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Supplementary Material

Article Title: Recovery and Recurrence Following a First Episode of Mania: A Systematic Review and Meta-Analysis of Prospectively Characterized Cohorts

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Supplementary Material

Supplementary eFigure 1: Prisma 2009 Checklist

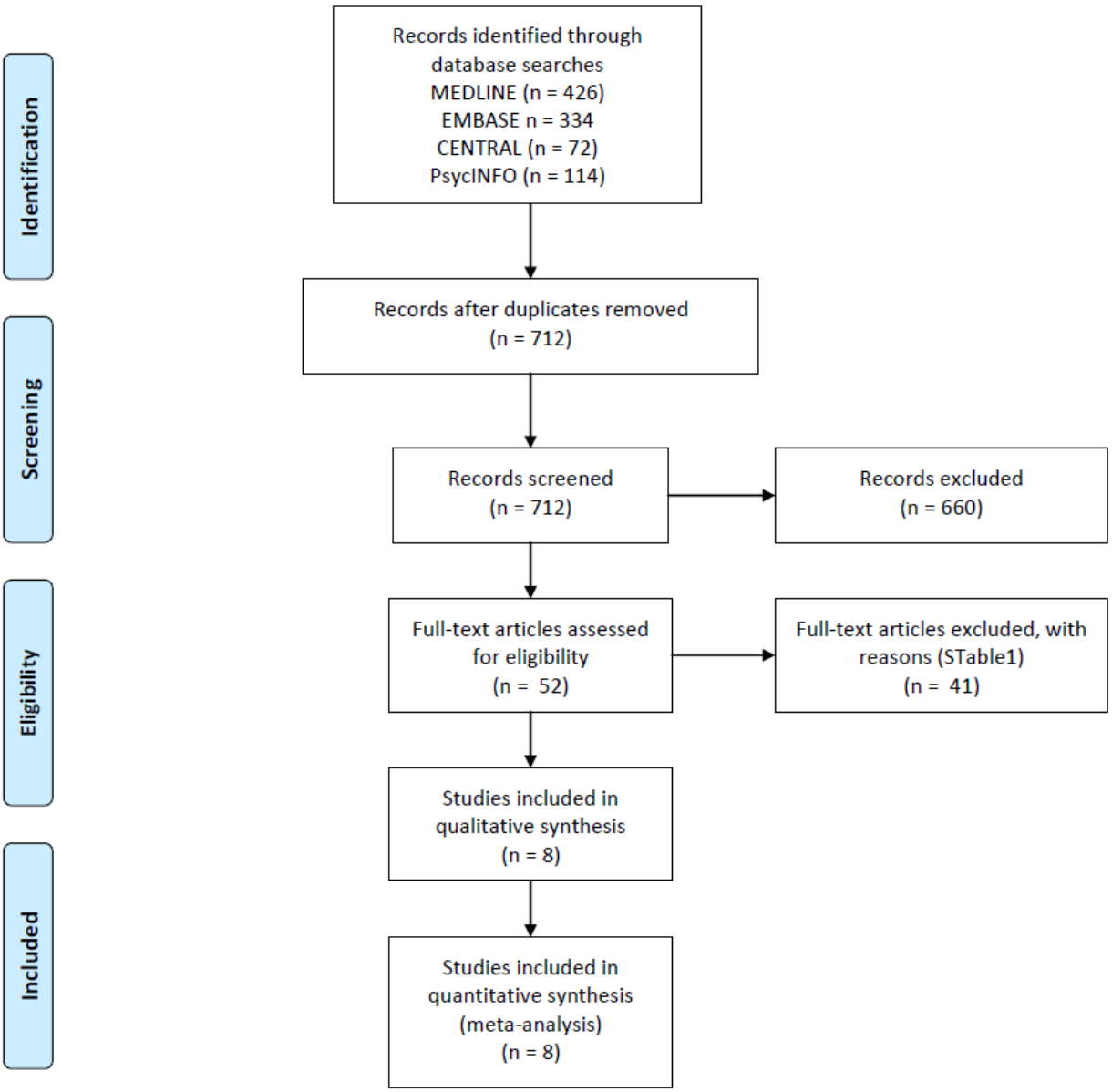
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Fig1, eF2-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8, eT3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10,eF-6, eT1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-13, Fig1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14, 18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

