Rapid and Non-Rapid Cycling Bipolar Disorder: A Meta-Analysis of Clinical Studies

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Background: Rapid cycling, defined as 4 or more mood episodes per year, is a course specifier of bipolar disorder associated with relative treatment resistance. Several risk factors have been suggested to be associated with rapid cycling. The purpose of this meta-analysis was to compare clinical studies for the evidence of discriminating factors between rapid and non-rapid cycling.

Data Sources and Selection: We searched MEDLINE and reference lists of articles and book chapters and selected all of the clinical studies published from 1974 to 2002 comparing subjects with rapid and non-rapid cycling bipolar disorder. Prevalence rates and mean random effect sizes for 18 potential risk factors that were reported by at least 3 studies were calculated. In addition, we differentiated between current and lifetime diagnoses of rapid cycling.

Data Synthesis: Twenty studies were identified. Rapid cycling was present in 16.3% of 2054 bipolar patients in 8 studies that included patients who were consecutively admitted to an inpatient or outpatient facility, without a priori selection of rapid cyclers and without matching the numbers of rapid cyclers to non-rapid cycling controls. Female gender and bipolar II subtype both had a small, but statistically significant, effect ($p < .000$ for female gender, $p < .001$ for bipolar II subtype). The further absence of recurrences with lithium prophylaxis was reported in 34% of rapid cyclers compared with 47% of non-rapid cyclers, a nearly significant difference, and a partial response was present in 59% and 65% of patients, respectively. The effect of hypothyroidism was significant ($p < .01$) in studies using current, but not lifetime, definitions of rapid cycling. In 46% of cases, a rapid cycling course was preceded by treatment with antidepressants, but systematic data on their causal role are lacking.

Conclusion: Rapid cycling is slightly more prevalent in women and in patients with bipolar II subtype. In contrast to common opinion, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients.

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The frequent recurrence of major mood episodes in some patients with manic-depressive illness (bipolar disorder) was described over a century ago in the pre-pharmacologic era, but it was not until 1974 that the term *rapid cycling* was introduced by Dunner and Fieve,[1] arbitrarily defined by them as the occurrence of at least 4 separate mood episodes within a given year. Since then, this definition has been used in most studies of rapid cycling and was included in DSM-IV[2] as a specifier of the longitudinal course of bipolar I or II disorder.

It is unclear whether rapid cycling is a distinct subtype of bipolar disorder or just a clinical phenomenon toward one extreme on a continuum of episode frequencies.[3–5] Cycle lengths (i.e., the time from the onset of one episode until the onset of the next episode of the same polarity) as short as 48 hours[6] or even 24 hours[7,8] have been described. These frequencies are sometimes referred to as ultra-rapid (episodes occurring within the course of days to weeks) and ultradian cycling (mood shifts within a day), respectively.[8]

In DSM-IV, rapid cycling is defined as the occurrence of at least 4 episodes in the previous 12 months that meet criteria for a major depressive, manic, mixed, or hypomanic episode and can be applied to bipolar I or II disorder. Episodes are demarcated by either partial or full remission for at least 2 months or a switch to an episode of opposite polarity. By definition, the recurrence of mood symptoms of the same polarity after a relatively brief period of remission is not regarded as a new episode, but rather as a relapse of the index episode. Likewise, patients who have very brief, although sometimes severe, episodes do not fall within the DSM-IV definition of rapid cycling, but are classified as having bipolar disorder not otherwise specified. Other diagnostic systems that have been used

during the last decades do not specify rapid cycling and may differ with regard to the required minimum duration of a mood episode, if specified.

If rapid cycling is a distinct subtype of bipolar disorder, one would assume that this condition is characterized not only by a high episode frequency, but also by other features distinguishing it from the non-rapid cycling forms of bipolar disorder. Indeed, several phenomena have been associated with a rapid cycling course. Dunner and Fieve[1] originally reported that rapid cyclers were disproportionately represented in a subgroup of bipolar patients with a poor response to lithium prophylaxis; this was followed by similar reports for other pharmacologic treatments.[9,10] In addition, rapid cycling has been associated with female gender, bipolar II subtype, a longer duration of illness, a positive family history of mood disorders, the presence of clinical or subclinical hypothyroidism, and the use of antidepressants.[9,11–16]

Over the last decades, many studies have addressed the issue of rapid cycling from the perspective of clinical and demographic features, neurobiological dysfunction, longitudinal course, and treatment response. Several nonsystematic reviews of rapid cycling have been published,[9,11–16] as well as 1 meta-analysis of gender in rapid cycling.[17] In the present systematic review, we performed a meta-analysis of all studies that made a direct comparison between rapid cycling versus non-rapid cycling bipolar disorder and fulfilled several additional methodological criteria. This meta-analysis included all clinical phenomena associated with rapid cycling that were addressed by at least 3 of the studies.

METHOD

Identification of Studies

Using MEDLINE searches (keywords: *rapid cycling, non-rapid cycling*) and the reference lists of original peer-reviewed publications, review articles, and relevant book chapters, we selected all clinical studies that were published from 1974 until 2002 and that compared subjects with rapid cycling and non-rapid cycling bipolar disorder, using the definition of rapid cycling as the occurrence of 4 or more mood episodes per year.[1,2] In addition, studies had to fulfill the following inclusion criteria: the study (1) was originally designed to address the issue of rapid cycling bipolar disorder either retrospectively or prospectively, (2) included a rapid cycling and a non-rapid cycling group and described the characteristics of these 2 groups separately, (3) gave a clear description of the patient samples and how subjects were selected for the study, (4) specified which criteria were used for the diagnosis of bipolar disorder and for the definition of rapid cycling, (5) stated whether rapid cycling was lifetime or current, and (6) addressed 1 or more factors that were potentially associated with a rapid cycling course (for a list of the factors, see Statistical Method). We examined all factors that were reported by at least 3 studies. Studies from the same research group were not allowed to refer to the same subjects; in such cases, or when there was doubt, the most representative study was chosen.

