

Manic Episode as a Result of Adding Trazodone to a Patient under Escitalopram Treatment

ABSTRACT

Antidepressants with hypnotic effects can often be added to treatment for sleep problems emerging in patients receiving antidepressant treatment. One of these is trazodone, which is an antidepressant that exhibits hypnotic effect by the effect of histamine H1 receptor antagonist and 5-HT_{2A} stimulation, which is a serotonin transporter protein inhibitor and 5-HT_{2A} and 5HT_{2C} antagonist. Some antidepressants can cause mania-like mood episodes when used singly or in combination. In this case report, we discussed a manic episode that developed after including trazodone for sleep problems in the treatment of a patient with an anxiety disorder who uses escitalopram.

Keywords: Anxiety disorders, mania, trazodone

Introduction

Available data indicate a high incidence of comorbidities between sleep problems and several mental illnesses, especially mood and anxiety disorders. Sleep-related symptoms, such as deterioration of sleep quality and continuity, cause advancement and exacerbation of psychiatric disorders. Similarly, these comorbidities may aggravate the diagnosis and treatment of the disorder.¹ In clinical applications, sleep-adherent antidepressants, such as trazodone, mirtazapine, and agomelatine, are commonly used. Moreover, mood dysregulation may occur with different antidepressant combinations.²

Trazodone is a serotonin antagonist used in the treatment of depressive disorders accompanied by anxiety and sleeping disorders and a well-tolerated antidepressant from the serotonin reuptake inhibitor medication group. It can be used as additional treatment in patients with psychiatric disorders who have sleep problems as hypnotic with H1 histamine antagonist effect.^{3,4} Furthermore, it has been determined in a study that the usage of trazodone for sleep is a quarter of its usage as an antidepressant.⁵ After trazodone intake, manic episode developed in two patients with bipolar depression and one patient with unipolar depression.⁶ In contrast, although it was indicated that there might be side effects, such as serotonergic syndrome risks, when trazodone is used in combination with selective serotonin reuptake inhibitor (SSRI) and that when it is overdosed, priapism might occur; manic symptoms were not mentioned in case of SSRI intake.⁷ Although the manic mechanism of trazodone is not fully known, it is accomplished with high doses of serotonin reuptake inhibitor effect and 5HT_{2a} blockade for its antidepressant activity.³

We aimed to examine a manic episode that occurred after adding trazodone in the treatment for sleep problems in a patient with anxiety disorder who uses escitalopram.

Case Presentation

A 72-year-old female patient with a diagnosis of anxiety disorder had been receiving her treatment with 10 mg/day escitalopram for approximately two years. Approximately one week ago, she was brought to our hospital for the complaint of increase in talking, decrease in sleep, non-eating occupation with chores, constant interference in other household members, not eating, making absurd and inappropriate jokes, and wandering off topic after



Filiz İzci 

Eda Ülger 

Sinem Yolcu 

Clinic of Psychiatry, Erenköy Mental and Neurological Disease Training and Research Hospital, Istanbul, Turkey

Corresponding Author:
Filiz İzci ✉ filizizci@yahoo.com

Received: June 11, 2020

Accepted: July 17, 2020

Published Online: January 19, 2021

Cite this article as: İzci F, Ülger E, Yolcu S. Manic Episode as a Result of Adding Trazodone to a Patient under Escitalopram Treatment. *Alpha Psychiatry* 2021;22(1):67-69.



Copyright@Author(s) - Available online at alpha-psychiatry.com.
Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