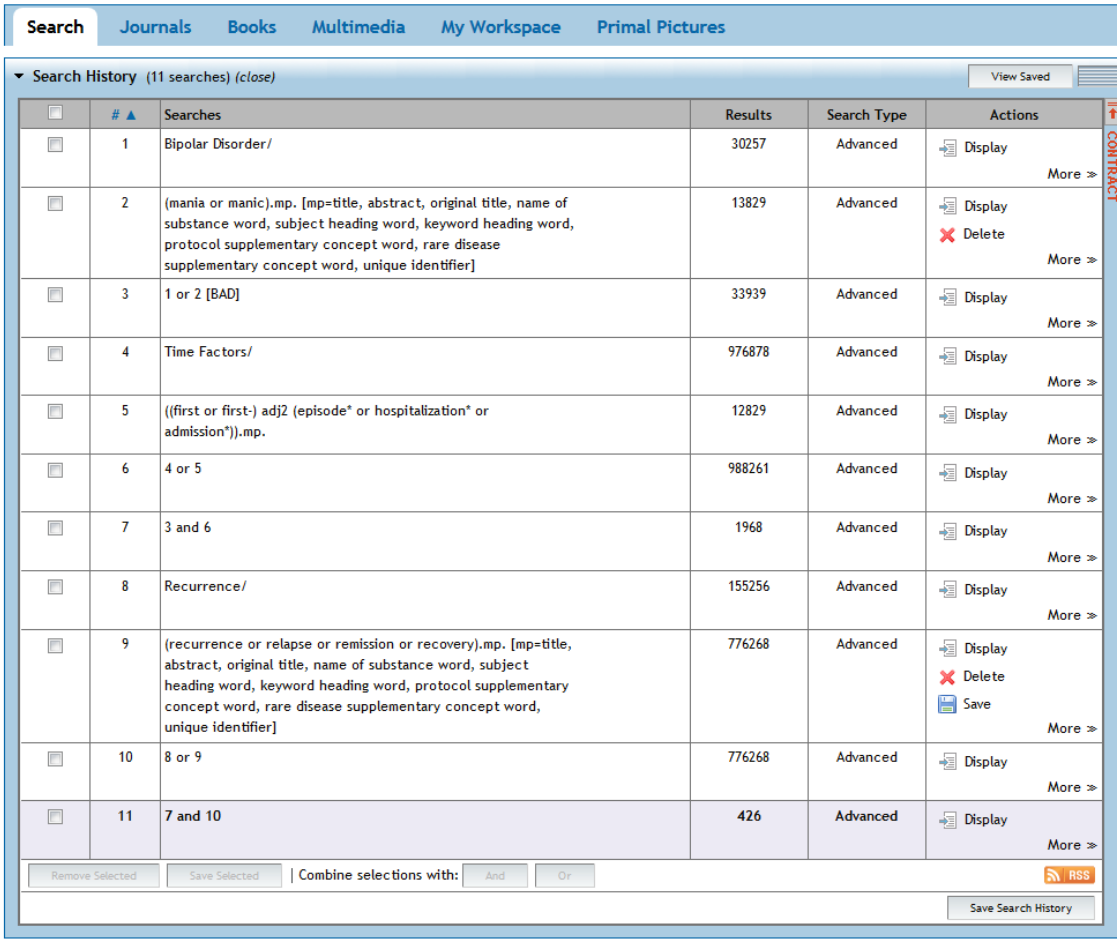
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplementary eFigure 2: Study Selection PRISMA Flowchart



Supplementary eFigure 3. MEDLINE (OVID interface) search strategy and results.



Search | Journals | Books | Multimedia | My Workspace | Primal Pictures

Search History (11 searches) *(close)* — View Saved

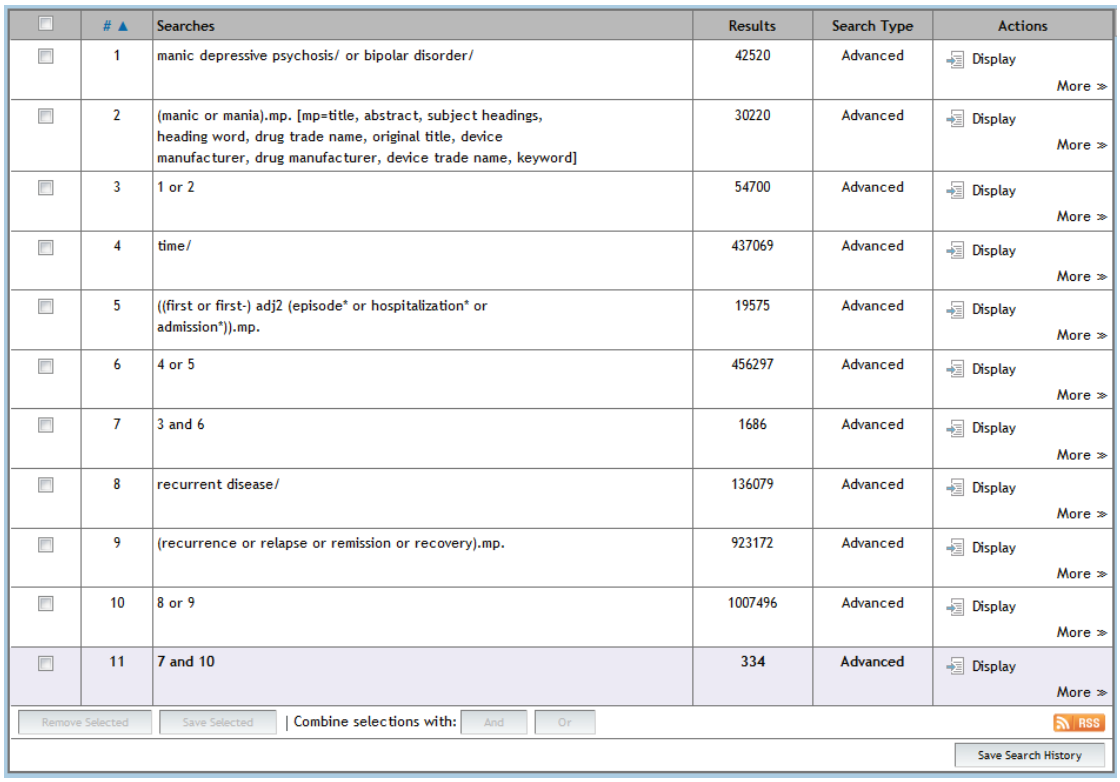
# ▲	Searches	Results	Search Type	Actions
1	Bipolar Disorder/	30257	Advanced	Display; More »
2	(mania or manic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	13829	Advanced	Display; Delete; More »
3	1 or 2 [BAD]	33939	Advanced	Display; More »
4	Time Factors/	976878	Advanced	Display; More »
5	((first or first-) adj2 (episode* or hospitalization* or admission*)).mp.	12829	Advanced	Display; More »
6	4 or 5	988261	Advanced	Display; More »
7	3 and 6	1968	Advanced	Display; More »
8	Recurrence/	155256	Advanced	Display; More »
9	(recurrence or relapse or remission or recovery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	776268	Advanced	Display; Delete; Save; More »
10	8 or 9	776268	Advanced	Display; More »
11	7 and 10	426	Advanced	Display; More »