Statistical Method

For all studies that included a particular risk factor, the results were pooled by adding the numbers of patients in the rapid cycling and non-rapid cycling groups and calculating mean percentages. To prevent bias, studies were included in the analysis only if they did not match rapid and non-rapid cycling subjects for that particular factor, e.g., gender.[18] Results are presented as group comparisons between rapid cyclers and non-rapid cyclers and as the prevalence of rapid cycling among subjects with and without a particular risk factor. For the subgroup of rapid cyclers, we also looked at whether rapid cycling had been present from the onset of bipolar illness and the association of rapid cycling with prior or current exposure to antidepressants. In addition, we compared the results of studies that used the definition of current rapid cycling with those that defined rapid cycling from a lifetime perspective, since this could explain some of the variance among studies.

Our main outcome measure was the effect size for each factor, as described by Rosenthal.[19] An effect size of 0.1 was considered as small; 0.3, as moderate; and 0.5, as large. We calculated the effect size for every study that reported on any of the following variables: female gender; bipolar II subtype; age; duration of bipolar illness; age at onset of mood disorder; occurrence of a depressive episode at onset of mood disorder; history of suicide attempt; histories of bipolar disorder, major depression, or any affective disorder among first-degree family members of bipolar probands; morbid risk of bipolar disorder, major depression, or any affective disorder among first-degree family members of bipolar probands; presence of clinical, subclinical, or any type of hypothyroidism; and nonresponse to prophylactic lithium treatment. Nonresponse to prophylactic lithium was differentiated into failure to achieve complete or near-complete prevention of further episodes (nonresponse type I) and failure to achieve at least 50% improvement (nonresponse type II), depending on which outcome measure was used in the studies that reported lithium response.

All effect sizes are presented as Pearson correlation coefficients (r), which can be calculated from chi-square tests for categorical variables [$\text{phi} = (\chi^2/N)^{1/2}$] and from Student t tests for continuous variables [$r = (t^2/[t^2 + df])^{1/2}$]. From the effect sizes of individual studies, we calculated weighted mean fixed and random effect sizes and tested for differences from zero and homogeneity based on methods described by Shadish and Haddock.[20] Weights were the inverse of the conditional variance for each study. Correlations were transformed

using Fisher z for all calculations, then converted back to r to report combined effect sizes. Subgroup analyses comparing lifetime and current rapid cycling were conducted using fixed effects contrasts described by Hedges.[21] A fixed-effects model was used for these contrasts in an attempt to understand the degree of heterogeneity explained by the contrasts.

Hochberg's adjusted Bonferroni procedure was used to adjust for multiple tests of significance.[22] The potential effect of publication bias was assessed by looking at the number of negative studies needed to negate any positive results from the random-effects models, as described by Rosenthal.[19] All statistical calculations were performed using SPSS 9.0 for Windows (SPSS Inc., Chicago, Ill., 1999).

RESULTS

Studies

We found 20 studies including 3709 subjects[23–42] meeting our inclusion criteria (Table 1), 9 from the United States, 7 from Italy, 2 from Canada, 1 from the United Kingdom, and 1 from India. One study[27] that reported results from 2 subsamples was treated as 2 separate studies with regard to different variables.

Eight studies[25,33–35,37,40–42] gave explicit details about criteria for severity and duration of individual mood episodes, and 9[24,25,32,33,35,37,40–42] gave details about criteria for the demarcation of episodes. In most studies, the criteria for severity and duration of mood episodes were defined according to the diagnostic system that was used (Table 1). However, the criteria for the duration of mood episodes and/or the interepisode remission were modified in some studies.[25,32–34,40] Criteria for the demarcation of individual mood episodes varied between studies, but generally included a switch to an episode of the opposite polarity, as well as a period of euthymia varying from 1 week to 2 months. One study[42] considered 2 episodes of opposite polarity that were separated by less than 8 weeks of remission as 1 mixed episode. Another study[33] included episodes lasting at least 24 hours and considered 24 hours of euthymia sufficient to separate episodes. Yet another study[40] used 4 definitions of rapid cycling: definition 1 was in accordance with DSM-IV, definition 2 included all episodes of at least 1 day of full severity, definition 3 added a requirement of at least 1 direct switch to an episode of the opposite pole, and definition 4 was the same as definition 2 but with the additional requirement of at least 8 weeks of full affective illness in the last year; we included only the rapid cycling group who fulfilled definition 1 (DSM-IV) in our meta-analysis.

Prevalence of Rapid Cycling

Rapid cycling was diagnosed in 335 (16.3%) of 2054 patients in 8 studies[23,24,27,29,32,38,40,41] that included patients who were consecutively admitted to an inpatient or outpatient facility, without a priori selection of rapid cyclers and without matching the numbers of rapid cyclers to non-rapid cycling controls (range between studies, 12%–24%). The average prevalence for the studies using the definition of current rapid cycling (including 795 subjects) was 16.4%, and for the studies using lifetime rapid cycling (including 1259 subjects), 16.3%.

Associated Factors

Table 1 gives details of 8 associated factors for every study. Lithium response was defined as the complete or nearly complete absence of further recurrences by 2 studies[24,26] and as at least 50% improvement by another 2,[29,40] while 1 study[41] gave both outcome measures.

Table 2 presents the studies that reported family history of affective disorders, either as the number of bipolar probands with at least 1 first-degree family member with a major affective disorder or as the morbid risk of interviewed first-degree relatives of bipolar probands.

Table 3 presents the studies that assessed thyroid function. In studies that used the definition of current rapid cycling,[25,31,35] rapid cycling occurred in 70.8% of patients with either clinical or subclinical hypothyroidism and in only 29.4% of euthyroid patients; in contrast, in studies that used the definition of lifetime rapid cycling,[28,30,36] these percentages were 34.6% and 54.7%, respectively. Wehr et al.[26] reported only clinical hypothyroidism. We did not include the thyroid data from Coryell et al.,[32] since they assessed thyroid function only by history (rate of clinical hypothyroidism of 16% in rapid cycling, compared with 10% in non-rapid cycling, a nonsignificant difference).

Table 4 gives the number of included studies and subjects for each risk factor, as well as the pooled prevalences, presented as the percentage of rapid cyclers in the subgroups with (e.g., women) and without (e.g., men) a potential risk factor, and also as the percentage of patients with each risk factor (e.g., female gender) in the subgroups of patients with rapid cycling and non-rapid cycling.

