = 0.348)



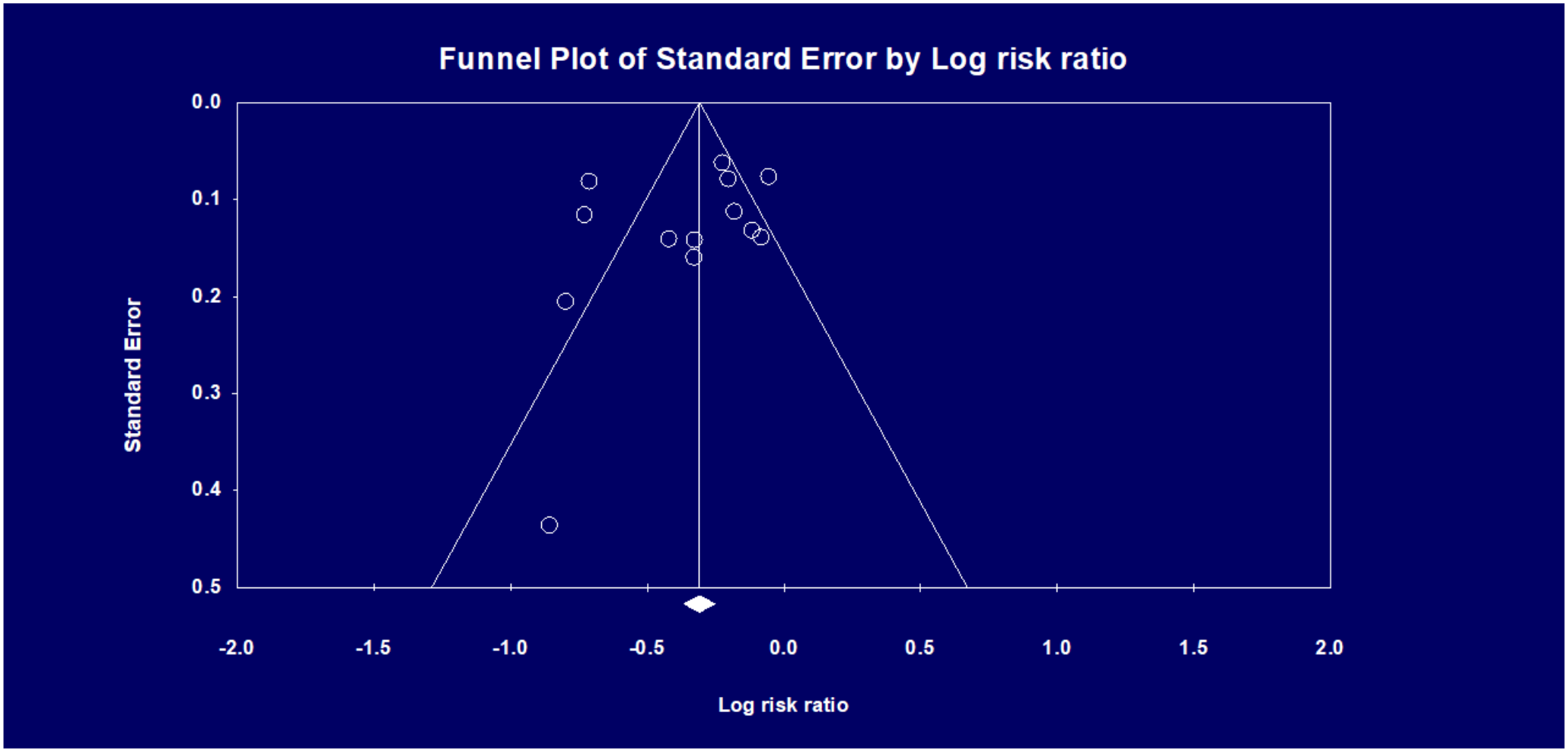
Recurrence of depressive episodes at 6 months (Egger's regression: p = 0.711)



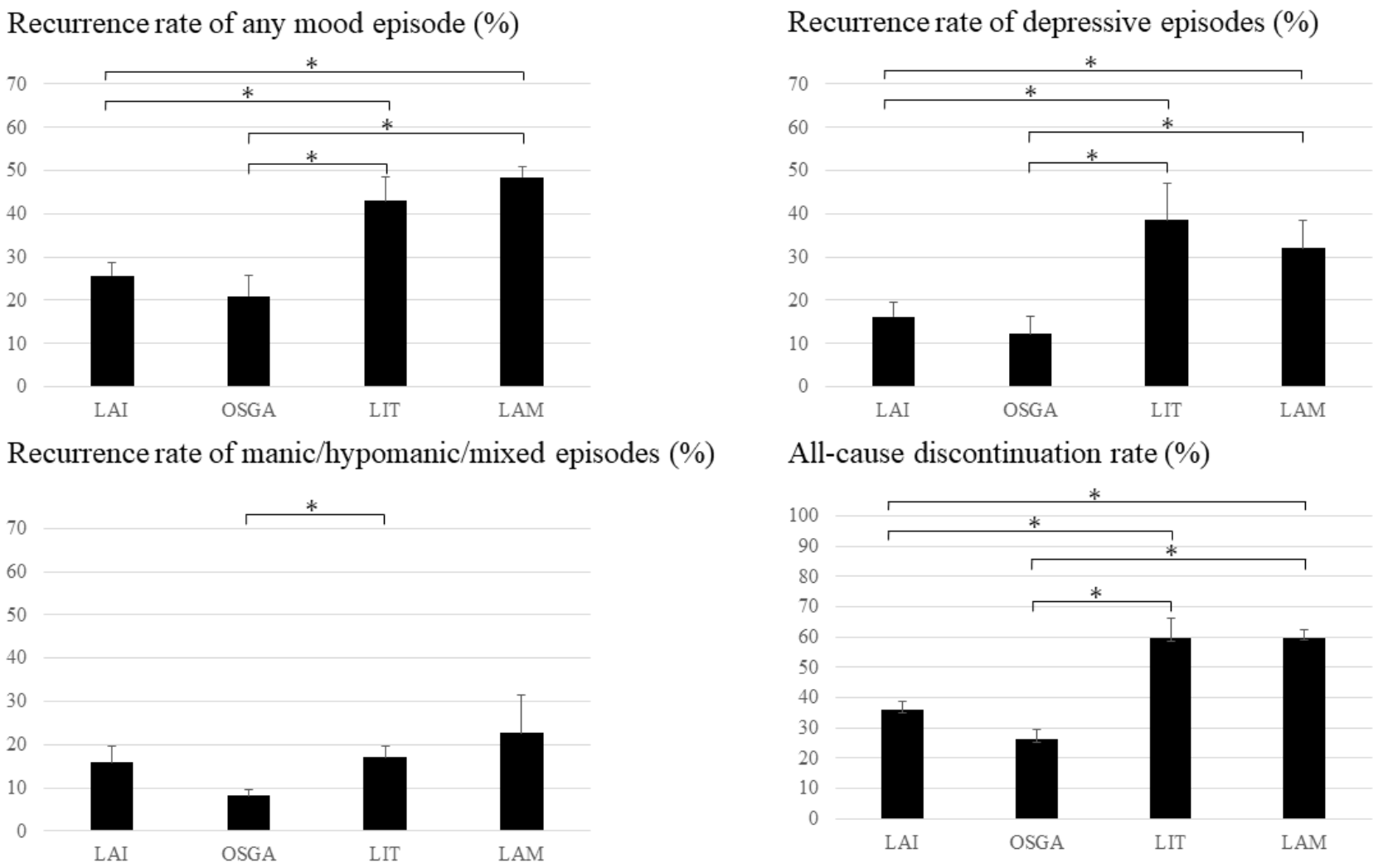
Recurrence rate of mania/hypomania/mixed episodes at 6 months (Egger's regression: p = 0.423)



