Background: Rapid cycling among patients with bipolar affective disorders is important because of its implications for long-term prognosis and for the use of antidepressants. To our knowledge, no prospective study has, as yet, described the course of this phenomenon beyond 5 years.

Methods: From 345 patients with bipolar I or bipolar II disorder followed up for a mean (SD) of 13.7 (6.1) years as part of the National Institute of Mental Health Collaborative Depression Study, 89 (25.8%) were identified who, during 1 or more years of follow-up, manifested a pattern that met DSM-IV criteria for rapid cycling. These patients were compared with the remaining bipolar patients by demographics, overall affective morbidity, morbidity during specific treatment conditions, and the likelihood of suicidal behavior. Analyses assessed whether the use of tricyclic antidepressants for depressive symptoms was associated with the persistence of rapid cycling or with tendencies to switch from depressive to manic or hypomanic phases.

Results: The 89 patients who showed a rapid cycling pattern were significantly more likely to have had an illness onset before 17 years of age and were more likely to make serious suicide attempts. In 4 of 5 cases, rapid cycling ended within 2 years of its onset. Resolutions were not associated with decreases in tricyclic antidepressant use. Throughout follow-up, patients prone to rapid cycling experienced more depressive morbidity than other bipolar patients, particularly when lithium carbonate was being used without tricyclic antidepressants. The use of these antidepressants was not more likely in the weeks preceding shifts from depression to mania or hypomania.

Conclusions: These results indicate that bipolar patients who develop a rapid cycling pattern suffer substantial depressive morbidity and are at high risk for serious suicide attempts. These findings do not implicate tricyclic antidepressants or, by inference, serotonin reuptake inhibitors in the promotion of affective instability.

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Several considerations give importance to the phenomenon of rapid cycling. In accord with the kindling hypothesis evoked to explain it, rapid cycling may reflect a sensitization produced by repeated episodes. If, as suspected, such sensitization is often an enduring change, the prognostic significance of rapid cycling should be long lasting as well. Some follow-up studies have supported this view, but others have shown rapid cycling to be time limited. Of perhaps greater concern to clinicians is the suggestion that antidepressants may both trigger and prolong rapid cycling. The pattern often begins while antidepressants are being taken, and cycle lengths, the period from the beginning of one episode to the beginning of the next, have been seen to increase after antidepressant treatment was withdrawn. These observations may be explained in other ways, however. Some investigators have noted that rapid cycling is likely to begin with depression and that episodes that do begin with depression are substantially more likely to develop a polyphasic or rapid cycling course than are those that begin with mania. Because all studies of rapid cycling have described patients who sought treatment, those who did so during depressive phases were likely to be receiving antidepressants. Thus, depression may predispose both to antidepressant treatment and, independently, to phase shifting. Data from the National Institute of Mental Health Collaborative Depression Study support this view. A regression analysis showed that the presence of depression preceding study intake, but not exposure to antidepressants, was an independent predictor of rapid cycling in the first year of follow-up. A subsequent regression...
analysis showed that depression during the first year of follow-up, but not antidepressant use in that year, predicted rapid cycling in the second year.\(^\text{11}\)

The conclusion that the discontinuation of antidepressants promotes the resolution of rapid cycling rests on 2 case series. In the first,\(^\text{7}\) 21 patients with rapid cycling were persuaded to discontinue antidepressant treatment, and 13 subsequently “stabilized.” The role of spontaneous stabilization could not be assessed, though, because the authors did not describe the course of patients who continued to take antidepressants. The second study\(^\text{6}\) described cycle lengths in 9 rapid cyclers before and after discontinuation of tricyclic antidepressants (TCAs). Cycle lengths were longer during periods without TCAs. Because cycle length is timed from the beginning of one phase to the beginning of the next, it necessarily encompasses any intervening euthymic period. If depression portends further rapid cycling, as previous results have shown, and if antidepressants were more likely to have been discontinued during periods of euthymia than during periods of depression, as might be expected, then the association between antidepressant discontinuation and longer cycle lengths may have been artifactual.