Two additional variables were not included in the formal meta-analysis because they did not compare rapid and non-rapid cyclers. A rapid cycling course was present from the onset of bipolar illness in 49 (27.1%) of 181 patients from 4 studies (range, 23%–34%).[24,26,29,38] Rapid cycling was associated with antidepressant use in 101 (45.5%) of 222 patients from 6 studies (range among the studies, 25%–70%), although the way in which this association was defined varied from study to study.[24–26,28,29,38]

Effect Size

Mean effect sizes according to the fixed- and random-effects models are presented in Table 5. These were calculated from the studies and subjects as summarized in Table 4.

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Table 1. Overview of 20 Selected Studies Comparing Rapid Cycling (RC) and Non-Rapid Cycling (NRC) Bipolar Disorder[a]

Study	Primary Focus	Subjects	Diagnosis	Patients With Rapid Cycling, N	Females, N (%)
Dunner et al, 1977, US[23]	Descriptive and effects of lithium	306 lithium outpatients followed up to 7 y	St Louis Criteria current RC	RC: 40 (13%) NRC: 266	RC: 28 (70) NRC: 123 (46) (p < .01)
Kukopulos et al, 1980, Italy[24]	Course of illness and influence of treatments	434 inpatients/ outpatients; follow-up 4.5 y	ICD-9 lifetime RC	RC: 87 (20%) NRC: 347	RC: 61 (70) NRC: 195 (56) (p = .02)
Cowdry et al, 1983, US[25]	Thyroid dysfunction	43 NIMH inpatients/ outpatients on lithium; follow-up 1 y	RDC current RC	RC: 24 (56%) NRC: 19	RC: 20 (83) NRC: 10 (53) (p < .05)
Wehr et al, 1988, US[26]	Descriptive and treatment response	66 NIMH inpatients; follow-up 1–12 y	RDC lifetime RC	RC: 47 (71%) NRC: 19	RC: 47 (100) NRC: 19 (100)
Nurnberger et al, 1988, US[27]	Family history	195 NIMH inpatients/ outpatients	RDC lifetime RC	RC: 29 (15%) NRC: 166	RC: 25 (86) NRC: 88 (53) (p < .001)
	Family history	58 matched subsample of whole group of N = 195	RDC lifetime RC	RC: 29 (50%) NRC: 29 (matched)	RC: 25 (50) NRC: 25 (50) (matched)
Joffe et al, 1988, Canada[28]	Thyroid dysfunction	42 outpatients	RDC lifetime RC	RC: 17 (40%) NRC: 25	RC: 7 (41) NRC: 20 (80) (p < .01)
Maj et al, 1989, Italy[29]	Course of illness and treatment response	118 outpatients; follow-up ≥ 2 y	DSM-III current RC	RC: 14 (12%) NRC: 104	RC: 9 (64) NRC: 59 (57)
Bartalena et al, 1990, Italy[30]	Thyroid dysfunction	22 outpatients	DSM-III-R lifetime RC	RC: 11 (50%) NRC: 11 (matched)	RC: 11 (100) NRC: 11 (100)
Kusalic, 1992, Canada[31]	Thyroid dysfunction	20 inpatients/outpatients	DSM-III current RC	RC: 10 (50%) NRC: 10 (matched)	RC: 7 (70) NRC: 7 (70) (matched)
Coryell et al, 1992, US[32]	Descriptive	243 NIMH inpatients/ outpatients; follow-up 1–5 y	RDC current RC	RC: 45 (19%) NRC: 198	RC: 32 (71) NRC: 98 (50) (p = .009)
Lish et al, 1993, US[33]	Family history	89 outpatients from 3 specialized clinics	DSM-III-R lifetime RC	RC: 45 (51%) NRC: 44	RC: 37 (82) NRC: 28 (64) (p < .05)
Wu and Dunner, 1993, US[34]	History of suicide attempts	220 outpatients	DSM-III-R lifetime RC	RC: 100 (45%) NRC: 120	RC: 60 (60) NRC: 64 (53)
Maj et al, 1994, Italy[35]	Validity of RC as course specifier	111 inpatients/outpatients; follow-up 2–5 y	RDC current RC	RC: 37 (33%) NRC: 74 (matched)	RC: 24 (65) NRC: 38 (51)
Post et al, 1997, US[36]	Thyroid dysfunction	67 NIMH inpatients, all medication-free	DSM-III lifetime RC	RC: 31 (46%) NRC: 36	All: 38 (58)
Kirov et al, 1998, UK[37]	Genetic (COMT gene)	165 outpatients from a genetic study	DSM-IV lifetime RC	RC: 55 (33%) NRC: 110	RC: 34 (62) NRC: 58 (53)
Avasthi et al, 1999, India[38]	Descriptive	270 inpatients/outpatients; follow-up ≥ 1 y	ICD-10 lifetime RC	RC: 33 (12%) NRC: 237	RC: 14 (42) NRC: 88 (37)
Bowden et al, 1999, US[39]	Efficacy of lamotrigine	75, open treatment trial; follow-up 48 wk	DSM-IV current RC	RC: 41 (55%) NRC: 34	RC: 25 (61) NRC: 20 (59)
Maj et al, 1999, Italy[40]	Validity of RC as course specifier	210 outpatients; follow-up ≥ 1 y	RDC current RC	RC: 31 (24%) NRC: 97	RC: 21 (68) NRC: 51 (53) (p < .05)
Baldessarini et al, 2000, Italy[41]	Response to lithium prophylaxis	360 outpatients; follow-up 4.5 y	DSM-IV lifetime RC	RC: 56 (16%) NRC: 304	RC: 41 (73) NRC: 188 (62)
Serretti et al, 2002, Italy[42]	Descriptive	595 inpatients from various studies pooled	DSM-IV lifetime RC	RC: 275 (46%) NRC: 320	RC: 175 (63) NRC: 176 (55) (p = .03)

[a]Percentages are rounded to whole numbers. Matched groups are indicated for each variable, if applicable. All p values shown indicate statistically significant differences between rapid cyclers and non-rapid cyclers.
[b]Lithium response I, defined as complete or near complete prevention of recurrences with lithium prophylaxis.
[c]Lithium response II, defined as at least 50% improvement with lithium prophylaxis.
Abbreviations: COMT = catechol-*O*-methyltransferase, NIMH = National Institute of Mental Health, RDC = Research Diagnostic Criteria.
Symbol: … = not reported.

