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

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ABSTRACT

Objective: Information about recurrence rates is useful in informing clinical practice, but most data with regard to recurrence rates in bipolar patients come from cohorts at different stages of illness. These data are of limited utility in estimating risk of relapse in first-episode bipolar disorder. Therefore, the objective of this investigation was to synthesize available recurrence data after a first episode of mania.

Data Sources: We searched MEDLINE, EMBASE, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) from 1980 to January 24th, 2014, for articles in English, French, or Spanish using (1) *bipolar disorder* (MeSH term) *OR manic/mania, AND* (2) *first** (*episode*, hospitalization* OR admission**) *OR time factor* (MeSH term), *AND* (3) *recovery, remission, recurrence OR relapse*.

Study Selection: 712 articles were screened. Prospective cohorts of first-episode mania were included.

Data Extraction: Syndromal recovery, symptomatic recovery, and recurrence rates were extracted by 2 independent raters at 6 months, 1 year, 2 years, and 4 years and analyzed using random effects models and meta-regression.

Results: We identified 8 studies representing a total of 734 first-episode patients. The syndromal recovery rates were 77.4% at 6 months and 84.2% at 1 year. Only 62.1% of patients had achieved a period of symptomatic recovery within 1 year. Recurrence rates were 25.7% within 6 months, 41.0% by 1 year, and 59.7% by 4 years. Younger age at first episode was associated with risk of recurrence after 1 year.

Conclusions: The majority of patients with first-episode mania exhibit syndromal recovery and, to a lesser extent, symptomatic recovery. The risk of recurrence is high, although the rates are slightly lower than those in mixed cohorts, with greater risk of recurrence associated with younger age at onset. Given lower recurrence than among mixed cohorts, there may be a window of opportunity to provide optimal treatment early and alter disease progression.

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Bipolar I disorder is a severe psychiatric disorder affecting about 0.6%[1] to 1.0%[2] of individuals worldwide. Onset peaks in adolescence and young adulthood, most often before the age of 21 years.[3,4] Bipolar disorder is a chronic recurrent illness that results in significant disability.[5] Bipolar disorder is associated with significant impairment in psychosocial functioning, even during euthymic periods that is often related to persistent cognitive dysfunction.[6] Moreover, bipolar disorder is associated with significant premature loss of life, with more than a third of bipolar disorder patients attempting suicide during their lifetime.[7]

Most of the information regarding the clinical characteristics, course, and natural history of bipolar disorder comes from cross-sectional or prospective cohort studies that included patients at different stages of illness.[8–17] Such naturalistic data suggest that lifetime manic recurrences occur in 85%–90% of patients.[18,19] Since the progression of bipolar disorder is accompanied by changes in its characteristics and severity, information from studies including individuals at different illness stages[20] is of limited value in determining relapse/recurrence risk estimates for patients who experience their first manic episode. Furthermore, adequate treatment early in the course of the disorder may lead to improved outcomes.[21,22] Therefore, careful characterization of the natural history of bipolar disorder from disease onset is critical to appropriately informing and educating patients and for tailoring interventions.

In the last 2 decades, there have been attempts to examine the natural history of bipolar disorder after a first episode of mania.[23–31] These studies have revealed significant heterogeneity in outcomes, with recurrence rates ranging between 37.5%[8] and 52%[25] after 1 year. Within these studies, a number of predictors of higher recurrence rates have emerged that include medication nonadherence,[29] comorbid substance use,[24–26,30] younger age,[23,26,27] psychosis,[30] and the absence of psychotherapeutic intervention.[25]

While there have been reviews of the first-episode mania literature,[32] to our knowledge, a synthesis of data ensuing from first-episode manic cohorts has not been reported. Therefore, the objective of this systematic review and meta-analysis was to synthesize the available data with regard to syndromal and symptomatic recovery, as well as recurrence rates after a first manic episode.

METHOD

Data Sources and Selection

This systematic review and meta-analysis was performed according to PRISMA guidelines (Supplementary eFigure 1, available at PSYCHIATRIST.COM).[33] We performed a systematic literature search using the following databases: MEDLINE, EMBASE, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) from 1980 to January 24th, 2014. The search was registered with

Clinical Points

- While the vast majority of patients with first-episode mania exhibit syndromal recovery within the first year, they are also at high risk of recurrence.
- Younger age at first manic episode predicts greater risk of recurrence at 1 year.
- Since there might be a window of opportunity to alter the progression of bipolar I disorder, intensive early intervention programs aimed at changing the course of this debilitating disease should be encouraged, and additional characterization of their efficacy should be monitored.

PROSPERO (CRD42014009038), and search procedures (including syntaxes, parameters, and results) are described in detail in the supplementary material (see Supplementary eFigures 2 to 6 and Supplementary eTable 1). We also reviewed the bibliography of studies retained for additional unidentified studies. The computerized search in MEDLINE combined 3 sets of terms: (1) *bipolar disorder* (MeSH term) *OR manic/mania*, *AND* (2) *first** (*episode*, hospitalization* OR admission**) *OR time factor* (MeSH term), *AND* (3) *recovery, remission, recurrence OR relapse*. Data extraction was performed by 2 independent raters (A.G. and A.M. or L.N.Y.), and inconsistencies were resolved by consensus review.

The studies were included if they recruited patients that met *DSM* or *ICD* diagnosis of bipolar I disorder with the index episode identified as the first manic or mixed episode, or as the first hospitalization for a manic or mixed episode. Only independent cohorts were selected, and corresponding authors were contacted in order to avoid independent consideration of dual publication samples. Studies needed to be prospective and longitudinal, peer-reviewed, written in English, French, or Spanish, and required a minimal follow-up duration of at least 6 months. Finally, raw data had to be available (or obtained after authors were contacted) for syndromal remission or recovery, symptomatic remission or recovery, or relapse or recurrence.

Studies were excluded if the sample involved exclusively pediatric patients or a very specific population (eg, postpartum, schizoaffective disorder). Patients with bipolar I disorder initially identified through a major depressive episode representing > 10% of the sample were excluded. Cohorts pooling bipolar I disorder and bipolar II disorder were also discarded.

In cases where potentially eligible studies were missing key data for our meta-analysis, their corresponding authors were contacted twice by e-mail at 2-week intervals. An expanded sample size and follow-up duration were obtained for 2 studies.[23,28] Study quality was assessed using Cochrane Collaboration's tool for assessing risk of bias in cohort studies (Supplementary eTable 2).[34]

Data Extraction

Data were recorded in a structured fashion. Demographic and clinical characteristics included were age, sex, type of first episode (manic vs mixed vs depressive), presence of psychotic features, rapid cycling, and comorbid substance use. The primary outcome consisted of the rates of recurrence, and these data were extracted at 6 months, 1 year, 2 years, and 4 years. The secondary outcome consisted of syndromal recovery, symptomatic recovery, and dropout rates/lost to follow-up.