The presumption that antidepressants trigger or prolong rapid cycling suggests that patients who experience this phenomenon may be particularly liable to exhibit mania or hypomania while taking antidepressants. This may be especially true for TCAs. These were expressly implicated in the series by Wehr et al\(^\text{8}\) and in a meta-analysis of placebo-controlled studies.\(^\text{13}\) The latter showed a significantly higher likelihood of switching during TCA treatment than during treatment with selective serotonin reuptake inhibitors (SSRIs).

If a liability to rapid cycling is inherent, then other features should distinguish bipolar patients who develop this pattern from those who do not. Of these, female sex has most consistently differentiated rapid cyclers from other bipolar patients.\(^\text{6,7,14-16}\) In contrast, bipolar patients with and without rapid cycling have generally not differed by current age or by age at illness onset. However, none of the relevant reports have presented the distributions of the ages at which bipolar illness first appeared. Observations that rapid cycling or, more specifically, continuous cycling is very common among children and early adolescents who have bipolar illness\(^\text{13,15}\) suggests 2 possibilities. Either childhood and adolescence have time-limited pathophysiological effects on bipolar illness that then resolve with adulthood, or very-early-onset bipolar illness carries a liability to rapid cycling that is lifelong. If the latter is true, patients with very early onset should be overrepresented among those who show rapid cycling as adults.

Because the identification of rapid cycling requires a careful mapping of episodes during a minimum time span of 1 year, a description of its natural course requires a lengthy observation period. In addition, conclusions as to the possible effects of treatment on the course of rapid cycling require that the members of a cohort be followed up prospectively regardless of whether they remain in treatment. The National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies recruited patients as they sought treatment for affective illness at any of 5 academic centers: Massachusetts General Hospital and Harvard University in Boston; Rush Presbyterian–St Luke’s Medical Center in Chicago, Ill; University of Iowa College of Medicine in Iowa City; New York State Psychiatric Institute and Columbia University in New York; and Washington University School of Medicine in St Louis, Mo. All patients were white, English speaking, and knowledgeable of their biological parents, and all met Research Diagnostic Criteria (RDC)\(^\text{17}\) for major depressive disorder, schizoaffective disorder, or manic disorder. Each participant provided informed consent.

The subjects described in the following analyses were limited to those who, at intake, met RDC for bipolar affective disorder, type I or II, or for schizoaffective disorder, manic type, other than the mainly schizophrenic subtype. Also included were subjects who met criteria for nonbipolar major depressive disorder at intake but who subsequently developed an episode of mania, hypomania, or schizoaffective disorder–manic type. We used DSM-IV criteria to identify as rapid cyclers those patients who manifested, during any 32-week period of the follow-up, 4 or more mood episodes, each lasting 2 or more weeks, during which RDC for major depressive disorder, mania, hypomania, schizoaffective mania, or schizoaffective depression were met. Episodes or phases were separated either by switches to an opposite pole or by remissions lasting 8 or more weeks. A remission required 8 contiguous weeks with no more than 2 symptoms present to no more than a mild degree.

## METHODS

### SUBJECTS

Between 1978 and 1981, the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies recruited patients as they sought treatment for affective illness at any of 5 academic centers: Massachusetts General Hospital and Harvard University in Boston; Rush Presbyterian–St Luke’s Medical Center in Chicago, Ill; University of Iowa College of Medicine in Iowa City; New York State Psychiatric Institute and Columbia University in New York; and Washington University School of Medicine in St Louis, Mo. All patients were white, English speaking, and knowledgeable of their biological parents, and all met Research Diagnostic Criteria (RDC)\(^\text{17}\) for major depressive disorder, schizoaffective disorder, or manic disorder. Each participant provided informed consent.