Bipolar II, N (%)	Age, Mean (SD), y	Duration of Illness, Mean (SD), y	Age at Onset, Mean (SD), y	Onset w/ Depression, N (%)	History of Suicide Attempt, N (%)	Lithium Response
RC: 16 (40) NRC: 87 (33)	…	…	RC: 29.9 (12.0) NRC: 31.3 (10.9)	…	…	RC: "poor" NRC: "good"
RC: 71 (82) NRC: 156 (45) (p < .0000)	…	…	…	RC: 53 (61) NRC: 179/308 (58)	…	RC: 36/65 (55)[b] NRC: 157/244 (64)[b]
…	RC: 45.3 (15.6) NRC: 41.1 (14.5)	…	…	…	…	…
RC: 22 (47) NRC: 6 (32)	RC: 49 (14) NRC: 47 (15)	…	RC: 30 (11) NRC: 27 (12)	RC: 46 (98) NRC: 13 (68)	RC: 32 (68) NRC: 7 (37) (p < .05)	RC: 12/51 (24)[b] NRC: 11/12 (92)[b] (p < .000)
…	…	…	…	…	…	…
RC: 12 (41) NRC: 8 (28)	… (matched)	…	…	…	…	…
…	All: 38 (12)	RC: 25.9 (52.3) NRC: 14.2 (11.0)	…	…	…	…
…	RC: 43.5 (11.9) NRC: 40.8 (9.8)	RC: 11.0 (7.2) NRC: 9.5 (5.6)	RC: 32.4 (6.0) NRC: 31.3 (4.6)	…	RC: 6 (43) NRC: 29 (28)	RC: 3/12 (25)[c] NRC: 53/87 (61)[c]
…	RC: 43 (22–78) NRC: 46 (21–75) (matched)	…	…	…	…	…
…	… (matched)	RC: 15 (9) NRC: 19 (11)	RC: 29 (6) NRC: 28 (8)	…	…	…
RC: 16 (36) NRC: 35 (18) (p = .008)	RC: 37.2 (11.4) NRC: 36.7 (13.2)	RC: 11.6 (8.4) NRC: 12.2 (10.4)	RC: 25.4 (8.4) NRC: 24.8 (10.0)	…	…	…
…	RC: 39 (15) NRC: 44 (11) (p < .05)	…	…	…	…	…
RC: 78 (78) NRC: 78 (65) (p < .003)	RC: 42 (10) NRC: 42 (13)	…	RC: 21 (12) NRC: 23 (12)	…	RC: 35 (35) NRC: 37 (31)	…
RC: 15 (41) NRC: 18 (24)	RC: 43.3 (8.8) NRC: 37.7 (8.7) (p < .002)	RC: 13.4 (7.2) NRC: 8.4 (6.8) (p < .001)	RC: 29.9 (4.7) NRC: 29.3 (5.2)	…	RC: 14 (38) NRC: 20 (27)	…
All: 25 (37)	…	…	…	…	…	…
RC: 10 (18) NRC: 6 (5)	RC: 47.9 (13.8) NRC: 46.2 (13.4)	RC: 17.1 (11.0) NRC: 19.4 (9.8)	…	…	…	…
RC: 8 (24) NRC: …	…	RC: 12.8 (10.7) NRC: 7.6 (8.8) (p < .01)	RC: 30.2 (7.1) NRC: 27.7 (11.2)	RC: 16 (48) NRC: 62 (26) (p < .01)	…	…
…	RC: 42.9 (11.7) NRC: 45.6 (9.4)	…	RC: 19.4 (8.8) NRC: 29.6 (11.2) (p < .00001)	…	…	…
RC: 13 (42) NRC: 28 (29) (p < .05)	RC: 43.9 (7.9) NRC: 38.3 (8.5) (p < .01)	RC: 12.9 (7.5) NRC: 9.9 (7.3) (p < .05)	…	…	RC: 12 (39) NRC: 30 (31)	RC: 13/22 (59)[c] NRC: 74/89 (83)[c]
RC: 43 (77) NRC: 99 (33) (p = .0001)	…	"No difference" All: 9	RC: 33.6 (12.5) NRC: 28.7 (11.9) (p = .005)	RC: 52 (93) NRC: 181 (60)	…	RC: 10/56 (18)[b] NRC: 96/304 (32)[b] RC: 37/56 (66)[c] NRC: 184/304 (61)[c]
RC: 49 (18) NRC: 63 (20)	RC: 47.6 (13.3) NRC: 41.5 (14.0) (p = .0001)	…	RC: 32.1 (11.8) NRC: 29.4 (10.9) (p = .004)	RC: 174 (77) NRC: 217 (70)	RC: 60 (27) NRC: 95 (31)	…

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Table 2. Family History of Major Affective Disorders in Rapid Cycling (RC) and Non-Rapid Cycling (NRC) Bipolar Disorder

		Subjects, N		Bipolar Disorder, N (%)		Major Depression, N (%)		Any Major Affective Disorder, N (%)	
Study	Method	RC	NRC	RC	NRC	RC	NRC	RC	NRC
Bipolar probands with first-degree relative with a major affective disorder									
Dunner et al[23]	Chart review	29	217	11 (37.9)	66 (30.4)	10 (34.5)	57 (26.2)	21 (72.4)	123 (56.7)
Wehr et al[26]	Various methods	47	19	12 (25.5)	7 (36.8)	19 (40.4)	5 (26.3)	28 (59.6)	12 (63.2)
Maj et al[29]	…	14	104	…	…	…	…	4 (28.6)	23 (22.1)
Maj et al[35]	FH-RDC	37	74	5 (13.5)	6 (8.1)	11 (29.7)	16 (21.6)	16 (43.2)	22 (29.7)
Kirov et al[37]	…	55	110	…	…	…	…	40 (72.7)	71 (64.5)
Maj et al[40]	FH-RDC	31	97	…	…	…	…	11 (35.5)	30 (30.9)
Avasthi et al[38]	Chart review	33	237	13 (39.4*)	16 (6.8)	2 (6.1)	9 (3.8)	15 (45.5*)	25 (10.6)
Serretti et al[42]	Clinical interview	188	290	…	…	…	…	165 (87.8)	243 (83.8)
Morbid risk in first-degree relatives of bipolar probands		N		N/N (%)		N/N (%)		N/N (%)	
		RC	NRC	RC	NRC	RC	NRC	RC	NRC
Nurnberger et al[27]	SADS-L	29	29	16/143 (11.2)	15/146 (10.3)	16/137 (11.7)	26/139 (18.7)	33/140 (23.5)	44/142 (31.0)
Coryell et al[32]	FH-RDC	45	198	11/268 (4.1)	54/1273 (4.2)	54/268 (20.1)	249/1273 (19.6)	66/268 (24.6)	303/1273 (23.8)
Lish et al[33]	FH-RDC	45	44	25/221 (11.3)	28/190 (14.7)	60/221 (27.1)	48/190 (25.3)	85/221 (38.5)	76/190 (40.0)