Definitions

Course and *outcome* were defined according to the International Society for Bipolar Disorders (ISBD) Task Force report.[35] Study definitions that varied from our predefined definitions were reclassified, or used as they were defined in the published manuscript if reclassification was not possible (Supplementary eTable 3). With respect to recurrence, specifically, an affective switch was not considered a recurrence.

Data Synthesis and Analyses

Analyses were performed using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, New Jersey) and IBM SPSS Version 20 (IBM Corporation, Chicago, Illinois).

A random-effects model was used because we assumed that the true rates of recovery and recurrence had most likely varied between the included studies.[36] For binary outcomes (ie, symptomatic recovery, syndromal recovery, recurrence, dropouts), we calculated the respective event rates (ie, the proportion of patients in whom the event was observed at a specific time point).[37] Weighting was performed for each study using the inverse variance method.[38] While we graphically represented data when only 2 or fewer studies were available per time point, we did not perform analyses because with 2 or fewer samples, it is not possible to produce funnel plots or estimate publication bias.[37]

Meta-regression using Q statistic was performed to predict the recurrence rate at 1 year.[37] We considered putative predictors of recurrence among variables repeatedly identified in first-episode and unselected cohorts, namely psychotic symptoms,[28] substance misuse,[39] rapid cycling,[40] and age at onset.[23] Meta-regression was contingent on the availability of the predictor in ≥ 5 cohorts.

Heterogeneity was assessed using the Q statistic and the I^2 index.[38] Values of $P < .10$ for the former and/or > 35% for the latter were deemed as indicative of study heterogeneity.[37] Finally, we used funnel plots and the fail-safe number to test for the presence of publication bias.[37,38]

RESULTS

Literature Search

Included trials: main characteristics. The literature search strategy is detailed in the supplementary material (see Supplementary eFigures 2–6 and Supplementary eTable 1). We identified 8 articles[23–30] that met inclusion criteria describing 9 cohorts (2 cohorts described in 1 article[24]). All articles included both manic and mixed episodes. Mixed episodes were described in 4 trials,[24,25,27,28] which represented 29% (148/502) of the total sample from these studies.

Table 1. Epidemiologic and Clinical Characteristics of Cohorts

Study	Study Design	Cohort	No. of Patients at Entry and Follow-Up	Follow-Up, y	Mean (SD) Age, y, at Admission	Sex (% of males)	% With Psychosis at First Episode (n/n)	% With Substance Use Disorder (n/n)	% of Dropout/Lost to Follow-Up (n)
Yatham et al, 2009[23,a]	1st mania	Systematic Treatment Optimization Program for Early Mania (STOP-EM)	53 45 (1 y)	1	22.2 (3.7) Inclusion: 14–35	50.9	67.9 (36/53)	54 (29/53)	11.3 (6)
Strakowski et al, 2007[24]	1st hospitalization for mania	Cincinnati	96 73 (1 y)	1	25 (7) Inclusion: 16–45	58	83 (80/96)	49 (47/96)	24.0 (23)
Strakowski et al, 2007[24]	1st hospitalization for mania	Taipei	46 44 (1 y)	1	26 (6) Inclusion: 16–45	43	85 (39/46)	10.9 (5/46)	4.3 (2)
DelBello et al, 2007[25]	1st hospitalization for mania	Cincinnati	71 62 (1 y)	1	15.2 (1.9) Inclusion: 12–18	42	41 (29/71)	8 (6/71)	9.4 (9)
Conus et al, 2006[26]	1st mania with psychotic features	Early Psychosis Prevention and Intervention Centre (EPPIC)	87 61 (1 y)	1	22.1 (3.5) Inclusion: 16–45	55.2	100[b] (87/87)	32.2 (28/87)	30.0 (26)
Bromet et al, 2005[27]	1st hospitalization for psychotic bipolar disorder	Suffolk County Mental Health Project (SCMHP)	123 106 (4 y)	4	29.7 (10.1) Inclusion: 15–60	47.2	100[b] (123/123)	50.4 (62/123)	…
Tohen et al, 2003[28,a]	1st hospitalization for mania	McLean/ Harvard 1st Episode Mania study	202 202 (2 y)	4[a]	31.6 (13.0) Inclusion: 18–75	53.5	90.1 (182/202)	21.3 (43/202)	6.6 (11)
Khess et al, 1997[29]	1st mania requiring hospitalization	Ranchi, India	51 32 (4 y)	4	28 (9.07) Inclusion: No limits	87.5	68.8 (22/32)	37.5 (12/32)	37.3 (19)
Tohen et al, 1990[30]	1st mania requiring hospitalization	Harvard, Belmont	24 24 (4 y)	4	26 Inclusion: >17	54	62.5 (15/24)	12.5 (3/24)	0 (0)

[a]With expanded sample and follow-up as provided by the corresponding author.
[b]Inclusion criteria.

Of the 9 cohorts, 8 assessed outcome after a first manic or mixed episode or hospitalization. One cohort[27] prospectively characterized hospitalized patients and included 11 patients (8.9%) in the final analyses whose first presentation of bipolar I disorder was a depressive episode.

Demographic and clinical characteristics are shown in Table 1. The 8 included studies represented a total of 753 patients with bipolar disorder identified during a first manic episode (n = 140, 19.1%) or first manic hospitalization (n = 613, 80.9%). This sample was composed of 388 males (52.8%) and 346 females (47.1%). For 1 study (n = 24), a mean age of 26 years was reported with no measure of variance; however, the remainder of the sample had a mean (SD) age of 24.92 (2.15) years.

Psychotic symptoms were reported in 613 of 734 patients (83.5%), and substance abuse was reported to be present in 31.6% of the sample (232 of 734 patients).

Description of the medication and adherence can be found in the supplementary material (see Supplementary eTable 4). The rates of nonadherence in the 9 different cohorts ranged from 21%[24] to 45.8%,[30] and up to 65% if partial adherence was included.[25] The majority of patients were treated with multiple medications, primarily mood stabilizers and antipsychotics. Regarding mood stabilizers, lithium appears to have been the most widely used.

Sample retention was reported in 7 studies representing 83.2% of the total sample. Pooled analyses revealed a dropout rate of 19.1% (95% CI, 15.8%–22.9%).

Data pertaining to syndromal recovery were presented in 5 cohorts, representing 64% (472/734) of patients included in this review.[23,25–28] Symptomatic recovery was described in 5 cohorts, representing 47% (347/734) of the sample.[24–26,28] Recurrence rates were detailed in 8 cohorts,[23–25,27–30] totaling 82% (385/472) of the sample that achieved recovery. Results for syndromal recovery, symptomatic recovery, and recurrence rates from these studies are summarized in Table 2.

