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Review Article

A systematic review of the evidence on the treatment of rapid cycling bipolar disorder

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Objective: Rapid cycling is associated with longer illness duration and greater illness severity in bipolar disorder. The aim of the present study was to review the existing published randomized trials investigating the effect of treatment on patients with rapid cycling bipolar disorder.

Methods: A MEDLINE search was conducted using combinations of the following key words: *bipolar* and *rapid* or *rapid-cycling* or *rapid cycling* and *randomized*. The search was conducted through July 16, 2011, and no conference proceedings were included.

Results: The search returned 206 papers and ultimately 25 papers were selected for review. Only six randomized, controlled trials specifically designed to study a rapid cycling population were found. Most data were derived from post hoc analyses of trials that had included rapid cyclers. The literature suggested that: (i) rapid cycling patients perform worse in the follow-up period; (ii) lithium and anticonvulsants have comparable efficacies; (iii) there is inconclusive evidence on the comparative acute or prophylactic efficacy of the combination of anticonvulsants versus anticonvulsant monotherapy; (iv) aripiprazole, olanzapine, and quetiapine are effective against acute bipolar episodes; (v) olanzapine and quetiapine appear to be equally effective to anticonvulsants during acute treatment; (vi) aripiprazole and olanzapine appear promising for the maintenance of response of rapid cyclers; and (vii) there might be an association between antidepressant use and the presence of rapid cycling.

Conclusion: The literature examining the pharmacological treatment of rapid cycling is still sparse and therefore there is no clear consensus with respect to its optimal pharmacological management. Clinical trials specifically studying rapid cycling are needed in order to unravel the appropriate management of rapid cycling bipolar disorder.

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Rapid cycling is a descriptive term that refers to the presence of four or more discrete mood episodes during a one-year period in the context of bipolar disorder. In the DSM-IV, rapid cycling is a course specifier for bipolar disorder and is defined by the occurrence of at least four mood episodes (mania, hypomania, depression, or mixed) during the preceding year (1). The term rapid cycling was first coined in 1974, when Dunner and Fieve (2) described a group of lithium-unresponsive manic-depressive patients who were noted to have at least four episodes of mania and/or depression per year. Clinical studies which thereafter investigated the correlates of rapid cycling bipolar disorder have suggested that it is more frequent in women and is associated with hypothyroidism and bipolar II disorder (3). The clinical importance of this condition derives from its relatively high point prevalence (ranging from 10% to 20% among clinical samples) (1) and its associations with longer illness duration (4) and greater illness severity. Indeed, patients who experience a rapid cycling course have been reported to demonstrate a worse global functioning

(5) and may be at a higher risk for serious suicide attempts (6). However, controversies still exist regarding the necessary criteria for diagnosis, the etiology, the longitudinal stability (7), and treatment of rapid cycling.

Several strategies have been used to treat this condition, given that a rapid cycling course has been recognized as an independent predictor of inadequate treatment response in bipolar disorder (2, 8). Studies have investigated the effects of the standard mood stabilizers (lithium, divalproex, and carbamazepine) used either as monotherapy or in combination, and also the utility of atypical antipsychotics and antidepressants (9). The role of antidepressants in the development of rapid cycling still remains an issue of debate, with some studies associating them with the onset or worsening of rapid cycling (10, 11), while others fail to replicate this association after controlling for major depression (6, 12). In the search for more effective treatment approaches, even experimental agents such as levothyroxine or melatonin have been employed, with mixed results (9, 13–16). The number of studies that have investigated the pharmacological management of rapid cycling is limited, and there are only a few that have directly compared specific treatment alternatives for rapid cycling patients. Additionally, the number of trials using a randomized design was also few. Consequently, there is no clear consensus with respect to the optimal pharmacological management of rapid cycling.

The aim of the current paper was to review published randomized clinical trials assessing the efficacy of various treatments in acute mood episodes and in prevention of relapse of mood episodes in patients with rapid cycling bipolar disorder.

Materials and methods

A MEDLINE search was conducted using combinations of the following key words: *bipolar* and *rapid* or *rapid-cycling* or *rapid cycling* and *randomized*. The search was conducted through July 16, 2011, and no conference proceedings were included.

Results

The search returned 206 papers for initial evaluation. Papers from randomized studies and their post hoc analyses reporting separate data on acute or maintenance treatment response for patients with a rapid cycling course or in which the majority of patients were rapid cyclers were selected. Twenty-five papers that presented such results were found, 24 of which reported on the original or post hoc analysis data, and one of which was a meta-analysis that included randomized as well as non-randomized studies. It is important to mention that most studies presented the effects of treatments in rapid cycling patients; however, there were also studies comparing the efficacy of treatment in rapid versus non-rapid cycling bipolar disorder patients (17–27). Table 1 lists the details of these studies; however, some of the studies shown in the table provide different analyses of pivotal trials and should not be considered separate trials (olanzapine studies).

Treatment of acute mood episodes in patients with rapid cycling bipolar course

Antidepressant monotherapy

Escitalopram. In the Parker et al. study (28), 10 outpatients having a diagnosis of bipolar II disorder and a history of mood episodes that occurred at least monthly were recruited. Patients were required to not have previously received any antidepressant, mood-stabilizing, or neuroleptic medication. The study was a randomized, double-blind, placebo-controlled, cross-over trial of escitalopram (10 mg) versus placebo with a nine-month duration. There was a no-treatment baseline period of three months (baseline phase) to ensure that subjects met criteria for episode frequency. Subjects compliant with and completing baseline period requirements were then randomized to receive escitalopram or placebo for three months (phase 2), and then crossed over to receive the alternative compound for the final three-month period (phase 3). Subjects were assessed at the start of the study, and every month thereafter for the entire nine-month period. Parker et al. reported that escitalopram reduced the severity of depressive episodes as measured by the Hamilton Depression Rating Scale (HDRS) and also reduced the percentage of days high or low and impaired when compared with placebo. A weak trend for reduction in hypomania failed to support concerns that prescriptions of antidepressants would increase switch rates in patients with bipolar disorder. The study did not provide data on the effects of escitalopram on depression remission rates. In terms of its funding, the study was not sponsored by a pharmaceutical company, but rather, the manufacturer of escitalopram provided the study capsules, as acknowledged by the authors. However, it should be noted that the small sample size should be taken into account when interpreting these findings, and the fact that the study was not

