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REVIEW

Recurrence rates in bipolar disorder: Systematic comparison of long-term prospective, naturalistic studies versus randomized controlled trials

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Abstract
Bipolar disorder (BD) is a recurrent, lifelong illness with high risks of disability and excess mortality. Despite many treatment options with demonstrated short-term efficacy, evidence concerning long-term treatment effectiveness in BD remains limited and the relative value of naturalistic studies versus randomized, controlled trials (RCTs) in its assessment, uncertain. Systematic computer-searching yielded 10 naturalistic studies and 15 RCTs suitable for analysis of recurrence rates and their association with treatments and selected clinical factors. In naturalistic studies (3904 BD subjects, 53.3% women, 85.8% BD-I, mean onset age 29.1, followed up to 2.1 years), the pooled recurrence rate was 55.2% (26.3%/year). In RCTs (4828 subjects, 50.9% women, 96.0% BD-I, mean onset age 23.1, followed up to 1.9 years), the pooled recurrence rate was 39.3% (21.9%/year) with mood-stabilizing drug-treatment versus 60.6% (31.3%/year) with placebo; drug-versus-placebo outcomes favored antipsychotics over lithium, and disfavor an approved anticonvulsant. Depressive episode-polarity increased from 27.7% at intake to 52.0% at first-recurrence ($p<0.0001$). Recurrence rate (%/year) did not differ by study-type, was greater with younger onset and rapid-cycling, and paradoxically *declined* with longer observation. In short, recurrences of major affective episodes up to two years during putative mood-stabilizing treatment of BD patients in prospective, naturalistic

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studies and RCTs were substantial and similar (26.3 vs. 21.9%/year). Episode-polarity shifted strongly toward depressive first-recurrences. These findings support the value of naturalistic studies to complement long-term RCTs, and add to indications that control of depression in BD remains particularly unsatisfactory.

1. Introduction

Bipolar disorder (BD), including types I (with mania) and II (with hypomania), is characterized by severe alterations in mood and behavior, with a prevalence of approximately 2.4% in the general population (Merikangas et al., 2011). BD typically follows a lifelong episodic course, produces significant dysfunction, and can increase mortality owing to suicide and later adverse outcomes of co-occurring medical illnesses (Goodwin et al., 2007; Hayes et al., 2015). More than 90% of BD patients experience at least two lifetime acute affective episodes, and most have multiple recurrences of mania-like, depressive, affectively mixed, or psychotic episodes, even with treatments of proven short- and probable long-term efficacy (Perlis et al., 2006; Baldessarini, 2013). Incomplete prevention of recurrences probably reflects limitations in the effectiveness of available treatments, particularly with respect to preventing bipolar depressive episodes, as well as major contributions of incomplete or inconsistent adherence to recommended treatments (Yatham et al., 2013; Pacchiarotti et al., 2013; Forte et al., 2105).

Experimental evaluation of long-term or maintenance treatments with prophylactic intent in BD has yielded variable results. A common limitation is that participants in trials for long-term treatment are often selected for responding to and tolerating short-term treatment in acute, index episodes, usually of mania, possibly exaggerating apparent effectiveness of particular treatments (especially of antimanic agents) and greatly limiting ability to generalize observed effects (Kulkarni et al., 2012). Moreover, complex cases, such as with co-occurring anxiety or substance abuse disorders, marked behavioral dyscontrol, and high suicidal risk, typically are excluded from long-term, randomized, controlled trials (RCTs), potentially further limiting generalizability of findings to broader clinical populations (Persons & Silberschatz, 1998; Moller, 2011; Baldessarini, 2013; Baldessarini et al., 2014).

In response to the uncertain generalizability of results of controlled, long-term trials in BD to broader and more clinically realistic samples and conditions, there is growing interest in findings from naturalistic studies. Although there are reviews and meta-analyses of findings from limited numbers of controlled, long-term, treatment trials in BD (Vieta et al., 2011; Popovic et al., 2012; Baldessarini, 2013; Cipriani et al., 2014), systematic comparisons with corresponding naturalistic studies are lacking. Accordingly, we carried out a systematic review of outcomes in long-term, naturalistic studies of treated BD patients in order to assess treatment effectiveness under clinically realistic, non-experimental conditions, and compared their results with those of long-term RCTs in BD. We also considered selected clinical and sociodemographic factors for associations with recurrence rates and the polarities of index and recurrent episodes.

2. Experimental procedures

2.1. Data sources and eligibility criteria

A systematic, computerized literature search was carried out using the MEDLINE/PubMed®, EMBASE, PsycINFO, and ClinicalTrials.gov databases through May 2015. For naturalistic studies, searching employed combinations of the key words: “bipolar disorders,” “follow up,” “long term,” “maintenance treatment,” “naturalistic,” “recurrence,” “relapse,” and “survival”. For reports of RCTs we used combinations of the keywords: “bipolar disorders,” “follow up,” “prevention,” “maintenance treatment,” “recurrence,” “relapse,” “efficacy,” “randomized or randomised,” and “trial,” as well as names of specific medicines: “aripiprazole, carbamazepine, divalproex, lamotrigine, lithium, olanzapine, placebo, quetiapine, risperidone, and valproate,” as well as medication classes (“anticonvulsants, antipsychotics, mood-stabilizers”). Both searches were supplemented by review of bibliographies of included research reports and of relevant reviews (Geddes et al., 2004; Popovic et al., 2011; Vieta et al., 2011; Cipriani et al., 2014; Forte et al., 2015). Included for analysis were studies of maintenance treatment of patients diagnosed with type I or II BD with at least 15 subjects per treatment-arm, and nominally lasting 18–30 months. Searches were reviewed independently by two investigators (JH, GHV), and any disagreements were resolved by consensus.