Syndromal and symptomatic recovery. With respect to syndromal recovery, pooled rates were 84.2% (95% CI, 80.3%–87.5%) at 6 months and 87.5% (95% CI, 78.1%–93.2%) at 1 year (Figure 1A). There was no evidence of significant improvement from 6 months to 1 year ($Q = 0.28$, $df = 1$, $P = .59$). Heterogeneity between the studies exceeded that expected by chance at 6 months ($Q = 25.93$, $df = 2$, $P < .001$, $I^2 = 92.28$) and at 1 year ($Q = 15.21$, $df = 3$, $P < .01$, $I^2 = 80.28$), and examination of the funnel plots revealed an asymmetric distribution at 6 months (Supplementary eFigure 7). The fail-safe number was 107, meaning that 107 unpublished trials would be required to significantly change the estimate.

Table 2. Outcome of Prospective Studies on Bipolar Disorder After a First Manic Episode

Time Point	Yatham et al, 2009[23]	Strakowski et al, 2007[24] Cincinnati setting	Strakowski et al, 2007[24] Taipei setting	DelBello et al, 2007[25]	Conus et al, 2006[26]	Bromet et al, 2005[27]	Tohen et al, 2003[28]	Khess et al, 1997[29]	Tohen et al, 1990[30]
Syndromal recovery									
0.5 year	88.9%	…	…	…	89.6%	62.8%	85.5%	…	…
1 year	97.8%	…	…	84.5%	88.5%	74.8%	91.6%	…	…
2 years	…	…	…	…	…	…	97.6%	…	…
4 years	…	…	…	…	…	83.7%	…	…	…
Symptomatic recovery									
0.5 year	…	…	…	…	58.2%	…	…	…	…
1 year	…	65.8%	100%	39.4%	59%	…	…	…	…
2 years	…	…	…	…	…	…	71.7%	…	…
Recurrence									
0.5 year	44.4%	…	…	…	…	24.3%	17.8%	…	20.8%
1 year	55.8%	43.8%	40.9%	51.7%	…	35.9%	28.2%	…	37.5%
2 years	…	…	…	…	…	…	49.0%	…	41.7%
4 years	…	…	…	…	…	61.2%	…	59.4%	54.2%

Pooled symptomatic recovery rates were 62.1% (95% CI, 41.9%–78.9%) at 1 year (Figure 1B). Heterogeneity between studies exceeded that expected by chance ($Q = 19.53$, $df = 3$, $P < .001$, $I^2 = 84.63$), and examination of the funnel plot (Supplementary eFigure 8) revealed that the Strakowski's Taipei sample[24] was the contributor to significant heterogeneity. When analyses were repeated excluding this sample, a symptomatic recovery rate of 54.1% (95% CI, 47.5%–61.4%) at 1 year was observed. The fail-safe number was 4.

We did not compute pooled syndromal recovery rates at 2 years or 4 years, or symptomatic recovery rates at 6 months, 2 years, or 4 years, due to data being available from an insufficient number of studies.

Recurrence. Pooled rates of patients who experienced a manic, mixed, or depressive recurrence were 25.7% (95% CI, 16.3%–38.2%) at 6 months, 41.0% (95% CI, 33.0%–49.5%) at 1 year, and 59.7% (95% CI, 51.9%–67.1%) at 4 years (Figure 1C). Recurrence rates were not computed at 2 years due to an insufficient number of studies. The increase in recurrence rate between 6 months and 1 year was statistically significant ($Q = 4.09$, $df = 1$, $P < .05$), as was the increase between 1 year and 4 years ($Q = 10.05$, $df = 1$, $P < .01$).

Heterogeneity was examined within these time points, and there was evidence of heterogeneity exceeding chance at 6 months ($Q = 13.89$, $df = 3$, $P < .01$, $I^2 = 78.40$) and at 1 year ($Q = 19.37$, $df = 6$, $P < .01$, $I^2 = 69.02$), but not at 4 years ($Q = 0.39$, $df = 2$, $P = .82$, $I^2 = 0.00$). The funnel plots at 6 months and 1 year were symmetrical (Supplementary eFigure 9); the trim and fill procedure did not remove studies at either time point. The fail-safe number was 69 at 6 months, and 25 at 1 year.

We sought to explain the variance in recurrence rates using multiple linear meta-regression. We focused on recurrence at 1 year to maximize the studies available for association. Age was inversely proportional to the risk of recurrence ($Q = 15.70$, $df = 1$, $P = .00007$; slope = −0.06, 95% CI, −0.10 to 0.40, $z = 3.96$, $P = .00007$; intercept = 1.32, 95% CI, 0.40–2.23, $z = 2.83$, $P = .004$; Figure 2). Our regression model predicts a 49.3% risk of recurrence at 1 year for a first episode at 20 years of age, 40.9% for a first episode at 25 years of age, and 33.1% for a first episode at 30 years of age. Nonsignificant associations were found with respect to psychotic symptoms at first presentation ($Q = 0.41$, $df = 1$, $P = .518$) and comorbid substance use disorders ($Q = 0.12$, $df = 1$, $P = .72$).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of first-episode mania cohorts. Our analyses suggest that while the majority of patients achieve syndromal recovery within 6 months to 1 year of first-episode mania, symptomatic recovery is less often achieved and patients remain at high risk for recurrence. Specifically, syndromal recovery was achieved within 6 months for the majority of patients (77.4%) with only incremental improvement thereafter, while symptomatic recovery rates were lower with only 62% of patients classified as achieving recovery within 1 year. Our analyses further suggest that 26% of patients experience a recurrence of mood episode by 6 months, 41% within 1 year, and 60% within 4 years.

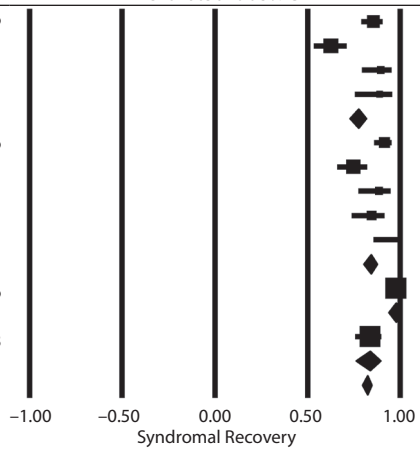
The large difference observed between syndromal and symptomatic recovery rates highlights one of the major challenges in the management of bipolar disorder. Indeed, the functional impairment associated with bipolar disorder cannot be overstated, highlighted by ongoing occupational impairment experienced by approximately 40% of patients in long-term follow-up.[40] Similarly, significant and enduring deficits in self-esteem are observed in patients with bipolar disorder, despite symptom remission.[41] Though poorer outcomes have been associated with illness characteristics such as the presence of mixed episodes[42] and rapid cycling,[40] the current data highlight the need for aggressive treatment using a comprehensive biopsychosocial approach.

