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Comorbidity in Pediatric Bipolar Disorder: An Unmet Challenge in Need of Treatment Studies

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In this edition of *Acta Psychiatrica Scandinavica,* Fahrendorff and colleagues report findings from their systematic review examining psychiatric comorbidity in pediatric bipolar disorder (1). The scientific literature regarding pediatric bipolar disorder has increased significantly over the past two decades, and this manuscript provides a helpful synopsis regarding psychiatric comorbidity in children and adolescents with bipolar disorder.

Before turning to the details of the current study, it is important to provide context from the international epidemiology of psychiatric comorbidity in adult bipolar disorder. A World Mental Health Survey Initiative study, which included 61,392 community adults from 11 countries in the Americas, Asia, and Europe, examined psychiatric comorbidity among individuals with bipolar spectrum disorders (2). The most common comorbidities were anxiety disorders, behavior disorders, and substance use disorders. Comorbidity patterns for anxiety disorders and substance use disorder showed substantial international consistency, although rates of comorbid behavior disorders were much higher in the U.S. and New Zealand than in most other countries. Over three-quarters of adults with bipolar disorder had at least one psychiatric comorbidity, and nearly half had three or more comorbidities. This is remarkable for a number of reasons, including the fact that the sample was community based, rather than clinical, and the fact that these data are not constrained to one country or one sample, but rather reflective of a highly consistent pattern of multi-comorbidity in bipolar disorder.

Discourse regarding psychiatric comorbidity in pediatric bipolar disorder often focuses on differential diagnosis in general, and the issue of overlapping diagnostic criteria in particular (3). This relates especially to attention deficit hyperactivity disorder (ADHD) and diagnoses characterized by severe irritability (e.g. disruptive mood dysregulation disorder [DMDD], oppositional defiant disorder [ODD]). Interwoven within this discourse are the themes of international differences in diagnostic practices and concerns around so-called over-diagnosis (i.e. false positives). While the aforementioned findings regarding comorbidity in adult bipolar disorder do not resolve debates around differential diagnosis or international differences in diagnostic approaches, they do establish that multi-comorbidity is a reality

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of bipolar disorder. That is, high rates of comorbidity in pediatric bipolar disorder are not primarily driven by confounding methodologic or diagnostic factors. Moreover, it has been well established, in both clinical and epidemiologic studies, that onset of bipolar disorder in childhood and/or adolescence is associated with increased burden of psychiatric comorbidity among adults with bipolar disorder (4).

Fahrendorff and colleagues reviewed 20 pediatric bipolar disorder studies that collectively included 2722 youth, with an average age of 12 years. Study quality was determined using a standardized approach (STROBE), and all but one study had moderate or high quality. If both lifetime and point prevalence were reported, point prevalence was used. The authors hypothesized that there would be high rates of comorbidity and that comorbidity would be associated with functional impairment.

The findings are largely aligned with the adult bipolar disorder comorbidity literature, but there were exceptions (note: percentages reflect weighted mean prevalence based on the studies that addressed each of the comorbidities below). Anxiety disorders are the most common comorbidity in adults, followed by behavior disorders. While behavior disorders, including ADHD (60%) and ODD (47%), were the most common type of comorbidity in pediatric bipolar disorder, comorbid anxiety disorders (43%) were also highly prevalent. The relatively low rate of comorbid substance use disorders in pediatric bipolar disorder (13%) as compared to adult bipolar disorder (37%) underscores the important opportunities for prevention. There was substantial between-study variability in terms of which comorbidities were reported. Among the 20 studies identified and reviewed by Fahrendorff and colleagues, 19 reported rates of comorbid anxiety disorders, and most studies reported on behavior disorders. However, less than half of the studies reported rates of substance use disorders, and information regarding comorbid eating disorders (three studies) and autism spectrum disorders (two studies) was sparse.

Fahrendorff and colleagues acknowledged a number of methodologic limitations, including the requirement for research-based diagnoses, the limited number of included studies, and the fact that most samples were derived from specialized centers/groups. The issue of research-based diagnoses is especially important for pediatric bipolar disorder, given that there has been evidence of increased rates of pediatric bipolar disorder in studies based solely on clinical or administrative diagnoses, which has not been paralleled in epidemiologic studies using research-based diagnoses (5, 6). While the preponderance of studies emerged from specialized centers conducting research on pediatric bipolar disorder, unfortunately there are only a few such centers, which is in turn related to the small number of studies.

