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Brief report

Characteristics of rapid cycling bipolar-I patients in a bipolar speciality clinic☆

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Abstract

Objective: To investigate the characteristics of patients with rapid cycling bipolar illness. *Method:* The charts of bipolar patients treated at the Massachusetts General Hospital Bipolar Clinic were reviewed for age of the first affective episode, demographics and history of rapid cycling. *Results:* Data from 223 bipolar-I–II patients, of whom 11.7% were bipolar-II, were obtained, and only the data from 197 bipolar-I patients were analyzed. Forty-three percent of them had a positive history of rapid cycling. Rapid cycling was more common in women, with rapid cycling females having an earlier age of onset than non-rapid cycling bipolar-I females. No such association was found in bipolar-I males. In addition, with respect to current age, rapid cyclers were younger than non-rapid cyclers in bipolar-I females. No association was found for duration of illness. *Conclusions:* Women with bipolar-I illness have an increased probability of rapid cycling, which may still be increased in those with an early onset. Therefore, biological factors, such as sex and age onset, appear to be relevant to the physiology of rapid cycling. The retrospective design and the selected population of bipolar-I patients from an academic tertiary-referral center may limit the generalizability of our results.

Keywords: Rapid cycling; Age of onset; Gender

1. Introduction

Rapid cycling, i.e. the occurrence of at least four distinct episodes a year, either demarcated by 8 weeks of wellness or by a switch in polarity, has been included in DSM-IV (American Psychiatric Association, 1994) as a course specifier for bipolar illness. By its current definition, it appears that rapid cycling identifies a special subgroup of bipolar patients. The factors involved in vulnerability to increased cycling have been searched. Among these, female gender, bipolar-II presentation, substance abuse, hypothyroidism, antidepressant use, longer duration of illness, and early age of onset are currently under investigation. Due to either a lack or inconsistencies of available clinical research data, none of these factors have been established or ruled out on an empirical basis (Lei-

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benluft, 1996; Maj et al., 1994; Coryell et al., 1992; Avasthi et al., 1999; Kukopulos et al., 1983; Suppes et al., 2001; Calabrese et al., 2001).

Because of the erratic nature of the disorder, with its waxing and waning pattern of rapid cycling, longitudinal study designs have been difficult to implement and carry through, but are finally under way (cf. the Stanley Foundation Bipolar Network, SFBN, and the Systematic Treatment Enhancement Program for Bipolar Illness, STEP). This, together with the differences in the criteria used to define age of onset across the studies (some defining age of onset as the first psychiatric outpatient contact, some as the first psychiatric hospitalization and some as the age at onset of rapid cycling pattern), may have contributed to the inconsistency of the data on the relationship of rapid cycling and age of onset.

In the present study the charts of bipolar patients treated at the Massachusetts General Hospital (MGH), Bipolar Clinic between the 1990–1999 for investigating the phenomenology of rapid cycling were reviewed for data on the relationship of rapid cycling with age, age of onset, gender, and duration of illness.

2. Method

The charts of all outpatients evaluated at the MGH, Bipolar Clinic between the years 1990–1999 were reviewed. All diagnoses were made using the Structured Clinical interview for DSM-III-R/IV, (Spitzer et al., 1987; First et al., 1995). These diagnoses were not made retrospectively at the time of chart review but prospectively by psychiatrists working at the MGH, Bipolar Clinic with expertise in bipolar illness during the clinical interview. Subjects were included in the analysis if the chart documented the type of bipolar illness, the presence or absence of rapid cycling either current or ever through the course of bipolar illness, and the age at onset of first affective episode, and gender. Rapid cycling was defined as four or more episodes (or two complete cycles) in a year as in DSM-IV. Patients who were diagnosed as bipolar-NOS were excluded from the analysis, as evaluation of the rapid cycling can only be valid for bipolar-I or -II patients by definition in DSM-IV. Subjects with unreliable information for the presence or absence of rapid cycling and/or age at onset of first affective episode were also excluded from the analysis.

For identifying age of first affective episode and current or lifetime histories of rapid cycling, we reviewed the Affective Disorders Evaluation Form, and Clinical Monitoring Form (Guille et al., 1999), which are routinely completed for each bipolar patient and include a modified version of SCID mood modules, and also elicit data regarding age of onset and course of the illness. Data included in these assessment forms came from clinical interview with the patient and outside report from family or other sources, including hospital charts and previous physician records.

Massachusetts General Hospital Institutional Review Board approved the study. Statistical analysis of data was performed by the independent samples Student's *t*-test, and chi-square test as appropriate using the Statistical Products for Service Solutions (SPSS), version 8.0. All reported *P* values are two-sided. Significance level was set at $P < 0.05$.