The search process yielded 5388 initial citations of naturalistic studies for preliminary screening. Of these, 5171 reports were excluded as not meeting our inclusion criteria, and 217 abstracts appearing to meet initial inclusion criteria were reviewed further. Following exclusion of another 48 reports, full texts of 169 reports were then reviewed, leaving 10 that met study criteria (e-Appendix Figure 1A). Initial searching for reports of relevant RCTs yielded 593 potential citations for preliminary screening; 358 were excluded as not meeting our inclusion criteria, leaving 235 abstracts for review, with another 176 exclusions. Review of the remaining 59 full reports yielded 15 reports of long-term RCTs for inclusion (e-Appendix Figure 1B).

2.2. Data extraction

From the 25 identified reports meeting study criteria, we extracted required data, including reference citation, year of reporting, numbers of subjects per subgroup, proportion diagnosed as BD-I, proportion of women, mean age at intake, estimated age at onset of BD, history of rapid-cycling (≥ 4 recurrences in any 12 month period) or of substance abuse or anxiety disorder, treatments given, months of observation and follow-up, and proportion of subjects with at least one recurrence of a syndromal episode of mania, hypomania, mixed-state, or depression during follow-up averaging two years. In addition, we included the polarity of index and first recurrent episodes when reported.

2.3. Statistical analysis

For categorical and continuous data, we calculated the average prevalence of each specified characteristic, with 95% confidence intervals (CIs). Factors of interest were tested for relationship to recurrence rate by bivariate linear regression (slope function, β with CI) or ANOVA

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Table 1 Subject characteristics in naturalistic studies of long-term outcome in bipolar disorder.

Study	Subjects N	% BD-I	F/U Yrs	Onset Age	Intake Age	% of Subjects					% Depressed		Dropout Rate (%)	Recurrence rate (%)
						Fem	RC	Suicidal	Anx Dx	SUD	Intake	Recur		
Silverstone et al. (1998)	120	100	2.0	21.0	40.0	63.3	2.50	-	-	-	-	32.1	10.0	48.3
Dittmann et al. (2002)	152	72.1	2.5	24.4	42.1	51.7	40.7	36.6	12.5	26.3	-	-	35.5	55.9
Tohen et al. (2003)	166	30.5	2.0	-	32.5	45.8	-	4.0	20.6	18.7	75.3	50.0	16.8	40.4
Fekadu et al. (2006)	312	100	2.5	-	29.5	43.9	-	-	-	-	-	-	7.00	66.0
Perlis et al. (2006)	858	71.0	2.0	16.7	39.9	59.0	27.4	35.6	37.0	49.3	63.3	71.6	24.9	48.5
Altamura et al. (2008)	232	39.2	2.0	31.2	51.9	65.1	-	-	-	-	-	-	44.0	54.7
Hong et al. (2010)	1379	100	2.0	36.2	45.2	39.2	15.4	27.0	-	3.60	100	-	7.30	54.3
Kulkarni et al. (2012)	175	100	2.0	42.0	42.0	61.1	-	58.9	-	18.3	40.0	65.0	7.10	64.5
Li et al. (2014)	210	81.0	2.0	27.8	39.4	59.5	-	-	-	-	48.1	-	38.1	61.0
Simhandl et al. (2014)	300	52.7	2.0	33.3	45.2	71.3	-	-	9.30	19.7	39.7	60.0	18.0	58.0
***Totals/Means* [95% CI]**	**3904**	**74.6 [56-94]**	**2.06 [1.9-2.2]**	**28.2 [24-32]**	**41.9 [41-43]**	**51.5 [49-60]**	**19.9 [14-26]**	**30.9 [24-38]**	**27.0 [11-43]**	**20.9 [15-26]**	**69.6 [58-88]**	**55.7 [46-67]**	**20.9 [11-31]**	**55.2 [50-61]**

Abbreviations: *N*, number of subjects; *F/U*, years of follow-up; *Fem*, women; *RC*, rapid-cycling ($\geq$ 4 episodes in any year); *Recur*, recurrence, *suicidal*, ideation; *Anx Dx*, lifetime anxiety disorder; *SUD*, lifetime substance use disorder; *Dep*, depression. Averages and 95% confidence intervals (CI) are weighted by N/study. Active treatments employed were: [a] mood-stabilizing anticonvulsants or lithium (59.0% [CI: 52.7-65.3]), [b] antidepressants (50.6% [45.2-55.9]), [c] antipsychotics (38.0% [32.6-43.4]), and [d] miscellaneous other psychotropics (43.75 [37.6-49.8]); total exceeds 100% since there was an average of 1.9 drugs/patient.

Table 2 Characteristics of bipolar disorder subjects in 15 long-term, randomized, controlled trials.