Our data suggest that recurrence risk increases with time in 25.7% of first-episode patients experiencing a recurrence within 6 months. This rate steadily rises to 41% at 1 year and approximately 60% by 4 years. This information can be used to guide decisions with regard to continuation/maintenance

Figure 1. Forest Plot Demonstrating Rates of (A) Syndromal Recovery, (B) Symptomatic Recovery, and (C) Recurrence

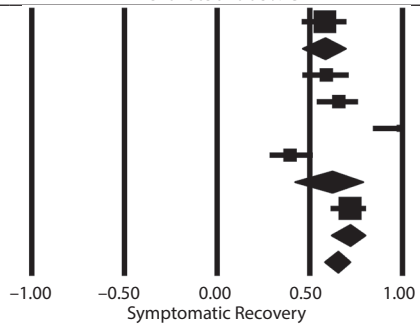
A

Group by Time Point	Study Name, Year (Citation no.)	Subgroup Within Study	Time Point	Event Rate	Statistics for Each Study: Lower Limit	Upper Limit	*P* Value	Total	Relative Weight
0.5 year	Tohen et al, 2003 (28)	…	0.5 year	0.855	0.793	0.901	.000	142/166	34.19
0.5 year	Bromet et al, 2005 (27)	…	0.5 year	0.626	0.537	0.707	.006	77/123	47.96
0.5 year	Conus et al, 2006 (26)	…	0.5 year	0.896	0.797	0.949	.000	60/67	10.44
0.5 year	Yatham et al, 2009 (23)	…	0.5 year	0.889	0.759	0.953	.000	40/45	7.40
0.5 year				0.774	0.727	0.816	.000		
1 year	Tohen et al, 2003 (28)	…	1 year	0.916	0.863	0.949	.000	152/166	24.43
1 year	Bromet et al, 2005 (27)	…	1 year	0.748	0.664	0.817	.000	92/123	44.19
1 year	Conus et al, 2006 (26)	…	1 year	0.885	0.778	0.944	.000	54/61	11 .81
1 year	DelBello et al, 2007 (25)	…	1 year	0.845	0.741	0.912	.000	60/71	17.71
1 year	Yatham et al, 2009 (23)	…	1 year	0.978	0.858	0.997	.000	44/45	1.86
1 year				0.842	0.803	0.875	.000		
2 years	Tohen et al, 2003 (28)	…	2 years	0.976	0.938	0.991	.000	162/166	100.00
2 years				0.976	0.938	0.991	.006		
4 years	Bromet et al, 2005 (27)	…	4 years	0.837	0.761	0.893	.000	103/123	100.00
4 years				0.837	0.761	0.893	.000		
Overall				0.822	0.796	0.846	.000		



B

Group by Time Point	Study Name, Year (Citation no.)	Subgroup Within Study	Time Point	Event Rate	Statistics for Each Study: Lower Limit	Upper Limit	*P* Value	Total	Relative Weight
0.5 year	Conus et al, 2006 (26)	…	0.5 year	0.582	0.462	0.694	.181	39/67	100.00
0.5 year				0.582	0.462	0.694	.181		
1 year	Conus et al, 2006 (26)	…	1 year	0.590	0.464	0.706	.161	36/61	30.73
1 year	Strakowski et al, 2007 (24)	Cincinnati	1 year	0.658	0.542	0.757	.008	48/73	31 .10
1 year	Strakowski et al, 2007 (24)	Taipei	1 year	0.989	0.846	0.999	.002	44/44	6.97
1 year	DelBello et al, 2007 (25)	…	1 year	0.394	0.288	0.512	.077	28/71	31.20
1 year				0.621	0.419	0.789	.239		
2 years	Tohen et al, 2003 (28)	…	2 years	0.717	0.617	0.800	.000	66/92	100.00
2 years				0.717	0.617	0.800	.000		
Overall				0.652	0.580	0.719	.000		



C

Group by Time Point	Study Name, Year (Citation no.)	Subgroup Within Study	Time Point	Event Rate	Statistics for Each Study: Lower Limit	Upper Limit	*P* Value	Total	Relative Weight
0.5 year	Tohen et al, 1990 (30)	…	0.5 year	0.208	0.089	0.413	.008	5/24	17.09
0.5 year	Tohen et al, 2003 (28)	…	0.5 year	0.178	0.131	0.237	.000	36/202	29.84
0.5 year	Bromet et al, 2005 (27)	…	0.5 year	0.243	0.170	0.335	.000	25/103	28.03
0.5 year	Yatham et al, 2009 (23)	…	0.5 year	0.444	0.308	0.590	.457	20/45	25.04
0.5 year				0.257	0.163	0.382	.000		
1 year	Tohen et al, 1990 (30)	…	1 year	0.375	0.208	0.578	.226	9/24	9.67
1 year	Tohen et al, 2003 (28)	…	1 year	0.282	0.224	0.348	.000	57/202	18.61
1 year	Bromet et al, 2005 (27)	…	1 year	0.359	0.273	0.456	.005	37/103	16.81
1 year	Strakowski et al, 2007 (24)	Cincinnati	1 year	0.438	0.305	0.579	.388	21/48	13.65
1 year	Strakowski et al, 2007 (24)	Taipei	1 year	0.409	0.275	0.558	.230	18/44	13.11
1 year	DelBello et al, 2007 (25)	…	1 year	0.517	0.392	0.639	.796	31/60	14.83
1 year	Yatham et al, 2009 (23)	…	1 year	0.556	0.410	0.692	.457	25/45	13.33
1 year				0.410	0.330	0.495	.039		
2 years	Tohen et al, 1990 (30)	…	2 years	0.417	0.241	0.617	.416	10/24	10.36
2 years	Tohen et al, 2003 (28)	…	2 years	0.490	0.422	0.559	.778	99/202	89.64
2 years				0.482	0.418	0.548	.597		
4 years	Tohen et al, 1990 (30)	…	4 years	0.542	0.346	0.725	.683	13/24	15.62
4 years	Khess et al, 1997 (29)	…	4 years	0.594	0.419	0.747	.292	19/32	20.24
4 years	Bromet et al, 2005 (27)	…	4 years	0.612	0.514	0.701	.025	63/103	64.14
4 years				0.597	0.519	0.671	.015		
Overall				0.477	0.436	0.518	.276		

