Clinical Psychopharmacology and Neuroscience - Manuscript Submission

- **Manuscript ID**: CPN-21-876
- **Title**: Vortioxetine Induced Hypomania; A Case Presentation and Review of the Literature
- **Running Title**: Vortioxetine induced Hypomania
- **Article Type**: Case Report
- **KeyWords**: vortioxetine, hypomania, adverse drug event, manic episode

Vortioxetine Induced Hypomania; A Case Presentation and Review of the Literature

Abstract

Antidepressant-induced hypomania/ mania is a complex issue that can be seen in mood disorders but is not clarified. There are case reports in the literature regarding vortioxetine-induced mania and hypomania; however, there is insufficient data. Here, we aim to present a case of vortioxetine-induced hypomania in a major depressive disorder patient who previously used various antidepressants but did not experience hypomania or mania. Our case is expected to contribute to the literature.

Introduction

The antidepressant-induced hypomania/ mania (AIHM) had been a contentious issue in the major depressive disorder (MDD) process. Antidepressants are likely to cause mood instability, revealing affective episodes. The incidence of AIHM in MDD range from 3.72% to 24.4% and can occur with all antidepressants (1–4)

It is not yet understood whether AIHM occurs due to the psychopharmacological effects of drugs or patients with previously undiagnosed bipolar disorder (BD). Some studies indicate that the potential risk factors for AIHM are female gender, having a younger age onset of depression, BD history in the family, having psychosis, severe depressive symptoms with hospitalization, and psychomotor retardation (4,5).

Vortioxetine is a novel strain multimodal antidepressant that positively affects cognitive functions in elderly patients with MDD (6,7). It also causes less sexual dysfunction compared to other antidepressants (8). Selective serotonin reuptake inhibitors (SSRIs) and serotonin & noradrenaline reuptake inhibitors (SNRIs) are accepted to have a risk of hypomanic /manic switch. However, there is not enough evidence about vortioxetine-induced hypomania/ mania (2,3). Here, we aimed to present a vortioxetine-induced hypomania case, who had used various antidepressants (SSRIs and SNRIs) for recurrent depression in the past but had no hypomanic/manic shifts.

Case Presentation

The 59-year-old female patient was married and had three children. Her depressive episode firstly started when she was 32 years old. She had used various antidepressants such as escitalopram, fluoxetine, paroxetine, and duloxetine due to recurrent depressive episodes in the last 27 years. The patient had been on 40 mg fluoxetine treatment for the previous two years. Due to sexual dysfunction and cognitive complaints such as amnesia, distraction, inability to focus, fluoxetine was discontinued by gradually decreasing from 40 mg in two weeks, and vortioxetine 10 mg was started. When the patient came to the outpatient clinic 20 days later, she complained of increased speech volume, distraction, increased energy, hyperactivity, euphoria, and decreased need for sleep in the last four days. Young Mania Rating Scale (YMRS) was applied, and the score was 15. There was no psychiatric or medical illness family history. Besides, there was no history of hypo/manic episodes associated with previous antidepressant therapies. Lab tests, complete blood count (CBC), renal function tests, hepatic function tests, electrolytes, and thyroid function tests were within the normal range. There was no extra medication, other life events, or stressor factors that triggered the patient's condition. We assumed that the patient had a hypomanic shift induced by vortioxetine. Therefore, we discontinued vortioxetine treatment. We observed for two weeks without any treatment. YMRS dropped to 5. Since the patient's depressive complaints recurred, Bupropion XL 150 mg was started. The patient benefited from the treatment. She had been followed for two years and had no hypomanic/ manic shift. The written informed consent was obtained from our case for this case report.

Discussion

Antidepressant-induced hypomania/ mania means meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) hypomania/ hypomania criteria immediately after initiating antidepressants or increasing dose (9). Here, we present a case of the hypomanic switch after vortioxetine treatment. The patient had taken fluoxetine, escitalopram, paroxetine, and duloxetine in the past. However, there was no hypomanic/manic switch with these agents before.

Vortioxetine is thought to work by blocking serotonin reuptake, while it differs pharmacologically from other SSRIs. At the same time, it works by directly stimulating different receptor profiles. Vortioxetine involves several pharmacological actions: serotonin (5-HT) transporter (SERT) inhibition and partial 5-HT1B agonism, 5-HT1A agonism, and 5-HT1D, 5-HT3, 5-HT7 antagonism. Also, dopaminergic, noradrenergic, histaminergic, cholinergic, GABAergic, and glutamatergic systems can be regulated by vortioxetine (10,11). There are four case reports on this subject in the literature. One of them reported a vortioxetine-induced mania in a patient with a previous BD diagnosis (12), while the other three reported vortioxetine-induced hypomania (13,14) and mania (15,16) in unknown BD history. A study conducted with 66 MDD patients reported that treatment was discontinued in 3 patients (12%) due to a manic switch (17). Since our knowledge about this drug is limited, more studies are needed.