Study	Subjects (*N*)	% BD-I	Onset Age	Intake Age	F/U Yrs	% Fem	% RC	% Suicidal	% Depressed		Dropout Rate (%)	Recurrence Rate (%)
									Intake	Recur		
Quitkin et al. (1981)	75	100	-	36.8	2.0	52.0	-	-	-	34.7	52.0	26.7
Lithium	38											21.1
Lithium + Imipramine	37											32.4
Prien et al. (1984)	114	-	24.9	38.1	2.0	58.0	-	-	53.0	48.8	31.0	61.5
Lithium	42											54.8
Imipramine	36											80.6
Lithium + Imipramine	36											50.0
Greil et al. (1997)	144	58.0	-	44.0	2.5	52.0	-	32.2	-	-	28.5	36.1
Lithium	74											28.0
Carbamazepine	70											47.0
Bowden et al. (2003)	175	100	-	40.7	1.5	53.1	-	27.4	0.00	46.1	23.4	45.1
Lamotrigine	59											40.7
Lithium	46											34.8
Placebo	70											61.4
Calabrese et al. (2003)	454	100	-	44.0	1.5	56.0	-	31.7	-	72.3	33.7	51.0
Lamotrigine	215											53.5
Lithium	120											46.7
Placebo	119											55.5
Hartong et al. (2003)	94	76.6	31.6	41.9	2.0	54.0	10.6	-	53.2	55.3	30.9	35.1
Lithium	44											31.8
Carbamazepine	50											42.0
Tohen et al. (2004)	99	100	21.0	41.3	1.5	51.5	41.4	-	0.00	68.7	48.5	47.5
Lithium or Valproate	51											55.3
Both + Olanzapine	48											36.7
Findling et al. (2005)	60	91.7	7.3	10.7	1.5	35.0	50.0	-	0.00	10.6	26.7	63.3
Lithium	30											60.0
Valproate	30											66.7
Keck et al. (2007)	160	100	-	40.0	2.0	67.0	-	-	0.00	54.6	68.9	32.5
Aripiprazole	77											26.0
Placebo	83											43.4
Vieta et al. (2008)	703	100	-	42.1	2.0	55.0	23.9	-	29.3	45.2	16.2	34.4
Lithium or Valproate	367											49.0
Either + Quetiapine	336											18.5
Suppes et al. (2009)	623	100	-	40.1	2.0	52.5	51.0	-	30.7	63.4	35.5	36.3
Lithium or Valproate	313											52.1
Either + Quetiapine	310											20.3
Geddes et al. (2010)	320	100	-	43.1	2.0	52.0	-	-	33.6	62.1	42.4	60.6
Lithium	110											59.0

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Valproate	110											69.0
Lithium+Valproate	100											54.0
Quiroz et al. (2010)	303	100	31.5	39.0	2.0	49.0	-	-	0.00	47.4	-	38.9
Risperidone	154											27.3
Placebo	149											51.0
Weisler et al. (2011)	1172	100	-	39.5	2.0	53.3	13.9	-	27.7	48.8	21.1	46.1
Quetiapine	404											20.8
Lithium	364											24.5
Placebo	404											50.0
Vieta et al. (2012)	398	100	-	36.9	1.5	52.4	-	-	-	43.9	18.3	39.4
Risperidone	132											38.9
Olanzapine	131											23.8
Placebo	135											56.4
Totals/Means [95% CI]												
Overall	4894	94.7	26.7	40.2	1.90	53.5	26.5	30.8	20.7	58.8	34.1	39.3 [32-46]
Drugs	3934	[88-100]	[11-36]	[34-43]	[1.7-2.0]	[49-56]	[18-46]	[29-32]	[6.2-35]	[33-84]	[26-43]	34.1 [28-40]
Placebo	960											60.6 [38-84]

Overall recurrence rates are for active treatments only (excluding the imipramine-only arm in Prien et al., 1984).

(*t*-score), followed by stepwise, multivariate linear regression modeling of factors in order of significance in preliminary bivariate analyses. We also tested for drug-placebo differences when available, using random-effects meta-analysis when trial count was ≥ 3, and fixed-effect models with only 1 or 2 trials. Analyses were based on Statview.5® spreadsheets (SAS Institute, Cary, NC), and commercial statistical software, R.3.0.1® (R Foundation, Vienna, Austria), SAS.9.4® (SAS Institute), and Stata.13® (StataCorp., College Station, TX).

3. Results

3.1. Comparison of naturalistic with controlled trials

Systematic searching yielded 10 long-term, naturalistic studies (e-Appendix Figure 1A) and 15 RCTs (e-Appendix Figure 1B) involving a total of 8798 BD patients followed up to 2.1 [95% CI: 1.9-2.2] or 1.9 [1.7-2.0] years, respectively. Salient characteristics of these studies are summarized in Tables 1-3. Of note, demographic and clinical characteristics of subjects in the two samples were similar with respect to age at intake, approximate age at onset, proportion of women, and reported length of follow-up, although RCT participants more often had type I BD (94.7% [CI: 87.6-100] vs. 74.6% [55.7-93.6]; $t=2.50$, $p=0.02$) and higher study-dropout rates (34.1% vs. 20.9%; $t=2.30$, $p=0.03$; Tables 1-3). Data on co-occurring psychiatric conditions (mainly anxiety or substance use disorders) was found only in the naturalistic studies (Table 3).

