

Tramadol-associated mania: A case report

Jamaluddin Nimah, MD; Alexander Chen, BA; Kelly N. Gable, PharmD, BCPP; Alan R. Felthous, MD

ARTICLE INFO

Keywords:
tramadol
bipolar disorder
mania
adverse drug effects

DOI:10.5055/jom.2017.0386
© 2017 Journal of Opioid Management,
All Rights Reserved.

ABSTRACT

A variety of medications, most notably tricyclic antidepressants, and other antidepressants including venlafaxine have been reported to have triggered manic episodes in patients with bipolar disorder. The synthetic opioid tramadol has also been associated with mania activation. This report describes an unusual case of tramadol-associated mania in a patient without a charted diagnosis of bipolar disorder. However, she had a history of two prior episodes of mania following administration of tramadol that were also believed to be related to medication-induced mood disorder rather than underlying bipolar disorder. We hypothesize that tramadol-associated mania may have an underlying mechanism involving monoamine neurotransmission and increased oxidative stress.

INTRODUCTION

Medication-induced manic episodes have been of increasing concern in recent years. Studies and case reports have suggested mood-elevating effects of various medications including atypical antipsychotics, antidepressants, and recently various analgesic agents.¹⁻³ Tramadol is a centrally acting synthetic opioid that binds weakly to μ -opioid receptors. Case reports of tramadol-associated mania in patients with a pre-existing diagnosis of bipolar disorder exist.⁴⁻⁵ Here, we report an episode of tramadol-associated mania in a patient with no previous diagnosis of bipolar disorder.

CASE PRESENTATION

A 61-year-old African American female with no previous psychiatric history presented to the emergency department (ED) in a manic episode and was subsequently admitted to the psychiatric inpatient unit. The patient was prescribed tramadol 50 mg 4 times a day for headache pain associated with a fall that occurred 1 week prior to initiating the pain medication. She received no further workup from her primary care physician. Manic symptoms began approximately 4 days after her prescription for tramadol was initiated. She presented to the ED 2 weeks after initiating treatment, reporting manic symptoms

and suicidal thoughts. The patient presented with markedly decreased need for sleep, increased energy, euphoric mood, pressured speech, and aggressive behavior. The patient also described acute disorganization and verbal aggression toward family members. The patient began drinking alcohol excessively, and was found disheveled and unclothed in the lobby of her apartment building during the day. During her stay on the inpatient psychiatric unit, she displayed a decreased need for sleep, euphoric mood, and tangential thought process with episodes of inappropriate laughter. She also reported vivid nightmares. Further investigation revealed that this was this patient's third medication-associated manic episode. Approximately one and half years prior to her current hospitalization, the patient experienced similar symptoms after taking tramadol for the first time for lower back pain. The patient's daughter, who describes her mother as a pleasant, calm, and collected woman, reported that tramadol use correlated with a decreased need for sleep, excessive energy, and verbal aggression in her mother. The patient discontinued the treatment due to memory impairment and disorganization, causing her to misplace items. Upon discontinuation of tramadol, she regained her ability to sleep and became euthymic within 2 weeks.

The patient's primary care physician again prescribed tramadol for back pain 5 months prior to her

current admission. She once again described experiencing a decreased need for sleep and “happier” than usual mood. She reported feeling “ups” while taking the medication and “downs” a few days after stopping the tramadol. She discontinued the medication with a similar report of memory loss and reported feeling better within 2 weeks. The patient and her daughter report no episodes of elevated mood or decreased need for sleep when she is not taking tramadol.

Upon admission to the psychiatric unit during her most recent manic event, the patient was administered haloperidol 5 mg and lorazepam 2 mg due to agitation. She was subsequently initiated on risperidone 1 mg twice daily. This was increased to 2 mg twice daily after 2 days. The patient was discharged from the hospital displaying euthymia after 5 days of treatment with risperidone. She was evaluated by outpatient psychiatry 2 weeks after hospital discharge and displayed no signs or symptoms of mania.

DISCUSSION

The temporal relationship between the use of tramadol and the three manic episodes in this patient suggests a possible cause-effect link between the two. Previous studies on this topic include a retrospective study that showed nine of 33 previously diagnosed patients with bipolar disorder who took opioid analgesics experienced a significant hypomanic/manic reaction, including one patient who was taking tramadol.³ Two other case reports have described patients with a diagnosis of bipolar disorder who were not taking a mood stabilizer as having a manic episode within 1 week of starting tramadol.^{4,5} The emergence of manic symptoms in our case subject could suggest that tramadol has the potential to induce manic symptoms in patients who have undiagnosed bipolar disorder, subclinical bipolar disorder, or at higher risk of developing bipolar disorder.