Table 1. Treatment of rapid cycling bipolar disorder

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Acute treatment					
Antidepressant monotherapy					
Escitalopram					
Parker et al. 2006 (28)	Escitalopram versus PLA 9-month RCT with cross-over (3 months drug-free, 3 months escitalopram, 3 months PLA) N = 10 medication -naïve BD-II rapid cycling patients (at least monthly episodes): Depressed (n = 6) Euthymic (n = 4) Primary outcome: not defined	Escitalopram: (i) significant reduction in depression (HDRS) severity, percentage of days depressed or high, and percentage of days impaired versus PLA; (ii) no worsening of illness course; (iii) remission of depression: not reported	No	Escitalopram > PLA	Switching to (hypo)mania: weak reduction with escitalopram
Venlafaxine					
Amsterdam et al. 2009 (17)	VENLF versus LITH Post hoc analysis of one 12-week randomized, parallel-group, open-label study Rapid cyclers versus non-rapid cyclers (lifetime history) presenting with a BD-II MDE VENLF (n = 12) LITH (n = 15) Primary outcome: HDRS-28 rating	VENLF: (i) greater reduction in HDRS-28 versus LITH, higher rate of responders and remitters; (ii) equal pro portion of mood conversions versus LITH in rapid cyclers; (iii) no significant differences in mean YMRS change scores over time, between rapid and non-rapid cycling patients; (iv) remission of depression: higher rates of remitters in VENLF-treated patients	No	VENLF > LITH	No difference in mood switch between VENLF and LITH
Antipsychotic monotherapy					
Aripiprazole					
Suppes et al. 2008 (29)	ARI versus PLA Post hoc analysis of two pooled 3-week RCTs in rapid cyclers (past 12 months) with an acute manic or mixed BD-I episode N = 103: ARI (n = 52) PLA (n = 51) Primary outcome: YMRS change	ARI: significantly reduced mean YMRS total scores at endpoint in rapid cycling patients and greater responder and remitter rates versus PLA	Yes	ARI > PLA	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Olanzapine					
Suppes et al. 2005 (21)	OLAN versus DIVAL Post hoc analysis for rapid cyclers (past 12 months) of one 47-week RCT comparing OLAN to DIVAL for bipolar manic or mixed episodes Rapid cyclers (n = 144): OLAN (n = 76) DIVAL (n = 68) Non-rapid cyclers (n = 106) Primary outcome: YMRS change	(i) Rapid cycling patients did less well during the extended observation period than non-rapid cycling patients, regardless of treatment; (ii) rapid cycling patients receiving DIVAL appeared to be at some advantage over non-rapid cycling patients receiving DIVAL in terms of manic symptoms improvement; (iii) among rapid cycling patients, OLAN and DIVAL appeared equal in YMRS change while among non-rapid cycling patients OLAN appeared superior; (iv) there was a difference in response over time in HDRS, independently of treatment; (v) no differences in CGI severity scale between rapid cycling groups; (vi) remission: not reported	Yes	OLAN = DIVAL	Rapid cyclers demonstrate a non-significant trend to switch into depression more often, regardless of treatment
Vieta et al. 2004 (19)	OLAN versus PLA Post hoc analysis for rapid cycling (past 12 months) manic patients from two randomized clinical trials Rapid cyclers (n = 90): OLAN (n = 44) PLA (n = 46) Non-rapid cyclers (n = 164) Primary outcome not defined	Clinical response rates: OLAN = 76.7% PLA = 50% (i) Improvement of mania was similar in rapid cyclers and non-rapid cyclers; (ii) rapid cyclers showed an earlier response; (iii) remission: in fewer patients with a rapid cycling course	Yes	OLAN > PLA	Rapid cyclers more likely to switch into depression
Shi et al. 2004 (20)	OLAN versus PLA Post hoc analysis of one 3-week and one 4-week RCT to determine the effect of olanzapine on the PANSS-Cognitive score N = 254 (35% rapid cyclers) Primary outcome: PANSS-Cognitive score	OLAN-treated patients experienced modest but significant improvement in PANSS-Cognitive score, regardless of course (rapid or non-rapid cycling) Remission: not applicable	Yes	OLAN > PLA	Not applicable

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Baldessarini et al. 2003 (18)	OLAN versus PLA Post hoc analysis of pooled data from one 3-week and one 4-week RCT in manic patients among 10 subgroup pairs of interest (including rapid cyclers during the previous year) Rapid cyclers (n = 54): OLAN (n = 33) PLA (n = 21) Primary outcome: antimanic treatment efficacy (proportion of subjects attaining ≥ 50% YMRS reduction)	(i) Similar drug/PLA superiority and responsiveness to OLAN was found and responses were independent of recent rapid cycling; (ii) patients who were relatively more responsive to OLAN were younger at illness onset, lacked prior substance abuse, and had not previously received AP treatment; (iii) remission: not reported	Yes	OLAN > PLA	Not reported
Sanger et al. 2003 (31)	OLAN versus PLA *A priori* planned secondary sub -analysis for patients with a rapid cycling course (in the preceding year) recruited in one 3-week RCT in acutely ill manic or mixed BD patients Rapid cyclers (n = 45): OLAN (n = 19) PLA (n = 26) Primary outcome: change in YMRS	Clinical response rates: OLAN = 58% PLA = 28% (i) Significantly fewer PLA patients completed treatment, and more than half discontinued due to lack of efficacy; (ii) OLAN reduced YMRS total scores significantly more than PLA; (iii) clinical responses, defined as ≥ 50% improvement in YMRS, were achieved in 58% of OLAN patients, compared with 28% of PLA patients; (iv) remission: not reported	Yes	OLAN > PLA	Not reported
Quetiapine					
Suppes et al. 2010 (22)	QUET versus PLA Post hoc analysis of one 8-week RCT in acutely depressed adults with BD-I or BD-II, with or without rapid cycling in the previous 12 months Rapid cyclers (n = 74): QUET (n = 36) PLA (n = 38) Primary outcome: change in MADRS	QUET XR 300 mg once daily was significantly more effective (change in MADRS) than PLA in patients with a rapid cycling course Remission: not reported for rapid cyclers	Yes	QUET > PLA	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Vieta et al. 2007 (33)	QUET versus PLA *A priori* planned secondary analysis for a rapid cycling course during the previous year in one 8-week RCT in acute BD-I or BD-II depression Rapid cyclers (n = 108): QUET 300 mg (n = 42) QUET 600 mg (n = 31) PLA (n = 35) Primary outcome: change in MADRS	QUET: significantly greater mean reductions from baseline to week 8 in the MADRS and second ary efficacy measures Clinical response rates: QUET = 66.8% PLA= 40% Remission: not reported	Yes	QUET > PLA	Inconclusive effect of QUET on treatment-emergent mania due to small number of patients
Mood stabilizer–anticonvulsant monotherapy					
Lamotrigine					
Suppes et al. 2008 (23)	LTG versus LITH Post hoc analysis for rapid cyclers in a 16-week randomized, open-label, monotherapy trial in patients with a current depressed episode of BD-II Rapid cyclers within the past 12 months (n = 68): 83% of the LTG group 69% of the LITH group The primary outcome variable was change in the HDRS-17	44% completed the study: 51% in the LTG group and 19 (39%) in the LITH group (p = 0.29) For rapid cyclers: (i) both groups showed significant improvement on the HDRS, with no between-group differences in improvement; (ii) both groups demonstrated significant improvement on the MADRS, with no between-group differences in improvement; (iii) both groups showed significant improvement on the YMRS, with no significant differences between groups; (iv) both groups showed significant improvement in overall mood severity (CGI scale), with no between-group differences; (v) significant improvement on GAF scores; (vi) there was also a significant group-by-visit interaction for the GAF, with the LTG rapid cycling group showing a greater improvement on the GAF; (vii) remission in rapid cyclers: not reported	Pharmaceutical company provided medication and reviewed the paper	LTG = LITH	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Lithium					
Amsterdam et al. 2009 (17)	VENLF versus LITH (see above)			VENLF > LITH	
Suppes et al. 2008 (23)	LTG versus LITH (see above)			LTG = LITH	
Valproate					
Muzina et al. 2011 (34)	VAL versus PLA 6-week RCT in BD-I or BD-II depression N = 54: BD-I (n = 20) BD-II (n = 34) (67% rapid cycling during the previous 12 months) VAL (n = 26) PLA (n = 28) The primary outcome measure was mean change from baseline to week 6 on the MADRS total score	(i) No separate results for rapid cyclers; however, the majority were rapid cyclers; (ii) DIVAL treatment produced statistically significant improvement in MADRS scores compared with placebo from week 3 onward; (iii) no separation between VAL and PLA for those with BD-II diagnoses; (iv) remission: no separate results for rapid cyclers Response rates: VAL: 38.5% PLA: 10.7% (3 of 28) p = 0.017 Remission rates: VAL: 23.1% PLA: 10.7% (3 of 28) p = 0.208	Yes	VAL > PLA	6 patients on PLA and 8 on VAL switched into (hypo) mania; their rapid cycling status was not reported
Suppes et al. 2005 (21)	OLAN versus DIVAL (see above)			OLAN = DIVAL	
Mood stabilizer–anticonvulsant combinations					
Wang et al. 2010 (35)	LTG ± (LITH ± VAL) versus PLA ± (LITH ± VAL) Rapid cycling de pressed patients with a recent SUD not meeting criteria for MADRS, YMRS, and GAF response after 16 weeks of open-label treatment with LITH + VAL were randomized to a 12-week, double-blind addition N = 36: LTG (n = 18) PLA (n = 18) Primary outcome: change in MADRS	Eight patients per arm completed the study The changes in MADRS and YMRS total scores and rates of response and remission did not differ	No	LTG = PLA	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Mood stabilizer–anticonvulsant ± antidepressant					
Post et al. 2006 (24)	BUP ± MS versus sertraline ± MS versus VENLF ± MS Post hoc analysis for rapid cycling (prior history) patients with BD-I or BD-II depression in a 10-week randomized trial N = 174 (27% with a prior history of rapid cycling) Primary outcomes: AD response, AD remission, and AD-related switch into mania or hypomania	(i) Separate results for AD response and remission not reported for rapid cycling patients; (ii) the difference between the three medications in the risk for switching was highly significant among rapid cycling patients; (iii) BUP had a significantly lower risk than VENLF, whereas there was no significant difference between BUP and sertraline or between sertraline and VENLF; (iv) remission: not reported for rapid cyclers	Pharmaceutical companies provided medications	BUP > VENLF in avoiding switching	BUP > VENLF in avoiding mood switching
Mood stabilizer–anticonvulsant ± ethyl-eicosapentanoate					
Keck et al. 2006 (36)	MS versus MS ± EPA 4-month, RCT, adjunctive trial of EPA 6 g/day in the treatment of bipolar depression and rapid cycling (within the previous 12 months) BD N = 59: EPA (n = 31) PLA (n = 28) Efficacy measures: early study discontinuation, changes from baseline in depressive symptoms (IDS total score) and in manic symptoms (YMRS total score), and manic exacerbations (*switches*)	No significant differences were found on any outcome measure between the EPA and PLA groups Remission: not reported	Yes	MS = MS + EPA	No significant differences in manic switch rates between EPA and PLA