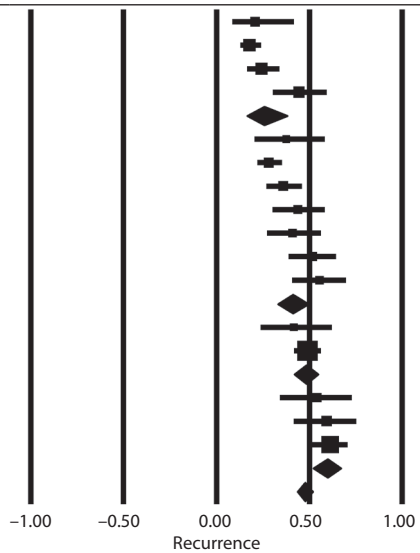
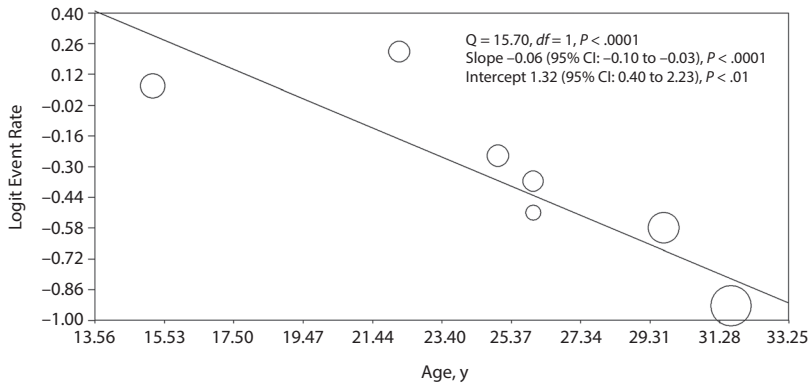


Figure 2. Meta-Regression Demonstrating the Relationship Between Age and Risk of Recurrence at 1 Year



treatment of bipolar disorder. An unanswered question is what characterizes the protective factors in the 40% of patients that stay well for up to 4 years. Unfortunately, the first-episode mania literature has not focused on protective factors. At present, this literature principally suggests minimizing risk factors as the target for recurrence prevention. The lone exception is psychotherapeutic intervention, which emerged as a significant protective factor in 1 study.[25] The role of psychosocial interventions in bipolar disorder has been recently reviewed,[32] and while there is a limited evidence base on which to draw, psychosocial interventions may play a disease-altering role in bipolar disorder.

These findings also suggest that recurrence rates are slightly lower in first-episode mania cohorts compared with the recurrence rates reported from unselected (not first episode) samples. Indeed, Keller et al (n = 172) found that recurrences rates were between 47%–58% at 1 year and 81%–91% at 5 years.[9] The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort (n = 858) had a recurrence rate of 48.5% at 2 years,[43] while Tohen et al (n = 75) described a recurrence rate of 72% at 4 years.[8] Higher rates of recurrence in unselected populations are consistent with previous observations that suggest that the interval between episodes tends to shorten with successive episodes[12,44,45] and that the effectiveness of lithium may be reduced with successive episodes.[46] Thus, early optimized pharmacotherapy and psychotherapy intervention, with the objective to prevent recurrence, should be the primary goal for managing patients with bipolar disorder with the hope of altering the disease progression and improving outcomes.

Our data suggest that age at onset carries important prognostic implications with respect to recurrence risk. Indeed, a strong relationship emerged between risk of recurrence at 1 year and age, with our regression model predicting that a first episode at age 20 is associated with a 49.3% risk of recurrence, compared to 40.9% for a first episode at 25 years of age, and 33.1% at 30 years of age. This association is consistent with previous reports suggesting that early age at onset is associated with poorer outcomes.[3,23,26,28,47–52] However, it is important to note that there is inconsistency in the literature, with several older studies finding no association[53] or a better prognosis[54,55] with early age at onset. Nevertheless, early age at onset has been associated with several negative prognostic factors including higher rates of comorbidity, particularly with substance use disorders,[50,56] illness features including rapid-cycling course,[50] and lower rates of medication adherence.[23] Increased risk with early age of onset is also consistent with the hypothesis that the genetic liability and familial environment associated with early onset of mania are associated with poorer prognosis.[4,56–58] Indeed, some have advocated for the addition of an early onset diagnostic specifier.[59]

Delay to treatment also has important clinical implications and has been associated with poorer outcomes.[26,51,60] Indeed, delay to treatment and age at onset are likely related factors, as early age at onset has been associated with longer delay to first treatment.[51,52] At-risk cohorts will possibly shed more light on the accurate warning signs or the order of transitional stages[61] to help refine early diagnosis and develop tailored approaches and treatments. Intensive programs for patients with first-episode mania might also help to reduce the burden and improve outcomes for a population that is in a critical period of development.[62]

Though rates of psychosis and substance use were not linearly related to the risk of recurrence at 1 year in our meta-regression, this may, in part, be due to their bimodal distribution across studies and the limited power of our meta-regression. Moreover, our analyses could not differentiate the impact of lifetime substance use history relative to substance abuse at the time preceding admission or during follow-up.[24–26,30] We caution against minimizing the importance of psychosis and substance use as predictors of recurrence. Indeed, both have clearly been associated with serious adverse events in this population, including death, prolonged hospitalization, and congenital anomalies in offspring.[63]

Limitations

One limitation is that selected cohorts differed in their characteristics. For example, 1 study[27] included a small

percentage (8.9%) of bipolar I disorder prospectively characterized patients who were initially identified after a depressive episode. Of the 9 cohorts, 7 included only hospitalized patients, and 2 selected only patients presenting with psychotic features; therefore, generalizability to the subset of patients who do not experience psychosis or to the minority that do not require hospitalization is limited. Moreover, considering only first hospitalization may have resulted in a biased sample by ignoring patients with unrecognized illness and, conversely, incorrectly identifying patients with previous episodes as first-episode mania. Our meta-regression of age at onset utilized mean age of each cohort, as individual patient data were not available, and therefore replication, as well as collaboration and pooling of individual data to confirm the association, is required. Further, future studies should examine other clinical features associated with early age at onset. Medication adherence was variably defined across studies, and therefore, we could not provide pooled analyses or meta-regression controlling for treatment adherence. Similarly, substance comorbidity was presented differently across studies. Further, our meta-analysis did not consider important indicators of functioning, such as employment, nor did it consider factors such as quality of life.

A limitation of the meta-analytic method is the combination of heterogeneous studies, poor-quality or unrepresentative studies, or the potential of publication bias. While we cannot definitively rule out these influences, we have attempted to temper these by using a comprehensive systematic review of the literature, assessing the quality of studies and examining both publication bias and heterogeneity.

CONCLUSION

First-episode mania is associated with limited rates of symptomatic recovery and a high risk of recurrence that is strongly associated with younger age at onset. Further study of first-episode cohorts is required, as is additional characterization of the efficacy of intensive early intervention programs aimed at changing the course of this debilitating disorder.

Drug names: lithium (Lithobid and others).

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Supplementary material: Available at PSYCHIATRIST.COM.