Tramadol is a synthetic codeine analog thought to have analgesic effects as a weak μ -opioid agonist as well as an inhibitor of serotonin and norepinephrine uptake.⁶ μ is one of three opioid receptors, the others being δ and κ , implicated in the pharmacology of pain management. Prepared as a racemic mixture, the (+)-enantiomer binds to the serotonin receptor and inhibits its uptake, whereas the (-)-enantiomer inhibits norepinephrine uptake and stimulates α_2 adrenergic receptors.⁷ The racemic mixture is a more effective analgesic than either enantiomer alone.⁶

A possible mechanism for the emergence of manic symptoms could involve tramadol's effect in enhancing dopamine release via μ -opioid receptor mechanisms,⁸ inhibiting serotonin reuptake,⁹ and inhibiting norepinephrine reuptake.⁸ Contemporary models of bipolar disorder theorize that excessive dopaminergic, glutamatergic, norepinephrine, and possibly serotonergic signaling are significant components of disease pathogenesis.¹⁰⁻¹⁴ Certain postsynaptic receptors including monoamine (D_2 -like,¹⁵ 5-HT_{2A/2C},¹⁶ β_2 ¹⁷), N-methyl-D-aspartate,¹⁸ and astrocytic receptors (TNF α ,¹⁹ IL-1 β ²⁰) have been demonstrated to be coupled to phospholipase A₂ (PLA₂) and glycogen synthase kinase-3 (GSK3) activation.²¹ PLA₂ metabolizes polyunsaturated fatty acids (PUFAs) found in cellular membranes into eicosanoid metabolites. Arachidonic acid (AA) is an omega-6 PUFA that is an integral part of neuronal cell membranes and found in higher ratios in bipolar patients.²¹ When it is metabolized by PLA₂, AA is turned into proinflammatory eicosanoid metabolites.²² GSK3 is a serine/threonine protein kinase that activates proapoptotic signaling pathways by phosphorylating various transcription factors involved in regulating apoptosis.²³ These processes lead to increased apoptosis,²⁴ decreased neuronal plasticity, cortical atrophy^{25,26}, and ventricular atrophy,²⁷ resulting in the cognitive deficits and mood symptoms observed in bipolar disorder.²⁸ Increased monoamine signaling from mania pathology and medication mechanisms could result in the activation of some of the PLA₂ and GSK3 coupled receptors, leading to the production of a net proinflammatory and proapoptotic state that cause neuronal damage and mania symptom progression. Tramadol's induction of manic symptoms could then potentially be explained in part by the drug's effect in increasing the activation of PLA₂ and GSK3 through coupled monoamine receptors. Additionally, tramadol has been shown to increase brain oxidative stress that could augment the neuronal apoptosis,²⁹ further contributing to symptom progression. Tramadol's monoamine activity profile is similar to some antidepressants³⁰ and antidepressant-associated switch processes in bipolar disorder have been similarly attributed to activation of monoamine receptors.³¹⁻³³ Tricyclic antidepressants,^{34,35} monoamine oxidase inhibitors,^{35,36} and serotonin and norepinephrine reuptake inhibitors³⁷ were associated with greater conversion rates from depression to mania compared to selective serotonin reuptake inhibitors, possibly due to the increased range of monoamine receptors they activate. The hypothesis of monoamine receptor

coupled signaling being significant mechanisms of tramadol and antidepressant-associated mania is further supported by the protective effects of mood stabilizers like lithium and valproic acid. Evidence from current literature suggests that GSK3 inhibition is a critical component of the mechanism in which lithium and valproic acid exert their mood stabilizing and neuroprotective effects.³⁸ This could explain the ability of mood stabilizers to reduce switch to mania when patients with bipolar disorder are treated with a combination of mood stabilizer and antidepressant compared to antidepressant alone.³⁹ Lithium and valproic acid would, in theory, allow antidepressants to exert their efficacy in treating depression while inhibiting downstream inflammatory and apoptotic pathways that are associated with mania development.