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Relapse prevention					
Reviews					
Tondo et al. 2003 (27)	Meta-analysis of 16 studies for effects of rapid cycling status and treatment type on clinical outcome (non-improvement or recurrence per exposure-time)	(i) Rapid cycling was associated with clinical non-improvement with all active treatments evaluated; (ii) rapid cycling was associated with higher recurrence under all treatments evaluated; (iii) time to relapse: no data	No	LITH = CBZ	Not reported
	3/16 studies were randomized	The crude rate-estimate for recurrence for rapid cycling subjects pooled across all study arms was higher (by 1.85-fold) than for non-rapid cycling subjects (2.31/1.25%/month)			
		Pooled recurrence rates from low to high, ranked: LITH: 2.09%/month CBZ: 2.87%/month VAL: 3.63%/month LTG: 8.57%/month PLA: 12.5%/month			
Antipsychotic monotherapy					
Aripiprazole					
Muzina et al. 2008 (37)	ARI versus PLA Post hoc analysis of one 100-week, RCT in rapid cycling (previous 12 months) patients with BD-I (most recently manic/mixed)	No data on number of relapses	Yes	ARI > PLA	Not reported
		Time to relapse was significantly longer with ARI versus PLA at week 100			
	Rapid cyclers (n = 28): ARI (n = 14) PLA (n = 14)				
	Primary measure: time to relapse				
Olanzapine					
Vieta et al. 2004 (19)	OLAN versus PLA (see above)	(i) Non-rapid cyclers had a better long-term outcome; (ii) non-rapid cyclers were more likely to experience a symptomatic remission in one year and were less likely to experience a recurrence, especially depression; (iii) they also were less likely to be hospitalized and to make a suicide attempt; (iv) no data on time to relapse	Yes	Non-rapid cyclers > rapid cyclers	Rapid cyclers were more likely to experience a depressive switch

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Quetiapine					
Langosch et al. 2008 (38)	QUET versus VAL 12-month, open-label, randomized, parallel-group monotherapy N = 38 remitted or partly remitted patients with rapid cycling BD (not specified whether it referred to lifetime or past year cycling history): QUET (n = 22) VAL (n = 16) Primary outcome: not defined	(i) Life Chart Method data: QUET: significantly fewer moderate to severe depressive days than patients on VAL while they did not differ in the number of days with manic or hypomanic symptoms; (ii) no significant differences in responder rates, YMRS, MADRS, HDRS reductions and the frequency of mood swings; (iii) no results were provided regarding time to relapse	Yes	QUET > VAL and QUET = VAL	No significant differences in the frequency of mood swings
Mood stabilizer–anticonvulsant monotherapy					
Carbamazepine					
Denicoff et al. 1997 (25)	LITH versus CBZ versus LITH ±CBZ Post hoc sub-analysis in patients with a past history of rapid cycling of one double-blind randomized cross-over study One-year treatment with either LITH or CBZ to one-year cross-over to one-year LITH + CBZ in bipolar prophylaxis N = 52 BD outpatients: Rapid cyclers (n = 31) No primary measure defined	(i) Rapid cyclers showed a better treatment response to combination than to either monotherapy, according to CGI ratings; (ii) a past history of rapid cycling predicted a CBZ non-response; (iii) the number of relapses and the time to relapse for rapid cyclers were not reported	Yes	LITH + CBZ > LITH > CBZ	Not reported
Lamotrigine					
Goldberg et al. 2008 (40)	LTG versus PLA Randomized trial in current manic, hypomanic, depressive, or mixed-episode rapid cyclers (previous year), assessing daily and weekly mood shifts. Post hoc comparison in subjects who achieved euthymia across weeks Rapid cyclers (n = 177): LTG (n = 90) PLA (n = 87) Primary measure: not specified	(i) Patients taking LTG were 1.8 times more likely than those taking PLA to achieve euthymia at least once/week in 6 months as assessed by the Life Chart Method; (ii) subjects taking LTG had an increase of 0.69 more days per week euthymic as compared with those taking PLA; (iii) number of relapses and time to relapse were not reported	Yes	LTG > PLA	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Calabrese et al. 2000 (39)	LTG versus PLA 6-month double-blind, randomized, placebo-controlled study in rapid cycling (previous year) BD-I and BD-II patients. Initially, LTG was added to current regimens during an open-label treatment and then the other psychotropics were tapered off N = 177: LTG (n = 90) PLA (n = 87) Primary measure: time to additional pharmacotherapy for emerging symptoms	6-month stabilization rates: LTG = 41% PLA = 26% (i) No difference between treatment groups in time to additional pharmacotherapy for emerging symptoms (primary outcome measure); (ii) time to any premature discontinuation was significantly longer for LTG; (iii) more patients without relapse in the LTG group for BD-II but not BD-I subtype; (iv) no data were reported in terms of number of relapses	Yes	LTG > PLA May be effective in BD-II but not in BD-I subpopulation	Not reported
Walden et al. 2000 (41)	LTG versus LITH One-year open, randomized trial in manic patients with rapid cycling (past year) disorder N = 14: LTG (n = 7) LITH (n = 7) Primary measure: not defined	LITH group: 3/7 (43%): fewer than 4 affective episodes (depressive, manic, hypomanic, or mixed 4/7: (57%) 4 or more episodes LTG group: 6/7 (86%) fewer than 4 episodes 1/7: (14%) more than 4 affective episodes 3/7 (43%): without any further affective episodes There was no evidence of a preferential AD versus antimanic efficacy; time to relapse not reported	Not reported	LTG > LITH	Not reported
Lithium					
Kemp et al. 2009 (42)	LITH versus LITH ± DIVAL 6-month, double-blind, randomized parallel-group study in rapid cycling (past 12 months) patients with co-occurring substance abuse or dependence and recently stabilized disorder following combination treatment with LITH and VAL Rapid cyclers (n = 31): LITH (n = 16) LITH + DIVAL (n = 15) Primary measure: time to treatment for a mood episode	Relapse rates: LITH = 56% LITH + DIVAL = 53% LITH monotherapy did not differ from LITH + DIVAL in terms of rates or time to relapse No data for treatment effects on the number of relapses were presented	Pharmaceutical industry provided study medication	LITH = LITH + DIVAL	Not reported

Table 1. (Contiuned).