In addition to these limitations, it appears that the current search strategy resulted in the exclusion of many publications that could have bolstered the representativeness and conclusions of the current article. The small number of studies included in the current review is especially pertinent for comorbidities that are under-represented, such as autism spectrum disorders and eating disorders (7). Moreover, among the 20 studies identified, only three were published within the past decade, which is discordant from the overall growth in publications on pediatric bipolar disorder. While recency is an important consideration when

examining any topic, it is especially important for pediatric bipolar disorder as this was a nascent field not long ago and consensus within the field has increased meaningfully over recent years (8). Most groups currently conducting research on pediatric bipolar disorder are aligned in terms of requiring discrete episodes of mania/hypomania, concordant with contemporary DSM and ICD criteria. Similarly, most groups take the approach that in order for symptoms that overlap with other diagnoses (e.g. distractibility, irritability, hyperactivity) to count toward mania/hypomania, a mood-related increase in the severity of those symptoms is required. That is, overlapping symptoms are not automatically "double counted". Huge between-study differences in rates of comorbid ADHD (0–87%), for example, are likely a vestige of debates from 20 years ago. Regarding the concern about high rates of comorbidity comprising a reflection of specialized centers conducting pediatric bipolar disorder research, it is clear from representative epidemiologic studies that high rates of comorbidity are not limited to clinical samples (9–11).

The distinction between pediatric bipolar disorder and DMDD is highlighted by Fahrendorff and colleagues as a topic of ongoing debate. While there is some truth to this assertion, the issue of differential diagnosis should be parsed from that of comorbidity. By specifying that as little as one day of full manic or hypomanic symptoms is an exclusion criterion for DMDD, DSM5 enshrines a false dichotomy. However, it is clear that these phenotypes frequently co-occur, as evidenced by a study reporting 25% prevalence of DMDD phenotype among adolescents with bipolar disorder (12). Moreover, rates of DMDD are elevated among children of parents with bipolar disorder, independent of demographic variables or parental comorbidity (13). Future studies focused on DMDD comorbidity in pediatric bipolar disorder are warranted to build on the limited literature in this area.

As previously mentioned, studies of adults and of youth with bipolar disorder are aligned in terms of both the high rates of psychiatric comorbidity and the leading categories of comorbidities. In contrast, while medical comorbidity has been widely examined in epidemiologic and clinical studies of adult bipolar disorder, the literature on this topic is comparatively sparse in youth. This relates to a variety of conditions that manifest clinically in childhood and adolescence, such as atopic disorders, diabetes, epilepsy, and migraine headaches, but also extends to subclinical cardiovascular risk factors. Generally speaking, measurement of cardiovascular risk factors among youth with bipolar disorder is undertaken in relation monitoring medication side effects. Whereas, the concept that cardiovascular risk factors can impact the course of pediatric bipolar disorder, and vice versa, is not yet widely integrated into clinical practice. In comparison to the significant amount of time that is required to evaluate psychiatric comorbidity using research diagnostic interviews, common medical comorbidities can be evaluated using brief self- and/or parent-reported screeners. Similarly, anthropometric measurements can be easily and reliably measured, ideally together with lipids and glycemic indices (e.g. glucose, insulin, glycosylated hemoglobin). Given that cardiovascular risk factors have been adversely associated with brain structure, neurocognition, and symptomatic burden (including suicidality), in pediatric bipolar disorder, increasing the scope of research on this topic is imperative (14).

In contemplating future research foci, Fahrendorff and colleagues highlight differences relating to current vs. lifetime comorbidity, and relating to the assessment of comorbidity

during symptomatic vs. asymptomatic intervals. There is surely valuable information and precision to be gained from such approaches. However, it is already safe to conclude that the issue of comorbidity in pediatric bipolar disorder is of massive importance, and it is highly unlikely that this conclusion would be altered by incremental differences in methodologic approaches. Whereas, the knowledge base regarding treatment of psychiatric comorbidity in pediatric bipolar disorder is miniscule relative to the magnitude of the problem. A handful of studies regarding adjunctive treatment of comorbid ADHD with psychostimulants suggest that this approach is efficacious and relatively well tolerated (15). However, larger studies are needed to generate accurate estimates of adverse events such as treatment-emergent mania. The same applies to the pharmacologic treatment of anxiety and depression in pediatric bipolar disorder, presenting challenging decisions for which existing evidence provides little guidance. The gap in knowledge regarding treatment extends to all psychiatric (and medical) comorbidities of pediatric bipolar disorder. A combination of observational naturalistic treatment studies and randomized controlled trials, each with their relative strengths and limitations, is needed to make progress in mitigating the burden of comorbidity in pediatric bipolar disorder. All clinical trials in pediatric bipolar disorder, including those focused on acute mood episodes and maintenance treatment, should minimize comorbidity-related exclusion criteria and plan for comorbidity-related secondary analyses. Such studies would both ensure that findings are generalizable to all youth with bipolar disorder, and enable clinicians to make more evidence informed, personalized treatment decisions.

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