Among the 10 naturalistic studies analyzed, overall recurrence risk (% of subjects) averaged 55.2% [CI: 49.6-60.8], and ranged from 40.4% to 66.0% (Table 1), (Perlis et al., 2006; Kulkarni et al., 2012; Silverstone et al., 1998; Dittmann et al., 2002; Tohen et al., 2003; Fekadu et al., 2006; Altamura et al., 2008; Hong et al., 2010; Li et al., 2014; Simhandl et al., 2014) annualized recurrence rates averaged 26.3 [23.6-29.0] %/year. Most subjects in these clinical trials (69.6%) presented with depressive index episodes, and a majority (55.7%) of their first recurrent episodes during two years of follow-up also were depressive (Table 1). Types of treatments used in these naturalistic studies (Table 1, footnotes) ranked: lithium or anticonvulsants with putative mood-stabilizing activity (carbamazepine, gabapentin, lamotrigine, topiramate, or valproate; 59.0%), with or without antidepressants (mainly serotonin reuptake inhibitors or bupropion; 50.6%), unspecified, or combined treatments (43.7%), or atypical antipsychotics (mostly olanzapine, quetiapine, or risperidone; 38.0%); more than one medicine was used by approximately 91% of participants. Recurrence rates in naturalistic studies did not correlate significantly with proportions of mood-stabilizers, antipsychotics, or antidepressants used ($r=0.257$ to 0.366, all $p \geq 0.37$; not shown).

In the 15 RCTs, with active medications, the overall recurrence rate (omitting one trial-arm testing imipramine alone; Prien et al., 1984) averaged 39.3% [CI: 32.3-46.3] %, or 21.9 [CI: 19.2-24.6] %/year, and ranged from 18.5-20.3% (with quetiapine added to lithium or valproate) to 66.7% (with valproate alone; Table 2), (Quitkin et al., 1981; Prien et al., 1984; Greil et al., 1997; Bowden et al., 2003; Calabrese et al., 2003; Hartong et al., 2003; Tohen et al., 2004; Findling et al.; 2005; Keck et al., 2007; Vieta et al., 2008; Suppes et al., 2009; Geddes et al., 2010; Quiroz

Table 3 Comparison of naturalistic and controlled trials of long-term treatment of bipolar disorder patients.

Characteristic	Naturalistic	Controlled	*p*-value (*t*-score)
Drug-treated groups (*n*)[a]	10	31	-
Subjects (*N*)	3904	4828	-
Onset age (yrs)	29.1±8.30	23.1±8.97	0.15 (1.49)
Intake age (yrs)	43.2±4.17	34.8±12.0	0.08 (1.87)
Women (%)	53.3±10.5	50.9±6.33	0.56 (0.35)
Bipolar-I (%)	85.8±16.4	96.0±8.09	0.08 (1.84)
Ever rapid-cycling (%)	21.5±16.3	32.0±16.5	0.27 (1.14)
Initially depressed (%)	69.6±25.0	0.00±0.00	0.005 (4.71)
First recurrence depression (%)	55.7±15.4	51.5±14.5	0.55 (0.74)
Years followed	2.06±0.18	1.77±0.26	0.01 (2.71)
Dropout rate, drugs (%)[a]	20.9±14.0	33.2±12.8	0.01 (2.58)
Recurrence risk, drugs (%/yr)[a]	26.3±3.14	21.9±2.70	0.50 (0.68)

[a]Placebo arms of controlled trials not included.

Table 4 Meta-analyses of placebo-controlled long-term trials in bipolar disorder.

Treatment	Trials (*n*)	Subjects (*N*)	RR [95% CI]	NNT [95% CI]	*p*-value [z-score]
Antipsychotics	4	996	0.56[0.092-0.45]	4.3[3.3-6.1]	<0.0001[5.28]
Lithium	2	1123	0.62[0.42-0.91]	4.9[3.1-11]	0.01[2.76]
Anticonvulsant	3	463	0.87[0.73-1.0]	13[6.0-56]	0.12[1.56]
All drugs	9	2582	0.63[0.51-0.77]	5.1[3.8-7.7]	<0.0001[4.45]

Based on meta-analysis (random-effects when $n \geq 3$), with statistics based on the ratio of drug/placebo recurrence risk (% of subjects), as shown in Table 2. Findings are ranked in descending order of apparent efficacy. The only anticonvulsant tested vs. placebo was lamotrigine; antipsychotics included aripiprazole, olanzapine, and risperidone.

et al., 2010; Weisler et al., 2011; Vieta et al., 2012). In the placebo arms of the six trials with such controls, recurrence rates averaged 60.6% [CI: 46.4-59.5], or 31.3 [CI: 22.8-39.8] %/year. Although most controlled trial participants were initially treated for mania or hypomania (79.3%), a majority of first-recurrences were depressive (58.8%; Table 2).

Based on summarized characteristics, the 10 naturalistic and 15 controlled trials were quite similar (Table 3). Of particular note, annualized recurrence rates (%/year) were similar in naturalistic and controlled trials (26.3 vs. 21.9%/year; $t=0.50$, $p=0.68$), whereas dropout rates were significantly more prevalent in the active medication arms of the controlled trials (33.2% vs. 20.9%, $t=2.58$, $p=0.01$; Table 3). Overall, there was a marked increase in the proportion of depressive episodes between intake and first-recurrences, especially in the randomized, controlled trials (overall, 28.4% vs. 51.9%, paired-$t=3.66$, $p<0.0001$; Table 3).