	Study design	Efficacy	Funding from the pharmaceutical industry	Conclusions[a]	Affective switching rates
Calabrese et al. 2005 (43)	LITH versus DIVAL 20-month, double-blind, randomized, parallel-group comparison in rapid cycling (previous year) patients with recently stabilized disorder following combination treatment with LITH and VAL Rapid cyclers (n = 60): LITH (n = 32) DIVAL (n = 28) Primary outcome measure: time to treatment for a mood episode (relapse)	Relapse rates: LITH = 56% DIVAL = 50% There were no significant group differences in rates or time to relapse The comparative treatment effects on the number of relapses were not presented	Industry provided only study medications	LITH = DIVAL	Not reported
Walden et al. 2000 (41)	LTG versus LITH (see above)			LTG > LITH	
Denicoff et al. 1997 (25)	LITH versus CBZ versus LITH ± CBZ (see above)			LITH + CBZ > LITH > CBZ	
Valproate					
Calabrese et al. 2005 (43)	LITH versus DIVAL (see above)			LITH = DIVAL	
Mood stabilizer–anticonvulsant combination					
Kemp et al. 2009 (42)	LITH versus LITH ± DIVAL (see above)			LITH = LITH + DIVAL	
Denicoff et al. 1997 (25)	LITH versus CBZ versus LITH ± CBZ (See above)			LITH + CBZ > LITH > CBZ	
Antidepressant continuation/discontinuation					
Ghaemi et al. 2010 (26)	Planned subgroup analyses for rapid cyclers (during the previous year) in a 1–3-year open, random assignment study in bipolar depression. MS were continued in both groups N = 35 Primary outcome: mean change on the depressive subscale of the STEP-BD Clinical Monitoring Form	Rapid cycle course predicted 3 times more depressive episodes with AD continuation Rapid cyclers had more depressive episodes, shorter episode latency, and fewer weeks in remission, independently of treatment	No	AD discontinuation > AD continuation	Not reported for rapid cyclers

AD = antidepressant; AP = antipsychotic, ARI = aripiprazole; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BUP = bupropion; CBZ = carbamazepine; CGI = Clinical Global Impression; DIVAL = divalproex; EPA = ethyl-eicosapentanoate; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; IDS = Inventory for Depressive Symptomatology; LITH = lithium; LTG = lamotrigine; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; MS = mood stabilizer; OLAN = olanzapine; PANSS = Positive and Negative Syndrome Scale; PLA = placebo; QUET = quetiapine; RCT = randomized, controlled trial; STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder; SUD = substance use disorder; VAL = valproate; VENLF = venlafaxine; XR = extended release; YMRS = Young Mania Rating Scale.
[a]The = sign indicates equal efficacy; >indicates more effective; <indicates less effective.

adequately powered is noted as a limitation by the authors.

Venlafaxine. In another randomized trial of 12 weeks' duration, Amsterdam et al. (17) compared the safety and antidepressant efficacy of venlafaxine versus lithium monotherapy in patients presenting with a major depressive episode of bipolar II disorder. The study was not specifically powered to detect differences in efficacy or mood conversion between groups with and without a lifetime history of rapid cycling, and the post hoc analyses of these groups were exploratory. The primary outcome measure of the study was the HDRS-28 rating score suggesting that venlafaxine was associated with a greater reduction in HDRS-28 scores ($p = 0.001$) when compared with the lithium group which was independent of cycling status ($p = 0.358$). Amsterdam et al. also reported a higher rate of responders ($p = 0.021$) and remitters ($p = 0.001$) in the rapid cycling group. Interestingly, venlafaxine did not result in a higher proportion of mood conversions when compared to lithium in either the rapid or non-rapid cycling patients. This study received no funding from the pharmaceutical industry.

Antipsychotic monotherapy

Aripiprazole. In a post hoc analysis of two three-week randomized, controlled trials, Suppes et al. (29) assessed the efficacy and safety of aripiprazole in subpopulations of patients experiencing an acute bipolar I manic or mixed episode. The primary efficacy outcome measure for this study was mean change from baseline to week 3 in Young Mania Rating Scale (YMRS) total scores. Patients with a rapid cycling course during the previous year demonstrated significantly greater improvements in YMRS with aripiprazole than placebo ($p < 0.01$). In addition, in the rapid cycling subgroup, both responder and remitter rates were statistically significantly greater in patients receiving aripiprazole ($p = 0.0018$ and $p = 0.0070$, respectively). This study did not present data on mood conversion and was funded by a pharmaceutical company.

Olanzapine. Tohen et al. (30) studied the effects of olanzapine in the treatment of acute mania in a random-assignment, double-blind, placebo-controlled parallel group study of three weeks' duration. Following a two- to four-day screening period, qualified patients were assigned to either olanzapine ($n = 70$) or placebo ($n = 69$).

In the secondary analysis of this data set, Sanger et al. (31) suggested that olanzapine was effective in reducing symptoms of mania (change in YMRS total score from baseline to endpoint which was the primary efficacy measure) and was well tolerated in patients with bipolar I disorder with a rapid cycling course in the preceding year. The authors did not report whether olanzapine affected conversion rates into the opposite polarity. This analysis was funded by the pharmaceutical industry.

Data from the Tohen et al. study (30) and a second study that used a similar design (32) were pooled to conduct a post hoc analysis of differences in treatment responses in patient subgroups by Baldessarini et al. (18). They found similar olanzapine superiority to placebo in responsiveness (proportion of subjects attaining $\geq 50\%$ reduction in YMRS scores, which was the primary outcome measure) in patients with a rapid cycling course during the previous year, compared to non-rapid cycling patients. In this study, which had received funding from the pharmaceutical industry, no data on affective switch rates were shown.

Similarly, Vieta et al. (19) analyzed data pooled from the same studies with the aim to compare demographic, clinical, and outcome measures between bipolar disorder patients with a manic episode that had either a rapid or a non-rapid cycling course during the previous year. This analysis also included an open-label treatment study with olanzapine which followed patients for up to a year after completion of the first trial (30). The resulting total number of patients was 254; 90 of whom were rapid cyclers (44 had received olanzapine and 46 had received placebo). Vieta et al. (19) found that improvement of mania was similar in rapid cyclers and non-rapid cyclers, but rapid cyclers showed an earlier response. Rapid cyclers were more likely to convert into depression compared with non-rapid cyclers. This study had received sponsorship, in part, from the pharmaceutical industry.

In another post hoc analysis of the two above-mentioned randomized, controlled trials examining olanzapine, Shi et al. (20) investigated the effects of olanzapine on the cognitive factor of the Positive and Negative Syndrome Scale (PANSS) which was the primary outcome of the relevant study and presented results for patients with a rapid cycling status. They reported that olanzapine-treated patients showed modest but significant improvement in PANSS-Cognitive score regardless of rapid cycling course. However, it should be noted here that the authors did not clarify whether rapid cycling course involved the previous year or patients' lifetime history. This study also received funding from the pharmaceutical industry.

