

## Short report

## Early course of bipolar disorder in high-risk offspring: prospective study

Anne Duffy, Martin Alda, Tomas Hajek and Paul Grof

**Summary**

We studied the course of major mood disorders in the offspring of parents with well-characterised bipolar disorder prospectively for up to 15 years. All consenting offspring were assessed annually or anytime symptomatic. The participants began to develop major mood episodes in adolescence and not before. The index major mood episode was almost always depressive, as were the first few recurrences. Onsets and recurrences continued

throughout the observation period into adulthood. We did not find evidence of pre-pubertal mania. In summary, adolescence marks the beginning of the high-risk period for major mood episodes related to bipolar disorder.

**Declaration of interest**

None.

Knowledge of the clinical course of bipolar disorder is important for practical and theoretical reasons including the validation of the diagnosis, determination of onset and recurrence risks, as well as for the development of clinical services and mental health policy. Moreover, mapping the early clinical course is crucial for improving early detection, and for the prevention of substantial burden of illness effects and excess mortality associated with established illness.

Long-term follow-up studies show that individuals experience a recurrence of mood episodes throughout their lifetime in patterns that are highly variable between individuals.<sup>1</sup>

Currently, little is known about the early clinical stages of the illness and descriptions of the onset and early course are largely based on patient recall.<sup>2</sup> Retrospective data about the natural course of illness is confounded by memory biases and distortions that are amplified by recurrent episodes, medication and psychosis. In addition, there is ongoing debate with regard to the validity of the bipolar disorder diagnosis in referred pre-pubertal children;<sup>3–5</sup> a clinical presentation not reported retrospectively by adults with bipolar disorder. As bipolar disorder is highly heritable,<sup>6</sup> children of affected parents are an important high-risk group. This is the first study to describe the onset and early course of major mood episodes in the offspring of parents with well-characterised bipolar disorder longitudinally, prospectively studied for up to 15 years.

**Method**

Parents with bipolar disorder were identified from their involvement in a mood disorders subspecialty programme and/or genetic studies as previously described.<sup>7</sup> Briefly, suitable families were identified through a proband who met DSM-IV<sup>8</sup> criteria for bipolar disorder based on Schedule for Affective Disorders and Schizophrenia – Lifetime version (SADS-L)<sup>9</sup> research interviews conducted by an experienced research psychiatrist. Final diagnosis was made on masked consensus review involving two additional research psychiatrists using all available clinical information.

All consenting children ( $n=207$ ) from eligible families ( $n=105$ ) between the ages of 8–25 years were enrolled.<sup>7</sup> The duration of the longitudinal study ranged from 1 to 15 years. Children completed Kiddie-SADS-PL (Present and Lifetime version)<sup>10</sup> interviews conducted by a child and adolescent psychiatrist at enrolment, annually or at any time symptoms developed, up until their 30th birthday. DSM-IV diagnoses were

made using all available clinical information on a masked consensus basis. Sixty-four per cent of all major episodes were prospectively captured. Any retrospective data used were based on participant and parent recall, and verified through a review of all available clinical documentation.

Only major mood episodes (major depression, hypomania or mania) meeting full DSM-IV criteria were analysed. We used Mann-Whitney  $U$  to compare continuous variables. Wilcoxon signed rank test was used to assess differences between neighbouring cycle lengths and cycle length ratios. Cycle length was calculated as time between the onset of two subsequent episodes. Survival analysis (life table method with 1-year intervals) was used to assess the risk of onset of the initial mood episode and the risk of recurrence thereafter.

**Results**

Of the 207 participants, 67 met DSM-IV lifetime criteria for at least one major mood episode. Their mean age at analysis was 24 (s.d. = 5) years and 67% were females. In total, 16% had been admitted to hospital at least once in their lifetime and 18% had a lifetime history of psychotic symptoms in episodes.

The mean age at onset of the first major mood episode was 17 (s.d. = 4) years and no one experienced an onset prior to 12 years. In 90% of the 67 cases, the first episode was major depression. Of the 67 participants, 61 had a remitting or partially remitting course for whom we could calculate the mean duration of the first major mood episode. Among these 61 first episodes, 54 were depressive with a mean duration of 6.1 (s.d. = 4.8) months, which was significantly longer than the mean duration of 1.7 (s.d. = 1.3) months for first activated (hypomanic/manic or mixed) episodes ( $U=3.07$ ,  $P<0.01$ ). For these 61 individuals with a remitting or partially remitting course, we compared the polarity of mood episodes across the first five episodes, collapsed across course and gender subgroups, and found that the majority were depressive. Specifically, 89% of 61 first episodes were depressive, as were 68% of 34 second episodes, 78% of 18 third episodes and 58% of 12 fourth episodes. There were no gender differences in the proportion of depressive, hypomanic/manic or mixed episodes.

Medication could not have influenced the course of illness significantly, as less than 20% of acute mood episodes were treated with a mood stabiliser (lithium, anticonvulsant or antipsychotic)

and less than 20% of intervals were associated with any exposure to a mood stabiliser.