Remove Selected | Save Selected | Combine selections with: And | Or | RSS

Save Search History

CONTRACT

Supplementary eFigure 4. EMBASE (Ovid Interface) search strategy and results.

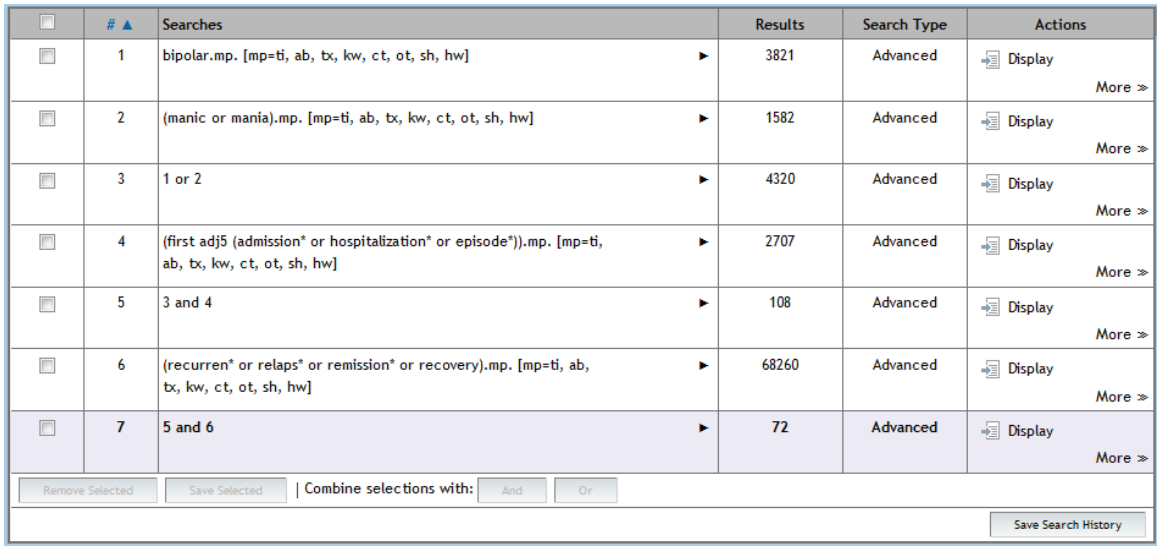


# ▲	Searches	Results	Search Type	Actions
1	manic depressive psychosis/ or bipolar disorder/	42520	Advanced	Display More »
2	(manic or mania).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	30220	Advanced	Display More »
3	1 or 2	54700	Advanced	Display More »
4	time/	437069	Advanced	Display More »
5	((first or first-) adj2 (episode* or hospitalization* or admission*)).mp.	19575	Advanced	Display More »
6	4 or 5	456297	Advanced	Display More »
7	3 and 6	1686	Advanced	Display More »
8	recurrent disease/	136079	Advanced	Display More »
9	(recurrence or relapse or remission or recovery).mp.	923172	Advanced	Display More »
10	8 or 9	1007496	Advanced	Display More »
11	7 and 10	334	Advanced	Display More »

Remove Selected | Save Selected | Combine selections with: And Or RSS

Save Search History

Supplementary eFigure 5. EBM CENTRAL (Ovid Interface) search strategy and results.



# ▲	Searches	Results	Search Type	Actions
1	bipolar.mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] ▸	3821	Advanced	Display More »
2	(manic or mania).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] ▸	1582	Advanced	Display More »
3	1 or 2 ▸	4320	Advanced	Display More »
4	(first adj5 (admission* or hospitalization* or episode*)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] ▸	2707	Advanced	Display More »
5	3 and 4 ▸	108	Advanced	Display More »
6	(recurren* or relaps* or remission* or recovery).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] ▸	68260	Advanced	Display More »
7	5 and 6 ▸	72	Advanced	Display More »

Remove Selected | Save Selected | Combine selections with: And Or

Save Search History

Supplementary eFigure 6. PsychINFO (EBSCO Interface) search strategy and results.