Suppes et al. (21) conducted a post hoc analysis of one 47-week, randomized, double-blind study

that compared olanzapine (5–20 mg/day) to divalproex sodium (500–2500 mg/day) in 251 patients suffering from a bipolar manic or mixed episode. The objective of this study was to examine whether rapid cycling during the previous year affects treatment response. The change in YMRS was used as the primary outcome measure. Of the 251 randomized patients, 144 were classified as rapid cyclers (76 had received olanzapine and 68 had received divalproex). This post hoc analysis showed that rapid cycling patients did less well during the extended observation period than non-rapid cycling patients, regardless of treatment. Of note, rapid cycling patients receiving divalproex appeared to be at some advantage over non-rapid cycling patients receiving divalproex in terms of manic symptom improvement. However, continued improvement was not observed beyond the first few weeks, though initial effects were sustained. Another significant finding was that among rapid cycling patients, olanzapine and divalproex appeared equal in terms of YMRS changes from baseline to endpoint, while among non-rapid cycling patients, olanzapine appeared superior. No significant difference between rapid and non-rapid cyclers was revealed in Clinical Global Impression (CGI) Mania or Bipolar Severity (CGI-BP), or HDRS. Rapid cyclers were shown to respond differently from non-rapid cyclers over time, independent of treatment. They also demonstrated a non-significant trend to experience depression more often than non-rapid cyclers, independent of treatment. This study received pharmaceutical company funding.

In summary, the secondary analyses of the pivotal olanzapine trials showed that olanzapine is equally effective in reducing manic symptoms in rapid and non-rapid cyclers. There is evidence that its antimanic effect appears earlier in rapid cyclers who are also more likely to experience a switch into depression. Olanzapine is similar to divalproex against manic symptoms and could have a positive effect on cognitive symptoms in this bipolar disorder subpopulation.

Quetiapine. Vieta et al. (33) conducted an *a priori* sub-analysis of data from adult patients with a diagnosis of bipolar depression and a rapid cycling disease course during the previous year. The subjects were recruited from a multicenter trial that examined the efficacy of quetiapine. Patients were randomized to eight weeks of treatment with either quetiapine at 600 mg/day (n = 31), quetiapine at 300 mg/day (n = 42), or placebo (n = 35). The primary efficacy variable was change from baseline to week 8 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score. The analysis suggested that quetiapine monotherapy (600 or 300 mg/day) was clinically more effective than placebo in terms of both MADRS reductions ($p < 0.001$) and changes in other secondary measures (CGI, HDRS, Hamilton Rating Scale for Anxiety, Pittsburgh Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire scales) and was also well tolerated in the short-term treatment of depressive episodes in patients with bipolar I or II disorder who had a rapid cycling disease course. The administration of quetiapine was associated with a very low propensity to cause treatment-emergent mania. Two patients in the 600-mg group, two in the 300-mg group, and one patient receiving placebo switched into mania. This finding suggests that quetiapine probably does not increase the risk of a manic switch, although a larger sample is needed to draw safer conclusions. This study was funded by the pharmaceutical industry.

Similarly, in a more recent study on patients with bipolar depression that was also sponsored by the pharmaceutical industry, Suppes et al. (22) reported that quetiapine monotherapy (300 mg) was found to be more effective than placebo. A post hoc analysis for patients with and without a rapid cycling disease course during the previous year revealed that quetiapine was associated with significantly greater reductions than placebo in the MADRS total score change from baseline to week 8. This was the primary efficacy measure. Although quetiapine was not associated with treatment-emergent hypomania or mania for the whole sample, its specific effect on switch rates in patients with a rapid cycling course was not reported.

Mood stabilizer–anticonvulsant monotherapy

Lamotrigine. Suppes et al. (23) presented results involving rapid cycling patients in a study comparing open-label lamotrigine and lithium monotherapy in bipolar II disorder depression. Patients were titrated to 200 mg/day of lamotrigine over eight weeks or at least 900 mg/day of lithium over two weeks (serum level 0.6–1.2 mEq/L), and were seen biweekly for 16 weeks. The evaluable number of patients for efficacy analyses was 90; 41 for the lamotrigine group and 49 for the lithium group. Of the 90 patients evaluated, 72% (n = 71) showed rapid cycling within the previous 12 months; 79.6% in the lamotrigine group, and 66.7% in the lithium group. A total of 40 patients (44%) completed the study: 21 (51%) in the lamotrigine group and 19 (39%) in the lithium group ($p = 0.29$). The primary outcome variable was

change in the HRDS-17. Both groups showed significant improvement from baseline to endpoint on the HDRS-17 ($p < 0.0001$), with no between-group differences ($p = 0.95$). No differences in response were noted between rapid cyclers and non-rapid cyclers. For the subset of patients with a history of rapid cycling, both groups showed significant improvement on the HDRS-17 ($p < 0.001$) at week 16, with no between-group differences in improvement ($p = 0.39$). Similarly, in rapid cycling patients both groups demonstrated significant improvement on the MADRS ($p < 0.001$) at week 16, with no between-group differences in improvement ($p = 0.96$). Patients with a history of rapid cycling experienced significant improvement on the YMRS ($p < 0.001$), with no significant differences between groups ($p = 0.74$). Patients with a history of rapid cycling also showed significant improvement in overall mood severity (CGI scale) ($p < 0.001$), with no between-group differences ($p = 0.43$). Patients experiencing rapid cycling showed significant improvement on Global Assessment of Functioning (GAF) scores ($p < 0.001$). There was also a significant group-by-visit interaction for the GAF ($p = 0.019$), with the lamotrigine rapid cycling group showing a greater improvement on the GAF. The specific treatment impact on the probability of hypomanic switch in rapid cycling patients was not reported, although both lithium and lamotrigine were associated with a limited switch rate in the whole sample. No patient in the lamotrigine group and only one patient in the lithium group met mood switch criteria. Although the manufacturer of lamotrigine did not provide funding for the study, it provided medication and had the opportunity to review this paper and to give editorial feedback (23).

Lithium. Two studies (17, 23) investigated the acute efficacy of lithium monotherapy against bipolar II major depressive episodes in rapid cycling patients and have been discussed above.

Valproate. Further to the study of Suppes et al. (21) (see above), which compared valproate with olanzapine, Muzina et al. (34) conducted an exploratory investigation of the acute efficacy of extended-release divalproex sodium compared with placebo in patients with bipolar I or II depression that had never been treated with a mood stabilizer. Fifty-four patients with bipolar I ($n = 20$) or bipolar II ($n = 34$) disorder were randomly assigned to six-week divalproex or placebo monotherapy, while 67% met DSM-IV criteria for rapid cycling. Although the authors did not report separate results for patients with a rapid cycling course, this study was selected for our review due to the fact that the majority of patients were rapid cyclers. The primary outcome measure of the study was mean change from baseline to week 6 on the MADRS total score. Secondary outcomes included rates of response and remission, changes in the CGI-BP scores and changes in anxiety symptoms as measured by the Hamilton Anxiety Rating Scale. Divalproex treatment was associated with significant improvement in MADRS scores compared with placebo from week 3 onward, which included patients with bipolar I disorder, albeit not bipolar II disorder. Similarly, a significantly higher percentage of patients in the divalproex group met response criteria compared with the placebo group (38.5% versus 10.7%, $p = 0.017$). However, the two groups did not differ in the proportion of patients achieving remission. Six patients receiving placebo and eight receiving divalproex met criteria for treatment-emergent hypomania/mania; however, the authors did not report whether they were rapid cyclers or not. The study was funded by the pharmaceutical industry.