3.2. Efficacy of treatments

The six controlled trials with a placebo-control arm yielded nine drug-placebo paired comparisons (Table 4). Based on meta-analyses, there was a strong overall drug-placebo difference in annualized recurrence rates (risk reduced by 37%), with a pooled drug/placebo risk ratio [RR] of 0.63 [CI: 0.41-0.77]. This highly significant difference ($z=4.45$, $p<0.0001$) was associated with a favorable estimated number-needed-to-treat (NNT, reciprocal of the meta-analytically pooled risk-difference [RD], of 5.1 [3.8-7.7]; Table 4). Of the limited range of drugs tested against placebo, antipsychotics (only aripiprazole, olanzapine, risperidone were tested) in 4 trials provided the most robust apparent efficacy (RR=0.56 [0.092-0.45], NNT=4.3 [3.3-6.1]), followed by lithium carbonate in 2 trials (RR=0.62 [0.42-0.91]), NNT=4.9 [3.1-11], and then by non-significant effects of lamotrigine as the only anticonvulsant tested and the only such drug with regulatory approval as having long-term mood-stabilizing effects (RR=0.87 [0.73-1.0]; NNT=13 [6.0-56.0]; Table 4).

Descriptive analyses of recurrence rates associated with particular treatments in the RCTs yielded the following ranking: combinations of antipsychotic and mood-stabilizing agents (3 trials; 14.6%/year [0.0-3.6]) ≤ antipsychotics alone (5 trials; 15.8%/year [8.3-23.3]) < lithium (14 trials; 23.8%/year [18.6-29.0]) < anticonvulsants (9 trials; 29.9%/year [23.4-40.4]) < placebo (6 trials; 31.9%/year [23.4-40.4]) < imipramine (1 trial; 40.3%/year). Moreover, between-treatment differences in recurrence rates were significant ($t=1.84$, $p=0.01$; Table 5). Overall, treatments including an antipsychotic yielded significantly lower recurrence rates than treatment with lithium or an anticonvulsant (15.8 [8.3-23.3] vs. 26.8 [22.1-31.5] %/year; $t=2.19$, $p=0.04$). These findings are also summarized graphically (Figure 1).

Table 5 Factors associated with recurrence rate.

Factor	Recurrence (%/year) or Slope (β)[a] [CI]	Statistic (*t*-score)	*p*-value
Longer follow-up (years)	$\beta = -15.9$[-23.8 to −8.05]	4.07	0.002
% Ever rapid-cycling	$\beta = +0.388$[−0.146 to +0.629]	3.40	0.004
Older onset age	$\beta = -0.563$[−0.925 to −0.200]	3.26	0.004
Treatment type (trials)[b]		1.84	0.01
Antipsychotic+Mood-stabilizer (3)	14.6[0-35.8]		
Antipsychotics (5)	15.8[8.34-23.3]		
Lithium (14)	23.8[18.6-29.0]		
Anticonvulsants (9)	29.9[23.4-36.4]		
Placebo (6)	31.9[23.4-40.4]		
Imipramine (1)	40.3 [-]		
Treatment group (trials)		2.19	0.04
Antipsychotics (5)	15.8[8.34-23.3]		
Mood-stabilizers (23)	26.8 [22.1-31.5]		
Older current age	$\beta = -0.361$ [-0.730 to −0.007]	1.97	0.05

Factors are in descending rank-order of association with recurrence rate.
Factors not associated significantly with recurrence rate: [a] study type, [b] study size, [c] % women, [d] substance abuse, [e] suicidal, [f] anxiety disorder, [g] diagnosed bipolar-I, and [h] reporting year.
Factors associated with recurrence risk in these preliminary, bivariate analyses were also entered, step-wise into multivariate linear regression modeling, with recurrence rate as the outcome measure; three factors were sustained as significantly and independently associated with *higher* recurrence rates: [a] treatment with an anticonvulsant or lithium vs. an atypical antipsychotic (slope [β]=8.99 [CI: 2.69-15.3]; t=3.46, p=0.01); [b] younger onset-age (β=0.566 [0.084-1.05]; t=2.87, p=0.03); and [c] *shorter* exposure time (β=16.8 [0.84-32.7]; t=2.58, p=0.04), possibly owing to "temporal dilution" of morbidity with longer follow-up in an episodic illness.
[a]Slope (β) from bivariate linear regression.
[b]Antipsychotics and lithium sometimes combined with other agents.

