Weight Loss Medication Phentermine–Induced Hypomania in Bipolar Depression

Wisam Al Jumaili, MD; Nibras Al Gburi, MD; and Shailesh Jain, MD

Weight gain is common in patients with bipolar disorder.[1] Patients with bipolar disorder may gain weight due to their chronic condition or medication side effects. Obesity can exacerbate bipolar depression and limit patient compliance with treatment.[1] Phentermine was approved by the US Food and Drug Administration as a short-term antiobesity appetite suppressant medication in 1959.[1] Additionally, it was reapproved in 2013 for adults and in 2022 for adolescents after revision of its satiety profile.[2,3] Phentermine is approved as an antiobesity medication when the initial body mass index (BMI) is ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with obesity comorbidity.[1–3] Phentermine is a sympathomimetic that shows significant effect on the norepinephrine, dopamine, and serotonin neurotransmitter release and reuptake balance, similar to the amphetamine-based group of medications.[1]

Phentermine is a controlled substance per the US Drug Enforcement Administration and has abuse potential due to its high dopamine potency. It can worsen psychosis or bipolar disorder alone or in combination with antidepressants.[1,4,5] In contrast, reports are conflicting regarding an effect on unipolar depression.[1,4,5] Phentermine is contraindicated with monoamine oxidase inhibitors and under precautionary warning when combined with selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants because of its blocking effect on cytochrome P450 2C19 and risk of serotonin syndrome and/or hypertensive crisis.[6] Phentermine can cause neuropsychiatric symptoms, including insomnia, mood swings, anxiety, panic attack, irritability, increased anger, agitation, and secondary parkinsonism.[1–7] Phentermine can cause mixed features, rendering the diagnosis of potential bipolar disorder with depression a challenge.[1,7] We report a case of phentermine-induced mania/hypomania in a woman with bipolar depression who was stable on a mood stabilizer and antidepressant.

Case Report

A 40-year-old White mother of 4 with bipolar II disorder and morbid obesity (BMI = 41 kg/m^2) presented to the outpatient psychiatry clinic seeking treatment for clinical depression. She had been stable on fluoxetine and aripiprazole for over a year after several failed medication trials that included lithium and valproate. She stopped taking her medication after a 2-month hypomanic episode. She had several episodes with extreme symptoms between age 18 and 20 years but resisted hospitalization.

The patient had been prescribed phentermine 37.5 mg for obesity and had a hypomanic episode with various symptoms, including euphoric mood, low sleep, pressured speech, high energy, racing thoughts, irritability, disinhibition, elevated libido, and unsafe sexual practice. Over 2 months she had problems with her mental health, lost her job and insurance, and stopped taking her medication. The patient denied any active medical condition, use of illegal recreational substances or alcohol, psychosis, or any psychiatric family history. All laboratory values were within normal range except a hemoglobin A_{1c} level of 6.7%.

Discussion

Phentermine-induced hypomania has been documented previously; however, this is the first time we have evaluated a manic break with phentermine in a bipolar disorder patient previously stabilized with aripiprazole. The patient's Naranjo probability score was 6.[8] Patients with bipolar disorder can experience manic/hypomanic episodes when taking antidepressants or sympathomimetic agents.[1,7]

Phentermine is one of the most widely prescribed short-term (3 months) appetite suppressant antiobesity medications in adults[1] and was recently approved in combination with topiramate for adolescents as early as age 12 years.[3] While there are controversial data on the benefit of phentermine in attention-deficit/hyperactivity disorder, several cases report the connection of phentermine to psychosis, mania/hypomania, and worse depression in both sexes and with different age groups.[1,4–7] Taking phentermine with antidepressants like venlafaxine or fluoxetine can cause severe neuropsychiatric complications.[4] Phentermine overuse

can cause reversible psychosis in young patients with no psychiatric illness.[5] While the phentermine/topiramate combination has been reported to be effective for obesity with eating disorder, including binge and night eating disorder,[9] currently, there are no safety data on the long-term use of phentermine. Mania/hypomania is a common complication of stimulant use with bipolar disorder.[10] In a retrospective chart review (N = 137) of bipolar disorder patients taking mood stabilizers, Wingo et al[10] found that 40% developed hypomania after use of stimulants such as amphetamine, methylphenidate, or modafinil. In a systematic review, Corp et al[11] found a nonsignificant mood fluctuation secondary to the addition of sympathomimetic stimulant in patients with bipolar depression.

Around one-third of bipolar patients are struggling with obesity that needs treatment,[12] and primary care providers, endocrinologists, obesity specialists, and patients should be aware of the serious side effects of sympathomimetic medication in destabilizing or triggering manic/hypomanic episodes, which has a serious safety consequence.[5,9] Many people with bipolar disorder seek treatment for comorbid obesity, but some medications for obesity can trigger manic or hypomanic episodes in bipolar patients. Patients taking phentermine with or without topiramate should be counseled about possible side effects and monitored for hypomanic phases, especially in children. Close monitoring and long-term future study are needed to evaluate the safety of phentermine treatment for obesity in patients with an underlying mental disorder.

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Author Affiliations: Texas Tech University Health Science Center at Permian Basin, Odessa, Texas (Al Jumaili, Jain); Core Clinical Research Center (Al Gburi).

Corresponding Author: Wisam Al Jumaili, MD, 2301 W Michigan Ave, Midland, TX 79707 (waljumai@ttuhsc.edu).

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