Mood stabilizer–anticonvulsant combinations

Lamotrigine addition to lithium and valproate. The acute efficacy of mood stabilizer–anticonvulsant combinations was examined in a recent study by Wang et al. (35) which reported the results of a trial comparing a 12-week adjunctive treatment with lamotrigine to ongoing treatment with lithium plus valproate in depressed patients with rapid cycling bipolar disorder comorbid with a substance use disorder. The patients recruited had failed to meet the criteria for a bimodal response following a 16-week open-label treatment with lithium plus divalproex, and were thereafter randomized to receive adjunctive lamotrigine or placebo. These criteria comprised a MADRS score lower than 19, a YMRS score < 12, and a GAF score > 51 for four weeks. Of the 98 patients enrolled into the study, 36 were randomized to receive either lamotrigine ($n = 18$) or placebo ($n = 18$). No significant differences were found in terms of the MADRS or YMRS change from baseline to endpoint or rates of response and remission between lamotrigine- and placebo-treated patients. The effects of treatment on affective mood switch were not reported. The study did not receive funding from any pharmaceutical company.

Mood stabilizer–anticonvulsant plus antidepressant

Bupropion or sertraline or venlafaxine addition to mood stabilizers. Post et al. (24) examined the

relative risks of switching into hypomania or mania associated with second-generation antidepressant drugs in bipolar depression. More specifically, they investigated the acute effects of bupropion, sertraline, and venlafaxine as adjuncts to mood stabilizers in a 10-week randomized trial and presented results on patients with a prior positive history for rapid cycling. Antidepressant response, antidepressant remission, and antidepressant-related switch into mania or hypomania were the primary outcomes of this study. However, the separate results for rapid cycling patients were reported only for switch rates. A strong interaction between the rapid cycling status of patients and the relative risk of switching was revealed for the three medication groups. The difference between the three medications was highly significant among rapid cycling patients [log rank $\chi^2 = 9.66$, degrees of freedom (df) $= 2$, $p < 0.01$]. The pattern of this difference for the rapid cycling group was that bupropion had a significantly lower risk for switching than venlafaxine (log rank $\chi^2 = 9.07$, df $= 1$, $p < 0.01$), whereas there was no significant difference between bupropion and sertraline (log rank $\chi^2 = 1.9$, df $= 1$, $p < 0.17$) or between sertraline and venlafaxine (log rank $\chi^2 = 2.1$, df $= 1$, $p < 0.15$). Three pharmaceutical companies that manufacture bupropion, sertraline, and venlafaxine provided the medications and placebo, but were not involved in the funding of the study.

Mood stabilizer–anticonvulsant plus ethyl-eicosapentanoate (EPA)

In a four-month, randomized, placebo-controlled trial, Keck et al. (36) examined the effects of 6 g/day EPA augmentation of treatment with mood stabilizers in patients with bipolar depression with a rapid cycling course within the previous 12 months and reported negative results. In this study, 31 rapid cycling patients receiving EPA and 28 subjects receiving placebo did not show any difference in any of the outcome measures [early study discontinuation, changes from baseline in depressive symptoms measured by the Inventory for Depressive Symptomatology total score, manic symptoms assessed by YMRS total score, and manic exacerbations (*switches*)] thus lending no support to the antidepressant efficacy of omega-3 fatty acid addition for patients with rapid cycling bipolar disorder. The study was partly sponsored by the pharmaceutical company that also provided the study medication.

Relapse prevention in rapid cycling bipolar disorder

Antipsychotic monotherapy

Aripiprazole. The effects of aripiprazole in rapid cycling (course within the previous year) bipolar disorder patients who had experienced a recent manic or mixed episode were investigated by Muzina et al. (37) in a post hoc analysis of a 100-week, randomized, controlled trial. This analysis suggested that aripiprazole maintained efficacy and was generally well tolerated in the long-term treatment of rapid cycling bipolar disorder. Time to relapse was significantly longer with aripiprazole versus placebo at week 100, but it should be mentioned that the study had a small sample size of only 28 patients. The authors did not report whether there was a difference between aripiprazole and placebo in the number of relapses or mood switches. This study was supported by the pharmaceutical industry.

Olanzapine. In a study comparing olanzapine with placebo among patients who continued open-label olanzapine therapy for one year after three weeks of double-blind therapy for acute mania, Vieta et al. (19) reported that rapid cyclers were less likely to experience a symptomatic remission within one year ($p = 0.014$) and were more likely to experience a recurrence, especially into a depressive phase during the one-year period. Patients were also more likely to be hospitalized and to make a suicide attempt. Interestingly, the mean number of new episodes in rapid cyclers during the open-label olanzapine treatment was 1.44, suggesting that they no longer met the criteria for the diagnosis of rapid cycling. This study was partly supported by the pharmaceutical industry.

Quetiapine. The long-term efficacy and safety of quetiapine were compared with those of sodium valproate in an open-label, randomized, parallel-group monotherapy pilot study by Langosch et al. (38). The study included 38 remitted or partly remitted patients diagnosed with bipolar disorder with a rapid cycling course. However, the study did not mention whether this course referred to the past 12 months or to a lifetime history. Twenty-two patients were treated with quetiapine and 16 were treated with valproate for 12 months, with 41% of the quetiapine patients and 50% of the valproate patients completing the trial. Life Chart Method data showed that patients being treated with quetiapine had significantly fewer

moderate-to-severe depressive days than patients receiving valproate [mean ± standard deviation (SD) = 11.7 ± 16.9 days versus 27.7 ± 24.9 days; $p = 0.04$], while they did not differ in the number of days with manic or hypomanic symptoms or the frequency of mood swings. No differences were found in responder rates or HDRS, MADRS, or YMRS reductions between the two groups.

Mood stabilizer–anticonvulsant monotherapy

Carbamazepine. In a prospective study of 52 outpatients with bipolar disorder, Denicoff et al. (25) evaluated the prophylactic efficacies of lithium, carbamazepine, and a combination of both drugs. The patients were randomly assigned in the double-blind study to either lithium or carbamazepine for the first year. In the second year, there was a cross-over to the opposite drug, and then all patients received the combination of lithium and carbamazepine during the third year. More than half of these patients had a past history of rapid cycling which was associated with a better response as assessed by CGI ratings on the combination therapy than on either monotherapy (56.3% for the combination, versus 28% for lithium and 19% for carbamazepine; $p < 0.05$). Notably, four out of nine rapid cycling patients who responded to the combination did not respond to either monotherapy. A past history of rapid cycling also predicted carbamazepine non-response. In general, patients experienced a significantly lower number of episodes on the combination compared with lithium therapy, and the mean number of days to the first manic episode was significantly higher during the combination phase. However, the specific effects of treatments on the time to relapse, on the number of relapses, and on mood switch were not reported for rapid cyclers. The authors received support for the study from the pharmaceutical industry.

Lamotrigine. Calabrese et al. (39) reported on the effects of lamotrigine monotherapy in bipolar maintenance in a sample of 182 bipolar disorder patients with a rapid cycling course within the previous year. The sample was derived from 324 patients with rapid cycling bipolar disorder who initially received an open-label lamotrigine addition to their current psychotropic regimens of four to eight weeks' duration. Thereafter, stabilized patients were tapered off other psychotropic agents and were randomly assigned to lamotrigine or placebo monotherapy for six months. The primary outcome measure of this industry-sponsored study was the time to additional pharmacotherapy for emerging symptoms and did not differ between the lamotrigine and placebo groups. Analyses that favored lamotrigine in secondary measures were the time to premature discontinuation for any reason and the percentage of patients who remained stable without relapse for six months of monotherapy. No data were presented for the effects of lamotrigine and placebo on the number of relapses or the prevention of affective mood switch. This trial also suggested that lamotrigine monotherapy may be effective in bipolar II disorder patients, but not in bipolar I disorder patients.