All-cause discontinuation 6 months (Egger's regression: p = 0.359)



Supplementary Figure 4. Pooled event rates in the maintenance subgroups stratified by assigned drug(s)



*Adjusted p after False Discovery Rate (Benjamini–Hochberg method) < 0.05

Error bar represents standard error.

LAI: long-acting injection-second generation antipsychotic, LAM: lamotrigine, LIT: lithium, OSGA: oral second generation antipsychotics

Supplementary Table 1. Half-lives of drugs included in the meta-analysis

Oral risperidone	The apparent half-life of risperidone is 3 hours. The apparent half-life of 9-hydroxyrisperidone is about 21 hours.
Risperidone-LAI	The apparent half-life of risperidone plus 9-hydroxyrisperidone following risperidone-LAI administration is 3 to 6 days. The elimination phase is complete approximately 7 to 8 weeks after the last injection.
Oral aripiprazole	The apparent half-life of aripiprazole is 75 hours. The apparent half-life of dehydro-aripiprazole is about 94 hours.
Aripiprazole-LAI	The mean aripiprazole terminal elimination half-life is 29.9 days and 46.5 days after every 4-week injection of aripiprazole-LAI 300 mg and 400 mg, respectively
Olanzapine	The half-life ranges of olanzapine are 21 to 54 hours (5th to 95th percentile; mean of 30 hours). The apparent plasma clearance ranges are 12 to 47 L/ hour (5th to 95th percentile; mean of 25 L/hour).
Paliperidone	The terminal elimination half-life of paliperidone is approximately 23 hours.
Quetiapine IR	Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range.
Lamotrigine	The terminal elimination half-life of lamotrigine is approximately 32.8 (single-dose) or 25.4 (multiple-dose) hours.
Lithium	The elimination half-life of lithium is approximately 18 to 36 hours.

Provided by the United States Food and Drug Administration (https://www.fda.gov/).

LAI: long-acting injection

Supplementary Table 2. Study characteristic

Study name, study duration, sponsor	Diagnosis (%BDII, criteria), mood status at recruitment	%female, mean age	%rapid cycling	Pre-randomization treatment	Double-blind treatment (n)*	Definition of recurrence
Amsterdam 2010, 50 wk, AC	BDII (100%, DSM-IV-TR), DE	46.3%, 38.0 yr	ni	FLU 20-80 mg/d	(1) LIT 0.5-1.5 mmol/L (26) (2) PLA (27)	(1) MDE in DSM-IV-TR and HAMD ≥ 14 (2) HME in DSM-IV-TR (≥ 4d with symptoms ≥ 4) and YMRS ≥ 12
Berwaerts 2012*, 171.4 wk, IN	BDI (0%, DSM-IV), MaE or MiE	53.4%, 40.0 yr	0%	PAL 3-12 mg/d	(1) PAL 3-12 mg/d (152) (2) PLA (148)	(1) YMRS ≥ 15 and CGI-BP-S for mania ≥ 4 (2) YMRS < 15 and MADRS ≥ 16 and CGI-BP-S for depression ≥ 4 (3) Hospitalization (4) Additional therapeutic intervention
Bowden 2000, 52 wk, IN	BDI (0%, DSM-III-R), MaE, MiE or EU	50.9%, 39.2 yr	ni	LIT or DIV	(1) DIV 71-125 μg/mL (187) (2) LIT 0.8-1.2 mmol/L (91) (3) PLA (94)	(1) Depression : Additional AD intervention or discontinuation because of symptoms (2) Mania: MRS ≥ 16 or hospitalization
Bowden 2003, 76 wk, IN	BDI (0%, DSM-IV), MaE or HME	52.8%, 41.1 yr	ni	LAM 100-200 mg/d	(1) LAM 100-400 mg/d (59) (2) LIT 0.8-1.1 mEq/L (47) (3) PLA (70)	(1) Additional therapeutic intervention including ECT
Calabrese 2000, 26 wk, IN	BDI or II (28.9%, DSM-IV), MaE, HME, MiE, DE or EU	57.2%, 38.0 yr	100%	LAM 100-200 mg/d	(1) LAM 100-500 mg/d (93) (2) PLA (89)	(1) Additional pharmacological intervention
Calabrese 2003, 76 wk, IN	BDI (0%, DSM-IV), DE	54.9%, 43.4 yr	ni	LAM ≥ 100 mg/d	(1) LAM 200-400 mg/d (171) (2) LIT 0.8-1.1 mEq/L (121) (3) PLA (121)	(1) Additional therapeutic intervention including ECT

Study name, study duration, sponsor	Diagnosis (%BDII, criteria), mood status at recruitment	%female, mean age	%rapid cycling	Pre-randomization treatment	Double-blind treatment (n)*	Definition of recurrence
Calabrese 2017, 52 wk, IN	BDI (0%, DSM-IV-TR), MaE or MiE	57.5%, 40.6%	0%	AOM 400 mg/4w	(1) AOM 400 mg/4w (133) (2) PLA (133)	(1) YMRS ≥ 15 (2) MADRS ≥ 15 (3) CGI-BP-S > 4 (4) Hospitalization (5) Additional therapeutic intervention (6) SAE of worsening BDI (7) Discontinuation due to lack of efficacy (8) Active suicidality
Cundall 1972, 26 wk, AC	Manic-Depressive (ni, ni), ni	61.5%, 53.7 yr	ni	LIT	(1) LIT 0.5-1.2 mEq/L (8) (2) PLA (5)	(1) diagnosed clinically (2) Hospitalization
Dunner 1976, 65 wk, AC	BDII, BD others (100%, Feighner), EU	57.5%, 51.2 yr	15.0%	ni	(1) LIT 0.8-1.2 mEq/L (16) (2) PLA (24)	(1) Additional pharmacological intervention
Fieve 1976, 64 (mean) wk, AC	BDI or II (34.0%. Feighner), EU	50.9%, 46.6	3.8%	ni	(1) LIT 0.7-1.3 mEq/L (24) (2) PLA (29)	(1) Author defined
Kane 1982, 104 wk, AC	BDII (100%, RDC), EU	69.4%, 47.5 yr	ni	IMI 150 mg/d	(1) LIT 0.8-1.2 mEq/L (4) (2) PLA (7)	(1) Major depression for a wk (RDC) (2) Mania for a wk (RDC) (3) Minor depression for 4 wks (RDC) (4) Hypomania for 4 wks (RDC)
Keck 2007, 100 wk, IN	BDI (0%, DSM-IV), MaE or MiE	67.1%, 39.7 yr	17.5%	ARI 15-30 mg/d	(1) ARI 15-30 mg/d (78) (2) PLA (83)	(1) Hospitalization (2) Additional therapeutic intervention (3) Discontinuation due to lack of efficacy
Koyama 2011, 26 wk, IN	BDI (0%, DSM-IV-TR), MaE, MiE, DE or EU	56.3%, 42.8 yr	ni	LAM 100-200 mg/d	(1) LAM 100-200 mg/d (45) (2) PLA (58)	(1) Additional pharmacological intervention