*$p < .01$.
Abbreviations: FH-RDC = Family History-Research Diagnostic Criteria, SADS-L = Schedule for Affective Disorders and Schizophrenia-Lifetime Version. Symbol: … = not reported.

When effect sizes from the various studies were combined according to the fixed-effects model, a significant difference from zero after Hochberg's adjustment was found for female gender, bipolar II subtype, older age, depressive episode at onset, history of suicide attempt, family histories of bipolar disorder and any major affective disorder, and lithium nonresponse type I.

Homogeneity tests revealed significant between-studies variation for 12 of the 18 factors, which suggests the need to account for this variance by using random-effects models. Given the debate over when random-effects models are appropriate, we report these for all factors. All mean random-effects effect sizes with 95% confidence intervals are also presented in Figure 1.

Using a random-effects model, we found that effect sizes were significantly different from zero for female gender and bipolar II subtype after Hochberg's adjustment and nearly significant for lithium nonresponse type I, history of suicide attempt, family history of any major affective disorder, and depression at onset.

Since publication bias could play a factor in any of the results, the number of studies with null results required to make results nonsignificant was calculated. These numbers were 100 studies for gender and 36 for bipolar II subtype.

We tried to explain some of the high degree of heterogeneity using the 2 definitions of rapid cycling. Specifically, some studies counted patients as rapid cyclers only if they were currently rapid cycling, while others counted anyone with a lifetime history of rapid cycling (Table 1). When we compared effect sizes for all factors between subgroups of patients with a current versus lifetime diagnosis of rapid cycling, the only significant differences occurred for any hypothyroidism. Thus, for hypothyroidism, a significant portion of the between-studies variation was explained by the definition of rapid cycling used. Specifically, hypothyroidism had a larger effect with current rapid cycling (Table 5).

DISCUSSION

This is the first meta-analysis of clinical studies comparing patients with rapid cycling and non-rapid cycling bipolar disorder to cover most of the factors that have been associated with a rapid cycling illness course in previous publications. There are several limitations to a meta-analytic approach to these studies. First, most studies had a naturalistic design, especially with regard to treatment outcome. Second, although studies may have investigated the same phenomenon, the methodology and outcome criteria varied, thus limiting the comparability of the results. Third, we could only look at all of the factors individually, although some of these factors may have been related to each other, e.g., female gender and hypothyroidism. Finally, our selection criteria set aside studies that included only rapid cycling bipolar subjects and had no comparison group of non-rapid cyclers or otherwise did not fulfill our criteria (e.g., references 7 and 43–46); we discuss these studies below. In particular, one of the major studies in this area,[45] a multisite reanalysis, was excluded because it included patients from some of the original studies in our analysis (written communication, M. S. Bauer, M.D., December 2002). That study reported more women and subjects from higher social classes in

Table 3. Prevalence of Hypothyroidism in Rapid Cycling (RC) and Non-Rapid Cycling (NRC) Bipolar Disorder

	Subjects, N		% Female		Age, Mean (y)		Clinical Hypothyroidism, N (%)		Subclinical Hypothyroidism, N (%)		Any Hypothyroidism, N (%)		
Study	RC	NRC	RC	NRC	RC	NRC	RC	NRC	RC	NRC	RC	NRC	Comments
Cowdry et al[25]	24[a]	19	83	53	45	41	12 (50‡)	0 (0)	10 (42‡)	6 (32)	22 (92‡)	6 (32)	All patients received lithium for at least 3 mo
Wehr et al[26]	47[b]	19	100	100	49	47	22 (47)	7 (37)	…	…	…	…	Hypothyroidism began during lithium treatment in 18 subjects (62%)
Joffe et al[28]	17[b]	25	41†	80	…	…	0 (0*)	5 (20)	0 (0)	3 (12)	0 (0†)	8 (32)	All patients received lithium for at least 3 mo
Bartalena et al[30]	11[b]	11	100	100	43	46	0 (0)	0 (0)	4 (36)	3 (27)	4 (36)	3 (27)	All patients with hypothyroidism received lithium for at least 1 y
Kusalic[31]	10[a]	10	70	70	(matched)		0 (0)	0 (0)	6 (60†)	0 (0)	6 (60†)	0 (0)	All patients received lithium
Maj et al[35]	37[a]	74	65	51	43†	38	2 (5)	1 (1)	4 (11)	7 (9)	6 (16)	8 (11)	N = 7 (50%) of all hypothyroid patients received lithium
Post et al[36]	22[b,c]	15	…	…	…	…	0 (0)	0 (0)	5 (23)	6 (40)	5 (23)	6 (40)	All patients were medication-free for an average of 6 wk

[a]Current rapid cycling.
[b]Lifetime rapid cycling.
[c]Data on both clinical and subclinical hypothyroidism (thyroid-stimulating hormone level) were available for 37 of 67 patients.
*p < .05.
†p < .01.
‡p < .001.
Symbol: … = not reported.