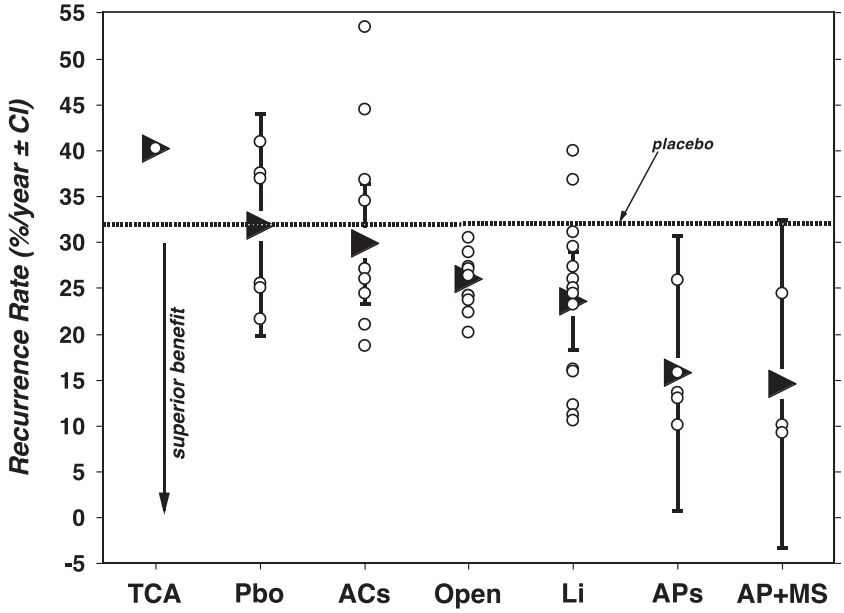

Figure 1 Summary of recurrence rates in long-term trials in bipolar disorder with various treatments. In descending rank by recurrence rate (%/year): a tricyclic antidepressant alone (TCA; 1 trial, N=36 subjects); placebo (Pbo; 6 trials, N=960); anticonvulsants with putative mood-stabilizing effects (ACs; 9 trials, N=899); naturalistic studies (Open; 10 studies, N=3904); lithium carbonate (Li; 14 trials, N=1307); antipsychotic drugs alone (APs; 6 trials, N=898); and combination treatments with antidepressants+mood-stabilizers (AP+MS; 3 trials, N=694), including 6 trials with placebo-arm, all based on data reported in Tables 1-3. Small circles are mean recurrence rates for each study, and large filled triangles are means (with 95% CI) for each treatment-type.

3.3. Factors associated with recurrence rates

In addition to differences among treatments, annualized recurrence rates (%/year) differed significantly in bivariate comparisons for only four other factors. In order of strength of associations, they were: [a] longer follow-up (with lower recurrence risk) [b] a history of rapid-cycling (higher risk) [c] older at onset (lower risk) [d] a weak effect of older current age (lower risk; Table 5).

Factors not significantly related to recurrence rate were: study type (naturalistic vs. controlled), study size, proportion of subjects diagnosed as BD-I, women, history of substance abuse, anxiety disorder or suicide attempt, reporting year, and proportions of subjects with manic or depressive polarity at either intake or first-recurrence (Table 5). There also was an unexpected lack of effect of more years-at-risk on the observed risk (%) of having a recurrence ($\beta = -0.154$ [CI: -0.168 to $+0.165$], $t = 0.055$, $p = 0.98$), albeit over a limited range of trial-durations.

Further assessments of the same factors in multivariate, linear regression modeling found that: [a] older age at onset (as expected), [b] treatment with an antipsychotic versus a mood-stabilizer (lithium or anticonvulsant), and [c] longer follow-up all remained associated significantly and independently with more favorable outcomes as lower %/year recurrence rates (Table 5). Again notably, the type of trial (RCT vs. naturalistic) and other factors tested in Table 5 were not related to outcome with active treatments (placebo-arms excluded).

4. Discussion

Several interesting findings arose from this review of risks of new illness episodes among BD patients in 10 prospective, long-term naturalistic, follow-up studies lasting up to an average of 2.1 years and 15 RCTs averaging up to 1.9 years. The naturalistic studies reported a mean risk of at least one new syndromal BD episode of 55.2% (26.3%/year) with clinically determined treatments. Their outcomes were quite consistent, with recurrence rates ranging between 20.2%/year (Tohen et al., 2003) and 30.5%/year (Li et al., 2014; Table 1). In the long-term RCTs, recurrence risk during treatment with a mood-stabilizing or antipsychotic drug averaged 39.3% (21.9%/year). This risk ranged more widely (4.8-fold) than the naturalistic trials (1.5-fold), from 9.25%/year (with a combination of lithium or valproate with quetiapine; Vieta et al., 2008), to 44.5%/year (with valproate alone; Findling et al., 2005). Recurrences averaged 30.3%/year with placebo, ranging from 21.7 (Keck et al., 2007) to 40.9%/year (Bowden et al., 2003), with strong separation of active treatments from placebo in the six trials that included a placebo condition (Table 4; Figure 1). The findings suggest more heterogeneity among RCTs in comparison to naturalistic studies, although recurrence rates with active treatments [20.2–30.5%/year (naturalistic) vs. 9.25–42.2%/year (RCTs)] overlapped. Such heterogeneity may be a consequence of specific, limited, randomized treatment options in RCTs versus flexible and individualized treatments in naturalistic studies. A particularly noteworthy finding from these comparisons was the lack of statistical difference in annualized recurrence rates between naturalistic studies and the active treatment arms of controlled trials (Table 3).