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## PROCEDURES

Intake assessments included the Schedule for Affective Disorders and Schizophrenia.\(^\text{18}\) Ratings on this scale reflected information from direct patient interview, from informants, and from a review of medical records.
Raters recontacted probands at 6-month intervals for the first 5 years of follow-up and annually thereafter. They used information from direct patient interview and from medical records to complete the Longitudinal Interval Follow-up Evaluation (LIFE) during the first 2 years, the LIFE II in years 2 to 5, and the Streamlined Longitudinal Interval Continuation Evaluation in the sixth year and beyond. The LIFE II and Streamlined Longitudinal Interval Continuation Evaluation differed from the LIFE in the omission of some psychosocial comparators. These instruments tracked each RDC syndrome on a weekly basis. The interviewers identified change points for each syndrome active since the last assessment and derived symptom levels for each interval. The Psychiatric Status Rating used 6 levels for major depressive disorder, manic disorder, and schizoaffective disorder. A score of 1 indicated no symptoms and a 2 indicated the presence of no more than 1 or 2 symptoms to a mild degree. A 5 indicated a full syndrome and a 6, a relatively severe, full syndrome. Other RDC syndromes were rated on 3-point scales, and, for these, a 3 indicated the presence of a full syndrome. Eight consecutive weeks with no ratings greater than 2 indicated recovery from a specified syndrome, and a recurrence required the redevelopment of a full syndrome.

The LIFE instruments also quantified psychosocial functioning in discrete areas of employment, household maintenance, academic work, interfamilial relationships, relationships with friends, and recreation. The LIFE–Range of Impaired Functioning Tool condenses these various domain ratings to a single score with demonstrable reliability and validity.20 Participation did not determine or influence treatment. Patients, though, systematically quantified all somatic treatment directed at mental disorders and, for each week, listed all individual drugs and their doses.21 The following analyses entered treatment dichotomously as present or absent for any given week and separately considered lithium carbonate, valproate sodium, carbamazepine, TCAs, monoamine oxidase inhibitors, and SSRIs.

**ANALYSIS**

Survival analyses were used to quantify the persistence of rapid cycling patterns. These describe the time from the end of the first year in which rapid cycling was observed to the beginning of the first year in which rapid cycling was absent. Loss to follow-up was a censoring variable. In the absence of any widely accepted definition of rapid cycling resolution, we used 2 provisional ones. A narrow one specified the first year that encompassed no more than 1 episode and in which no switching occurred. The second, broader one identified the first year that encompassed no more than 2 episodes and no more than 1 switch.

To determine whether patients who were prone to rapid cycling were more likely to develop manic or hypomanic symptoms while taking antidepressants, we focused on lithium and the TCAs. As will be shown, lithium was by far the dominant mood stabilizer prescribed for this cohort, and TCAs were used more than any other class of antidepressants. Moreover, the TCAs have been more strongly implicated than have the SSRIs in the provocation both of manic switches22 and of rapid cycling.21 Exposure to other mood stabilizers during this observation period was too limited to support analyses concerning their effects.

The analyses compared those with any rapid cycling during follow-up with the remaining bipolar patients by the proportion of weeks in which manic or hypomanic symptoms co-occurred with antidepressant use. Thus, the number of weeks during which both Psychiatric Status Ratings for mania, hypomania, or schizoaffective mania were greater than 2, and any TCA treatment was ongoing, composed the numerator. The number of weeks with ongoing TCA treatment, regardless of coincident symptoms, composed the denominator. A daily TCA dose greater than an imipramine hydrochloride equivalent of 100 mg constituted ongoing TCA treatment. The likelihood of depressive symptoms during TCA treatment was similarly quantified. Depression was considered present when the Psychiatric Status Rating for major depressive disorder, schizoaffective depression, intermittent depression, or minor depression exceeded 2. To detect any association between the resolution of rapid cycling and changes in the use of TCAs, analyses focused on the use of TCAs in the final 52 weeks of the first rapid-cycling period observed during follow-up and on the subsequent 52 weeks representing the first year in which rapid cycling was no longer present. We chose not to simply compare the number of weeks of TCA use in the 2 periods because a resolution of rapid cycling implies less psychopathology generally and, because less morbidity leads to less treatment, an association between the resolution of rapid cycling and a decreased use of TCAs may have been artifactual. Instead, the analyses considered only weeks during which depressive symptoms were present and compared the 2 periods by the proportion of those weeks during which TCAs were prescribed.