No genetic testing was performed on this subject but future studies might consider genetic testing to establish a more complete understanding of the mechanism behind tramadol-associated mania. The molecular genetics of bipolar disorder are thought to be mediated through multiple small-effect genes rather than large-effect genes, even though it has a strong familial genetic link. Genetic contributions may include the serotonin transporter gene 5HTTLPR, but with other genes and mechanisms potentially involved, genetic testing was not considered practical for effective short-term hospital treatment of this patient.⁴⁰ Nonetheless the short allele of the serotonin transporter gene could, hypothetically, contribute to vulnerability to mania from tramadol and further exploration in future research may be warranted. Additionally, CYP2D6 and CYP3A4 testing may also be considered as these are some of the primary pathways in which tramadol undergoes metabolism and becomes conjugated before renal excretion.⁶ Phenotypical consequences could include a variety of effects such as an increased risk of toxicity and unanticipated side effects like manic symptoms.⁴¹

Our case report adds to the evidence of a relationship between tramadol and psychiatric manifestations. It also calls for the need for additional evidence to further clarify the etiology behind mania and how serotonergic and noradrenergic agents such as antidepressants and tramadol produce such effects.

CONCLUSIONS

To our knowledge, this is the first report of multiple repeatable episodes of tramadol, a synthetic opioid analgesic with central serotonergic and

norepinephrine activity, being associated with manifestation of mania in an individual without a prior diagnosis of bipolar disorder. The development of mania in this individual from tramadol administration was a repeatable phenomenon as she had two similar episodes in the past. This case suggests that caution should be exercised not only when prescribing tramadol for a patient with known bipolar disorder, as other reports have indicated, but also in patients without a bipolar disorder diagnosis as tramadol may precipitate psychiatric adverse effects in someone with no prior psychiatric history. Groups at risk for these tramadol-associated symptoms could include patients with undiagnosed bipolar disorder, subclinical bipolar disorder, or at high risk for bipolar disorder. Further research is necessary to better elucidate the mechanism behind tramadol-associated mania, biomarkers or identifiable risk factors for stratifying tramadol-associated mania risk in various patient populations, and adjunctive therapies that may decrease rates of tramadol-associated mania.

Jamaluddin Nimab, MD, Department of Medicine, University of California at Los Angeles, Los Angeles, California.

Alexander Chen, BA, Department of Psychiatry, School of Medicine, Saint Louis University, St. Louis, Missouri.

Kelly N. Gable, PharmD, BCPP, School of Pharmacy, Southern Illinois University at Edwardsville, Edwardsville, Illinois.

Alan R. Felthous, MD, Forensic Psychiatry Division, Department of Psychiatry, School of Medicine, Saint Louis University, St. Louis, Missouri.

REFERENCES

1. Rachid F, Gilles B, Bondolfi G, et al.: Possible induction of mania or hypomania by atypical antipsychotics: An updated review of reported cases. *J Clin Psychiatry*. 2004; 65: 1537-1545.
2. Saatcioglu O, Erim R, Nesrin T, et al.: Antidepressant-associated mania or hypomania: A comparison with personality and bipolarity features of bipolar disorder. *J Affective Disorders*. 2011; 134: 85-90.
3. Schaffer CB, Nordahl TE, Schaffer LC, et al.: Mood-elevating effects of opioid analgesics in patients with bipolar disorder. *J Neuropsychiatry Clin Neurosci*. 2007; 19(4): 449-452.
4. Watts B, Grady T: Tramadol-induced mania. *Am J Psychiatry*. 1997; 154: 1624.
5. Oronsky BT, Martin R: Intolerance to tramadol may herald bipolar disease. *Internet J Family Practice*. 2008; 6(2): 4.
6. Yaksh TL, Wallace MS: Opioids, analgesia and pain management. In Brunton LL, Chabner BA, Knollmann BC (eds.): *Goodman & Gilman's Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw Hill Medical, 2011: 481-564.