It is unclear whether the patient's hypomanic shift occurs in the disease's natural course or is triggered by vortioxetine. It has been reported that temporary mixed or agitated depression with antidepressants may occur (18). A mixed presentation of depressive and hypomanic symptoms may occur in the treatment of MDD patients (19). In DSM-5, the "mixed" specifier was added to the MDD, which consists of major depression based on the B criterion of BD (at least three hypomanic features) (20). Clinical features of depression with mixed features and hypomania of BD are very

similar, thus confusing (21). In our case, the patient had a euphoric mood, vitality, increased speech volume, and energy; there was no depressive symptom after vortioxetine use.

It is known that patients may develop an 'activation syndrome' in a few months of antidepressant therapy, characterized by agitation, akathisia, anxiety, insomnia, aggression, and impulsivity, suicidal thoughts and actions, hypomania/ mania (22). However, this syndrome is distinct from hypomania or mania. Euphoria and vitality seen in hypomania/ mania, as in our patient, are not seen in activation syndrome (23).

Antidepressant discontinuation syndrome is one of the subjects of exclusion. Discontinuation syndrome symptoms appear mostly in medications with a shorter half-life and rapidly occur after discontinuation. It consists of headache, dizziness, nausea-vomiting, insomnia, loss of balance, sensory disturbances, hyperarousal states, myalgia, blurry vision, loss of memory and perception, cognitive impairment, loose bowels, depression, suicidal ideas (24). Antidepressant discontinuation syndrome due to fluoxetine withdrawal was not considered in our case because fluoxetine is an antidepressant with a long half-life, and we had made a gradual dose reduction. Another reason is that the complaints of the patient did not match this syndrome. She did not have nausea, vomiting, depressive mood, suicidal thoughts, etc.

Hypomania or mania associated with rapid reduction or sudden withdrawal of antidepressant dose has been reported with SSRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Antidepressant discontinuation-related hypomanic/ manic states can be explained by increased cholinergic and noradrenergic activity (25,26). Also, decreased serotonin levels are associated with mania. As a result of the discontinuation of SSRIs, SNRIs, and MAOIs, serotonin levels may drop rapidly and cause mania (27). In this case, fluoxetine was gradually reduced and discontinued within two weeks. Besides, the patient's

hypomanic symptoms started shortly after vortioxetine initiation, and these symptoms disappeared entirely after discontinuation of it. Therefore, we believe that there was no hypomania in our case after dose reduction or complete discontinuation of AD.

In DSM-5, AIHM belongs to the category of Substance / Medication-Induced Bipolar and Related Disorder. Our patient had not hypomania/mania history with various antidepressants. Vortioxetine treatment was initiated after fluoxetine treatment which was gradually reduced and discontinued. Afterward, our patient applied again with complaints of elevated mood, hyperactivity, increased amount of speech, insomnia. There was no previous history of mental disorder. There was no acute change in cognition, disturbance of consciousness that tends to fluctuate during a day, so delirium was not considered. Laboratory tests were within normal range. With the discontinuation of vortioxetine, complaints were resolved. Vortioxetine-induced hypomania was considered because there was no drug use other than vortioxetine.

Since the AIHM seen in MDD patients impacts treatment and prognosis, the factors that may cause this condition should be recognized. In conclusion, our knowledge about Vortioxetine associated with hypomania and mania is limited, and more clarification is needed. Clinicians should be aware of vortioxetine-induced hypomania or mania.

Acknowledgments: None.

Conflict of interest: On behalf of all authors, the corresponding author states no conflict of interest.

Author's Contribution:

Conceptualization: EBT, ST. Data acquisition: EBT. Formal analysis: EBT, ST Funding: EBT, ST Supervision: ST. Writing—original draft: EBT. Writing—review & editing: EBT, ST.

References:

1. Baldessarini RJ, Faedda GL, Offidani E, Vázquez GH, Marangoni C, Serra G, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: A review. J Affect Disord. 2013;148(1):129–35.

2. Barbuti M, Pacchiarotti I, Vieta E, Azorin JM, Angst J, Bowden CL, et al. Antidepressant-induced hypomania/mania in patients with major depression: Evidence from the BRIDGE-II-MIX study. J Affect Disord. 2017;219:187–92.

3. Navarro V, Gastó C, Guarch J, Penadés R, Pintor L. Treatment and outcome of antidepressant treatment-associated hypomania in unipolar major depression: A 3-year follow-up study. J Affect Disord. 2014 Feb 1;155(1):59–64.

4. Valenti M, Pacchiarotti I, Del Mar Bonnin C, Popovic D. Risk Factors for Antidepressant-Related Switch to Mania Evolutive Bipolar Disorders View project Re-thinking therapies (twice) in bipolar proposals View project. J Clin Psychiatry. 2012;73(2):271–6.