Those who developed rapid cycling during follow-up were compared with those who did not by means of χ² tests for categorical variables and t tests for continuous variables. A 2-tailed α level of .05 was used for each statistical test.

**RESULTS**

Of 345 patients who met inclusion criteria for this analysis, 89 (25.8%) met DSM-IV criteria for rapid cycling during at least 1 of the years of prospective observation. Sixty-nine (78%) of these patients displayed rapid cycling in the first year of follow-up, and another 11 (12%) began rapid cycling in the second year. Only 1 patient had the onset of rapid cycling later than the eighth year of follow-up. The modal number switches in the first year of rapid cycling was 4 (40 subjects); 33 (37%) had fewer than 4 switches, and only 1 (1%) had 10 or more. Forty-six (52%) had no periods of remission (2 or more symptom-free months) during that year.

This group was followed up for a mean (SD) of 15.2 (4.9) years and the remaining bipolar patients were followed up for a shorter mean (SD) of 13.2 (6.4) years (t103 = −2.54, P = .01). More than two thirds of those who developed a rapid-cycling pattern were female, while the sex ratio for the remaining patients was nearly even (Table 1). Bipolar II disorder was not more frequent among those prone to rapid-cycling patterns. These patients were somewhat more likely to be in a depressed or mixed state at the beginning of follow-up and had had, on average, more than twice as many previous episodes of affective disorder.

Although the 2 groups were similar in ages at intake, those who developed rapid cycling were significantly younger when they first met criteria for an affective disorder. Distributions of age at onset showed that onsets in childhood and in early puberty accounted for this difference (Figure 1). With the threshold for early-onset bipolar disorder proposed by Geller et al.22 27 (30%) of the rapid-cycling patients and 40 (15.6%) of the remaining bipolar patients had an onset at age 16 years or younger (χ² = 9.75, P < .005).
Among rapid-cycling patients, the 27 with onsets before age 17 years did not differ from the remaining 62 by liability to switching or by the quantity of affective morbidity during follow-up. Rapid-cycling patients with early onsets and those with later onsets experienced means (SDs) of 2.5 (1.3) and 2.5 (1.5) switches per year, respectively. The respective mean (SD) proportions of follow-up weeks with depressive symptoms were 0.48 (0.26) and 0.39 (0.27) \((t_{11.4} = 1.48, P = .14)\). The mean (SD) proportions of weeks with manic symptoms were 0.11 (0.11) and 0.135 (0.14), respectively \((t_{13.3} = -0.93, P = .36)\).

Over all weeks of follow-up, those who at any time showed a rapid-cycling course experienced depressive symptoms for 0.42 (SD, 0.27) of the follow-up weeks, a significantly higher proportion than the 0.30 (SD, 0.30) seen among the remaining bipolar patients \((t_{133.2} = -3.31, P = .001)\). Rapid-cycling patients also tended to experience more weeks with manic or hypomanic symptoms. Such symptoms were present during 0.13 (SD, 0.13) of the follow-up weeks among rapid cyclers and during 0.09 (0.16) of the weeks among nonrapid cyclers \((t_{143.6} = -1.91, P = .06)\). The mean ratio of weeks depressed to weeks manic or hypomanic was 11.1 (SD, 18.7) for rapid cyclers and 21.6 (8.9) for non–rapid cyclers \((t_{14.0} = 2.05, P = .04)\).