adding 50 mg/day trazodone to her present treatment in the epicenter. It was acknowledged that the patient had not had a similar history and a memory problem, had been able to do chores, did not have an organic disease, and had no other regular treatment (other than escitalopram). It was noted that within two years, any hypomanic symptoms did not occur with the use of 10 mg escitalopram. In the mental status examination of the patient, her psychomotor activity had increased, her speaking speed had increased, her thought flow rate had increased, and her association of ideas tended to loosen. Refusing to eat and drink, insomnia, and hostile and irritable behavior against frustration were detected. Psychotic content and suicidal thoughts were not identified. Her young mania evaluation criteria point was 25. Her routine complete blood cell count, biochemical parameters, and thyroid hormone profile tests were normal. She was suggested to stay in the hospital with the prediagnosis of manic episode derived from drug usage and induced by trazodone. Because the patient and her relatives did not agree with inpatient treatment, her existing treatment was discontinued, and she was expected to check in daily for patient follow-up with the treatment of 10 mg/day aripiprazole and 2.5 mg/day lorazepam. Her relatives were informed about her disorder. On the 5th day of the patient's follow-up with her present treatment, it was determined that her mood was euthymic, her psychomotor activity was reduced, her sleep and appetite regulations were stable, and her associations and thought content were normal. The patient's lorazepam treatment was minimized, and she was called for a follow-up in 10 days. In addition, written consent was obtained from the patient to publish this information.

Discussion

The effects of an antidepressant on sleep have a crucial role to play in its clinical usage. For a quick recovery in sleep quality, this group of medications is indicated, especially in patients with depression who have insomnia, anxiety, agitation, and suicidal thoughts. In a study that compared the effects of trazodone on sleep in patients who are depressive with agomelatine, amitriptyline, doxepin, mianserin, and mirtazapine, it was monitored that adding low dosages of these medications that have a sedation-like characteristic to the treatment becomes a preventer against hypnotic addiction and treats agitation, anxiety, or sleep deprivation.⁸

With antidepressant usage, in addition to the possibility of inducing manic episodes, it may cause manic switches in patients with depression. Manic episodes resulting from antidepressants have been identified related to tricyclic antidepressants, monoamine oxidase inhibitors, SSRI, nefazodone, and mirtazapine.⁹ Similar to our patient, manic episodes may occur with antidepressants along with other groups of antidepressants. Accordingly, manic switches have been

detected with a combination of SSRI and mirtazapine, which has a hypnotic effect and are used with the purpose of toneup.¹⁰ In another similar phenomenon, a maniac case has been reported in the case of a combination of fluoxetine and mirtazapine.⁹

In our patient, manic episode was monitored after the addition of trazodone to the treatment of the patient using escitalopram who had an anxiety disorder and showed no kinds of mood episodes previously. It is believed that the hypnotic effect of trazodone is revealed under the influence of 5-HT_{2A} and H₁ histamine antagonist.¹¹ Moreover, it is indicated that trazodone promotes sleep continuity and slow-wave sleep but has no impact on rapid-eye-movement sleep. It has been observed that trazodone induced manic switches in a few cases so far.⁸ In addition, the mania induced by trazodone occurred at 50-400 mg/day range. This is a low risk for switch to mania during treatment with sleep-promoting antidepressants.¹² In our patient, manic episode was developed after 1 week of treatment with 50 mg/day trazodone. In the instance of mania phenomenon developing with a combination of SSRI and trazodone, it has been indicated that trazodone induced mania by increasing the serum concentration of sertraline.²

Manic switches were observed while using antidepressants as monotherapy in patients who are bipolar in the clinic.¹³ In particular, manic shifts have been shown to be more associated with tricyclic antidepressants and specific serotonin and noradrenaline reuptake inhibitors. Although some possible mechanisms have been proposed, the exact mechanisms for mood swings are still uncertain.^{14,15}

In a study in which trazodone, mirtazapine, and agomelatine were used in low doses for their hypnotic effects, a switch was only observed in patients with the risk of manic switch. It was indicated that low doses of trazodone and mirtazapine should be safe and that they can be used as an important alternative to hypnotics in sleep deprivation treatment. It has been mentioned that these antidepressants can confidently be used when taken with a mood stabilizer.¹² Moreover, despite having no bipolar history and no mood episodes while taking escitalopram regularly for two years, it must not be ignored that additional sleep deprivation might be the beginning of a manic stage. However, in our phenomenon, no risk factor causing a tendency to bipolarity was defined. In addition, after stopping trazodone, the patient's manic symptoms improved. Therefore, we believe that mania was induced after the usage of trazodone.