Study name, study duration, sponsor	Diagnosis (%BDII, criteria), mood status at recruitment	%female, mean age	%rapid cycling	Pre-randomization treatment	Double-blind treatment (n)*	Definition of recurrence
Melia 1970, 104 wk, IN	BD (ni, ICD-9), EU	90.9%, 51.5 yr	ni	LIT	(1) LIT 500-1500 mg/d (5) (2) PLA (6)	(1) Sufficient severity to admission to hospital
Prien 1973a, 104 wk, AC	Manic-depressive manic type (ni, ni), MaE or HME	35.1%, 44 (median) yr	ni	LIT	(1) LIT 0.5-1.4 mEq/L (101) (2) PLA (104)	(1) Additional pharmacological intervention (2) Hospitalization
Prien 1973b, 17.3 wk, AC	BD (ni, ni), DE	23.0%, 45.7 yr	ni	LIT or IMI	(1) LIT 0.5-1.4 mEq/L (18) (2) PLA (13)	(1) Additional pharmacological intervention (2) Hospitalization
Quiroz 2010, 104 wk, IN	BDI (0%, DSM-IV-TR), MaE, MiE or EU	48.5%, 39.0 yr	0%	RIS-LAI 12.5, 25, 37.5, 50 mg/2wk	(1) RIS-LAI 12.5-50 mg/2wk (154) (2) PLA (149)	(1) YMRS > 12 (2) MADRS > 12 (3) CGI-S > 4 (3) Hospitalization (4) Additional therapeutic intervention including increase dosage of RIS (5) Any mood episode in DSM-IV
Szegedi 2018, 26 wk, IN	BDI (0%, DSM-IV-TR), MaE or MiE	54.8%, 41.9 yr	0%	ASE 5 or 10 mg bid	(1) ASE 10-20 mg (126) (2) PLA (127)	(1) YMRS ≥ 16 (2) MADRS ≥ 16 (3) Hospitalization (4) Additional therapeutic intervention (5) Discontinuation because of a mood event
Tohen 2006, 48 wk, IN	BDI (0%, DSM-IV), MaE or MiE	61.2%, 40.6 yr	49.6%	OLA 5-20 mg/d	(1) OLA 5-20 mg/d (225) (2) PLA (136)	(1) HAMD ≥ 15 (2) YMRS ≥ 15 (3) Hospitalization

Study name, study duration, sponsor	Diagnosis (%BDII, criteria), mood status at recruitment	%female, mean age	%rapid cycling	Pre-randomization treatment	Double-blind treatment (n)*	Definition of recurrence
Vieta 2012, 78 wk, IN	BDI (0%, DSM-IV-TR), MaE, MiE or EU	52.1%, 36.9 yr	0%	RIS-LAI 25, 37.5, 50 mg/2wk	(1) OLA 10 mg/d (131) (2) RIS-LAI 25-50 mg/d (132) (3) PLA (135)	(1) YMRS > 12 (2) MADRS > 12 (3) CGI-S ≥ 4 (3) Hospitalization (4) Additional therapeutic intervention including increase dosage of RIS
Weisler 2011, 104 wk, IN	BDI (0%, DSM-IV), MaE, MiE, DE or EU	51.5%, 39.5 yr	13.4%	QUE 300-800 mg/d	(1) LIT 0.6-1.2 mEq/L (364) (2) QUE 300-800 mg/d (404) (3) PLA (404)	(1) YMRS ≥ 20 (2) MADRS ≥ 20 (3) Additional pharmacological intervention (4) Hospitalization (5) Discontinuation because of a mood event
Young 2014, 52 wk, IN	BDI or II (39.6%, DSM-IV), DE	59.6%, 40.1 yr	8.7%	QUE 300 or 600 mg/d	(1) QUE 300-600 mg/d (291) (2) PLA (294)	(1) YMRS ≥ 16 (2) MADRS ≥ 20 (3) Hospitalization (4) Additional therapeutic intervention (5) Discontinuation because of a mood event

* Studies with enrichment design were underlined

Enrichment design: patients are stabilized on the drug of interest during the open-label study, then randomized to revive the drug or comparators (e.g. placebo)

AC: academia, AD: antidepressant, AOM: aripiprazole once-monthly, ARI: aripiprazole, ASE: asenapine, BD: bipolar disorder, CGI-BP-S: Clinical Global Impressions of Bipolar Disorder-Severity, d: day, DIV: divalproex, DSM: Diagnostic and Statistical Manual of Mental Disorders, ECT: electroconvulsive therapy, EU: euthymia, FLU: fluoxetine, HAMD: Hamilton Rating Scale for Depression, HME: hypomanic episode, ICD: International Classification of Diseases, IN: industry, LAM: lamotrigine, LIT: lithium, MaE: manic episode/ (M)DE: (major) depressive episode, MiE: mixed episode, MRS: Mania Rating Scale, n: number of patients, ni: not information, PAL: paliperidone, PLA: placebo, QUE: quetiapine, RDC: Research Diagnostic Criteria, RIS-LAI: risperidone long-acting injectable, SAE: serious adverse event, YMRS: Young Mania Rating Scale, yr: year, wk: week.