	Search ID#	Search Terms	Search Options	Actions
☐	S9	(S6 OR S7) AND (S5 AND S8)	**Search modes** - Boolean/Phrase	View Results (114) | View Details | Edit
☐	S8	S6 OR S7	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S7	recurrence or relapse or remission or recovery	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S6	DE "Relapse (Disorders)"	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S5	S3 AND S4	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S4	((first or first-) N2 (episode* or hospitalization* or admission*))	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S3	S1 OR S2	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S2	mania or manic	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit
☐	S1	DE "Bipolar Disorder"	**Search modes** - Boolean/Phrase	Rerun | View Details | Edit

Supplementary eTable 1. Studies excluded after screening full-text.

Study	Reason
Alvarez-Jimenez M, Gleeson JF, Henry LP, et al. Road to full recovery: longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. *Psychol.Med.* 2012;42(3):595-606.	Not 1st Bipolar Disorder (BD) sample or no 1st BD sub-group for analysis
Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. *Biol.Psychiatry.* 2000;48(6):445-457.	Not 1st BD sample or no 1st BD sub-group for analysis
Arrasate M, Gonzalez-Pinto A, Mosquera F, et al. Prognostic value of affective symptomatology in first-admitted psychotic patients: A threeyear follow-up study. *European Neuropsychopharmacology.* 2008.;18(S4):S462-S463	Not 1st BD sample
Baethge C, Smolka MN, Gruschka P, et al. Does prophylaxis-delay in bipolar disorder influence outcome? Results from a long-term study of 147 patients. *Acta Psychiatr.Scand.* 2003;107(4):260-267.	Not 1st BD sample or no 1st BD sub-group for analysis
Baldessarini RJ, Salvatore P, Khalsa HM, et al. Episode cycles with increasing recurrences in first-episode bipolar-I disorder patients. *J.Affect.Disord.* 2012;136(1-2):149-154.	1st BD but not outcome looked for
Berk M, Hallam K, Malhi GS, et al. Evidence and implications for early intervention in bipolar disorder. *Journal of Mental Health.* 2010;19(2):113-126.	Not longitudinal prospective study
Birmaher B, Axelson D, Goldstein B, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am.J.Psychiatry.* 2009;166(7):795-804.	Not 1st BD sample or no 1st BD sub-group for analysis
Carlson GA, Bromet EJ, Driessens C, et al. Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. *Am.J.Psychiatry.* 2002;159(2):307-309.	1st BD but not outcome looked for
Carlson GA, Kotov R, Chang SW, et al. Early determinants of four-year clinical outcomes in bipolar disorder with psychosis. *Bipolar Disord.* 2012;14(1):19-30.	Not 1st BD sample or no 1st BD sub-group for analysis
Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am.J.Psychiatry.* 2000;157(2):213-219.	Not 1st BD sample or no 1st BD sub-group for analysis

Conus P, McGorry PD. First-episode mania: A neglected priority for early intervention. *Aust.N.Z.J.Psychiatry.* 2002;36(2):158-172.	Not longitudinal prospective study
Coryell W, Norten SG. Mania during adolescence. The pathoplastic significance of age. *Journal of Nervous & Mental Disease.* 1980;168(10):611-613.	Not longitudinal prospective study
Craig TJ, Grossman S, Mojtabai R, et al. Medication use patterns and 2-year outcome in first-admission bipolar disorder with psychotic features. *Bipolar Disord.* 2004;6(5):406-415.	Overlapping sample (See Bromet et al. 2005, 106-113)
Cruz Culebra N, Arrasate M, Vega P, et al. Prognostic value of affective symptomatology in first episodes of psychosis. *European Neuropsychopharmacology.* 2012.;22:S287-S288.	1st BAD sample, but not outcome looked for
Cruz N, Khalsa HM, Baldessarini RJ, et al. The McLean-Harvard first episode project: Two-year functional recovery in 152 first-episode bipolar-I disorder patients. *European Neuropsychopharmacology.* 2011.;21:S420.	1st BD sample, but not outcome looked for
Fiedorowicz JG, Endicott J, Solomon DA, et al. Course of illness following prospectively observed mania or hypomania in individuals presenting with unipolar depression. *Bipolar Disord.* 2012;14(6):664-671.	Including BD II population in analysis and no BD I sub-group
Geller B, Tillman R, Bolhofner K, et al. Pharmacological and non-drug treatment of child bipolar I disorder during prospective eight-year follow-up. *Bipolar Disord.* 2010;12(2):164-171.	Paediatric sample
(Geller B, Tillman R, Bolhofner K. Pharmacological and non-drug treatment of child bipolar I disorder during prospective 8-year follow-up. *J.Child Adolesc.Psychopharmacol.* 2009.;19(6):787-788	Paediatric sample
(Gette et al. 2008, 1125-1133) Gette B, Tillman R, Bolhofner K, et al. Child bipolar i disorder: Prospective continuity with adult bipolar i disorder; Characteristics of second and third episodes; Predictors of 8-year Outcome. *Arch.Gen.Psychiatry.* 2008;65(10):1125-1133.	Paediatric sample
Jiang HK. A prospective one-year follow-up study of patients with bipolar affective disorder. *Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal.* 1999;62(8):477-486.	Written in Chinese
Kauer-Sant'Anna M, Bond DJ, Lam RW, et al. Functional outcomes in first-episode patients with bipolar disorder: a prospective study from the Systematic Treatment Optimization Program for Early Mania project. *Compr.Psychiatry.* 2009;50(1):1-8.	1st BD but not outcome looked for
Keck PE,Jr, McElroy SL, Strakowski SM, et al. Outcome and comorbidity in first- compared with multiple-episode mania. *Journal of Nervous & Mental Disease.* 1995;183(5):320-324.	1st BD but not outcome looked for