Several factors were significantly associated with higher recurrence rates (Table 5). These included shorter follow-up, previous rapid-cycling, younger estimated age at onset as well as a weaker effect of younger current age, and variable outcomes by treatment-type. Some of these factors were sustained in multivariate regression modeling as well: treatment with antipsychotics versus established (lithium) or putative mood-stabilizers (anticonvulsants), younger onset-age, and shorter exposure (Table 5). Higher recurrence risk with younger onset, as well as a history of rapid-cycling are expected associations (Geoffroy et al., 2013; Carvalho et al., 2014), but it is remarkable that they were detected here in aggregate data from so few studies. The finding of lower recurrence rates with older current age seems inconsistent with the questionable view that the disorder may tend toward higher recurrence rates and shorter wellness intervals over years of illness (Oepen et al., 2004; Baldessarini et al., 2012a).

The effect of duration of exposure (lower recurrence rate with more years of treatment follow-up) may seem paradoxical since more time at risk would be expected to reveal more recurrences. However, the duration of observation, which was limited to the range 1.5–2.5 years among included studies, had little impact on detection of recurrences (%), suggesting that almost all of the observed risk occurred within the first 18 months of treatment. The observed relationship of lower recurrence rates with longer exposure in both types of studies probably reflects the episodic nature of BD, in that more time would tend to "dilute" morbidity per time expressed as episodes/year (Goodwin et al., 2007; Baethge et al., 2003; Bratti et al., 2003). In addition, as most new episodes of illness arise within the first months at risk (Baldessarini, 2013), prolonged overall follow-up would tend to diminish the average outcome as a ratio of first new episodes per time.

It is also important to point out that the studies reviewed intended to evaluate risk of recurrences of new episodes of illness, and not relapses into index episodes. This aim is supported by the difference in the distribution of polarities of initial and first-recurrent episodes, with a marked increase of depressive recurrences versus an excess of mania at or near intake. Nevertheless for observations as brief as 18 months or less, it is possible that some "recurrences" were actually relapses after brief remissions (rather than sustained recoveries) from initial episodes and within expected durations of many untreated acute episodes in BD (Tohen et al., 2003). The great increase in depressive polarity in recurrences to intake polarity in the present two-year trials, contrasts with earlier reports in which the intake and first-new episode polarities were similar, but may have included some instances of relapse, especially in shorter trials (Calabrese et al., 2004). We have encountered a similar shift from manic initial episodes to depression later during follow-up of first-episode patients over several years (Baldessarini et al., 2010). On the other hand, the polarity of first-lifetime episodes was remarkably predictive of predominant types of later morbidity among BD patients (Baldessarini et al., 2012b, 2014).

A critical consideration concerns the relationship of findings in naturalistic studies and controlled trials. The

RCT design is widely considered optimal for assessing therapeutic efficacy of active treatments, ideally against placebo controls, and may also contribute to efforts to compare efficacy of different active treatments. Nevertheless, RCTs present important limitations, especially for long-term assessments, including selection of cases, sometimes for responding initially to a tested treatment that is then continued, generally less complicated participants, artifacts associated with treatment-discontinuation (as to placebo) or other changes from previous treatments (Faedda et al., 1992; Viguera et al., 1997, 2007; Baldessarini et al., 2010). Some of these clinical differences in recruited study participants may contribute to the somewhat lower recurrence risks found in the RCTs. Risk of early discontinuation from studies presents a further limitation, especially of long-term trials, and dropout rates were greater in the present RCTs than in naturalistic studies. It is not known whether early dropping out is associated with higher risks of impending recurrences. Differences in dropout risks may reflect responses to limited, randomized treatment options in the RCTs versus the flexible and individualized treatments provided in naturalistic studies (Tables 1–3). It is particularly striking that we found no significant differences in recurrence rates/year between the markedly different RCT and naturalistic study designs (Tables 3 and 5). Indeed, it could be argued, ironically, that the similar outcomes of naturalistic and controlled studies support the value of RCTs.

In the present RCTs, if the limited findings available for analysis are taken at face value, drugs developed initially as antipsychotics appeared to be more effective than lithium or anticonvulsants with putative mood-stabilizing actions, especially when antipsychotics and were combined with mood-stabilizers (Tables 4 and 5; Figure 1). However, only four long-term trials directly compared monotherapy with an antipsychotic versus lithium or an anticonvulsant (Tohen et al., 2004; Vieta et al., 2008; Suppes et al., 2009; Weisler et al., 2011). Three of these RCTs involved adding an antipsychotic drug (olanzapine or quetiapine, but not risperidone, ziprasidone or aripiprazole) to a mood-stabilizer, and so did not evaluate each type of treatment separately, leaving open the question of superiority of antipsychotic treatment versus added benefits of combinations of potentially effective treatments. Nevertheless, these trials consistently found less, but more variable, recurrence risk with an antipsychotic agent included in treatment, with recurrence rates [%/year] averaging: 26.1 [CI: 22.2–30.0] with, versus 12.6 [0.15–25.0] without an antipsychotic (paired-$t=4.80$, $p=0.04$). Only one of the trials (Weisler et al., 2011) directly compared an atypical antipsychotic, quetiapine (10.5%/year recurrence rate) and lithium carbonate (12.2%/year) as monotherapies (Table 2). It found little difference in outcomes despite initial stabilization of subjects with open-label quetiapine treatment rather than lithium. This outcome suggests that the type of "enrichment" (favorable initial response to a selected treatment prior to randomization) involved is important for interpreting trial outcomes. Particular caution is required in comparing combined or clinically adjustable treatments to controlled monotherapies. In general, although tested treatments appeared to be effective in reducing risks of new episodes of illness in BD, the effects were far from ideal, with substantial mean recurrence rates found in treatment arms of not only RCTs (21.9%/year), but also naturalistic studies (26.3%/year), that were only moderately lower than in placebo arms of the RCTs (31.9%/year; Tables 1-3, and 5, Figure 1).

