

Need for further exploring at the intersection of ADHD medications and bipolar disorder

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Bipolar disorder (BD) and attention-deficit hyperactivity disorder (ADHD) may copresent and manifest as complex clinical presentations, often accompanied by further comorbidities such as anxiety and substance use disorders. ADHD/BD comorbidity not only relies on a widely reported symptomatological and neurobiological overlap, but it also creates an intricate interplay between ADHD, affective and other psychiatric conditions, requiring a more nuanced understanding of their comorbid nature. Moreover, clinical and nosological perspectives on the nature of the ADHD/BD comorbidity may significantly vary across developmental stages, ranging from an overestimated comorbidity (possibly due to the confound role of greater symptoms' overlap in childhood, adolescence and youth cases) to a prodromal developmental pattern (i.e., from ADHD to BD) or a separate nosological entity ("ADHD-BD").¹ In younger patients, in particular, recent literature also suggests a possible specific role of emotional dysregulation, a common key feature of ADHD and bipolar spectrum disorders, acting as a confound variable that may enhance the misconception of ADHD/BD comorbidity and favor the misdiagnosis of ADHD as a BD spectrum disorder.² Clearly, the emphasis on the need to disentangle the complex relationship between juvenile ADHD and BD highlights the challenges in delineating these disorders for better diagnostic characterization and therapeutic indications.

The systematic review by Miskowiak et al.³ addresses a highly relevant clinical topic, reporting on the available evidence on the efficacy and safety of ADHD pharmacotherapies to treat cognitive impairment and ADHD symptoms in juvenile and adult BD. Shared neurobiological dysregulations, particularly involving dopamine and norepinephrine signalling pathways, may significantly contribute to the symptomatic overlap between BD and ADHD. However, pharmacological interventions targeting dopamine and noradrenaline pathways (such as stimulants and alpha-2-adrenergic agonists) long

held promise to ameliorate cognitive deficits and ADHD symptoms in individuals with BD. Indeed, the evidence relative to dysfunctions of the dopamine transporter (DAT) gene and catechol-O-methyltransferase (COMT) gene variants underscores the intricate interplay between these disorders and prompts for therapeutic implications.⁴ Miskowiak et al.³ also report preliminary favorable evidence of efficacy of ADHD drugs in treating ADHD symptoms in BD, with a current lack of evidence for psychostimulants to trigger or exacerbate mania and insufficient evidence to conclude on their role in improving cognitive symptoms in BD.

Also in our previous work,⁵ we underscored the potential benefits of adjunctive therapy in alleviating ADHD symptoms in BD patients. Indeed, while mood stabilization should remain the main target of BD patients (as impulsivity, hyperactivity, and inattention symptoms may recede after stabilization), the presence of "residual" (and particularly cognitive) symptoms may require specific ADHD drugs. We agree that methylphenidate and mixed amphetamine salts represent the most promising options in the treatment of BD, with robust beneficial effects observed particularly in pediatric and adolescent populations. However, the paucity of data concerning atomoxetine, viloxazine, modafinil, armodafinil, and lisdexamfetamine (that, importantly, is the only stimulant marketed for use in ADHD to be studied as an add-on strategy for treatment-resistant bipolar depression) demands for a still cautious and highly individualized approach. On the other hand, we also highlighted a favorable safety profile of ADHD medications with no increased risk of manic episodes, especially when administered alongside mood stabilizers, and this evidence should favor their use in BD.

A more recent examination of comorbidities in youth with BD explored both clinical characteristics and pharmacological treatment approaches.⁶ This review underscores the relevance of customized interventions to effectively address the diverse needs of

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this patient cohort. However, it also highlights a notable gap in research concerning pharmacological interventions for BD and its concurrent conditions, particularly in the pediatric and adolescent age groups.

Despite the promising efficacy and safety profile of ADHD medications, significant gaps remain in our understanding of their cognitive effects and long-term outcomes in BD patients. Future research endeavors should prioritize comprehensive cognitive assessments, individual characterization of patients and larger sample sizes to elucidate the potential cognitive benefits of these medications. Also, specific attention should be devoted to develop controlled clinical trials sensitive to emotional dysregulation along different developmental stages, in order to really improve the prognosis of these highly complex patients, that require finely characterized diagnostic processes and highly personalized therapies. Indeed, tailored interventions addressing comorbidities and developmental nuances are imperative to optimize treatment outcomes and enhance the quality of life for individuals with BD and ADHD features.

In conclusion, a multifaceted approach encompassing neurobiological insights, clinical complexity, and treatment implications is essential in navigating at the intersection of ADHD medications and BD. By integrating findings from different clinical perspectives, we can advance personalized care paradigms, tailored to the unique needs of individuals within the BD spectrum. Embracing interdisciplinary collaboration and prioritizing specific research endeavors are crucial steps toward optimizing treatment outcomes and improving the quality of life for this complex patient population.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

REFERENCES

1. Comparelli A, Polidori L, Sarli G, Pistollato A, Pompili M. Differentiation and comorbidity of bipolar disorder and attention deficit and hyperactivity disorder in children, adolescents, and adults: a clinical and nosological perspective. *Front Psychiatry*. 2022;13:949375.
2. Masi G, Sesso G, Pfanner C, et al. An exploratory study of emotional dysregulation dimensions in youth with attention deficit hyperactivity disorder and/or bipolar spectrum disorders. *Front Psych*. 2021;12:619037.
3. Miskowiak KW, Obel ZK, Guglielmo R, et al. Efficacy and safety of established and off-label ADHD drug therapies for cognitive impairment or attention-deficit hyperactivity disorder symptoms in bipolar disorder: a systematic review by the ISBD Targeting Cognition Task Force. *Bipolar Disord*. 2024;00:1-24.
4. Hartman CA, Larsson H, Vos M, et al. Anxiety, mood, and substance use disorders in adult men and women with and without attention-deficit/hyperactivity disorder: a substantive and methodological overview. *Neurosci Biobehav Rev*. 2023;151:105209.
5. Salvi V, Ribuoli E, Servasi M, Orsolini L, Volpe U. ADHD and bipolar disorder in adulthood: clinical and treatment implications. *Medicina (Kaunas)*. 2021;57(5):466.
6. Sesso G, Brancati GE, Masi G. Comorbidities in youth with bipolar disorder: clinical features and pharmacological management. *Curr Neuropharmacol*. 2023;21(4):911-934.

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