Keck PE,Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am.J.Psychiatry.* 1998;155(5):646-652.	Not 1st BD sample or no 1st BD sub-group for analysis
Kessing LV. Recurrence in affective disorder. II. Effect of age and gender. *British Journal of Psychiatry.* 1998;172:29-34.	Not longitudinal prospective study
Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br.J.Psychiatry.* 2013;202(3):212-219	Not 1st BD sample
Khanna R, Gupta N, Shanker S. Course of bipolar disorder in eastern India. *J.Affect.Disord.* 1992;24(1):35-41.	Not 1st BD sample
Mander AJ. Is lithium justified after one manic episode?. *Acta Psychiatr.Scand.* 1986;73(1):60-67	Not longitudinal prospective study
McMurrich S, Sylvia LG, Dupuy JM, et al. Course, outcomes, and psychosocial interventions for first-episode mania. *Bipolar Disord.* 2012;14(8):797-808.	Not longitudinal prospective study
Morrison J, Winokur G, Crowe R, et al. The Iowa 500. The first follow-up. *Arch.Gen.Psychiatry.* 1973;29(5):678-682	Not 1st BD sample or no 1st BD sub-group for analysis
Pedersen J, Aarkrog T. A 10-year follow-up study of an adolescent psychiatric clientele and early predictors of readmission. *Nordic Journal of Psychiatry.* 2001;55(1):11-16.	Not 1st BD sample
Pogge DL, Insalaco B, Bertisch H, et al. Six-year outcomes in first admission adolescent inpatients: clinical and cognitive characteristics at admission as predictors. *Psychiatry Res.* 2008;160(1):47-54.	1st BD but not outcome looked for
Salvadore G, Drevets WC, Henter ID, et al. Early intervention in bipolar disorder, part I: Clinical and imaging findings. *Early Intervention in Psychiatry.* 2008;2(3):122-135.	Not longitudinal prospective study
Schimmelmann BG, Conus P, Cotton S, et al. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *European Psychiatry.* 2012;27(6):463-469.	Not 1st BD sample
Solomon DA, Leon AC, Coryell WH, et al. Longitudinal course of bipolar I disorder: duration of mood episodes. *Arch.Gen.Psychiatry.* 2010;67(4):339-347.	Not 1st BD sample or no 1st BD sub-group for analysis
Srinath S, Janardhan Reddy YC, Girimaji SR, et al. A prospective study of bipolar disorder in	Not 1st BD sample or no 1st BD sub-group for

children and adolescents from India. *Acta Psychiatr.Scand.* 1998;98(6):437-442.	analysis
Strakowski SM, Keck PE,Jr, McElroy SL, et al. Twelve-month outcome after a first hospitalization for affective psychosis. *Arch.Gen.Psychiatry.* 1998;55(1):49-55.	Include depression as 1st episode, and only data on recovery; no 1st manic sub-group
Strakowski SM, Keck PE,Jr, Sax KW, et al. Twelve-month outcome of patients with DSM-III-R schizoaffective disorder: comparisons to matched patients with bipolar disorder. *Schizophr.Res.* 1999;35(2):167-174	Not 1st BD sample or no 1st BD sub-group for analysis
Strakowski SM, Williams JR, Fleck DE, et al. Eight-month functional outcome from mania following a first psychiatric hospitalization. *J.Psychiatr.Res.* 2000;34(3):193-200.	Overlapping sample (See Strakowski et al. 2007, 820-827)
Tohen M, Waternaux CM, Tsuang MT. Outcome in Mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch.Gen.Psychiatry.* 1990;47(12):1106-1111.	Not 1st BD sample or no 1st BD sub-group for analysis
Tohen M, Stoll AL, Strakowski SM, et al. The McLean First-Episode Psychosis project: Six-month recovery and recurrence outcome. *Schizophr.Bull.* 1992;18(2):273-282.	Overlapping sample (See Tohen et al. 2003, 2099-2107)
Tohen M, Strakowski SM, Zarate J, et al. The McLean-Harvard First-Episode Project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biol.Psychiatry.* 2000;48(6):467-476.	Overlapping sample (See Tohen et al. 2003, 2099-2107)
Tohen M. Vieta E. Gonzalez-Pinto A. Reed C. Lin D. European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) Advisory Board. Baseline characteristics and outcomes in patients with first episode or multiple episodes of acute mania. *J.Clin.Psychiatry.* 2010;71(3):255-261.	Duration of follow-up less than 6 months
Wade D, Harrigan S, Harris MG, et al. Treatment for the initial acute phase of first-episode psychosis in a real-world setting. *Psychiatric Bulletin.* 2006;30(4):127-131.	Not 1st BD sample

Supplementary eTable 2: Risk of bias (Cochrane tool modified for naturalistic studies)

