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Rapid cycling bipolar disorder

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INTRODUCTION

Bipolar disorder (manic-depressive illness) is a severe and highly recurrent mood disorder characterized by the alternating occurrence of manic, hypomanic, depressive and mixed episodes. The illness has a heterogeneous course, with much inter-individual and intra-individual variations. The term rapid cycling, i.e. the occurrence of four or more separate mood episodes within a year, was introduced in 1974 by Dunner and Fieve to indicate a variant of bipolar disorder that was relatively unresponsive to lithium prophylaxis. Since then, the concept of rapid cycling has been widely studied, especially after it was included in DSM-IV as a course specifier of bipolar disorder.

CHARACTERISTICS OF RAPID CYCLING

As defined in DSM-IV and DSM-IV-TR, the specifier «with rapid cycling» can be applied to bipolar I disorder or bipolar II disorder. The essential feature of rapid cycling is the occurrence of four or more mood episodes during the previous 12 months, occurring in any combination and order. The episodes must meet both the duration and symptom criteria for a major depressive, manic, mixed, or hypomanic episode and must be demarcated by either a period of full remission or by a switch to an episode of the opposite polarity. Manic, hypomanic, and mixed episodes are counted as being of the same pole (e.g. a manic episode immediately followed by a mixed episode counts as only one episode in considering the specifier with rapid cycling).

A recent prospective study among 539 bipolar patients with various cycle frequencies revealed no clear boundary between those with non-rapid cycling (0-3 DSM-IV mood episodes per year) and rapid cycling (four or more DSM-IV mood episodes per year). This finding suggests that rapid cycling is not a distinct subtype; instead it is a dimensional course specifier, arbitrarily defined on a continuum of episode frequency.

PREVALENCE OF RAPID CYCLING

The true prevalence of rapid cycling in patients with bipolar disorder in the general population or in non-specialized treatment settings is unknown. A meta-analysis of studies that included patients who were consecutively admitted to an in- or outpatient facility, without a priori selection of rapid cyclers, and without matching the numbers of rapid cyclers to non-rapid cycling controls, reported an overall prevalence of rapid cycling of 16.3% (range between studies 12%-24%).

ASSOCIATED FEATURES AND POSSIBLE RISK FACTORS

In a meta-analysis of clinical studies published between 1974 and 2002 that compared rapid cycling and non-rapid cycling patients, female gender ($p = 0.000$) and bipolar II subtype ($p = 0.001$) were significant differentiating features, although the effect sizes of these differences were small. In addition, a family history of mood disorder, onset of bipolar illness with a depressive episode, a lifetime history of suicide attempts, and lithium non-responsiveness were more

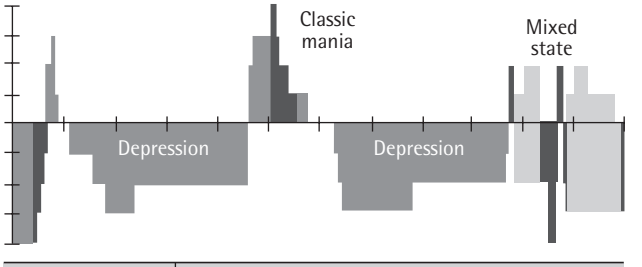

Figure 1 *Example of rapid cycling illness pattern in a patient with bipolar I disorder. Rapid cycling including mixed episodes (female, 47). Stanley Foundation Bipolar Network, one year prospective follow up.*