Supplementary Table 3. Data synthesis

Recurrence rate of any mood episode

	1 month	3 months	6 months	9 months	12 months	18 months	24 months
Amsterdam 2010							
Berwaerts 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Bowden 2000	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		
Bowden 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2000	4 weeks	12 weeks	26 weeks				
Calabrese 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2017	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		
Cundall 1972			26 weeks				
Dunner 1976						65 weeks	
Fieve 1976							
Kane 1982							104 weeks
Keck 2007	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	100 weeks
Koyama 2011	4 weeks	12 weeks	26 weeks				
Melia 1970							104 weeks
Prien 1973a							104 weeks
Prien 1973b		17.3 weeks					
Quiroz 2010	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Szegedi 2018	4 weeks	12 weeks	26 weeks				
Tohen 2006	4 weeks	12 weeks	26 weeks	39 weeks	48 weeks		
Vieta 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Weisler 2011	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Young 2014	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		

Recurrence rate of depressive episodes

	1 month	3 months	6 months	9 months	12 months	18 months	24 months
Amsterdam 2010	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		
Berwaerts 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Bowden 2000	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		
Bowden 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2000							
Calabrese 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2017					52 weeks		
Cundall 1972							
Dunner 1976						65 weeks	
Fieve 1976						64 weeks	
Kane 1982							104 weeks
Keck 2007	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	100 weeks
Koyama 2011	4 weeks	12 weeks	26 weeks				
Melia 1970							
Prien 1973a							
Prien 1973b							
Quiroz 2010	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Szegedi 2018	4 weeks	12 weeks	26 weeks				
Tohen 2006	4 weeks	12 weeks	26 weeks	39 weeks	48 weeks		
Vieta 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Weisler 2011	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Young 2014	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		

Recurrence rate of manic/hypomanic/mixed episodes

	1 month	3 months	6 months	9 months	12 months	18 months	24 months
Amsterdam 2010					50 weeks		
Berwaerts 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Bowden 2000					52 weeks		
Bowden 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2000							
Calabrese 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2017					52 weeks		
Cundall 1972							
Dunner 1976						65 weeks	
Fieve 1976						64 weeks	
Kane 1982							104 weeks
Keck 2007	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	100 weeks
Koyama 2011	4 weeks	12 weeks	26 weeks				
Melia 1970							
Prien 1973a							
Prien 1973b							
Quiroz 2010	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Szegedi 2018	4 weeks	12 weeks	26 weeks				
Tohen 2006	4 weeks	12 weeks	26 weeks	39 weeks	48 weeks		
Vieta 2012	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Weisler 2011	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Young 2014	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		

All-cause discontinuation

	1 month	3 months	6 months	9 months	12 months	18 months	24 months
Amsterdam 2010					50 weeks		
Berwaerts 2012							171.4 weeks
Bowden 2000					52 weeks		
Bowden 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2000	4 weeks	12 weeks	12 weeks				
Calabrese 2003	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	
Calabrese 2017	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		
Cundall 1972			26 weeks				
Dunner 1976							
Fieve 1976							
Kane 1982							104 weeks
Keck 2007							100 weeks
Koyama 2011	4 weeks	12 weeks	26 weeks				
Melia 1970							104 weeks
Prien 1973a							104 weeks
Prien 1973b							
Quiroz 2010	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Szegedi 2018			26 weeks				
Tohen 2006					48 weeks		
Vieta 2012						78 weeks	
Weisler 2011	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks	76 weeks	104 weeks
Young 2014	4 weeks	12 weeks	26 weeks	39 weeks	52 weeks		

Data from Kaplan-Meier curve was underlined.

Supplementary Table 4. Number of comparisons included in each discontinuation subgroup stratified by assigned drug characteristics

	Recurrence of any mood episode at 6 months	Recurrence of depressive episodes at 6 months	Recurrence of manic/hypomanic/mixed episodes at 6 months	All-cause discontinuation at 6 months
LAI-SGAs	2	1	1	2
Oral medications	12	11	10	8
LAI-SGAs	2	1	1	2
OSGAs	5	5	5	2
LAI-SGAs	2	1	1	2
Lithium	1	1	0	1
LAI-SGAs	2	1	1	2
Lamotrigine	2	1	1	2
OSGAs	5	5	5	2
Lithium	1	1	0	1
OSGAs	5	5	5	2
Lamotrigine	2	1	1	2
Lithium	1	1	0	1
Lamotrigine	2	1	1	2

LAI-SGAs: long acting injection second generation antipsychotics, OSGAs: oral second generation antipsychotics

Supplementary Table 5. Results of the primary meta-analysis and primary single-group summary meta-analysis

Recurrence rate of any mood episode

	Event rate in maintenance group				Event rate in discontinuation group				Maintenance–discontinuation difference				
	N	ER (%)	95% CI	I^2 (%)	N	ER (%)	95% CI	I^2 (%)	N	RR	95% CI	Unadjusted p*	I^2 (%)
1 month	19	6.9	4.7, 10.1	87.08	14	13.0	7.8, 20.8	93.80	19	0.59	0.42, 0.83	**0.002**	71.55
3 months	20	21.6	17.0, 27.0	90.17	15	33.1	28.1, 38.5	82.02	20	0.63	0.51, 0.77	**0.000**	79.53
6 months	20	32.3	26.2, 39.0	91.95	15	52.7	45.5, 59.8	89.02	20	0.61	0.54, 0.70	**0.000**	75.33
9 months	16	37.3	30.6, 44.5	92.22	11	60.7	52.7, 68.3	90.47	16	0.60	0.51, 0.70	**0.000**	85.07
12 months	16	42.2	36.1, 48.6	90.25	11	65.7	58.8, 72.0	87.52	16	0.63	0.55, 0.72	**0.000**	83.44
18 months	12	46.2	39.9, 52.6	84.40	8	73.7	65.8, 80.2	84.63	12	0.61	0.53, 0.72	**0.000**	85.06
24 months	8	38.9	36.2, 41.7	0.00	7	75.6	68.0, 81.9	75.28	8	0.49	0.45, 0.52	**0.000**	0.00

Recurrence rate of depressive episodes

	Event rate in maintenance group				Event rate in discontinuation group				Maintenance–discontinuation difference				
	N	ER (%)	95% CI	I^2 (%)	N	ER (%)	95% CI	I^2 (%)	N	RR	95% CI	Unadjusted p*	I^2 (%)
1 month	18	6.1	4.3, 8.5	75.58	13	9.5	6.2, 14.3	87.27	18	0.61	0.44, 0.85	**0.003**	55.52
3 months	18	15.3	11.1, 20.7	90.79	13	21.0	15.2, 28.4	90.54	18	0.71	0.59, 0.86	**0.000**	54.95
6 months	18	22.2	16.3, 29.5	93.27	13	30.6	22.2, 40.5	93.46	18	0.72	0.60, 0.87	**0.001**	73.15
9 months	16	25.5	18.8, 33.7	93.85	11	35.1	26.7, 44.7	92.19	16	0.71	0.58, 0.87	**0.001**	81.54
12 months	17	27.1	20.7, 34.6	93.20	12	37.0	28.0, 47.1	93.35	17	0.71	0.59, 0.84	**0.000**	78.45
18 months	13	26.3	18.7, 35.7	92.89	9	38.8	28.8, 49.8	90.98	13	0.65	0.50, 0.84	**0.001**	83.89
24 months	6	18.2	16.1, 20.6	0.00	5	35.4	25.4, 47.0	85.83	6	0.47	0.39, 0.58	**0.000**	34.72