	Yatham et al., 2009	*Strakowski et al., 2007Cincinnati setting*	*Strakowski et al., 2007 Tapei setting*	*Delbello et al., 2007*	*Conus et al., 2006*	*Bromet et al., 2005*	*Tohen et al., 2003*	*Khess et al., 1997*	*Tohen et al., 1990*
Assessment of prognostic factors	*+/?*	*+/?*	*+/?*	+	+	*+/?*	+	*+/?*	*+/?*
Assessment of outcome	*+/?*	*+/?*	*+/?*	+	+	*+/?*	+	*+/?*	*+/?*
Adequacy of follow-up, presence and management of missing data	*+/?*	*?*	+	+	*+/?*	+	+	-	+

+: Low risk of bias; - : High risk of bias; ?: Unclear risk of bias

Supplementary eTable 3. Definitions

The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorder [1] is the most up to date consensus on the topic. To summarize the ISBD consensus, remission has no duration criteria, while recovery is defined by 8 consecutive weeks with the virtual absence of depressive and manic or hypomanic symptoms.

Syndromal remission (or recovery) focuses on core affective symptoms (referring to DSM) while "symptomatic" remission (or recovery) is assessed via rating scales. Syndromal depressive remission is achieved when sad mood and\or loss of interest\pleasure are not present, and <3 of the 7 remaining core criteria may be meaningfully (score>3 within a range of 1-7) present. CGI has to be ≤ 2. Syndromal manic remission is defined by DSM criterions A ≤ 2; no B criterion rated >3; no more than two B criteria= 3. As well, CGI score must be ≤ 2.

Symptomatic bipolar depressive remission is attained when HAMD-17 (Hamilton rating scale for Depression) or MADRS (Montgomery-Asberg Depression Rating Scale) score is ≤ 5 or ≤ 7, or BDRS (Bipolar Depression Rating Scale) score is ≤ 8. Symptomatic recovery of mania is defined by YMRS (Young Mania Rating Scale) <5 or <8. Complete remission or recovery is achieved when both mania and depression are not present simultaneously.

Recurrences were always based on syndromal recurrences.

The definitions of symptoms were assessed differently in the included cohorts.

Studies included	Syndromal recovery	Symptomatic recovery

Yatham et al., 2009	DSM-IV criteria in updated results (not presented in 2009 article)	Not assessed
Strakowski et al., 2007 Cincinnati setting	Not assessed	Ratings combining: YMRS≤5 HAMD ≤7 SAPS <2 DSM criteria
Strakowski et al., 2007 Tapei setting	Not assessed	Ratings combining: YMRS≤5 HAMD ≤7 SAPS <2 DSM criteria
Delbello et al., 2007	DSM-IV criteria	Ratings combining: YMRS ≤5 HAMD-17 ≤10 SAPS ≤2 LIFE score ≤2 DSM-IV criteria
Conus et al., 2007	No score >2 on BPRS on these items: grandiosity, excitement, tension and conceptual disorganization Recovery defined as 4 weeks instead of 8.	BPRS ≤ 2 on any item. Recovery defined as 4 weeks instead of 8.
Bromet et al., 2005	DSM-IV criteria	Not assessed

Tohen et al, 2003	DSM-IV criteria (each criteria scored individually)	YMRS<=5 HAMD <=8
Khess and al., 1997	Not assessed	Not assessed
Tohen et al., 1990	Not assessed	Not assessed

DSM: *Diagnostic and Statistical Manual* of Mental Disorders

CGI: Clinical Global Impressions

HAMD: Hamilton rating scale for Depression

MADRS: Montgomery-Asberg Depression Rating Scale

BDRS: Bipolar Depression Rating Scale

YMRS: Young Mania Rating Scale

SAPS: Scale for the Assessment of Positive Symptoms

BPRS: Brief Psychiatric Rating Scale

[1] Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) task force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord.* 2009;11(5):453-473.

Supplementary eTable 4. Medication details for each cohort.

Study	Medication
Yatham et al., 2009	Non-adherence rate: 37% (10/27) after 1 year; defined as at least one event of discontinuation of medication against medical advice. Treatment: "Comprehensive care and evidenced-based pharmacotherapy and psychoeducation". Entry: 86.6% (46/53) on a mood stabilizer. 77.4% (41/53) on an antipsychotic. 0.6% (3/53) on an antidepressant. 62% (38/53) on a combination of one mood stabilizer and one antipsychotic. Psychoeducation: 43.4% completed 8-week program.
Strakowski et al., 2007 Cincinnati	Non-adherence rate: 41%; defined as taking medication less than 75% of time. Treatment not described.
Strakowski et al., 2007 Tapei	Non-adherence rate: 21%; defined as taking medication less than 75% of time. Treatment not described.
Delbello et al., 2007	Non-adherence rate: 23% (16/71), partial adherence 42% (30/71). Treatment during initial year of follow-up: 59% (42/71) with at least one mood stabilizer (95% {40/71} with lithium and/or valproic

	acid, 2.4% {1/71} with topiramate and 2.4% {1/71} with lamotrigine). 66% (47/71) with an atypical antipsychotic. 24% (17/71) with an antidepressant. 27% (19/71) with a psychostimulant. Psychotherapeutic intervention.
Conus et al., 2006	Adherence not described. Standard clinical care provided in a center specialized in the treatment of early psychosis. Treatment not described.
Bromet et al., 2005	Non-adherence rate not described. At discharge from hospital: 93% (115/123) with one or more medications. 55.3% (68/123) on an anti-manic. 81.3% (100/123) on an antipsychotic. 10.6% (13/123) on an antidepressant. 43.9% (54/123) on a combination of an anti-manic and an antipsychotic.
Tohen et al., 2003	Not taking medication at 2 years: 35.6% (45/138) Treatment at discharge from hospital: 95.2% (158/166) on at least 1 psychotropic agent.