Goldberg et al. (40) conducted a secondary analysis of data obtained during the course of the Calabrese et al. study (39) using the prospective Life Chart Method which assesses daily and weekly mood changes and found that, after adjusting for potential confounding factors, subjects taking lamotrigine were 1.8 times more likely to achieve euthymia than those taking placebo at least once per week over six months [95% confidence interval (CI): 1.03–3.13]. Subjects taking lamotrigine had an increase of 0.69 more days/week euthymic as compared with those taking placebo ($p = 0.014$). In addition to its positive findings with regard to lamotrigine efficacy, this study also supports the use of the prospective life chart as an informative measure for capturing fine-grained longitudinal variations in mood. The study provided no data on the number of relapses or time to relapse, and also received funding from the pharmaceutical industry.

In a preliminary study to explore the potential efficacy of lamotrigine in the treatment of patients with rapid cycling bipolar disorder (four or more mood episodes during the previous year), Walden et al. (41) assigned 14 patients with rapid cycling bipolar disorder to an open, randomized one-year treatment with either lithium or lamotrigine as a mood stabilizer. Out of the seven patients who received lithium, three (43%) had fewer than four episodes, and four (57%) had four or more episodes. In the lamotrigine group, six out of seven patients (86%) had fewer than four episodes, and one out of seven (14%) had more than four affective episodes (depressive, manic, hypomanic, or mixed). In fact, three out of seven (43%) of the patients who were on lamotrigine therapy were without any further affective episodes. No data concerning the effects of lithium or lamotrigine on time to relapse or on the probability of a mood switch were reported. The study produced no evidence of a preferential antidepressant versus antimanic efficacy, but the authors admitted that their sample size was too small to examine this issue. Although the study suggests that lamotrigine

is effective, it also suggests that lithium is associated with a suboptimal response in rapid cycling bipolar disorder. The authors did not report whether they had received any funding from the pharmaceutical industry.

Lithium. Further to the Walden et al. study (41), which compared lithium with lamotrigine, and that of Denicoff et al. (25), which compared lithium with valproate, a recent six-month, double-blind, parallel-group study by Kemp et al. (42) compared the prophylactic effects of lithium monotherapy with those of the combination of lithium plus divalproex in 31 patients suffering from rapid cycling bipolar disorder and co-occurring substance abuse or dependence. The study was a continuation of an open-label acute stabilization phase of 149 patients who initially received the combination of lithium with divalproex but were then randomly assigned either to remain on combination treatment or to discontinue divalproex and receive lithium monotherapy. Lithium monotherapy did not differ from the combination of lithium plus divalproex in preventing relapse of mood episodes. The rates of relapse into a mood episode were 56% for lithium versus 53% for the combination, with a median time to recurrence of 15.9 weeks versus 17.8 weeks, respectively. However, it should be noted that the majority of patients (79%) discontinued the preceding open-label phase, thus limiting the number of patients who participated in the following double-blind study. The authors did not provide comparative data on the number of relapses in the two groups, nor on the effects of treatments on mood switch. The study did not receive funding from the pharmaceutical industry, which only provided study medications.

In another double-blind, parallel-group trial, Calabrese et al. (43) reported on 60 recently hypomanic/manic patients with recently stabilized rapid cycling bipolar disorder who had experienced a persistent response for at least six months to combined treatment with lithium and divalproex. Patients were randomly assigned to either lithium or divalproex monotherapy for 20 months using a balanced design after stratification for illness type (bipolar I disorder versus bipolar II disorder). The results indicated that divalproex was not more effective than lithium in the long-term management of rapid cycling bipolar disorder since no significant differences were found in rates of, or time to relapse to, any mood episode between the two treatment groups. The relapse rates into any mood episode for those assigned to lithium versus divalproex were 56% and 50%, respectively. However, the relatively small sample size and the effects of lithium discontinuation limit the generalizability of these findings. The authors did not present the comparative effects of lithium on the number of relapses or on mood switch and acknowledge that the pharmaceutical industry provided study medications but not funding.

Valproate. The study by Calabrese et al. (43) assessed the effects of valproate in comparison with lithium monotherapy in the prevention of relapse in rapid cycling bipolar disorder and has been reviewed above.

Mood stabilizer–anticonvulsant combination

The results of two studies by Denicoff et al. (25) and Kemp et al. (42) that reported the efficacy and safety of mood stabilizer combination in the prevention of relapse in rapid cycling bipolar disorder have been discussed above. They included the combinations of lithium/carbamazepine (25) and lithium/valproate (42) and produced contradictory results. Whereas the lithium–valproate combination was not found to be superior to lithium monotherapy in preventing mood episodes in rapid cyclers, the history of rapid cycling was associated with a better response in the lithium–carbamazepine combination group than on either monotherapy.

Antidepressant continuation versus discontinuation

Ghaemi et al. (26) recently reported the effects of antidepressant discontinuation after acute recovery of bipolar depression in 70 patients with bipolar depression from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. They found that a rapid cycling course predicted three times more depressive episodes with antidepressant continuation. Rapid cycling was an independent predictor for shorter episode latency, increased number of depressive episodes, and fewer weeks in remission. However, the authors noted that these results need replication in a larger study of a rapid cycling population, since the number of patients with a rapid cycling course in their study was small ($n = 17$). This study did not receive any funding from the pharmaceutical industry.

Meta-analysis

Tondo et al. (27) conducted a review and meta-analysis of 16 studies examining the long-term treatment of rapid cycling, which included three

randomized trials and 13 non-random, open-label or naturalistic studies. They estimated that the prevalence of rapid cycling was 15.4%. The authors also confirmed that rates of recurrence were higher in rapid cyclers versus non-rapid cyclers, a finding indicating that rapid cycling bipolar disorder is a treatment-resistant condition. The crude rate estimate for recurrence for rapid cycling subjects pooled across all study arms was higher (by 1.85-fold) than for non-rapid cycling subjects (2.31 versus 1.25%/month). Pooled recurrence rates, from low to high, ranked as follows: lithium (2.09%/month), carbamazepine (2.87%/month), valproate (3.63%/month), lamotrigine (8.57%/month), and placebo (12.5%/month). The authors also report that no clear advantage was found for any treatment and, contrary to previous beliefs, anticonvulsants demonstrated no superiority over lithium. However, the studies reviewed did not permit a direct comparison of the treatment effects of different agents. Only lithium and carbamazepine could be directly compared meta-analytically in rapid cycling patients and this comparison revealed no difference in efficacy. This meta-analysis, which was not sponsored by the pharmaceutical industry, did not report mood-switching rates following treatments or the possible role of industry in the results. It also did not provide data on the time to relapse for the different treatments.

In terms of adverse events, the known adverse-effect profile of each agent was confirmed by most studies. Interestingly, one study found that rapid cyclers report severe adverse effects more frequently compared to non-rapid cyclers (19).

Discussion

This is the first paper to review the randomized trial clinical data on the efficacy of various treatments in patients with rapid cycling bipolar disorder. Most studies included in this paper examined the efficacy and adverse effects of various pharmacological treatments for patients with rapid cycling bipolar disorder. Our report also analyzed studies comparing treatment effects on rapid versus non-rapid cyclers, providing useful information on the comparative treatment responsiveness of these bipolar subpopulations. Previous reviews and meta-analyses that have examined the treatment responses of patients with rapid cycling have included mostly naturalistic studies (3, 27). Although the naturalistic design could provide important clinical information, especially when adequately randomized, controlled, and prospective trials are not available, it cannot control for numerous treatment factors, such as severity of illness, psychotropic dose, total time of drug exposure, types of medications used, or the presence of concomitant medications. Thus, it cannot establish causality in treatment response or effectively compare existing treatments, a limitation that can only be avoided by randomized studies.