More than 4 in 5 episodes of rapid cycling were observed to end whether the threshold for this required fewer than 3 episodes or 2 switches in a 1-year period, or fewer than 2 episodes and no switches (Figure 2). Six subjects had no follow-up beyond their first year of rapid cycling and were therefore omitted from this analysis. According to Kaplan-Meier estimates from the survival analyses, the median number of weeks from the end of the first year in which rapid cycling was observed, to the beginning of the first year of stabilization, was 6 for the first definition and 23 for the second, stricter definition.

Of patients whose rapid-cycling pattern was observed to resolve according to the broader definition, 64 had at least some weeks of depression during the year of stabilization. These patients were no less likely to have taken TCAs while depressed in the period after the resolution of rapid cycling than they had in the preceding year when rapid cycling was ongoing. Tricyclic antidepressants were prescribed for 32.1% (SD, 42.6%) of the 2035 person-weeks with depression observed during the first year of resolution; the corresponding percentage for the preceding year was 28.8% (SD, 34.8%) during 2003 person-weeks with depression. Nor did these 2 years differ
in the percentage of weeks during which mood stabilizers (lithium, carbamazepine, or valproate sodium) were prescribed. These were 48.7% (SD, 45.8%) for the rapid-cycling year and 49.3% (SD, 47.3%) for the following year.

Bipolar patients who displayed any rapid cycling took SSRIs, lithium with TCAs, and valproate for greater proportions of the follow-up weeks than did those who showed no rapid cycling (Table 2). Otherwise, the groups had similar treatment exposures. During periods when lithium was being taken without TCAs, patients prone to rapid cycling were significantly more likely to be experiencing depressive symptoms than were other bipolar patients (Table 3). During weeks when lithium was taken with a TCA, patients in the 2 groups had similar treatment exposures. During periods when lithium was being taken without TCAs, patients prone to rapid cycling were somewhat more likely than other bipolar patients to have manic or hypomanic symptoms in any given week during lithium treatment, but this was true both in the presence and in the absence of TCAs.

We considered whether patients prone to rapid cycling were more likely to have been taking a TCA during those weeks immediately preceding a switch from depression to mania or hypomania than they were during other weeks. The results did not implicate TCAs in these switches (Table 4). These patients were no more likely to have been taking a TCA, with or without lithium, during the weeks preceding a switch from depression to mania than they were during any other week when depression was present.

Although patients with rapid cycling were not more likely to commit suicide (Table 5), they were more likely than the remaining bipolar patients to have made attempts before study intake and to make them during the follow-up period. Group differences were particularly large for attempts rated as being high in intent or in potential medical lethality.

Sex is a well-known risk factor for attempted suicide, and females were overrepresented in the rapid-cycling group. A logistic regression analysis with sex and the presence or absence of rapid cycling as independent variables showed that both were significantly associated with the likelihood of suicide attempts during follow-up. The odds ratios were 2.0 (95% confidence interval, 1.2-3.2) for female sex (Wald \( \chi^2 = 16.1, P < .001 \)) and 1.5 (95% confidence interval, 1.0-2.2) for rapid cycling (Wald \( \chi^2 = 5.1, P = .02 \)).
COMMENT

Bipolar patients who developed a rapid-cycling pattern at any time during follow-up were more likely than those who did not to have had onsets before 17 years of age, were more likely to make serious suicide attempts during follow-up, and were much more likely to have depressive symptoms during any given week. The greater depressive morbidity experienced by patients prone to rapid cycling was reflected in their increased exposure to TCAs while taking lithium. They were somewhat more likely to experience mania or hypomania while taking lithium, but this was true whether or not TCAs were also present. Moreover, TCAs were no more often present in weeks preceding shifts from depression to mania or hypomania than in other weeks when depression was present.