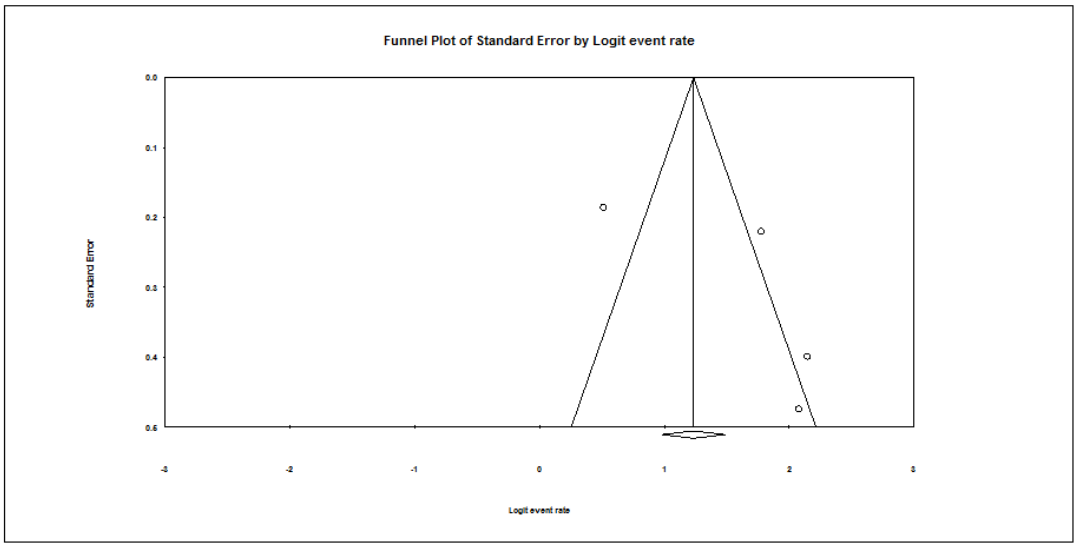
	75.3% (125/166) on an antipsychotic. 68.7% (114/166) on lithium. 23.5% (39/166) on valproate. 9.0% (15/166) on an antidepressant. 4.2% (7/166) on other anticonvulsant. 9.6% (16/166) on monotherapy (4.8% {8/166} lithium monotherapy) Treatment at 2 years of follow-up: 17.0% (23/135) on an antipsychotic. 38.5% (52/135) on lithium. 21.5% (29/135) on valproate. 3.7% (5/135) on another anticonvulsant. 20.0% (27/135) on an antidepressant. 28.1% (38/135) on monotherapy (Lithium monotherapy 17.0% {23/135})
Khess et all., 1997	Poor compliance rate: 34.4% (11\32); no definition given. Treatment during follow-up: 40.6% (13/32) on lithium. 53.1% (17/32) on other drugs. 6.3% (2/32) on no drugs.
Tohen et al., 1990	Not taking medication at 4 years: 45.8% (11/24). Treatment at discharge from hospital: 92% (22/24) on a psychotropic drug.

	87.5% (21/24) on lithium. Treatment at 4 years: 45.8% (11/24) with no psychotropic drugs. 92.3% (12/13) patients still taking medication were on lithium (58% {7/12} in monotherapy, 25% {3/12} in combination with a neuroleptic agent and 16.7% {2/12} with an antidepressant.0.8% {1/13} patient treated with carbamazepine and a neuroleptic).

Supplementary *eFigure 7. Syndromal recovery rate funnel plot. The funnel plots revealed an asymmetrical distribution at 6 months.*