Recurrence rate of manic/hypomanic/mixed episodes

	Event rate in maintenance group				Event rate in discontinuation group				Maintenance–discontinuation difference				
	N	ER (%)	95% CI	I^2 (%)	N	ER (%)	95% CI	I^2 (%)	N	RR	95% CI	Unadjusted p*	I^2 (%)
1 month	17	3.0	1.9, 4.7	66.76	12	5.7	3.2, 10.0	88.14	17	0.49	0.29, 0.83	**0.008**	53.41
3 months	17	8.5	6.5, 11.1	75.19	12	18.0	13.2, 24.0	88.07	17	0.44	0.34, 0.56	**0.000**	57.66
6 months	17	13.3	10.4, 16.9	82.28	12	28.9	22.8, 35.9	88.45	17	0.45	0.36, 0.57	**0.000**	71.74
9 months	15	18.0	14.6, 21.9	81.03	10	38.6	29.2, 48.9	93.33	15	0.46	0.37, 0.58	**0.000**	77.33
12 months	17	19.2	15.4, 23.7	85.31	12	39.7	31.4, 48.6	92.00	17	0.47	0.39, 0.58	**0.000**	77.17
18 months	13	26.2	21.8, 31.1	76.62	9	52.0	42.5, 61.4	88.56	13	0.49	0.41, 0.60	**0.000**	74.65
24 months	6	23.7	19.4, 28.8	62.83	5	58.5	47.8, 68.4	83.13	6	0.39	0.35, 0.44	**0.000**	0.67

All-cause discontinuation rate

	Event rate in maintenance group				Event rate in discontinuation group				Maintenance–discontinuation difference				
	N	ER (%)	95% CI	I^2 (%)	N	ER (%)	95% CI	I^2 (%)	N	RR	95% CI	Unadjusted p*	I^2 (%)
1 month	11	8.4	5.8, 12.0	79.21	8	14.8	9.2, 22.9	89.92	11	0.60	0.45, 0.80	**0.001**	48.77
3 months	11	35.3	28.0, 43.4	90.77	8	45.6	38.1, 53.4	85.53	11	0.75	0.65, 0.85	**0.000**	59.10
6 months	13	46.2	36.9, 55.9	93.46	10	61.9	54.6, 68.6	83.94	13	0.71	0.61, 0.82	**0.000**	81.92
9 months	9	56.9	48.1, 65.2	91.53	6	71.6	63.1, 78.8	87.64	9	0.76	0.67, 0.86	**0.000**	82.54
12 months	13	66.2	59.3, 72.4	90.11	9	79.3	72.6, 84.7	85.91	13	0.82	0.75, 0.88	**0.000**	76.31
18 months	9	65.0	53.2, 75.3	94.70	5	85.5	77.0, 91.2	86.00	9	0.72	0.61, 0.86	**0.000**	93.80
24 months	8	61.6	48.9, 72.9	92.52	7	85.7	80.9, 89.4	55.77	7	0.68	0.53, 0.86	**0.001**	94.78

*Boldface indicates associations that remained significant at $p < 0.05$ after FDR correction.

95% CI: 95% confidential interval, ER: event rate, N: number of comparisons

Supplementary Table 6. Subgroup analyses: characteristics of the assigned drugs

Recurrence rate of any mood episode at 6 months

	Event rate in maintenance group					Maintenance–discontinuation difference					
Subgroup	N	ER (%)	95%CI	I^2 (%)	Unadjusted p*	N	RR (%)	95%CI	Unadjusted p*	I^2 (%)	Unadjusted p*
LAI-SGAs	3	25.7	20.2, 32.1	48.50	0.107	3	0.61	0.47, 0.78	**0.000**	36.45	0.984
Oral medications	17	33.6	26.5, 41.5	92.79		17	0.62	0.53, 0.71	**0.000**	78.32	
LAI-SGAs	3	25.7	20.2, 32.1	48.50	0.418	3	0.61	0.47, 0.78	**0.000**	36.45	0.079
OSGAs	7	20.9	12.8, 32.0	94.59		7	0.45	0.36, 0.56	**0.000**	70.84	
LAI-SGAs	3	25.7	20.2, 32.1	48.50	**0.005**	3	0.61	0.47, 0.78	**0.000**	36.45	0.301
Lithium	5	43.0	32.5, 54.2	81.01		5	0.73	0.58, 0.92	**0.008**	67.02	
LAI-SGAs	3	25.7	20.2, 32.1	48.50	**0.000**	3	0.61	0.47, 0.78	**0.000**	36.45	0.093
Lamotrigine**	4	48.4	43.3, 53.5	0.00		4	0.78	0.68, 0.89	**0.000**	0.00	
OSGAs	7	20.9	12.8, 32.0	94.59	**0.005**	7	0.45	0.36, 0.56	**0.000**	70.84	**0.003**
Lithium	5	43.0	32.5, 54.2	81.01		5	0.73	0.58, 0.92	**0.008**	67.02	
OSGAs	7	20.9	12.8, 32.0	94.59	**0.000**	7	0.45	0.36, 0.56	**0.000**	70.84	**0.000**
Lamotrigine**	4	48.4	43.3, 53.5	0.00		4	0.78	0.68, 0.89	**0.000**	0.00	
Lithium	5	43.0	32.5, 54.2	81.01	0.390	5	0.73	0.58, 0.92	**0.008**	67.02	0.639
Lamotrigine**	4	48.4	43.3, 53.5	0.00		4	0.78	0.68, 0.89	**0.000**	0.00	

Recurrence rate of depressive episodes at 6 months

	Event rate in maintenance group					Maintenance–discontinuation difference					
Subgroup	N	ER (%)	95%CI	I^2 (%)	Unadjusted p*	N	RR (%)	95%CI	Unadjusted p**	I^2 (%)	Unadjusted p*
LAI-SGAs	2	16.2	10.5, 24.1	56.79	0.184	2	1.28	0.67, 2.44	0.462	58.19	0.071
Oral medications	16	23.1	16.5, 31.3	93.79		16	0.69	0.57, 0.82	**0.000**	71.67	
LAI-SGAs	2	16.2	10.5, 24.1	56.79	0.454	2	1.28	0.67, 2.44	0.462	58.19	**0.016**
OSGAs	7	12.2	6.4, 22.1	94.59		7	0.52	0.38, 0.72	**0.000**	70.31	
LAI-SGAs	2	16.2	10.5, 24.1	56.79	**0.010**	2	1.28	0.67, 2.44	0.462	58.19	0.290
Lithium	5	38.5	22.9, 56.9	93.18		5	0.88	0.73, 1.08	0.223	40.64	
LAI-SGAs	2	16.2	10.5, 24.1	56.79	**0.021**	2	1.28	0.67, 2.44	0.462	58.19	0.100
Lamotrigine**	3	32.1	21.0, 45.8	74.04		3	0.72	0.58, 0.89	**0.002**	0.00	
OSGAs	7	12.2	6.4, 22.1	94.59	**0.004**	7	0.52	0.38, 0.72	**0.000**	70.31	**0.006**
Lithium	5	38.5	22.9, 56.9	93.18		5	0.88	0.73, 1.08	0.223	40.64	
OSGAs	7	12.2	6.4, 22.1	94.59	**0.009**	7	0.52	0.38, 0.72	**0.000**	70.31	0.100
Lamotrigine**	3	32.1	21.0, 45.8	74.04		3	0.72	0.58, 0.89	**0.002**	0.00	
Lithium	5	38.5	22.9, 56.9	93.18	0.561	5	0.88	0.73, 1.08	0.223	40.64	0.163
Lamotrigine**	3	32.1	21.0, 45.8	74.04		3	0.72	0.58, 0.89	**0.002**	0.00	