In conclusion, even in patients without bipolar history and tendency, it must not be neglected that additional antidepressants with the purpose of taking advantage of their hypnotic effects or using them as a tone-up might cause manic switches during another antidepressant treatment. It must not be ignored that an antidepressant with a hypnotic effect, such as trazodone, which is included in the treatment for sleep problems, might induce a manic episode. Potential risks in terms of manic induction must be deeply evaluated.

MAIN POINTS

- *Escitalopram and trazodone combination therapy can increase the risk of inducing mania.*
- *If a second antidepressant is added to the treatment in individuals without a history of bipolar disorder, awareness of manic shift will be important.*
- *The use of trazodone in elderly individuals creates a risk of inducing mania or hypomania, even at low doses, due to decreased elimination rates.*

Informed Consent: Informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.İ.; Design - F.İ.; Supervision - F.İ.; Resources - F.İ.; Materials - E.Ü., S.Y.; Data Collection and/or Processing - E.Ü., S.Y.; Analysis and/or Interpretation - E.Ü., S.Y.; Literature Search - F.İ.; Writing Manuscript - F.İ.; Critical Review - F.İ., E.Ü., S.Y.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Satetia MJ. Update on sleep and psychiatric disorders. *Chest*. 2009;135(5):1370-1379. [\[Crossref\]](#)
2. Hu J, Lai J, Zheng H, et al. Fan the flame: trazo-done-induced mania in a unipolar depressed patient with stable sertraline treatment. *Neuropsychiatr Dis Treat*. 2017;13:2251-2254. [\[Crossref\]](#)
3. Stahl SM. Mechanism of action of trazodone: a multi-functional drug. *CNS Spectr*. 2009;14(10):536-546. [\[Crossref\]](#)
4. Fagiolini A, Comandini A, Dell'Osso MC, et al. Rediscovering trazodone for the treatment of major depressive disorder. *CNS Drugs*. 2012;26(12):1033-1049. [\[Crossref\]](#)
5. Wong J, Motulsky A, Abrahamowicz M, et al. Off label indications for anti-depressants in primary care: descriptive study of pre-scriptions from an indication based electronic prescribing system. *BMJ*. 2017;356:j603. [\[Crossref\]](#)
6. Knobler HY, Itzhaky S, Emanuel D, et al. Trazodone-induced mania. *Br J Psychiatry*. 1986;149:787-789. [\[Crossref\]](#)
7. Prapotnik M, Waschgler R, König P, et al. Therapeutic drug monitoring of trazodone: are there pharmacokinetic interactions involving citalopram and fluoxetine? *Int J Clin Pharmacol Ther*. 2004;42(2):120-124. [\[Crossref\]](#)
8. Wichniak A, Wierzbicka A. The effects of antidepressants on sleep in depressed patients with particular reference to trazodone in comparison to agomelatine, amitriptyline, doxepin, mianserine and mirtazapine. *Pol Merkur Lekarski*. 2011;31(181):65-70.
9. Bernardo NG. Mania associated with mirtazapine augmentation of fluoxetine. *Depress Anxiety*. 2002;15(1):46-47. [\[Crossref\]](#)
10. Liu CC, Liang KY, Liao SC. Antidepressant-associated mania: soon after switch from fluoxetine to mirtazapine in an elderly woman with mixed depressive features. *J Psychopharmacol*. 2009;23(2):220-222. [\[Crossref\]](#)
11. Wichniak A, Wierzbicka A, Jernajczyk W. Sleep and antidepressant treatment. *Curr Pharm Des*. 2012;18(36):5802-5817. [\[Crossref\]](#)
12. Wichniak A, Jarkiewicz M, Okruszek Ł, et al. Low risk for switch to mania during treatment with sleep promoting antidepressants. *Pharmacopsychiatry*. 2015;48(3):83-88. [\[Crossref\]](#)
13. Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. *J Affect Disord*. 2013;148(1):129-135. [\[Crossref\]](#)
14. Koszewska I, Rybakowski JK. Antidepressant-induced mood conversions in bipolar disorder: a retrospective study of tricyclic versus non-tricyclic antidepressant drugs. *Neuropsychobiology*. 2009;59(1):12-16. [\[Crossref\]](#)
15. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry*. 2006;189(2):124-131. [\[Crossref\]](#)