Despite having a randomized design, the studies that we examined for the purposes of the present review were not devoid of other limitations. The majority: (i) had a small sample size, (ii) presented post hoc analyses of data in rapid cyclers, (iii) lacked a placebo-control group, and (iv) had a short duration of follow-up periods. Notwithstanding these limitations, the main findings of the present review are: (i) rapid cycling patients do worse in follow-up than patients without rapid cycling; (ii) the acute responsiveness to treatment of rapid cycling patients in comparison with non-rapid cycling patients indeed remains inconclusive; (iii) lithium and anticonvulsants have comparable, albeit relatively low, efficacies in rapid cyclers; (iv) the data on the usefulness of the combination of anticonvulsants compared with anticonvulsant monotherapy in rapid cyclers are contradictory; (v) the atypical antipsychotics aripiprazole, olanzapine, and quetiapine are effective in acute bipolar episodes of rapid cyclers; (vi) olanzapine is equally effective to anticonvulsants during acute treatment; (vii) aripiprazole, olanzapine, and quetiapine appear promising for the maintenance of response in rapid cyclers; and (viii) there is an association between antidepressant use and the presence of rapid cycling, although the existence of a causal relationship cannot yet be established.

The few existing studies support the hypothesis that rapid cycling patients show a less favorable long-term outcome than non-rapid cycling patients and that initial responses do not predict long-term efficacy (19, 27). These findings have important therapeutic implications and, certainly, need replication in studies with adequate duration. Another important issue that also needs to be further investigated is whether rapid cycling is a characteristic that persists in time. During one randomized trial that explored this issue, Vieta et al. (19) found that the rapid cycling patients who received an open-label olanzapine treatment for one year experienced a mean number of fewer than four episodes. This is in agreement with the previous studies that suggested that rapid cycling status is not necessarily a sustained characteristic in all cases of rapid cycling bipolar disorder (6, 7, 44).

There are no clear data concerning the differential impact of treatment against acute states, of either mania or depression, in rapid cyclers versus

non-rapid cyclers. Although earlier reports suggested that rapid cycling is associated with inadequate treatment response (2, 8), two recent randomized studies showed similar treatment effects in both bipolar subgroups (19, 22). Interestingly, in one of the two, the improvement in manic symptoms was found to occur earlier in rapid cycling patients (19).

Recent data cast doubt on the initial opinion that rapid cyclers are refractory to lithium treatment and should be treated with other mood stabilizers (2, 10). This earlier view was mainly supported by comparing studies using lithium alone against studies using anticonvulsants alone without a direct comparison of the two treatments following a proper randomization. In the few randomized studies that have directly compared the effects of lithium with those of anticonvulsants, the two treatments appeared to be equivalent in efficacy in rapid cycling patients. Indeed, lithium prophylaxis was shown to be at least as effective as divalproex in rapid cycling bipolar disorder (43) and showed a comparable efficacy with carbamazepine (25). However, it should be noted here that in both studies monotherapy with either lithium or one of the other two mood stabilizers demonstrated a relatively low efficacy.

The study by Denicoff et al. (25) also examined another important issue: the comparative efficacy of lithium and carbamazepine combination versus monotherapy for treating rapid cycling bipolar disorder. It suggested that rapid cyclers show a better response to combination treatment than monotherapy. On the contrary, the prophylactic effect of lithium monotherapy was not found to differ from that of the combination of lithium plus valproate according to a more recent study (42), thus leaving the question of whether anticonvulsant co-treatment is better than monotherapy still unanswered. To the best of our knowledge, no randomized studies have examined the therapeutic value of combination treatments of mood stabilizers with atypical antipsychotics in rapid cycling patients.

Interest has been growing in the therapeutic potential of atypical antipsychotics in bipolar disorder (45, 46). Olanzapine is effective when used alone in the acute management of manic or mixed patients with a rapid cycling course (19, 31). Similarly, there have been positive results for aripiprazole (29) and quetiapine (22, 33) in bipolar mania and depression, respectively. The latter finding is particularly important, since patients with rapid cycling bipolar disorder present more often in the depressed phase of their disease (5, 26, 47). Recent studies also suggest that the acute treatment effects of mood stabilizers appear to be equal to those of olanzapine in rapid cyclers presenting with manic or mixed states (21). However, more studies are needed using other atypical antipsychotics and mood stabilizers in order to draw a safe conclusion on the relative efficacy of these agents in rapid cycling bipolar disorder.

The efficacy of aripiprazole (37), olanzapine (19), and quetiapine (38) monotherapy extends beyond the acute treatment to bipolar maintenance in rapid cycling bipolar disorder. An interesting finding that needs further exploration was that quetiapine seems more effective for the prophylaxis of exacerbations of depressive than manic symptoms. The role of typical or other atypical antipsychotics as well as their comparative efficacies in acute and prophylactic treatment of rapid cycling bipolar disorder remain to be investigated in future studies.

The most important issue in the management of rapid cycling bipolar disorder is probably not the acute efficacy of existing medications but their potential for relapse prevention. Indeed, the original paper by Dunner and Fieve (2) studied prophylactic treatment rather than acute responsiveness of rapid cyclers. The reason that the present review has mainly covered data concerning the acute treatment of rapid cycling bipolar disorder is that studies examining long-term stabilization of rapid cycling bipolar disorder patients are even fewer and therefore most needed.

A central question in the long-term treatment of bipolar disorder, and more specifically rapid cycling, is whether antidepressants are of benefit or if they destabilize the course of illness (10, 11). Previous observational studies have yielded inconsistent findings concerning antidepressant effects in rapid cycling patients (6, 48–51). Although the existing randomized studies have not systematically investigated this issue, they suggest that antidepressants might relate to rapid cycling (11, 26). The etiological nature of this relationship remains to be further delineated.

The above studies have additionally examined the side effects that emerged during treatment of rapid cycling bipolar disorder and, as expected, the known profiles of the agents used were confirmed. However, one study that examined the efficacy of olanzapine also found that rapid cyclers report severe adverse effects more frequently compared to non-rapid cyclers (19). This finding deserves further investigation since it has important clinical implications.

A philosophical issue is raised after reviewing the literature on the treatment of rapid cycling bipolar disorder. Undoubtedly, there is an utmost clinical

need to define the most effective treatments for this bipolar subtype. However, there are only seven randomized controlled clinical trials that have been designed to address it directly (28, 35, 36, 39, 40, 42, 43), two of which recruited rapid cycling patients with a substance abuse disorder, therefore limiting the generalizability of their findings (35, 42). Most existing data are derived from secondary analyses carried out mostly on results from industry-organized trials and open-label or naturalistic studies. Secondary analyses are usually not adequately powered to detect differences between subgroups. In these analyses, although a positive finding with regard to the treatment efficacy of any agent in rapid cycling subpopulations has clinical value, a negative one cannot rule out the possibility of a beneficial treatment effect. On the other hand, the presence of publication bias needs also to be taken into account. It is well known that secondary analyses of clinical trials are highly subject to publication bias, because generally only positive findings are published. Accordingly, should one attempt to extract some recommendations from this insufficient material, even if these recommendations will be questionable? We have positively answered this question, reviewed the existing data, and suggested some preliminary recommendations. However, we fully acknowledge that these recommendations unavoidably carry the risk of being rejected by future trials, free from methodological limitations. The pharmaceutical industry remains a major source of bias through selective reporting and publishing, which could influence the reliability of treatment guidelines and could also affect our recommendations (52). In order to facilitate the interpretation of our findings, the role of the pharmaceutical industry in the funding of each study is shown in Table 1.

In conclusion, the present review suggests that the current data on the treatment of rapid cycling bipolar disorder patients need to be enriched by more rigorously designed studies. The delineation of the benefits and risks of the existing medications and their combinations in different phases of rapid cycling bipolar disorder and, in particular, maintenance treatment through randomized controlled trials recruiting adequately powered samples of this specific patient population should be a research priority. Only when such research has been carried out may recommendations concerning treatment of rapid cycling bipolar disorder be safely given.

Disclosures

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