Recurrence rate of manic/hypomanic/mixed episodes at 6 months

	Event rate in maintenance group					Maintenance–discontinuation difference					
Subgroup	N	ER (%)	95%CI	I^2 (%)	Unadjusted p*	N	RR (%)	95%CI	Unadjusted p**	I^2 (%)	Unadjusted p*
LAI-SGAs	2	15.8	9.6, 24.7	65.10	0.483	2	0.43	0.25, 0.75	**0.003**	66.02	0.888
Oral medications	15	12.9	9.8, 16.9	83.88		15	0.45	0.35, 0.58	**0.000**	73,87	
LAI-SGAs	2	15.8	9.6, 24.7	65.10	0.027	2	0.43	0.25, 0.75	**0.003**	66.02	0.240
OSGAs	7	8.2	5.9, 11.2	65.17		7	0.30	0.23, 0.40	**0.000**	43.89	
LAI-SGAs	2	15.8	9.6, 24.7	65.10	0.766	2	0.43	0.25, 0.75	**0.003**	66.02	0.424
Lithium	4	17.1	12.7, 22.7	51.11		4	0.56	0.43, 0.72	**0.000**	19.59	
LAI-SGAs	2	15.8	9.6, 24.7	65.10	0.437	2	0.43	0.25, 0.75	**0.003**	66.02	0.050
Lamotrigine**	3	22.7	9,9, 44.0	89.35		3	0.81	0.61, 1.08	0.149	0.00	
OSGAs	7	8.2	5.9, 11.2	65.17	**0.001**	7	0.30	0.23, 0.40	**0.000**	43.89	**0.001**
Lithium	4	17.1	12.7, 22.7	51.11		4	0.56	0.43, 0.72	**0.000**	19.59	
OSGAs	7	8.2	5.9, 11.2	65.17	0.025	7	0.30	0.23, 0.40	**0.000**	43.89	**0.000**
Lamotrigine**	3	22.7	9,9, 44.0	89.35		3	0.81	0.61, 1.08	0.149	0.00	
Lithium	4	17.1	12.7, 22.7	51.11	0.513	4	0.56	0.43, 0.72	**0.000**	19.59	0.056
Lamotrigine**	3	22.7	9,9, 44.0	89.35		3	0.81	0.61, 1.08	0.149	0.00	

All-cause discontinuation at 6 months

	Event rate in maintenance group					Maintenance–discontinuation difference					
Subgroup	N	ER (%)	95%CI	I^2 (%)	Unadjusted p*	N	RR (%)	95%CI	Unadjusted p**	I^2 (%)	Unadjusted p*
LAI-SGAs	2	35.9	30.4, 41.8	0.00	0.052	2	0.69	0.57, 0.84	**0.000**	0.00	0.830
Oral medications	11	48.3	37.3, 59.6	94.34		11	0.71	0.60, 0.84	**0.000**	84.77	
LAI-SGAs	2	35.9	30.4, 41.8	0.00	0.032	2	0.69	0.57, 0.84	**0.000**	0.00	**0.003**
OSGAs	3	26.1	20.0, 33.2	76.18		3	0.48	0.43, 0.55	**0.000**	0.00	
LAI-SGAs	2	35.9	30.4, 41.8	0.00	**0.002**	2	0.69	0.57, 0.84	**0.000**	0.00	0.079
Lithium	4	59.6	45.8, 72.1	81.52		4	0.86	0.74, 0.99	0.041	48.71	
LAI-SGAs	2	35.9	30.4, 41.8	0.00	**0.000**	2	0.69	0.57, 0.84	**0.000**	0.00	0.121
Lamotrigine**	4	59.8	54.7, 64.7	0.00		4	0.82	0.74, 0.91	**0.000**	0.00	
OSGAs	3	26.1	20.0, 33.2	76.18	**0.000**	3	0.48	0.43, 0.55	**0.000**	0.00	**0.000**
Lithium	4	59.6	45.8, 72.1	81.52		4	0.86	0.74, 0.99	0.041	48.71	
OSGAs	3	26.1	20.0, 33.2	76.18	**0.000**	3	0.48	0.43, 0.55	**0.000**	0.00	**0.000**
Lamotrigine**	4	59.8	54.7, 64.7	0.00		4	0.82	0.74, 0.91	**0.000**	0.00	
Lithium	4	59.6	45.8, 72.1	81.52	0.985	4	0.86	0.74, 0.99	0.041	48.71	0.638
Lamotrigine**	4	59.8	54.7, 64.7	0.00		4	0.82	0.74, 0.91	**0.000**	0.00	

95% CI: 95% confidential interval, ER: event rate, LAI-SGAs: long acting injection second generation antipsychotics, N: number of comparisons, OSGAs: oral second generation antipsychotics

*Boldface indicates associations that remained significant at p <0.05 after FDR correction.

**Excluding the study enrolling only rapid cycling bipolar disorder patients, the effect sizes of the outcomes were as follows: recurrence rate of any mood episode; 0.75 (0.62,

0.92), unadjusted p=0.004, I^2 = 25.92% and all-cause discontinuation; 0.82 (0.72, 0.92), unadjusted p = 0.001, I^2 = 0.00%. The study did not include recurrence rates of depressive episodes and manic/hypomanic/mixed episodes. Multiple testing yields significance levels that are higher than nominal and hence this table is for presentation purposes only.