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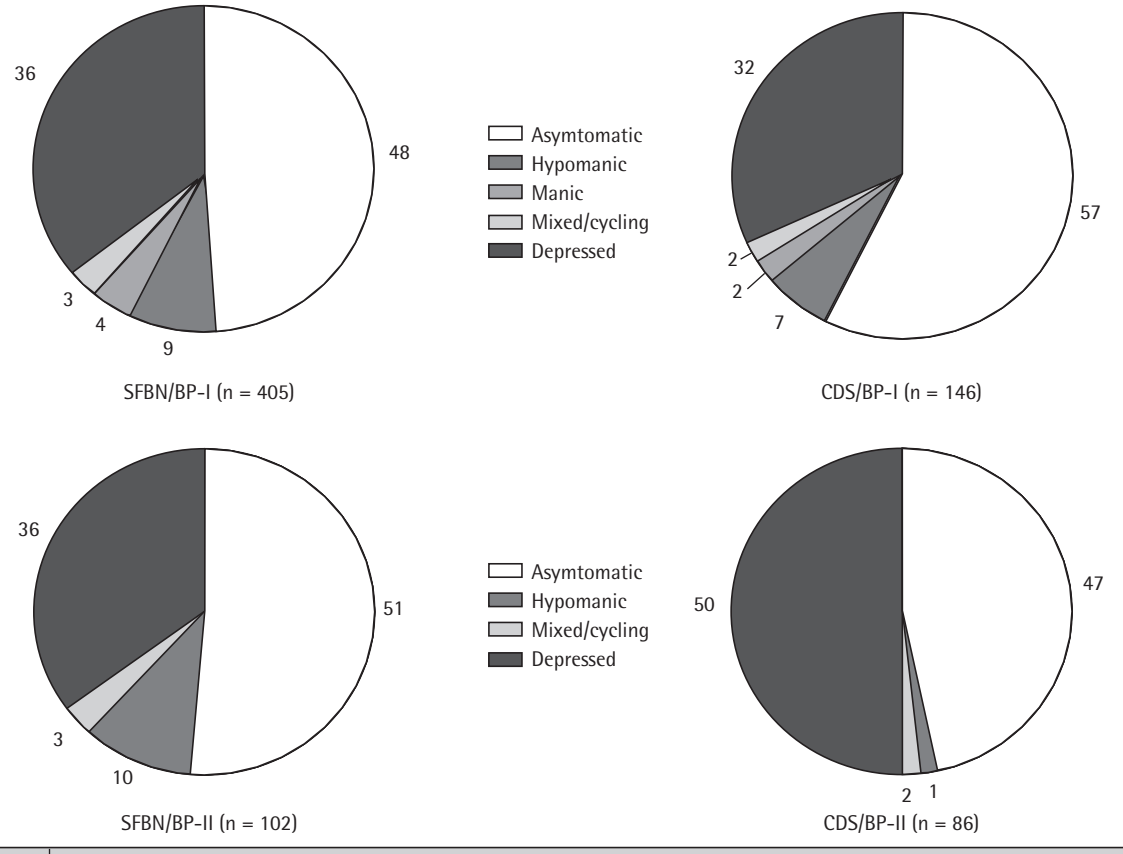

Figura 2 *Percentages of average time ill at follow-up in treated patients with bipolar I and II disorder in the Stanley Foundation Bipolar Network Naturalistic Follow-Up Study and the NIMH-Collaborative Depression Study.*

prevalent in rapid cyclers but these differences did not reach statistical significance. Studies investigating the association between rapid cycling and hypothyroidism reported very inconsistent results, thus lacking overall significance.

INDUCTION OF RAPID CYCLING BY ANTIDEPRESSANTS

The induction of rapid cycling by antidepressants is still subject to controversy. Alternatively, the association between rapid cycling and antidepressants may be related more to the frequent occurrence of depression or to a natural course of mania following depression than to the antidepressant itself. It is therefore difficult to differentiate the natural course of illness from switches into mania and cycle acceleration attributable to use of antidepressants. In a recent long-term follow-up, the use of tricyclic antidepressants was not associated with a switch from depression to (hypo-) mania.

TREATING RAPID CYCLING

As with bipolar disorder in general, treatment of rapid cycling is focused on acute episodes and prophylaxis. However, given the inherent nature of rapid cycling, and the likelihood of spontaneous remission of individual episodes within a relatively short time, prophylactic treatment is the greater challenge. It may even be counterproductive to focus on the treatment of individual episodes. While treatment of manic episodes is in general congruent with prophylaxis, the treatment of depression proves to be more difficult and may further destabilize a patient by inducing mania or faster cycling.

TREATMENT OPTIONS

Failure of lithium prophylaxis was one of the key features of rapid cycling when the term was introduced. In a meta-analysis, Tondo et al. conclude that lithium is no less effective than valproate, carbamazepine, lamotrigine, or topiramate, and that all these agents are relatively ineffective when total protection from episodes is the treatment goal. Patients with rapid cycling bipolar disorder may indeed benefit from long-term lithium treatment, alone or in combination with other mood stabilizers.

Combinations of mood-stabilizing agents which have predominantly antimanic and antidepressant properties ap-

pears to be the most promising approach if initial mood stabilizer monotherapy (lithium or valproate for bipolar I, and lamotrigine for bipolar II rapid cycling) is not successful. When evaluating treatment, significant reduction of symptoms (i.e. milder, briefer, and fewer episodes) is a more realistic goal than complete prevention of further episodes. Agents that show partial efficacy in a given patient should not be abandoned too soon but rather be part of a subsequent combination treatment. This strategy should be discussed with the patient to enhance treatment adherence.

CONCLUSIONS

Rapid cycling is relatively common in clinical populations of patients with bipolar disorder and is generally associated with unfavorable results when currently available pharmacologic treatments are used. These patients need careful assessment of previous illness course, elimination of potentially cycling-inducing factors (especially antidepressants and substance abuse), and systematic step-wise treatment planning with a focus on long-term stabilization rather than short-term remission. Despite a growing therapeutic armamentarium, patients with rapid cycling remain one of the great challenges in the treatment of bipolar illness.

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