Table 4. Overview of Studies and Prevalence of Rapid Cycling (RC) in Subgroups of Bipolar Subjects With and Without Potential Risk Factors

	No. of	Subjects in Studies,	Subjects With Risk Factor		Subjects With RC		RC in Group With Risk Factor		RC in Comparison Group		% of RC Subjects With	% of NRC Subjects With
Risk Factor	Studies	N	N	%	N	%	N	%	N	%	Risk Factor, %	Risk Factor, %
Female gender (vs male gender)	16	3394	1917	56.5	929	27.4	613	32.0	316	21.4	66.0	52.9
Bipolar II subtype (vs bipolar I)	11	2686	929	34.6	802	29.9	345	37.1	451	26.6	43.0	31.0
Age	11	1853	NA	NA	714	38.5	NA	NA	NA	NA	NA	NA
Duration of illness	9	1457	NA	NA	298	20.5	NA	NA	NA	NA	NA	NA
Age at onset	11	2384	NA	NA	697	29.2	NA	NA	NA	NA	NA	NA
Depression at onset (vs hypomania/mania)	5	1628	993	61.3	450	27.6	341	34.3	85	14.9	75.8	55.3
History of suicide attempt	6	1171	377	32.2	454	38.8	159	42.2	295	37.2	35.0	30.4
Family history of bipolar disorder	4	693	136	19.6	146	21.1	41	30.1	105	18.9	28.1	17.4
Family history of major depression	4	693	129	18.6	146	21.1	42	32.6	104	18.4	28.8	15.9
Family history of any affective disorder	8	1582	849	53.7	434	27.4	300	35.3	134	18.3	69.1	47.8
Family risk of bipolar disorder	3	2241[a]	149[a]	6.6	119[b]	30.5	NA	NA	NA	NA	8.2	6.0[c]
Family risk of major depression	3	2228[a]	453[a]	20.3	119[b]	30.5	NA	NA	NA	NA	20.8	20.2[c]
Family risk of any affective disorder	3	2234[a]	602[a]	26.9	119[b]	30.5	NA	NA	NA	NA	28.9	26.2[c]
Clinical hypothyroidism	7	341	49	14.4	168	49.3	36	73.5	132	45.2	21.4	7.5
Subclinical hypothyroidism	6	275	54	19.6	121	44.0	29	53.7	93	41.6	24.0	16.2
Any hypothyroidism	6	275	74	26.9	121	44.0	43	58.1	78	38.8	35.5	20.1
Lithium nonresponse I[c] (vs no further recurrences)	3	732	410	56.0	172	23.5	114	27.8	58	18.0	66.3	52.9
Lithium nonresponse II[d] (vs 50% improvement)	3	570	206	36.1	90	15.8	37	18.0	53	14.6	41.1	35.2

[a]Indicates number of interviewed first-degree relatives of 390 bipolar probands (see Table 2 for Ns in specific studies).
[b]Indicates number of rapid cyclers among 390 bipolar probands.
[c]Defined as complete or near-complete prevention of recurrences with lithium prophylaxis.
[d]Defined as at least 50% improvement with lithium prophylaxis.
Abbreviations: NA = not applicable for continuous variables, NRC = non-rapid cycling.

Table 5. Mean Fixed and Random Effect Sizes of Factors Potentially Associated With Rapid Cycling Bipolar Disorder[a]

	Fixed Effect Sizes							Random Effect Sizes				Current vs Lifetime[g]	
Risk Factor	Mean r[b]	95% CI	Z[c]	p (for Z)[d]	Q[e]	df	p (for Q)[f]	Mean r[b]	95% CI	Z[c]	p (for Z)[d]	χ^2	p
Female gender	.110	.143 to .076	6.380	.000[h]	25.769	15	.041	.107	.154 to .060	4.437	.000[h]	3.35	.067
Bipolar II	.154	.191 to .117	8.007	.000[h]	53.902	10	.000	.161	.250 to .068	3.392	.001[h]	1.00	.317
Age	.128	.173 to .082	5.485	.000[h]	32.220	10	.000	.084	.173 to –.005	1.841	.066	3.08	.079
Duration of illness	.069	.120 to .017	2.608	.009	23.381	8	.003	.081	.175 to –.015	1.647	.100	0.02	.900
Age at onset	.057	.097 to .016	2.747	.006	33.024	10	.000	.032	.112 to –.048	0.793	.428	7.07	.008
Depression at onset	.132	.179 to .084	5.326	.000[h]	19.256	4	.001	.166	.274 to .054	2.891	.004	NA	NA
History of suicide attempt	.084	.141 to .026	2.853	.004[h]	5.236	5	.388	.078	.137 to .018	2.543	.011	0.22	.641
Family history of bipolar disorder	.161	.233 to .087	4.244	.000[h]	18.797	3	.000	.110	.301 to –.089	1.084	.278	0.03	.856
Family history of major depression	.062	.137 to –.013	1.630	.103	0.572	3	.903	.062	.137 to –.013	1.630	.103	0.06	.812
Family history of any affective disorder	.113	.162 to .064	4.490	.000[h]	17.276	7	.016	.107	.188 to .025	2.547	.011	0.20	.654
Family risk of bipolar disorder	–.009	.032 to –.051	0.448	.654	0.941	2	.625	–.009	.032 to –.051	0.448	.654	0.11	.745
Family risk of major depression	–.004	.038 to –.046	0.192	.848	2.837	2	.242	–.009	.047 to –.065	0.327	.743	0.92	.339
Family risk of any affective disorder	–.009	.033 to –.050	0.402	.688	1.949	2	.377	–.009	.033 to –.050	0.402	.688	1.48	.223
Clinical hypothyroidism	.070	.178 to –.039	1.260	.208	10.824	6	.094	.057	.211 to –.098	0.721	.471	2.92	.087
Subclinical hypothyroidism	.074	.194 to –.049	1.182	.237	13.044	5	.023	.118	.321 to –.095	1.091	.275	3.65	.056
Any hypothyroidism	.165	.281 to .044	2.670	.008	33.951	5	.000	.225	.516 to –.112	1.315	.189		.000[h]
Lithium nonresponse I[i]	.137	.208 to .065	3.707	.000[h]	15.849	2	.000	.231	.432 to .008	2.030	.042		NA
Lithium nonresponse II[j]	.084	.165 to .001	1.988	.047	6.328	2	.042	.133	.291 to –.033	1.576	.115		.012

[a]All data refer to the same subjects as in Table 4.
[b]Pearson r effect size.
[c]Difference from zero of effect size.
[d]Significance indicates a true difference from zero.
[e]Homogeneity of studies.
[f]Significance indicates heterogeneity of results among individual studies.
[g]Current vs. lifetime: chi-square and p values for difference of fixed effect sizes between subgroups with a diagnosis of current and lifetime rapid cycling.
[h]Indicates statistical significance after Hochberg's adjustment for multiple comparisons.
[i]Defined as complete or near-complete prevention of recurrences with lithium prophylaxis.
[j]Defined as at least 50% improvement with lithium prophylaxis.
Abbreviation: NA = not applicable because the study used the current (not lifetime) definition of rapid cycling.