Supplementary Table 7. Analyses of the discontinuation subgroups stratified according to the drugs used before randomization

Recurrence rate of any mood episode

at 3 months*	N	ER (%)	95% CI	I^2 (%)
LAI-SGAs	3	25.6	21.5, 30.1	0.00
Oral medications	12	35.3	29.3, 41.9	83.61
LAI-SGAs	3	25.6	21.5, 30.1	0.00
OSGAs	6	27.3	22.3, 33.1	75.32
LAI-SGAs				
Lithium				
LAI-SGAs	3	25.6	21.5, 30.1	0.00
Lamotrigine	4	48.8	43.5, 54.1	0.00
OSGAs				
Lithium				
OSGAs	6	27.3	22.3, 33.1	75.32
Lamotrigine	4	48.8	43.5, 54.1	0.00
Lithium				
Lamotrigine				

at 6 months	N	ER (%)	95% CI	I^2 (%)	Unadjusted p**
LAI-SGAs	3	42.4	37.7, 47.3	0.00	**0.010**
Oral medications	12	55.8	46.8, 64.3	90.63	
LAI-SGAs	3	42.4	37.7, 47.3	0.00	0.297
OSGAs	6	49.9	37.0, 62.8	94.34	
LAI-SGAs	3	42.4	37.7, 47.3	0.00	0.068
Lithium	1	91.7	37.8, 99.5	na	
LAI-SGAs	3	42.4	37.7, 47.3	0.00	**0.000**
Lamotrigine***	4	62.9	57.6, 67.9	0.00	
OSGAs	6	49.9	37.0, 62.8	94.34	0.110
Lithium	1	91.7	37.8, 99.5	na	
OSGAs	6	49.9	37.0, 62.8	94.34	0.068
Lamotrigine***	4	62.9	57.6, 67.9	0.00	
Lithium	1	91.7	37.8, 99.5	na	0.207
Lamotrigine***	4	62.9	57.6, 67.9	0.00	

Recurrence rate of depressive episodes

at 3 months*	N	ER (%)	95% CI	I^2 (%)
LAI-SGAs	2	10.7	7.6, 15.0	0.00
Oral medications	11	23.5	16.9, 31.7	90.36
LAI-SGAs	2	10.7	7.6, 15.0	0.00
OSGAs	6	18.0	10.3, 29.6	94.17
LAI-SGAs				
Lithium				
LAI-SGAs	2	10.7	7.6, 15.0	0.00
Lamotrigine	3	33.0	27.4, 39.1	0.00
OSGAs				
Lithium				
OSGAs	6	18.0	10.3, 29.6	94.17
Lamotrigine	3	33.0	27.4, 39.1	0.00
Lithium				
Lamotrigine				

at 6 months	N	ER (%)	95% CI	I^2 (%)	Unadjusted p**
LAI-SGAs	2	12.7	9.2, 17.2	0.00	**0.000**
Oral medications	11	35.0	25.8, 45.5	92.84	
LAI-SGAs	2	12.7	9.2, 17.2	0.00	**0.015**
OSGAs	6	25.8	16.0, 38.9	94.57	
LAI-SGAs					
Lithium					
LAI-SGAs	2	12.7	9.2, 17.2	0.00	**0.000**
Lamotrigine***	3	46.8	33.6, 60.5	77.44	
OSGAs					
Lithium					
OSGAs	6	25.8	16.0, 38.9	94.57	0.026
Lamotrigine***	3	46.8	33.6, 60.5	77.44	
Lithium					
Lamotrigine***					

Recurrence rate of manic/hypomanic/mixed episodes

at 3 months*	N	ER (%)	95% CI	I^2 (%)
LAI-SGAs	2	20.1	15.7, 25.3	0.00
Oral medications	10	17.5	11.9, 24.9	90.14
LAI-SGAs	2	20.1	15.7, 25.3	0.00
OSGAs	6	15.5	8.3, 27.0	94.31
LAI-SGAs				
Lithium				
LAI-SGAs	2	20.1	15.7, 25.3	0.00
Lamotrigine	3	21.9	16.3, 28.9	29.41
OSGAs				
Lithium				
OSGAs	6	15.5	8.3, 27.0	94.31
Lamotrigine	3	21.9	16.3, 28.9	29.41
Lithium				
Lamotrigine				

at 6 months	N	ER (%)	95% CI	I^2 (%)	Unadjusted p**
LAI-SGAs	2	36.3	30.8, 42.2	0.00	0.080
Oral medications	10	27.5	20.6, 35.7	89.92	
LAI-SGAs	2	36.3	30.8, 42.2	0.00	0.128
OSGAs	6	26.4	17.3, 38.1	93.32	
LAI-SGAs					
Lithium					
LAI-SGAs	2	36.3	30.8, 42.2	0.00	0.523
Lamotrigine***	3	30.6	17.3, 48.2	85.44	
OSGAs					
Lithium					
OSGAs	6	26.4	17.3, 38.1	93.32	0.660
Lamotrigine***	3	30.6	17.3, 48.2	85.44	
Lithium					
Lamotrigine***					

All-cause discontinuation

At 3 months*	N	ER (%)	95% CI	I^2 (%)
LAI-SGAs	2	33.3	27.5, 39.6	14.27
Oral medications	6	50.0	41.6, 58.3	83.93
LAI-SGAs	2	33.3	27.5, 39.6	14.27
OSGAs	2	41.5	29.5, 54.6	91.42
LAI-SGAs				
Lithium				
LAI-SGAs	2	33.3	27.5, 39.6	14.27
Lamotrigine	4	56.1	50.5, 61.5	7.13
OSGAs				
Lithium				
OSGAs	2	41.5	29.5, 54.6	91.42
Lamotrigine	4	56.1	50.5, 61.5	7.13
Lithium				
Lamotrigine				

At 6 months	N	ER (%)	95% CI	I^2 (%)	Unadjusted p**
LAI-SGAs	2	52.2	46.3, 58.2	0.00	0.020
Oral medications	8	64.8	56.1, 72.6	85.59	
LAI-SGAs	2	52.2	46.3, 58.2	0.00	0.769
OSGAs	3	54.3	42.2, 65.8	90.94	
LAI-SGAs	2	52.2	46.3, 58.2	0.00	0.119
Lithium	1	91.7	37.8, 99.5	na	
LAI-SGAs	2	52.2	46.3, 58.2	0.00	**0.000**
Lamotrigine***	4	72.4	67.3, 76.9	0.00	
OSGAs	3	54.3	42.2, 65.8	90.94	0.137
Lithium	1	91.7	37.8, 99.5	na	
OSGAs	3	54.3	42.2, 65.8	90.94	**0.004**
Lamotrigine***	4	72.4	67.3, 76.9	0.00	
Lithium	4	72.4	67.3, 76.9	0.00	0.333
Lamotrigine***	1	91.7	37.8, 99.5	na	

95% CI: 95% confidential interval, ER: event rate, LAI-SGAs: long acting injection second generation antipsychotics, N: number of comparisons, OSGAs: oral second generation antipsychotics

*We did not plan this subgroup analysis because multiple-testing issues significance levels should be higher than nominal. To reveal the prerandomization drug effects on event rate at 3 and 6 months, we show event rate in each subgroup without statistical results. This table for the placebo group at 3 months is for presentation purposes only.

**Boldface indicates associations that remained significant at $p < 0.05$ after FDR correction.

***Excluding the study that included only rapid cycling bipolar disorder patients (Calabrese et al., 2000), the event rates of the outcomes were as follows: recurrence rate of any mood episode = 63.3% (57.1, 69.1) and all-cause discontinuation = 73.4% (67.5, 78.5). The study did not include the recurrence rates of depressive episodes and manic/hypomanic/mixed episodes. Multiple-testing issues significance levels should be higher than nominal and hence this table is for presentation purposes only.