Although duration of treatment was limited in range and was not related to outcome (Table 5), the mean duration of RCTs was slightly shorter than naturalistic studies (up to 1.9 vs. 2.1 years), raising the possibility that more subjects in RCTs may have experienced relapses of index episodes rather than new recurrences, and that such relapses included mania which may tend to favor the outcomes in RCTs enriched for initial antimanic responses. However, actual, individual latencies to new episodes are not provided in the studies analyzed, so that survival analysis was not possible. Indeed, it would be helpful in reports of such long-term studies to define actual latencies to new episodes of illness rather than requiring the potentially misleading assumption that nominal exposure times (or, more realistically, perhaps half of the nominal trial duration) can fairly be taken to represent latencies for all subjects.

4.1. Limitations and conclusions

This review has notable limitations. The numbers of studies of each type are small, reflecting the difficulty of organizing and completing studies in BD patients lasting up to 2.5 years, with particularly great clinical, ethical, and practical challenges in the use of placebo-controls long-term, as reflected in finding only six placebo-controlled trials. Moreover, characterizations of participants, outcomes, and latencies-to-outcome were available only as averages, precluding the possibility of relating clinical characteristics to latencies to new episodes in individual patients. Also, it is not always clear which new episodes of illness represent new-episode recurrences versus relapses of index episodes, particularly when treatments involved changes to a new drug or to placebo-arms and when actual times to new episodes probably often were less than 18 months following initial recovery from an index episode of illness. Incomparabilities of RCTs and naturalistic studies include the effects of limited and rigidly applied treatments in RCTs and sometimes complex and changing treatments to meet current clinical needs in naturalistic studies, as well as by effects of unreported treatment-discontinuation or lapses in both study-types. Also, differences in subject characteristics, including illness severity and complexity, represent important challenges to interpreting comparisons between RCTs and naturalistic studies. However, the similar average recurrence rates, corrected for exposure time, found in the naturalistic studies and in the RCTs, as well as other average characteristics of the participants of such trials do not suggest important systematic differences in average illness-severity between trial-types, or in sustained adherence to treatment. Nevertheless, long-term RCTs are likely to recruit participants who, due to clinical selection criteria, enrichment for initial response to a test treatment, and other factors, do not adequately represent unselected patients. The available RCTs also considered only a limited range of potential treatments, required rigid adherence to a single randomized drug, provided limited comparisons of

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specific monotherapies, and included placebo controls in only six trials. The present inclusion requirement for study duration of up to 18 months may tend to limit the impact of early relapses which would be more likely to occur in the considerable number of studies of 6–12 months duration that were not considered here.

Despite such limitations, the comparison between naturalistic, prospective studies and RCTs, both averaging two-years of follow-up, may provide realistic estimates of recurrence rates in treated BD, and it is reassuring that outcomes in both types of studies were similar. We propose that long-term RCTs in BD can generate findings whose plausibility is enhanced by their similarities to naturalistic findings, and that both types of study are of value. An important final observation is that recurrence risks with both the fixed treatments in RCTs and clinically adjusted treatments in the naturalistic trials were substantial, even though active treatments provided statistically lower recurrence risks than placebo. That there were substantial increases in depressive polarity between initial and first-recurrent episodes suggests that short-term predictability of episode polarity is limited and may be influenced by failing to distinguish relapses from recurrences. Moreover, the findings underscore the conclusion that depression was the dominant form of outcome morbidity with representative and even flexibly applied treatments. In short, these findings indicate that more effective treatments are required, especially to treat and protect against bipolar depression, as well as more effective methods to support long-term adherence to recommended medicinal and psychosocial treatments.

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Contributors

GV designed the protocol and plan of analysis, performed the electronic literature review, and contributed to manuscript construction and review. JH performed literature review, data analysis and interpretation, and manuscript construction. ML contributed to construction of the manuscript and manuscript review. TK contributed to construction of the manuscript and manuscript review. RB performed content design, data analysis, manuscript construction, and manuscript review. All authors read and approved the final manuscript.

Conflict of interest

Disclosures: Dr. Ketter has received research Support from the Agency for Healthcare Research and Quality, and from AstraZeneca, Cephalon, Eli Lilly, Pfizer, and Sunovion pharmaceutical corporations, consultant fees from Allergan, Avanir, DepotMed, Forest, Genentech, Janssen, Merck, Sunovion, and Teva corporations, lecture honoraria from Abbott, Otsuka, and Pfizer corporations, royalties from American Psychiatric Publishing Company, and his spouse is an employee and stockholder of Janssen Pharmaceuticals; no other author or family member has sources of potential conflicts of interest. Dr. Vazquez has served as a consultant or speaker for AstraZeneca, Gador, GlaxoSmithKline, Ivax, Eli Lilly, Lundbeck, Pfizer, Raffo, Servier and Novartis Corporations. No other authors or any immediate family members have financial or other potential conflicts of interest related to the material presented.

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Appendix A. Supporting information

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