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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

Author(s): Andréanne Gignac, MD; Alexander McGirr, MD, MSc; Raymond W. Lam, MD; and Lakshmi N. Yatham, MBBS

DOI Number: doi:10.4088/JCP.14r09245

List of Supplementary Material for the article

Supplementary Material

Supplementary eFigure 1: Prisma 2009 Checklist

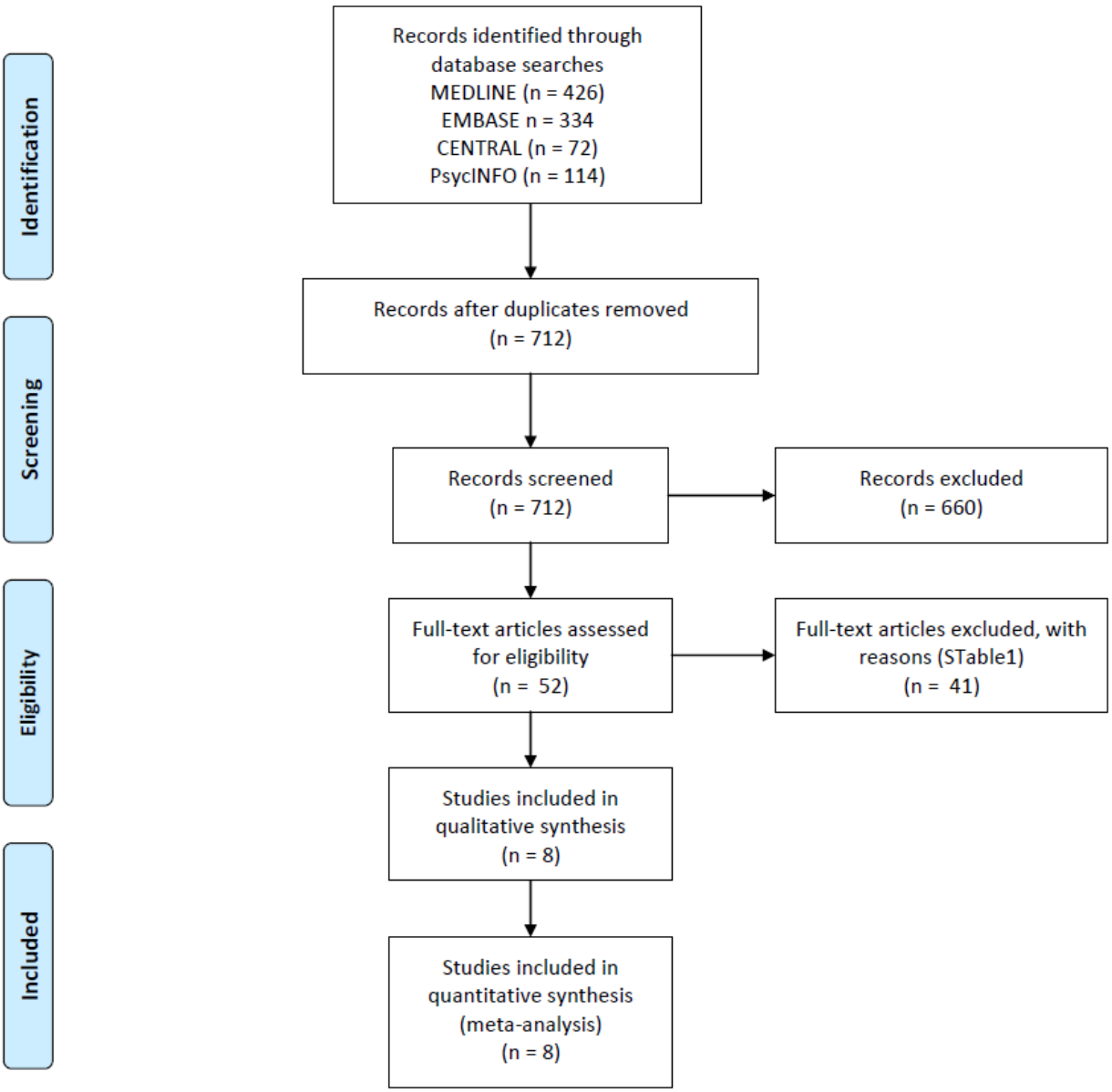
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, 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

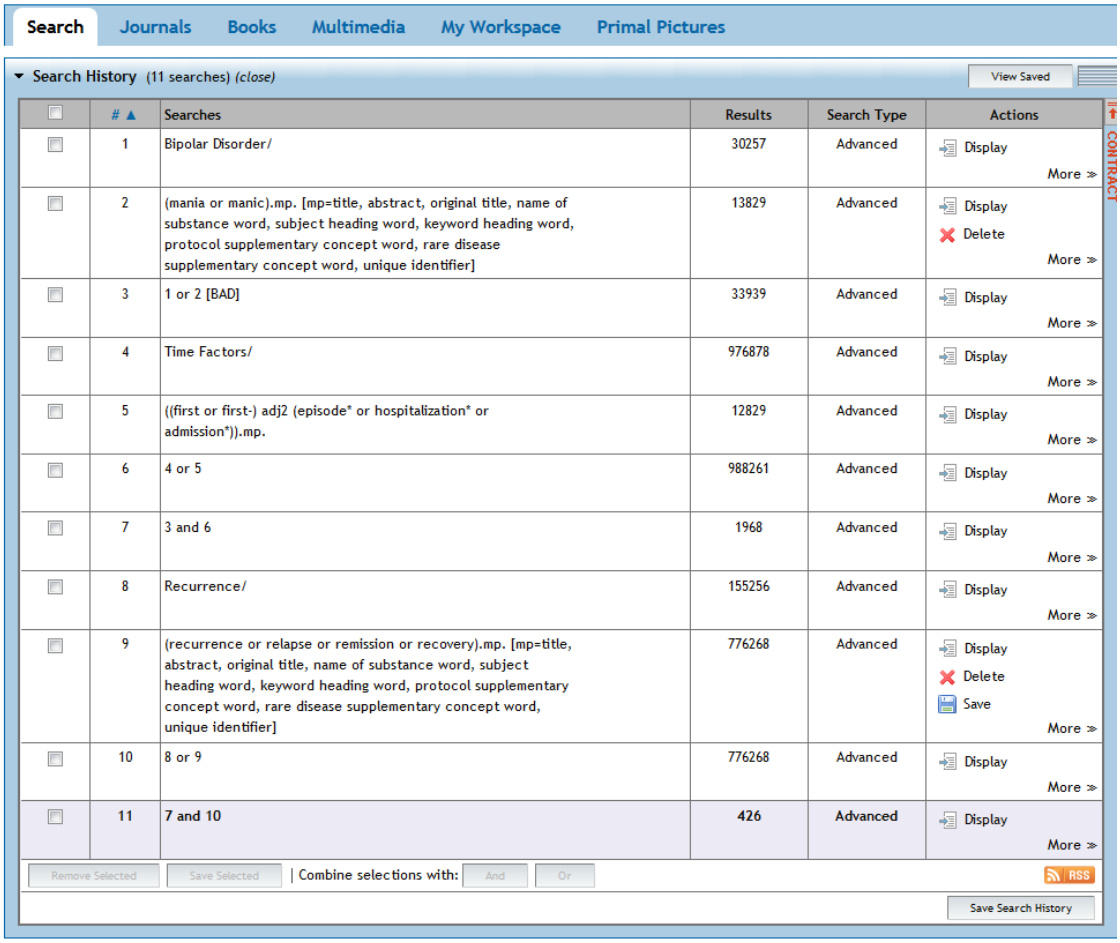
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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 »

