mhc MENTAL HEALTH CLINICIAN

APPLIED PSYCHOPHARMACOLOGY Open Access

Pharmacologic treatment of bipolar disorder and comorbid adult attention-deficit/hyperactivity disorder

Anuja Vallabh, PharmD, BCPP[1]

How to cite: Vallabh A. Pharmacologic treatment of bipolar disorder and comorbid adult attention-deficit/hyperactivity disorder. Ment Health Clin [internet]. 2024;14(2):82-4. DOI: 10.9740/mhc.2024.04.082.

Submitted for Publication: November 20, 2023; **Accepted for Publication:** December 11, 2023

Keywords: attention-deficit/hyperactivity disorder, bipolar disorder

[1] Psychiatric Clinical Pharmacist Practitioner, VISN 12 Clinical Resource Hub, Jesse Brown VA Medical Center, Chicago, Illinois, Anuja.Vallabh2@va.gov, ORCID: https://orcid.org/0000-0002-5878-5862

Disclosures: The author has no conflicts of interest to disclose.

Case Report

A patient, Mr. C, age 36, presented with a history of bipolar disorder (BD) I with psychotic features, attention-deficit/hyperactivity disorder (ADHD), and diabetes mellitus II. He works in construction. He presented to his follow-up appointment noting decreased productivity at work and home over the last several months with complaints from his supervisor and partner. He described often being late to work, having difficulty focusing on tasks, being easily distracted by the noise around him, misplacing tools, and relying on colleagues to complete the final details of a project.

He has been taking aripiprazole 30 mg daily, divalproex sodium 1500 mg at bedtime, and metformin XR 1000 mg daily with good adherence. His blood pressure was 118/76 mmHg, and his heart rate was 82 beats/min. All pertinent labs were within normal limits. His most recent valproic acid level was 82 µg/mL. His BD had recently stabilized, and he denied current affective and psychotic symptoms.

Discussion

Patients with BD and comorbid ADHD present a diagnostic and treatment challenge. Overlapping symptoms and phenomenology complicate the clinical picture; mainstay pharmacologic treatments of ADHD carry the potential to exacerbate BD, and patients with BD are excluded from clinical trials for ADHD treatments. Up to 1 in 5 adults with BD have comorbid ADHD, making this a common clinical presentation.[1,2] Research has found higher rates of comorbid ADHD among those with an onset of BD before 18 years of age. Achieving stability in BD can be difficult for many, and comorbid ADHD has been found to worsen the severity of BD with a greater number of depressive, manic, and mixed episodes and overall disease burden. In addition, evidence-based treatments for adult ADHD can induce psychosis and/or possibly "switch" patients into a hypomanic or manic state, thus making pharmacologic treatment planning difficult in this population.

Literature has defined a "manic switch" or treatment-emergent hypo/mania (TEM) as a transition from a depressive episode to a hypomanic, manic, or mixed episode within 12 weeks of medication initiation or dose escalation.[3] Risk factors for TEM include a history of hypo/manic switch or rapid cycling, BD I, earlier-onset BD, severe manic symptoms, suicide attempts, comorbid panic attacks, and amphetamine use. Not only are stimulants associated with inducing psychosis and TEM in patients with BD, but antidepressants and the noradrenergic agent atomoxetine have also been associated with TEM. Viloxazine is a selective norepinephrine reuptake inhibitor that was Food and Drug Administration (FDA)-approved for adult and pediatric ADHD in 2021; with the same mechanism of action, it theoretically carries a similar risk of TEM to atomoxetine. It is critical to assess for TEM risk factors and past responses to medications when considering initiation of agents associated with TEM. Significant irritability and anxiety soon after antidepressant initiation and a history of poor tolerability to antidepressants may signify risk for TEM.[3]

There are limited studies assessing treatment efficacy and safety of these comorbid conditions, especially in adults, and most studies that have been conducted are small, low quality, and/or less than 12 weeks in length, thus unable to fully assess TEM. Studies assessing the risk of methylphenidate in TEM in children and adults with BD and comorbid ADHD demonstrate mixed results.[2] However, it is clear that those on methylphenidate without mood stabilization

Practice Points:

- Treatment-emergent hypo/mania (TEM) or "manic switch" is a transition from a depressive episode to a hypomanic, manic, or mixed episode within 12 weeks of medication initiation or dose escalation.
- Risk factors for TEM include a history of hypo/manic switch or rapid cycling, bipolar disorder (BD) I, earlier-onset BD, severe manic symptoms, suicide attempts, comorbid panic attacks, and amphetamine use.
- Bupropion has been found to be the lowest-risk antidepressant in causing TEM compared with tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, and sertraline in adjunct to a mood stabilizer.
- A randomized, double-blind, placebo-controlled trial published in 2020 studied guanfacine XR in Japanese adults with attention-deficit/hyperactivity disorder (ADHD) and found a statistically significant reduction in ADHD symptoms with an effect size of 0.52.

had a nearly 7 times increased risk of TEM. Bupropion has been found to be the lowest-risk antidepressant in causing TEM compared with tricyclic antidepressants, monoamine oxidase inhibitors, venlafaxine, and sertraline in adjunct to a mood stabilizer.[3,4] Small, low-quality studies of atomoxetine in adolescents suggest a low risk of TEM when combined with a mood stabilizer. However, case reports of atomoxetine-induced TEM exist, even in the presence of a therapeutic mood stabilizer.