5. Gill N, Bayes A, Parker G. A Review of Antidepressant-Associated Hypomania in Those Diagnosed with Unipolar Depression—Risk Factors, Conceptual Models, and Management. Curr Psychiatry Rep. 2020;22(4):1–8.

6. Bennabi D, Haffen E, Van Waes V. Vortioxetine for Cognitive Enhancement in Major Depression: From Animal Models to Clinical Research. Vol. 10, Frontiers in Psychiatry. Frontiers Media S.A.; 2019.

7. Atique-Ur-Rehman H, Neill JC. Cognitive dysfunction in major depression: From assessment to novel therapies. Vol. 202, Pharmacology and Therapeutics. Elsevier Inc.; 2019. p. 53–71.

8. Salagre E, Grande I, Solé B, Sanchez-Moreno J, Vieta E. Vortioxetine: A new alternative for the treatment of major depressive disorder. Vol. 11, Revista de Psiquiatria y Salud Mental. Ediciones Doyma, S.L.; 2018. p. 48–59.

9. Gill N, Bayes A, Parker G. A Review of Antidepressant-Associated Hypomania in Those Diagnosed with Unipolar Depression. Risk Factors, Conceptual Models, and Management. Vol. 22, Current Psychiatry Reports. Springer; 2020. p. 1–8.

10. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: Review of preclinical and clinical data. Vol. 145, Pharmacology and Therapeutics. Elsevier Inc.; 2015. p. 43–57.

11. Sowa-Kućma M, Pańczyszyn-Trzewik P, Misztak P, Jaeschke RR, Sendek K, Styczeń K, et al. Vortioxetine: A review of the pharmacology and clinical profile of the novel antidepressant. Vol. 69, Pharmacological Reports. Elsevier B.V.; 2017. p. 595–601.

12. Maud C. Vortioxetine in bipolar depression induces a mixed/manic switch. Australas Psychiatry. 2016;24(2):206–7.

13. Aydın EP, Dalkıran M, Özer A, Karamustafalıoğlu KO. Hypomanic switch during vortioxetine treatment: a case report. Psychiatry Clin Psychopharmacol. 2018;29(1):114–6.

14. Baldwin DS, Chrones L, Florea I, Nielsen R, Nomikos GG, Palo W, et al. The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol. 2016;30(3):242–52.

15. D'Andrea G, De Ronchi D, Giaccotto L, Albert U. Vortioxetine treatment-emergent mania in the elderly: a case report. Vol. 27, Australasian Psychiatry. SAGE Publications Inc.; 2019. p. 413.

16. Sobreira G, Oliveira J, Brissos S. Vortioxetine-induced manic mood switch in patient with previously unknown bipolar disorder. Vol. 39, Revista Brasileira de Psiquiatria. 2017. p. 86.

17. De Carlo V, Vismara M, Grancini B, Benatti B, Bosi MF, Colombo A, et al. Effectiveness, tolerability, and dropout rates of vortioxetine in comorbid depression: A naturalistic study. Hum Psychopharmacol. 2020;35(5).

18. Sani G, Vöhringer PA, Napoletano F, Holtzman NS, Dalley S, Girardi P, et al. Koukopoulos' diagnostic criteria for mixed depression: A validation study. J Affect Disord. 2014 Aug 1;164:14–8.

19. Zimmerman M. Measures of the DSM-5 mixed-features specifier of major depressive disorder. Vol. 22, CNS Spectrums. Cambridge University Press; 2017. p. 196–202.

20. Shim IH, Bahk W-M, Woo YS, Yoon B-H. Pharmacological Treatment of Major Depressive Episodes with Mixed Features: A Systematic Review. Clin Psychopharmacol Neurosci. 2018;16(4):376–82.

21. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: A farewell to mixed depression. Acta Psychiatr Scand. 2014;129(1):4–16.

22. Administration F and D. Worsening depression and suicidality in patients being treated with antidepressant medications. 2004; Available from: https://www.pogustmillrood.com/worsening-depression-suicidality-patients-treated-antidepressant-medications/

23. Harada T, Sakamoto K, Ishigooka J. Incidence and predictors of activation syndrome induced by antidepressants. Depress Anxiety. 2008;25(12):1014–9.

24. Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Ther Adv Psychopharmacol. 2020;10:2045125320980573.

25. Kwok C, Chan HN, Lim L. Antidepressant-discontinuation Mania in Two Patients with Depression. Eur Psychiatry. 2015 Mar 28;30:1591.

26. Narayan V, Haddad PM. Antidepressant discontinuation manic states: A critical review of the literature and suggested diagnostic criteria. J Psychopharmacol. 2011;25(3):306–13.

27. Shiah IS, Yatham LN. Serotonin in mania and in the mechanism of action of mood stabilizers: A review of clinical studies. Vol. 2, Bipolar Disorders. Blackwell Munksgaard; 2000. p. 77–92.