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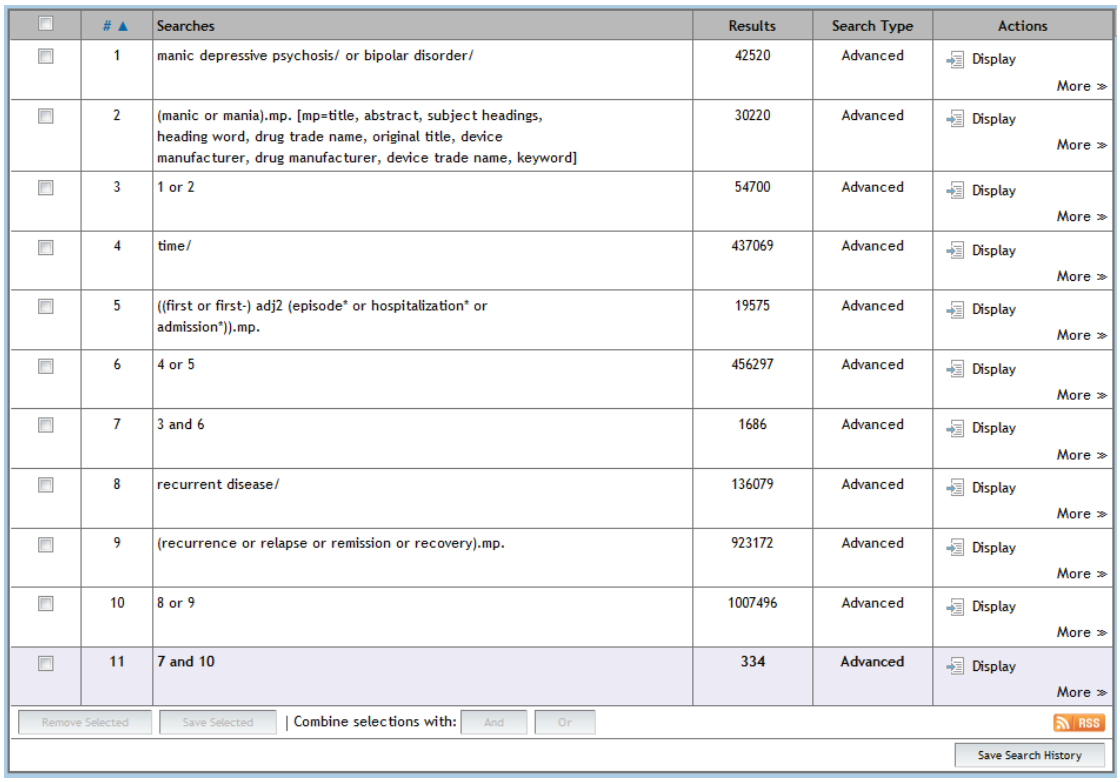
CONTRACT

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

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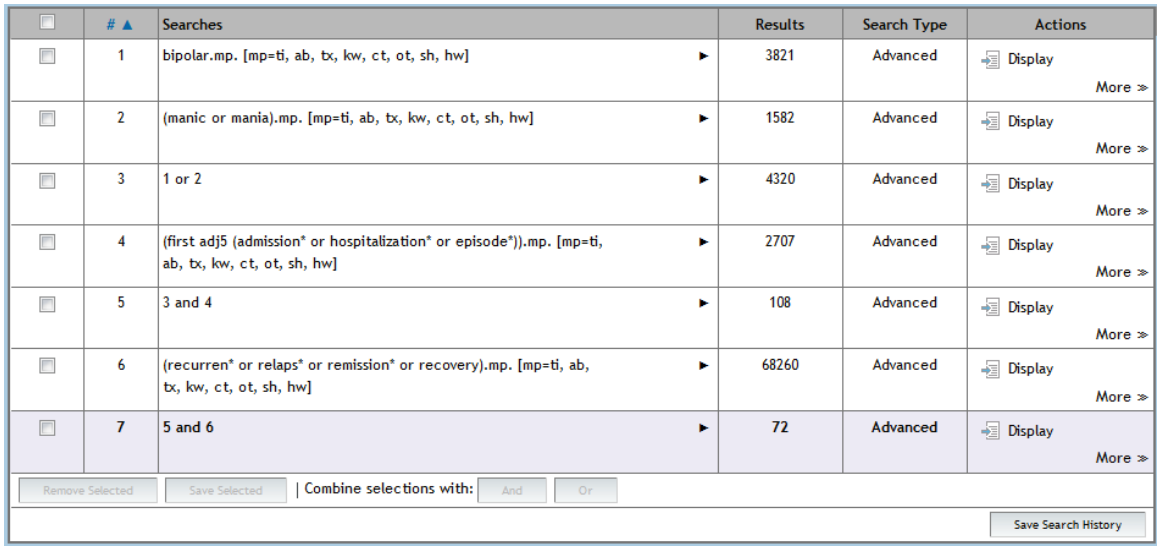
Supplementary eFigure 5. EBM CENTRAL (Ovid Interface) search strategy and results.



# ▲	Searches	Results	Search Type	Actions
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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.

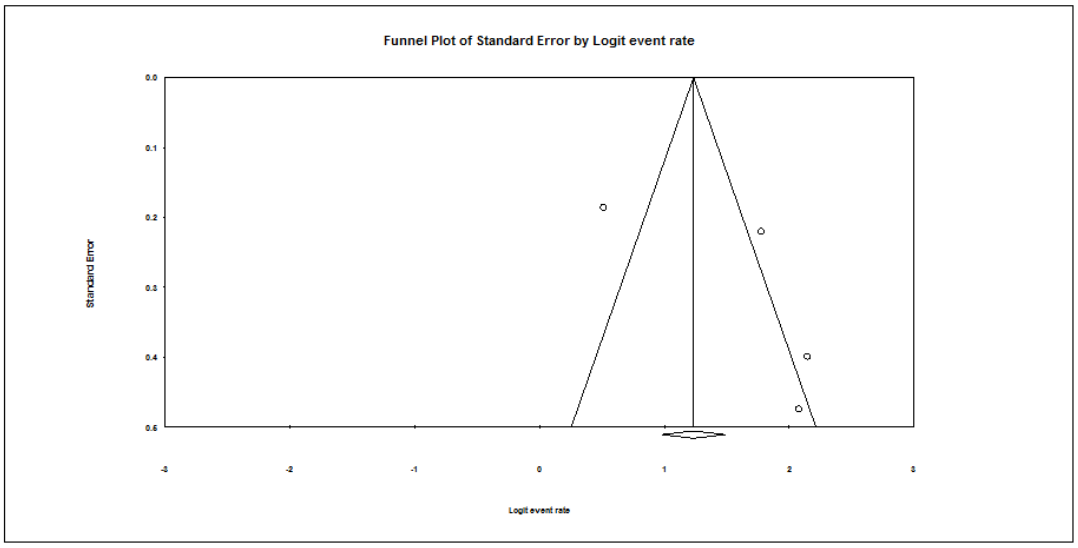
	75.3% (125/166) on an antipsychotic. 68.7% (114/166) on lithium. 23.5% (39/166) on valproate. 9.0% (15/166) on an antidepressant. 4.2% (7/166) on other anticonvulsant. 9.6% (16/166) on monotherapy (4.8% {8/166} lithium monotherapy) Treatment at 2 years of follow-up: 17.0% (23/135) on an antipsychotic. 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.*