When treating comorbid BD and ADHD, it is critical to take a step-wise approach and first achieve mood stabilization before initiating ADHD treatment.[5] Mood stabilization with a mood stabilizer and/or antipsychotic serves as a protective factor against TEM and offers the opportunity to reassess the severity and treatment of ADHD symptoms that may have otherwise been difficult to ascertain because of their overlapping presentations. However, there is limited guidance on how to subsequently treat ADHD because of the paucity of data in this area. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force put forth recommendations for the management of ADHD in patients with comorbid BD in 2012, with the 2018 guidelines referring to the same.[5,6] Based on safety and efficacy data in adolescents and adults and the workgroup's clinical experience, bupropion was suggested as a first-line agent after mood stabilization is achieved. Amphetamine products and methylphenidate were recommended as second-line agents and, with caution, could be considered first line in patients deemed low risk for TEM. Atomoxetine and lisdexamfetamine were recommended as third-line options due to limited data. Guanfacine, an alpha-2 agonist FDA-approved for pediatric ADHD, was not addressed by the CANMAT task force. When assessing the effect of BD treatment on ADHD, the task force found mood stabilizers and antipsychotics to be ineffective for ADHD symptoms. A study published in 2022 did not find improvement in ADHD symptoms with the addition of brexpiprazole to stimulants in treatment-resistant adult ADHD.[7] The place in therapy of guanfacine XR in adult ADHD has been unclear because it has only been studied in adolescent populations. However, a randomized, double-blind, placebo-controlled trial published in 2020 studied guanfacine XR in Japanese adults with ADHD and found a statistically significant reduction in ADHD symptoms with an effect size of 0.52.[8] Despite its limitations, the effects found in this trial are promising, and considering the lack of TEM risk, it is reasonable to trial guanfacine XR, particularly in a patient at higher risk for TEM.

Thoughtful and careful consideration must be given to the treatment of BD with comorbid adult ADHD to provide effective treatment while minimizing the risk for treatment-emergent adverse effects.

Case Continued

Mr. C's provider discussed treatment options for ADHD and the risks and benefits of each with comorbid BD. Mr. C reported having discontinued an antidepressant in the past due to feeling extremely irritable and anxious within a week of starting it, thus giving suspicion for TEM. Owing to Mr. C's history of BD I with psychosis, stimulants are avoided. Bupropion and atomoxetine were considered in the setting of effective mood stabilization with 2 agents, but they were ultimately avoided as first-line options due to his past reaction to an antidepressant. They decided to initiate guanfacine XR 1 mg daily due to Mr. C's multiple risk factors for TEM and psychosis. There were no drug–drug interactions. Mr. C was educated to take guanfacine XR at bedtime due to the risks of sedation and to monitor for dizziness and hypotension.

References

1. Brus MJ, Solanto MV, Goldberg JF. Adult ADHD vs. Bipolar Disorder in the DSM-5 Era. J Psychiatric Pract. 2014;20(6):428-37. DOI: 10.1097/01.pra.0000456591.20622.9e
2. Salvi V, Ribuoli E, Servasi M, Orsolini L, Volpe U. ADHD and bipolar disorder in adulthood: clinical and treatment implications. Medicina. 2021;57(5):466. DOI: 10.3390/medicina57050466
3. Niitsu T, Fabbri C, Serretti A. Predictors of switch from depression to mania in bipolar disorder. J Psychiatr Res. 2015;66-67:45-53. DOI: 10.1016/j.jpsychires.2015.04.014
4. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation

trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry. 2006;163(2):232-9. DOI: 10.1176/appi.ajp.163.2.232
5. Bond DJ, Hadjipavlou G, Lam RW, McIntyre RS, Beaulieu S, Schaffer A, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry. 2012;24(1):23-37. PMID: 22303520
6. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170. DOI: 10.1111/bdi.12609
7. Reimherr FW, Gift TE, Steans TA, Reimherr ML, Rosenberg LI, Wilson M, et al. The use of brexpiprazole combined with a stimulant in adults with treatment-resistant attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2022;42(5):445-53. DOI: 10.1097/JCP.0000000000001592
8. Iwanami A, Saito K, Fujiwara M, Okutsu D, Ichikawa H. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults. J Clin Psychiatry. 2020;81(3):19m12979. DOI: 10.4088/JCP.19m12979