For individuals with more than one remitting or partially remitting episode ( $n = 34$ ), the mean cycle length calculated from intra-individual means was 31.0 (s.d. = 21.3) months and the median cycle length for the group as a whole was 26.3 months. For participants with at least three lifetime mood episodes ( $n = 18$ ), using a criterion of a 20% or more decrease in cycle length, 72% of individuals showed a significant amount of shortening in cycle two compared with cycle one and 75% of individuals had shortening in cycle three compared with cycle two; these differences were not statistically significant. A subsequent analysis using a Wilcoxon signed ranks test to compare the cycle length ratios of cycle 2:1 with cycle 3:2 revealed that there was no significant difference between these ratios. Because of the within-participant nature of these approaches, both analyses avoided Slater's Fallacy,<sup>11</sup> that is, an artifactual progressive shortening of cycles caused by averaging values from participants with different numbers of episodes.

We entered all 207 participants into a survival analysis using 1-year intervals starting from birth. This analysis revealed a heightened risk of new onsets of major mood episodes from age 12 that continued through the observation period to age 30 (online Fig. DS1(a)). A similar analysis revealed a continuing recurrence risk in those having had one major mood episode. By 5 years the risk of recurrence was 61% (online Fig. DS1(b)).

## Discussion

Some of our findings confirm previous reports from large studies of adults<sup>12,13</sup> and high-risk studies with a longitudinal component.<sup>14,15</sup> Specifically, in this study the index mood episode was almost always major depression, as were the majority of the first few recurrences. Index depressive episodes lasted significantly longer than did index activated episodes. This highlights that a substantial amount of morbidity early in the course is related to the depressive polarity of the illness. These findings underscore the importance of including the family history in the diagnosis of young people with depression to improve the recognition of a bipolar diathesis.

The risk of onset of major mood episodes in high-risk individuals started around 12 years of age and markedly increased through adolescence into early adulthood. Given that new onsets continued throughout the observation period, the estimated age at onset is expected to increase with longer prospective follow-up. As in other high-risk studies,<sup>14-16</sup> we did not find evidence of pre-pubertal mania.

Finally, we confirmed a high recurrence risk (over 60% in 5 years) of major mood episodes and continuity through adolescence into early adulthood. These findings emphasise the need to identify children at familial risk of bipolar disorder and to provide continuity of expert psychiatric surveillance and assessment over this period. This involves programmes spanning child and adult institutions, and close collaboration between child and adult psychiatry services.

However, these findings cannot simply be generalised to other populations. This was a naturalistic study, the families were highly selected for research, and exposure to pharmacotherapy in the affected offspring was minimal. Furthermore, despite a clear tendency of shortening cycle lengths for the first few cycles, the number of participants with more than three episodes was small, reducing our power to show a statistical difference.<sup>17</sup>

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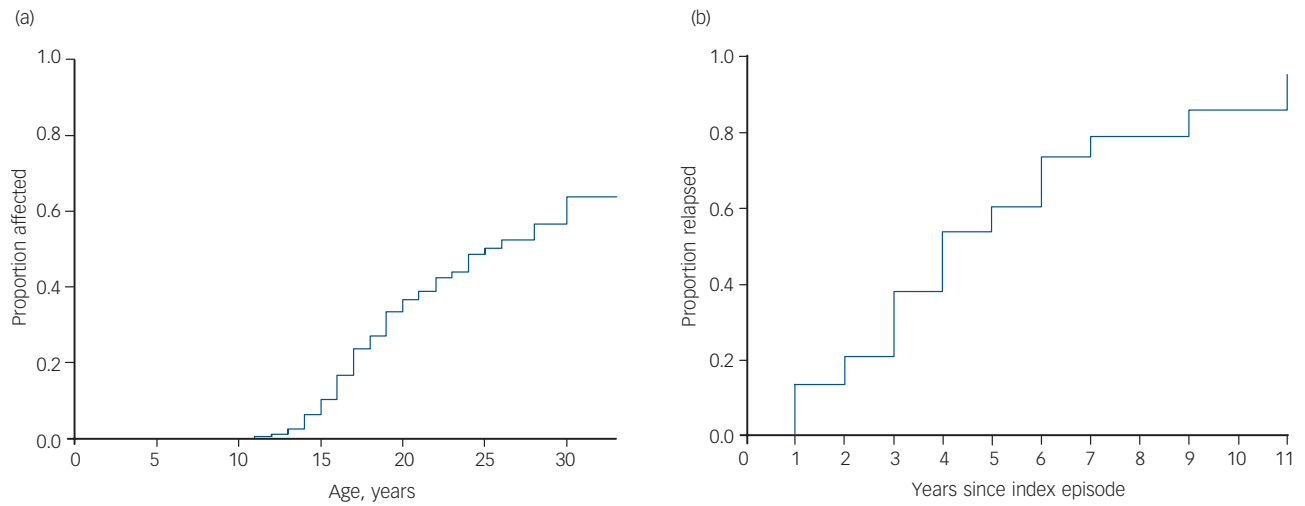
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## Data supplement



**Fig. DS1** (a) Risk of onset as a function of age and (b) risk of recurrence as a function of age.

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### Supplementary Material

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