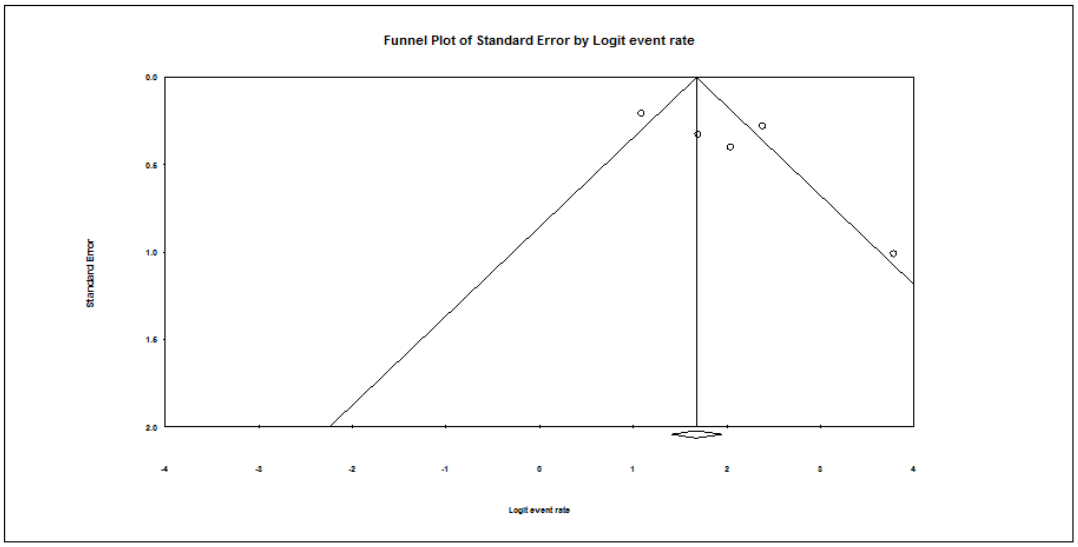
A

6 Months

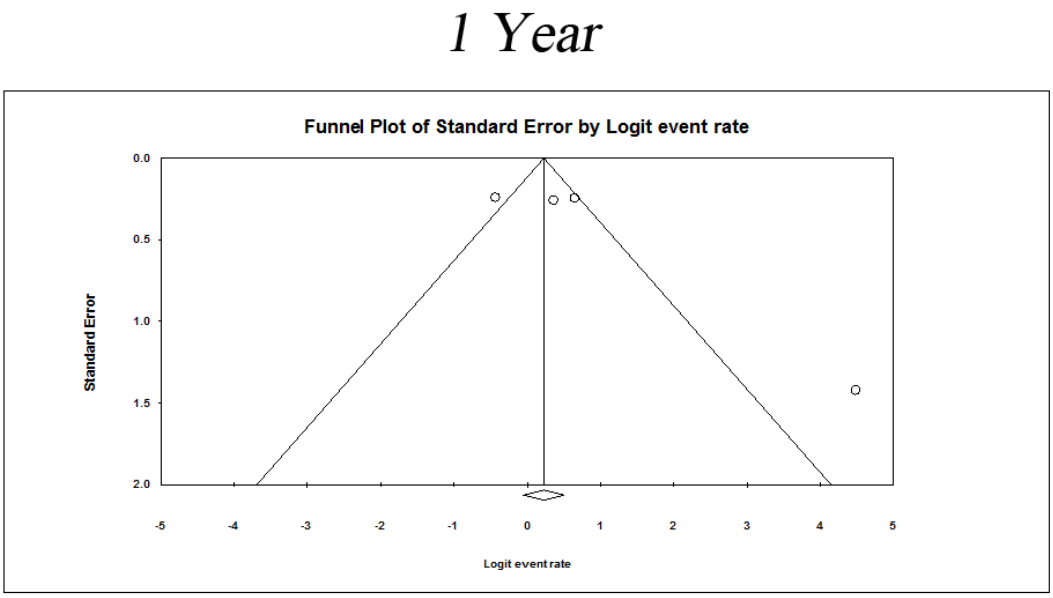


B

1 Year



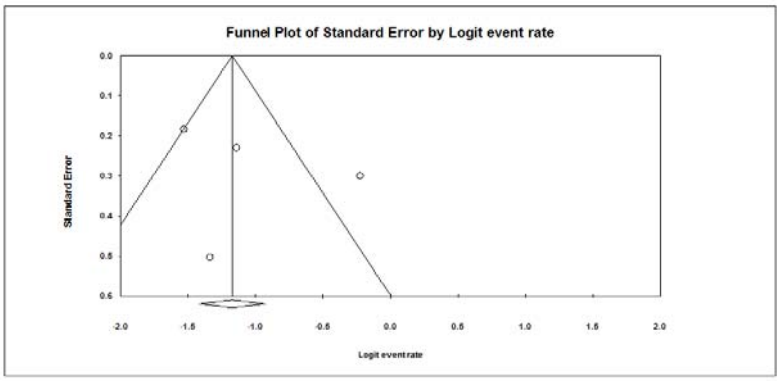
Supplementary eFigure 8. Symptomatic recovery rate funnel plot. Examination of the funnel plot revealed that the Strakowski Taipei sample was the contributor to significant heterogeneity.



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

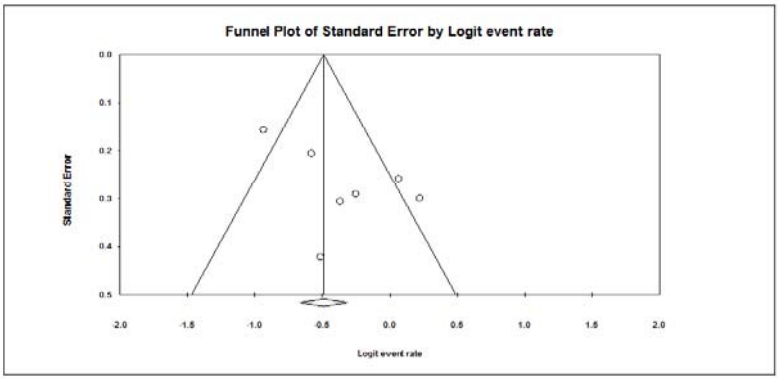
A

6 Months



B

1 Year



C

4 Years