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Debate: No bipolar disorder in prepubertal children at high familial risk

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How do we classify school-aged children with severe emotional dysregulation, attention deficits, and irritability? Over the last two decades, a huge increase in pediatric bipolar disorder (PBD) diagnoses has been observed, especially in the United States. From a historical perspective, a shift toward an earlier age of onset of bipolar disorder (BD) is observed. This is also confirmed in a recent study in which a birth cohort effect toward an earlier age of onset has also been observed in European multicenter clinical observational studies. However, no prepubertal onset was found (Scott, Etain, Azorin, & Bellivier, 2018). While the diagnostic criteria of bipolar disorder during adulthood are generally accepted, the term PBD is inconsistently used applying to either prepubertal children or under the age of 18. Here, PBD is referred to as prepubertal (or preadolescent) bipolar disorder.

The rise in PBD prevalence rates and the related treatment regimen has an impact on a whole generation of severely affected young children. Indeed, bipolar disorder is a chronic, severe mood disorder which often requires lifelong treatment with second generation antipsychotics or mood stabilizers which are associated with a broad range of serious side effects. In Europe, we also see such emotional dysregulated children with a broad range of explosive disruptive behavior. However, classification within the bipolar disorder spectrum is rare. These children are rather diagnosed within the disruptive behavior ADHD/ODD/CD spectrum and treated accordingly.

Why are these prepubertal children diagnosed with mania and how does this fit with findings from bipolar offspring studies? Bipolar disorder in adolescents has been well described and there are convergent findings indicating that mania presents with similar symptoms as in adulthood. In addition, we know that experiencing (hypo)manic symptoms is a common adolescent phenomenon that infrequently predicts mental health care use (Tijssen et al., 2010). Context and multi-informants are therefore crucial in the interpretation of these typical adolescent experiences. Interestingly, adolescent BD patients often have a high familial load for bipolar disorders. Since a first-degree family member with BD is the strongest risk factor for bipolar disorder, longitudinal offspring studies are ideal to study the development of BD. Children at the highest genetic and environmental risk (offspring of BD parents) constitute, therefore, a population in which childhood mania, if valid, should present more often and clear as compared to the general population. Worldwide, all six longitudinal BD offspring studies from different countries (Switzerland, Canada, USA Amish, USA Pittsburgh, Australia, and The Netherlands) show a mean age of onset of the narrow-defined BD type I after the age of 12 years.

However, cross-national variation is an issue with BD-NOS, as studies show more variation when BD-NOS is included as a result of different methods, interpretation of criteria, and prevalence rates across countries. This was also the case in our study comparing categorical and dimensional psychopathology from the Pittsburg BIOS study and the Dutch Bipolar Offspring Study (Mesman et al., 2016). BD-NOS prevalence rate in the Pittsburgh sample was high (6.7%), but was not assessed in Dutch offspring because of unclear criteria and could therefore not be compared directly. However, both offspring studies used the Achenbach Child Behavior Checklist (CBCL) and the K-SADS-PL, a semistructured psychiatric interview. After controlling for age, rates of bipolar I (2.2% Pittsburgh, 1.5% Dutch) and bipolar II (1.8% and 0.7) were similar. By contrast, other disorders were significantly more common in the Pittsburgh sample, as was the prevalence of comorbidity in the bipolar offspring. In general, the Pittsburg offspring was more severely affected compared to the Dutch offspring based on the psychiatric interview. Surprisingly, however, parent scores on the CBCL did not differ significantly between samples, whereas they should have as the symptom rates by interview were different. Also, in the Pittsburgh sample, fewer index-parents had bipolar I (vs. bipolar II or NOS disorder), they had an earlier age of onset, higher comorbid substance abuse rates, and lower rates of employment. In addition, the prevalence of psychopathology in the co-parent was higher in the Pittsburgh sample and recruitment by advertisement was common, while recruitment in the Dutch sample was through a patient advocacy group. These differences illustrate the importance of the psychopathology load of both the parents, the level of family functioning, and stress and effect of the recruitment strategy in understanding rates of offspring psychopathology and comparing cohorts.

Recently, results were published from the Danish High Risk and Resilience Study - VIA 7, a nationwide population-based cohort study of 522 seven-year-old (age range 6.9–8.4 years) children, who were born and living in Denmark, with no, one, or two biological parents diagnosed with schizophrenia spectrum or bipolar disorder. They were identified using the Danish Civil Registration System and the Danish Psychiatric Central Research Register (Ellersgaard et al., 2018). The BD offspring showed a higher prevalence of anxiety disorders, stress, and adjustment disorders – compared with controls. No bipolar

disorder was diagnosed in these offspring with a mean age of seven. Again, in this study recruitment and severity of the bipolar disorder are relevant. The BD parents in the Danish study were recruited through the registers and likely to be more heterogeneous in terms of severity of the disorders, which may affect the levels of psychopathology in the offspring.

The research and clinical field of child and adolescent psychiatry would benefit from more uniform methods of assessing symptoms and determining bipolar disorder diagnoses. Keeping in mind that questionnaires are not reliable, multiple informants are essential, and a clinical interpretation is more important than the sum of symptoms which needs to define an episode with a clear "change from the usual state". Longitudinal studies in high-risk offspring and across diagnostic domains and countries, with a focus on harmonizing parental characteristics, recruitment procedures, and clear BD criteria are needed to completely understand the international perspective on pediatric bipolar disorder (Maciejewski, Hillegers, & Penninx, 2018).

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