Supplementary Table 8. Meta-regression analysis

Recurrence rate of any mood episode at 6 months

Modulator	Event rate in maintenance group					Event rate in discontinuation group					Maintenance–discontinuation difference				
	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)
Number of total patients	20	-0.01	-0.00, 0.00	0.314	91.33	15	-0.00	-0.00, 0.00	0.553	89.79	20	-0.00	-0.00, 0.00	0.190	71.19
%placebo	20	-0.03	-0.06, -0.00	0.023	90.43	15	-0.02	-0.05, 0.01	0.275	87.99	20	-0.02	-0.03, -0.00	0.025	72.20
%female	20	0.01	-0.06, 0.08	0.734	92.16	15	0.04	-0.03, 0.10	0.266	89.74	20	-0.00	-0.04, 0.03	0.779	76.70
Mean age	20	0.05	-0.06, 0.15	0.381	91.59	15	0.12	-0.02, 0.26	0.093	89.34	20	-0.01	-0.06, 0.05	0.832	76.25
Duration of preliminary phase	19	-0.02	-0.09, 0.04	0.475	92.33	14	-0.00	-0.07, 0.06	0.891	90.08	19	-0.02	-0.05, 0.01	0.167	74.34
Publication year	20	-0.07	-0.10, -0.04	**0.000**	80.89	15	-0.06	-0.10, -0.03	**0.001**	81.99	20	-0.02	-0.04, -0.00	0.003	60.83

Recurrence rate of depressive episodes at 6 months

Modulator	Event rate in maintenance group					Event rate in discontinuation group					Maintenance–discontinuation difference				
	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)
Number of total patients	18	-0.00	-0.00, 0.00	0.082	91.94	13	-0.00	-0.00, 0.00	0.629	93.89	18	-0.00	-0.00, -0.00	0.013	65.40
%placebo	18	-0.02	-0.06, 0.02	0.292	92.64	13	-0.01	-0.06, 0.04	0.669	93.69	18	-0.00	-0.03, 0.01	0.435	73.42
%female	18	-0.02	-0.11, 0.07	0.705	93.52	13	-0.00	-0.09, 0.08	0.980	93.66	18	-0.01	-0.06, 0.03	0.482	73.02
Mean age	18	0.12	-0.06, 0.31	0.201	91.76	13	0.18	-0.05, 0.41	0.127	92.21	18	-0.05	-0.15, 0.06	0.375	74.72
Duration of preliminary phase	18	-0.06	-0.14, 0.02	0.153	92.80	13	-0.06	-0.16, 0.04	0.216	93.55	18	-0.02	-0.06, 0.02	0.316	73.57
Publication year	18	-0.11	-0.17, -0.06	**0.000**	87.38	13	-0.08	-0.17, -0.00	0.044	91.98	18	-0.03	-0.07, 0.00	0.078	68.13

Recurrence rate of manic/hypomanic/mixed episodes at 6 months

Modulator	Event rate in maintenance group					Event rate in discontinuation group					Maintenance–discontinuation difference				
	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)
Number of total patients	17	-0.00	-0.00, 0.00	0.936	83.37	12	-0.00	-0.00, 0.00	0.830	89.41	17	-0.00	-0.00, 0.00	0.977	73.06
%placebo	17	-0.03	-0.06, -0.00	0.022	79.37	12	-0.01	-0.05, 0.02	0.487	88.19	17	-0.03	-0.05, -0.00	0.039	68.96
%female	17	-0.06	-0.12, 0.01	0.074	80.14	12	-0.01	-0.08, 0.05	0.701	89.16	17	-0.03	-0.09, 0.02	0.232	71.01
Mean age	17	-0.02	-0.17, 0.14	0.822	83.30	12	-0.07	-0.26, 0.12	0.467	88.81	17	0.04	-0.09, 0.17	0.533	72.81
Duration of preliminary phase	17	0.01	-0.05, 0.07	0.794	83.28	12	0.04	-0.02, 0.11	0.192	87.15	17	-0.02	-0.07, 0.03	0.415	72.45
Publication year	17	-0.08	-0.13, -0.02	**0.004**	78.45	12	-0.04	-0.10, 0.03	0.252	88.03	17	-0.05	-0.09, -0.01	0.011	64.54

All-cause discontinuation at 6 months

Modulator	Event rate in maintenance group					Event rate in discontinuation group					Maintenance–discontinuation difference				
	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)	N	β	95% CI	Unadjusted p*	I^2 (%)
Number of total patients	13	-0.00	-0.00, 0.00	0.555	93.86	10	-0.00	-0.00, 0.00	0.840	84.89	13	-0.00	-0.00, 0.00	0.364	81.29
%placebo	13	-0.04	-0.08, -0.00	0.043	91.67	10	-0.03	-0.06, 0.00	0.053	74.73	13	-0.01	-0.03, 0.01	0.221	80.84
%female	13	-0.03	-0.15, 0.10	0.689	93.89	10	0.01	-0.09, 0.10	0.884	84.71	13	-0.02	-0.07, 0.03	0.505	83.41
Mean age	13	0.02	-0.10, 0.15	0.713	93.24	10	0.10	-0.04, 0.25	0.165	85.32	13	-0.01	-0.06, 0.05	0.839	81.82
Duration of preliminary phase	12	-0.00	-0.09, 0.09	0.974	94.49	9	0.01	-0.06, 0.07	0.856	85.62	12	0.00	-0.03, 0.03	0.982	84.41
Publication year	13	-0.04	-0.08, -0.01	0.015	88.09	10	-0.06	-0.09, -0.03	**0.000**	56.44	13	-0.02	-0.03, 0.01	0.178	76.57

95% CI: 95% confidential interval, N: number of comparisons

*Boldface indicates associations that remained significant at $p < 0.05$ after FDR correction.

Supplementary Table 9. Subgroup analysis excluding study using abrupt discontinuation strategy

Recurrence rate of any mood episode at 6 months

	RR	95% CI	Unadjusted p	I^2 (%)
Original analysis	0.61	0.54, 0.70	**0.000**	75.33
Sensitivity analysis	0.58	0.51, 0.67	**0.000**	73.09

Recurrence rate of depressive episodes at 6 months

	RR	95% CI	Unadjusted p	I^2 (%)
Original analysis	0.72	0.60, 0.87	**0.001**	73.15
Sensitivity analysis	0.70	0.57, 0.86	**0.001**	74.59

Recurrence rate of manic/hypomanic/mixed episodes at 6 months

	RR	95% CI	Unadjusted p	I^2 (%)
Original analysis	0.45	0.36, 0.57	**0.000**	71.74
Sensitivity analysis	0.42	0.33, 0.53	**0.000**	70.41

All-cause discontinuation rate at 6 months

	RR	95% CI	Unadjusted p	I^2 (%)
Original analysis	0.71	0.61, 0.82	**0.000**	81.92
Sensitivity analysis	0.71	0.61, 0.82	**0.000**	81.92

95% CI: 95% confidential interval, ER: event rate

Multiple-testing issues significance levels should be higher than nominal and hence this table is for presentation purposes only.