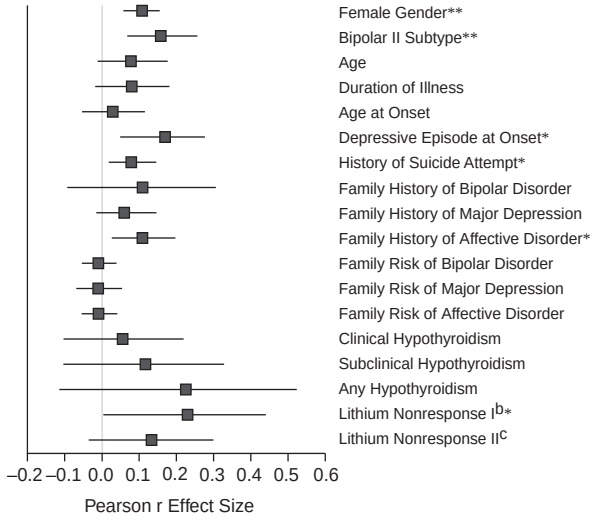
the rapid cycling group, but found no differences with regard to bipolar I and II subtypes or family history. A study that was available only in Chinese[46] reported that rapid cycling was associated with bipolar II disorder, but not with thyroid abnormalities assessed by thyroid-stimulating hormone levels, and thus confirms our findings.

The definition of rapid cycling of at least 4 episodes per year has been unchanged since its introduction in 1974. Studies that specifically addressed the issue of rapid cycling as a course modifier in DSM-IV endorsed this definition,[35,40,45] but suggested that the predictive validity of rapid cycling would be enhanced by a more valid definition of remission and its minimum duration[45] and the requirement of a pole-switching pattern.[35,40]

The true prevalence of rapid cycling in patients with bipolar disorder in the general population and in nonspecialized treatment settings is unknown. Among unselected patients, we found an overall prevalence of rapid cycling of 16.3%, which is the same prevalence calculated by Tondo and Baldessarini[17] from unselected samples and which corresponds with most reviews that suggest a prevalence of 13% to 20%.[9,11–16] Nevertheless, this percentage may still be at the upper limits of the true prevalence in bipolar disorder due to selection bias of research clinics. There are some indications that rapid cycling has become more frequent in recent years, at least in inpatient settings,[47,48] which may be due to the fact that the treatment of bipolar disorder is now common practice in nonresearch settings, leaving the more difficult cases for treatment in specialized centers. The equal prevalences of current and lifetime diagnosed rapid cycling suggest a certain stability of the phenomenon, although the studies refer to different subjects and considerable interconversion has been reported.[26,32,35,45]

An unfavorable response to lithium prophylaxis was the original feature associated with rapid cycling.[1] More recently, it has been estimated that as many as 72% to 82% of rapid cyclers have a poor response to lithium.[16] However, these numbers may only refer to a failure in fully preventing further manic and depressive recurrences, as reflected by the rate of 66% for nonresponse type I in the studies we reviewed. The differential effects that we found in our meta-analysis, 0.23 for nonresponse type I and 0.13 for nonresponse type II, indicate that

Figure 1. Mean Random Effect Sizes of Factors Potentially Associated With Rapid Cycling Bipolar Disorder[a]



[a]Bars indicate confidence intervals.
[b]Defined as complete or near-complete prevention of recurrences with lithium prophylaxis.
[c]Defined as at least 50% improvement with lithium prophylaxis.
*$p < .05$.
**Significant after Hochberg's adjustment for multiple tests.

although many rapid cycling patients may not be free of recurrences with lithium prophylaxis, lithium does have beneficial effects when severity and duration of subsequent episodes are taken into account, as reflected by the 59% of patients that achieved at least 50% improvement in the studies reviewed (i.e., 41% showed nonresponse type II). Dunner et al.[23] reported an overall poor prophylactic response in rapid cyclers; still, most of the patients experienced a reduction in severity and duration of manic and depressive episodes after 1 or 2 years of lithium treatment. Wehr et al.[26] observed that even in nonresponders to lithium, the drug abbreviated and attenuated the manic episodes. Baldessarini et al.[41] found that although rapid cyclers in comparison to non-rapid cyclers experienced more depressive episodes and less full response during lithium prophylaxis, the overall relative improvement from the previous course was equal in both groups. Moreover, response to lithium appears to be more favorable when antidepressants are avoided.[24,26,41,44] Kukopulos et al.[24] reported that lithium response in rapid cyclers increased from 16% to 78% after the patients' antidepressants were stopped, and Baldessarini et al.[41] suggested that a positive response to lithium may reflect their conservative use of antidepressants. There is accumulating evidence that rapid cycling appears to be a differential predictor of response to lithium and other mood stabilizers, with good efficacy in mania and hypomania but poor efficacy in the depressed phase.[49] Thus, lithium still may be effective in rapid cyclers, especially when given in combination with other mood stabilizers like valproate,[49] carbamazepine,[49,50] or lamotrigine.[39,49]

It is beyond the scope of this meta-analysis to give an overview of the pharmacotherapy of rapid cycling (recently reviewed by Shelton and Calabrese,[9] Post et al.,[10] and Calabrese et al.[16]). However, given the fact that some guidelines[51] recommend carbamazepine next to valproate as a first-line treatment for rapid cycling, it is of interest that in a recent open, retrospective study comparing the prophylactic efficacy of lithium and carbamazepine, Okuma[52] reported that current or past continuous-type rapid cycling was associated with an unfavorable response to both agents. Overall, current evidence suggests that patients with rapid cycling will benefit most from combinations of mood stabilizers to achieve a bimodal response.[9,10,16]

A modest overrepresentation of women in samples of rapid cyclers is a relatively consistent finding among studies and contrasts with the even sex distribution in bipolar disorder in general.[17,53,54] The possible endocrine or other factors that may account for this gender difference have not been delineated. No association has been found between menstrual cycle and rapid cycling.[26,55] Female gender has been associated with some other suggested concomitants of rapid cycling such as bipolar II pattern, hypothyroidism, preponderance of depression, and exposure to antidepressants. In addition, the occurrence of faster cycle frequencies has been reported in bipolar patients with a history of early physical and sexual abuse, and such early traumas were more prevalent in women.[56] Nonetheless, the preponderance of females among rapid cyclers tends to be overstated, and from the small effect found in our meta-analysis (0.11), it is obvious that men also have a substantial risk to develop a rapid cycling course.