3. Results

Among the 476 charts evaluated, reliable data on the age of first affective episode and presence or absence of rapid cycling course could be obtained only for 248 bipolar patients, of whom 25 were diagnosed as bipolar-NOS and excluded from the analysis. This left a sample of 223 bipolar patients. The sample was 59.2% female and mainly (88.3%) comprised of bipolar-I patients and a small number of bipolar-II (11.7%) patients. Overall, 39.9% ($n = 89$) of the sample had a positive lifetime history of rapid cycling while 43.9% ($n = 98$) had a positive life time history of psychosis. Of those with a positive history of rapid cycling, 94% were bipolar-I. The proportion of bipolar-I subtype among the patients with a positive history of psychosis was 96%. These values obviously reflect an over-presentation of bipolar-I patients in this sample. There may be two explanations for this: First, most of the bipolar-II patients may have been excluded from the sample owing to the unreliable or insufficient historical information on the age of first affective episode and/or the cycling pattern since, in the bipolar-II presentation of the illness distinct episodes are somewhat more difficult to identify histor-

ically. Second, being an academic tertiary-referral center our bipolar population might have been over-presented with more severe and difficult to-treat type of patients. Either one, or both of these factors may have contributed to the high proportion of bipolar-I subtype in our sample. As sample comprised of an unusual proportion of bipolar-I and -II patients (as well as the rapid cyclers in each subtype) would limit the generalizability of findings, we restricted our analysis to bipolar-I patients only ($n=197$, 43% with a positive history of rapid cycling).

The mean age of first affective episode (age of onset) for bipolar-I patients with a positive history of rapid cycling was significantly lower than the mean age of first affective episode of the patients with a negative history of rapid cycling. Additional analysis carried out separately by gender, found a significant difference for the females but not for the males. Rapid cycling bipolar-I females had the first affective episode at a younger age than the non-rapid cycling bipolar-I females (Table 1).

Further analysis of the sample was carried out according to the criterion previously applied by Fujiwara et al. (1998) for dichotomous division of the sample into early versus late-onset age groups: an early-onset group, consisting of patients aged 25 years or younger; and late-onset group, consisting of patients aged 26 or older. For the bipolar-I sample ($n=197$), there were 145 subjects in the early-onset group, and 48% of them had a positive history of rapid cycling. In the late-onset group there were 52 subjects of whom 27% had a positive history of rapid cycling, and the difference was statistically significant (chi-square test, $\chi^2=7.135$, df=1, $P=0.008$). When the same analysis carried out separately by gender, the chi-square test revealed significance for the females but not for the males. For the females there were 84 subjects in the early-onset group, 56% of them having a positive history of rapid cycling, while only 28% out of 29 subjects having a positive history of rapid cycling in the late-onset group ($\chi^2=6.943$, df=1, $P=0.008$). For the males there were 61 subjects in the early-onset group, 38% of them having a positive history of rapid cycling, while 26% of the 23 subjects in the late-onset group had a positive history of rapid cycling ($\chi^2=0.997$, df=1, $P=0.318$).

In accordance with previous reports, the analysis of the sample for the proportion of rapid cycling by gender revealed greater prevalence of rapid cycling in women (Calabrese et al., 2001). Among the 84 rapid cycling bipolar-I patients 65% were females. Among the bipolar-I females the rate of rapid cycling was 49%, while among the bipolar-I males the rate of rapid cycling was only 35% ($\chi^2=3.944$, df=1, $P<0.05$). Of note, among the 26 bipolar-II patients (73% females), only five patients had a positive history of rapid cycling, and they were all females.

In terms of current age and duration of illness, our analysis found no significant differences between the rapid cycling and non-rapid cycling bipolar-I patients

Table 1
Demographics of the rapid cycling bipolar-I patients

	Rapid cycling		Non-rapid cycling		*t* value	df	*P* value
	Mean ± S.D. (years)	*n*	Mean ± S.D. (years)	*n*			
Age of onset							
Both sexes	18.87 ± 8.68	84	21.84 ± 9.33	113	2.276	195	0.024
Female	19.13 ± 8.14	55	22.52 ± 9.05	58	2.089	111	0.039
Male	18.38 ± 9.76	29	21.13 ± 9.65	55	1.236	82	0.220
Current age							
Both sexes	37.77 ± 11.41	84	41.98 ± 14.45	113	− 1.682	195	0.094
Female	38.62 ± 12.34	55	43.52 ± 13.12	58	− 2.043	111	0.043
Male	39.07 ± 9.58	29	40.36 ± 15.71	55	− 0.405	82	0.686
Duration of illness							
Both sexes	19.90 ± 11.02	84	20.14 ± 13.56	113	− 0.131	195	0.896
Female	19.49 ± 10.77	55	21.00 ± 12.96	58	− 0.671	111	0.503
Male	20.69 ± 11.63	29	19.24 ± 14.23	55	0.473	82	0.638

overall (Table 1). However, splitting by gender found female rapid cyclers to be at a younger age than the female non-rapid cyclers (Table 1).