Although the course of patients who showed rapid cycling patterns differed in several ways from the course of bipolar patients without it, rapid cycling in itself was a transient phenomenon in the majority of cases. It is likely, though, that the persistence of rapid cycling when identified prospectively, as in this study, will be less than that seen in samples selected for a current rapid-cycling pattern, as the latter method will oversample patients whose rapid cycling is truly chronic. It is notable, then, that the only other report to quantify the persistence of rapid cycling during a lengthy follow-up found that a similar 19% continued to show this pattern.4 On the other hand, the current sample was recruited at tertiary care centers and the patients described by Maj et al4 all attended a clinic specializing in affective disorders. As such, patients with refractory disease were probably overrepresented in both samples relative to patients typically seen by private practitioners.

These analyses found no association between the cessation of rapid-cycling patterns and any decrease in the use of TCAs to treat depressive symptoms during lithium maintenance. Notably, another recent report found that the discontinuation of antidepressants in a group of bipolar patients was associated, not with a decrease in cycling, but with an increase in depressive morbidity.24

Bipolar patients who manifested rapid cycling resembled those who did not by the proportion of follow-up weeks during which they were treated with lithium and/or TCAs. The proportion of weeks with SSRI treatment was low in both groups but significantly higher for those with rapid cycling. This may have reflected the fact that the somewhat longer observation period for this group extended further into the period when SSRIs were displacing TCAs. The numbers of weeks observed during SSRI treatment were quite small for both groups, though, and this precluded efforts to determine their effects on affective stability.

While taking lithium, patients prone to rapid cycling were not significantly more likely to manifest manic or hypomanic symptoms when TCAs were also present than were patients who showed no such liability. Nor was the use of TCAs associated with an increased risk for switching in this affectively unstable group. Because TCAs have been more strongly implicated than other antidepressants in the promotion of such switches, these results probably apply as well to the newer antidepressants. This has important implications for the management of bipolar depression generally and for rapid cycling in particular. Switches did indeed occur while TCAs were being used, but they occurred no less frequently when TCAs were not in use. These findings are quite consistent with those of studies with placebo control. Three groups have randomly assigned bipolar patients to treatment with lithium with placebo or lithium with TCAs for prophylaxis, and none found manic episodes to be significantly more likely among the latter patients.25-27 Similarly, a naturalistic study of outpatients with bipolar I maintained on a regimen of mood stabilizers (predominantly lithium) found that depressive episodes in which TCAs were used were no more likely to end in switches than were depressive episodes managed without antidepressants.28

Rapid-cycling patients were more than twice as likely as other bipolar patients to have a history of severe suicide attempts at the beginning of follow-up, and to make further serious attempts during follow-up. This is consistent with our finding that rapid-cycling patients were depressed for significantly greater proportions of the follow-up period, presumably, experienced more depression before they entered follow-up. The abrupt transitions from mania or hypomania to depression that many of these patients experience may further predispose to suicidality. It is notable, though, that no trend emerged to indicate that rapid cyclers were at greater risk for completed suicide despite the large effect sizes observed in this population.29-31

A clear association between suicidality and rapid cycling has not emerged in earlier descriptions, although Bauer et al32 and Maj et al33 described strong trends in this direction. Wu and Dunner34 specifically sought an association between rapid cycling and suicide attempts in a
chart review of bipolar patients and found none. Their sample was drawn from a well-known specialty clinic and contained a large proportion of patients with treatment-refractory disease, however. Whether such an association is characteristic of more representative samples awaits further study.

Early onsets were overrepresented among adult patients prone to rapid cycling, and yet rapid-cycling patients with an onset of bipolar illness before the age of 17 years resembled other rapid-cycling patients in their propensity to switching and in overall manic or depressive morbidity over time. Although these data cannot determine the direct effects of prepubertal and early pubertal periods on the propensity to rapid cycling, they do indicate that the very early onset of bipolar disorder may convey a lifelong propensity to this phenomenon.

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