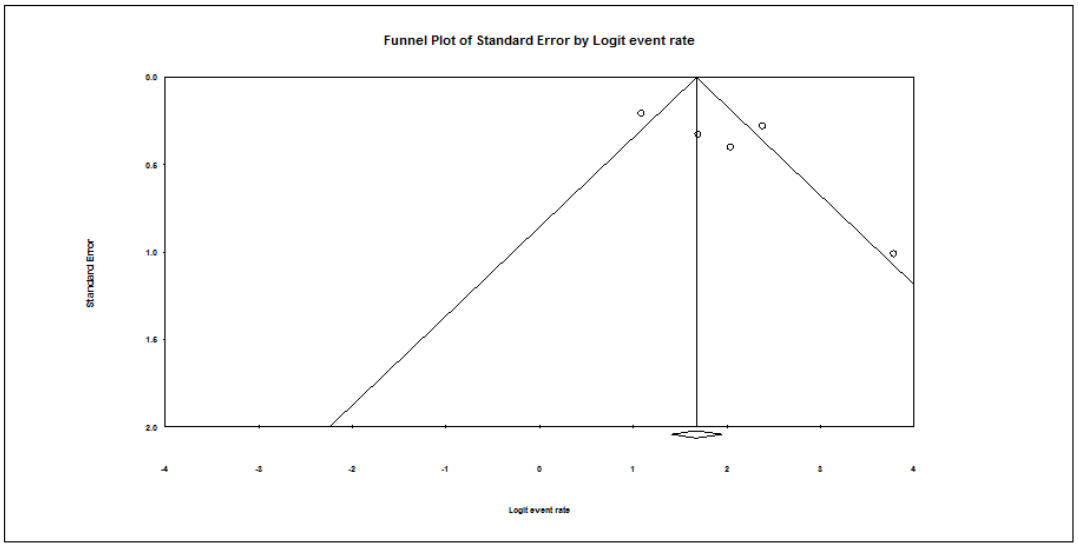
A

6 Months

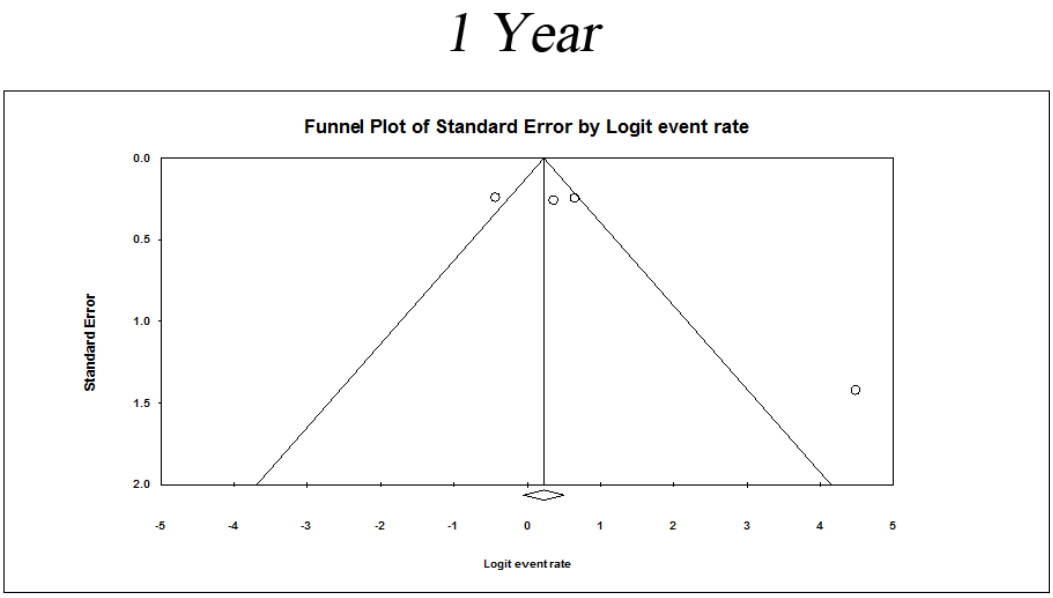


B

1 Year



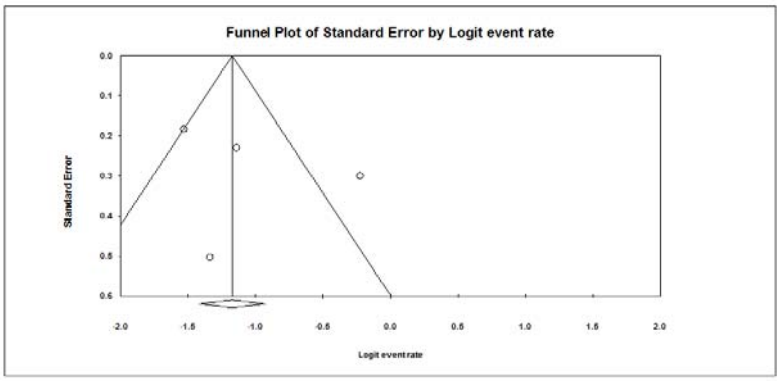
Supplementary eFigure 8. Symptomatic recovery rate funnel plot. Examination of the funnel plot revealed that the Strakowski Taipei sample was the contributor to significant heterogeneity.



Supplementary eFigure 9. Recurrence funnel rate plot. The funnel plots at 6 months and 1 year were symmetrical.

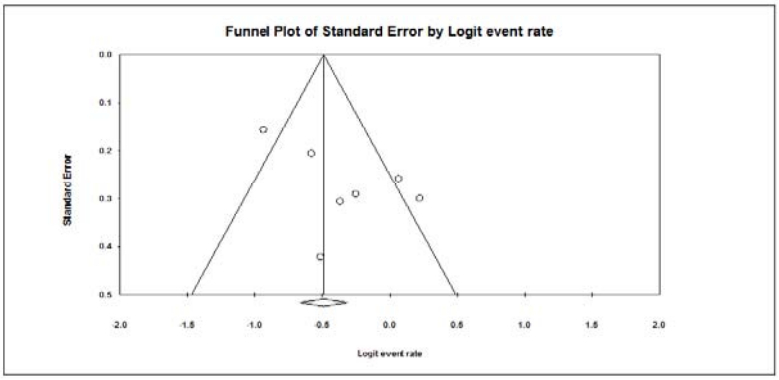
A

6 Months



B

1 Year



C

4 Years