4. Discussion

The prevalence of rapid cycling in our bipolar-I population was found to be 43%. This comparatively high rate of rapid cycling (other studies give figures between 9.5% and 31.2%, with a meta-analysis stating 24.2%; cf. Coryell et al., 1992; Persad et al., 1996; Wehr et al., 1988; Tondo and Baldessarini, 1998) in this sample may be a reflection of our definition of rapid cycling as current or ever through the course of illness, and/or MGH, bipolar clinic being an academic tertiary-referral center, to be over-presented with such difficult to-treat patients.

Our findings suggest an association between early age at onset and subsequent rapid cycling. Rapid cycling bipolar-I illness may represent a severe form of the illness with an earlier age of onset. Initial data from the Stanley Foundation Bipolar Network also suggest an association between the early onset and severity of bipolar illness (Suppes et al., 2001).

Intriguingly, a significant difference in age of onset of rapid cycling versus non-rapid cycling bipolar-I patients was found in females only. Dichotomous division of the sample as the early and late-onset groups strengthened this gender specific association between the early-onset and rapid cycling. This is compatible with the findings of Fujiwara et al. (1998), who reported a possible association between the early-onset, female gender and rapid cycling in a small sample of bipolar patients. In keeping with these findings, Altshuler et al. (1995) reported antidepressant induced cycle acceleration being associated with a younger age at first treatment and more likely to occur in women. Although, they used a much younger cut of point than ours for the early versus late-onset groups, the initial data from the SFBN is not supportive of such a gender specific finding. Data from a larger cohort of bipolar patients will be available by the SFBN and STEP in the near future, and will hopefully clarify if there exist such a gender specific association between the rapid cycling and early age of onset in bipolar illness.

In accordance with the previous reports, we found rapid cycling to be more common in women than men among the patients with bipolar-I illness (Calabrese et al., 2001).

Our results suggest that bipolar-I women may have a greater diathesis toward rapid cycling than bipolar-I men. This may reflect effects of gonadal steroids on the brain development and/or function (Leibenluft, 1996; Pillard et al., 1993). The mechanisms underlying such effects are not yet clear. However, there is some data suggesting that contribution of gonadal steroids on the pathogenesis of mood cycling to be through their prenatal/postnatal effects on the circadian rhythms (Leibenluft, 1993, 1996; Persad et al., 1996; Morin et al., 1977; Zucker et al., 1980). Neurotransmitters, circadian rhythms and neurophysiological predispositions aided by factors such as age, sex, developmental vulnerability to bipolar illness, thyroid status, substance abuse and use of antidepressants may interact to provoke a predisposition toward or an actual appearance of rapid cycling. This, in turn, may explain the waxing and waning of cycling under the influence of the non-developmental factors in addition to the developmental ones.

These findings may be relevant for the pharmacological treatment of rapid cycling bipolar patients. Dunner and Fieve (1974) first described rapid cyclers as having four or more episodes per year and found them to be refractory to lithium treatment. Later, Fujiwara et al., 1998, divided rapid cycling bipolar patients into early- (≤ 25) and late-onset groups (≥ 26); and reported a poor lithium response in the early onset group, whilst reporting a better lithium response in the late-onset group. We found a relationship between early age at onset and rapid cycling in bipolar-I women. Within this framework, it may be inferred that bipolar-I patients whose rapid cycling course is more likely to be associated with internal biologic factors (who may also be called as 'endogenous rapid cyclers') are the ones who became sick at an earlier age and have a poor lithium response. Bipolar-I rapid cyclers with a later age at onset, by contrast, may be more likely to experience cycle acceleration mediated by exogenous factors, and may have a good response to lithium. Thus, demographic and illness characteristics of rapid cycling bipolar illness may contribute to assess the prognosis and to develop predictors of treatment response.

A number of factors limit the interpretation and generalizability of these data. Firstly, this is a selected sample of patients studied in an academic, tertiary-referral center. Second, owing to the retrospective design, it is likely that many bipolar-II patients were excluded from the analysis due to insufficient data, which left the sample almost totally with bipolar-I patients. Nonetheless, given the paucity of the available data on the matter and difficulty of designing an ideal study to investigate the relationship of age/age of onset/duration of illness and rapid cycling because of the transient and erratic pattern of rapid cycling, this study may serve to provide background data on a relatively large cohort of systematically assessed bipolar patients.

As the prospective follow up data becomes available with the currently ongoing studies of bipolar illness with larger samples, we will hopefully gain a better understanding of the factors involved in vulnerability to increased cycling and the predictors of treatment response in this population.

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