The association of rapid cycling with bipolar II subtype is compatible with the observation that depressive features appear to be a core element of rapid cycling.[44,49] The near-significant finding that patients with a lifetime history of rapid cycling often have a depressive episode at the onset of illness is consistent with longitudinal course of illness data from the National Institute of Mental Health (NIMH)[57] and with a retrospective study of 320 subjects with bipolar I disorder[58] that reported significantly higher rates of rapid cycling in patients who presented with depression at onset and showed a predominantly depressive course. The authors of the latter study suggested that induction of rapid cycling by antidepressants may have contributed to this association, since these patients had received significantly higher rates of psychopharmacologic treatment.[58] Congruent with the overrepresentation of depressive features, rapid cyclers have a somewhat higher rate of attempted suicide.

We found only a weak association of rapid cycling with duration of bipolar disorder: 3 studies reported a

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longer duration in rapid cyclers. It has been hypothesized that the frequency of mood episodes increases as a function of illness duration, due to a process of kindling and sensitization.[59–61] However, this shortening of the interval between episodes would largely take place during the early years of the illness[62] and thus not necessarily lead to an association between illness duration and rapid cycling in later years. Moreover, in 27% of cases, rapid cycling was present from the onset of the illness.

Only 1 study[38] in our review found a significantly increased prevalence of mood disorders among first-degree relatives of rapid cyclers when compared with non-rapid cyclers, while 6[23,29,35,37,40,42] found only nonsignificant differences in the same direction. The 3 studies[27,32,33] that were specifically designed to assess the morbid risk among first-degree relatives and had a more rigorous methodology reported no differences. Taking all these results together, it appears that a family history of mood disorders does not substantially increase the risk of rapid cycling.

Whether rapid cycling is associated with hypothyroidism is the subject of ongoing controversy. There are 2 hypotheses explaining this possible association: (1) patients with rapid cycling are predisposed to the development of clinical or subclinical hypothyroidism, especially when treated with lithium, and (2) patients with (impending) thyroid failure become more susceptible to developing a rapid cycling course. The first hypothesis was proposed by Cho et al.,[43] who reported 5 cases of thyroxine-treated hypothyroidism that began after lithium exposure in 16 women with rapid cycling, in comparison to 2 cases among 99 non-rapid cycling bipolar and unipolar women (31% vs. 2%, $p < .01$). Interestingly, the 4 women who had clinical hypothyroidism before they were exposed to lithium were all non-rapid cyclers (4%), as were the 2 patients with hypothyroidism in a comparison sample of 39 women without lithium treatment, suggesting that rapid cycling is associated with lithium-induced but not spontaneous hypothyroidism. The second hypothesis was suggested by Bauer et al.,[7] who found rates of 23% clinical and 37% subclinical hypothyroidism in a sample of 30 rapid cycling patients. Fifty-six percent of cases with hypothyroidism were lithium-associated. However, these authors used a literature-based non-rapid cycling comparison group.

The results from the presently reviewed studies are inconsistent: only 2[25,31] of 7 studies found significantly more cases of hypothyroidism among rapid cyclers. Although we could not calculate the exact female-to-male ratios of hypothyroidism from these reports, it was our impression that the vast majority occurred in females. However, it must be taken into account that women were overrepresented in these studies. Moreover, the only study that found more cases of hypothyroidism among non-rapid cyclers was also the only study with an atypical overrepresentation of women among non-rapid cyclers and more male than female rapid cyclers.[28]

In general, 8% to 19% of lithium-treated bipolar patients exhibit clinical hypothyroidism, and up to 23% exhibit subclinical hypothyroidism.[63] Sixty-one percent of cases of hypothyroidism in the reviewed studies were related to ongoing lithium treatment (Table 3). Still, the only study of medication-free patients[36] also reported 30% subclinical hypothyroidism, but this prevalence did not differ between groups, and there was no relationship of subclinical hypothyroidism to previous lithium exposure or duration of time off lithium.

Interestingly, a significant effect of hypothyroidism was seen in current but not in lifetime diagnosed rapid cycling. This association between hypothyroidism and the presence of a current rapid cycling course suggests that thyroid dysfunction may contribute to mood destabilization in vulnerable subjects. In addition, studies[25,26,36] that were conducted in NIMH inpatient samples found high rates of hypothyroidism in both rapid and non-rapid cyclers, suggesting that thyroid dysfunction may be associated with various forms of refractory bipolar disorder, including rapid cycling.

Given the paucity of controlled prospective data[64] supporting the induction of rapid cycling by antidepressants, this assumption is largely based on retrospective case series and clinical observations.[3] The reviewed studies indeed suggest that a rapid cycling course is not infrequently preceded by treatment with antidepressants, but give no evidence of a causal role. Women and bipolar II patients may be at greater risk, as well as those patients who typically have mania or hypomania following depression, and/or premorbid hyperthymic or cyclothymic temperament.[24,44,65] However, it has also been suggested that the association between rapid cycling and antidepressants may be related more to the frequent occurrence of depression[32] or to a natural course of mania following depression[24,44] than to the antidepressant. It is therefore difficult to differentiate the natural course of illness from switches into mania and cycle acceleration attributable to use of antidepressants.

In conclusion, female gender and bipolar II subtype emerged as the most consistent factors associated with rapid cycling, even if the effects of these factors were small. Hypothyroidism appears to be associated with current rapid cycling and possibly with treatment resistance in general. Although lithium fails to prevent recurrences in many cases of rapid cycling, it still may lead to considerable improvement. To further investigate the interrelationships among these factors, we are currently performing a large-scale, prospective study comparing outpatients with rapid and non-rapid cycling bipolar disorder.

Drug names: carbamazepine (Tegretol, Epitol, and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), thyroxine (Synthroid, Levo-T, and others).

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