7. Lewis KS, Han NH: Tramadol. A new centrally acting analgesic. *Am J Health Syst Pharm.* 1997; 54: 643-652.
8. Frink MC, Hennies HH, Englberger W, et al.: Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung.* 1996; 46(11): 1029-1036.
9. Reimann W, Schneider F: Induction of 5-hydroxytryptamine release by tramadol, fenfluramine and reserpine. *Eur J Pharmacol.* 1998; 349(2-3): 199-203.
10. Rao JS, Harry GJ, Rapoport SI, et al.: Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol Psychiatry.* 2010; 15(4): 384-392.
11. Post RM, Jimerson DC, Bunney WE Jr, et al.: Dopamine and mania: Behavioral and biochemical effects of the dopamine receptor blocker pimozide. *Psychopharmacology.* 1980; 67(3): 297-305.
12. Bunney WE Jr, Garland-Bunney BL: Mechanisms of action of lithium in affective illness: Basic and clinical implications. In Meltzer HY (ed.) *Psychopharmacology: The Third Generation of Progress.* New York: Raven Press, 1987: 553-565.
13. Redmond DE Jr, Katz MM, Maas JW, et al.: Cerebrospinal fluid amine metabolites. Relationships with behavioral measurements in depressed, manic, and healthy control subjects. *Arch Gen Psychiatry.* 1986; 43(10): 938-947.
14. Tolmunen T, Joensuu M, Saarinen PI, et al.: Elevated mid-brain serotonin transporter availability in mixed mania: A case report. *BMC Psychiatry.* 2004; 4: 27.
15. Vial D, Piomelli D: Dopamine D2 receptors potentiate arachidonate release via activation of cytosolic, arachidonate-specific phospholipase A2. *J Neurochem.* 1995; 64(6): 2765-2772.
16. Felder CC, Kanterman RY, Ma AL, et al.: Serotonin stimulates phospholipase A2 and the release of arachidonic acid in hippocampal neurons by a type 2 serotonin receptor that is independent of inositolphospholipid hydrolysis. *Proc Natl Acad Sci USA.* 1990; 87(6): 2187-2191.
17. Pavoine C, Magne S, Sauvadet A, et al.: Evidence for a beta2-adrenergic/arachidonic acid pathway in ventricular cardiomyocytes. Regulation by the beta1-adrenergic/camp pathway. *J Biol Chem.* 1999; 274(2): 628-637.
18. Basselin M, Chang L, Bell JM, et al.: Chronic lithium chloride administration attenuates brain NMDA receptor-initiated signaling via arachidonic acid in unanesthetized rats. *Neuropsychopharmacology.* 2006; 31(8): 1659-1674.
19. Lüschen S, Adam D, Ussat S, et al.: Activation of ERK1/2 and cPLA(2) by the p55 TNF receptor occurs independently of FAN. *Biochem Biophys Res Commun.* 2000; 274(2): 506-512.
20. Dinarello CA: Interleukin-1. *Ann N Y Acad Sci.* 1988; 546: 122-132.
21. Jope RS, Roh M: Glycogen Synthase Kinase-3 (GSK3) in Psychiatric Diseases and Therapeutic Interventions. *Curr Drug Targets.* 2006; 7(11): 1421-1434.
22. Sobczak S, Honig A, Christophe A, et al.: Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. *Psychol Med.* 2004; 34(1): 103-112.
23. Jope RS, Johnson GV: The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci.* 2004; 29(2): 95-102.
24. Kim HW, Rapoport SI, Rao JS: Altered expression of apoptotic factors and synaptic markers in postmortem brain from bipolar disorder patients. *Neurobiol Dis.* 2010; 37(3): 596-603.
25. Coyle TR, Kochunov P, Patel RD, et al.: Cortical sulci and bipolar disorder. *Neuroreport.* 2006; 17(6): 1739-1742.
26. Lyoo IK, Sung YH, Dager SR, et al.: Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disord.* 2006; 8(1): 65-74.
27. Strakowski SM, DelBello MP, Zimmerman ME, et al.: Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. *Am J Psychiatry.* 2002; 159(11): 1841-1847.
28. Osuji IJ, Cullum CM: Cognition in bipolar disorder. *Psychiatr Clin North Am.* 2005; 28(2): 427-441.
29. Ghoneim FM, Khalaf HA, Elsamanoudy AZ, et al.: Effect of chronic usage of tramadol on motor cerebral cortex and testicular tissues of adult male albino rats and the effect of its withdrawal: Histological, immunohistochemical and biochemical study. *Int J Clin Exp Pathol.* 2014; 7(11): 7323-7341.
30. Wehr TA, Goodwin FK: Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry.* 1987; 144(11): 1403-1411.
31. Bunney WE Jr, Murphy DL, Goodwin FK, et al.: The switch process from depression to mania: relationship to drugs which alter brain amines. *Lancet.* 1970; 1(7655): 1022-1027.
32. Bunney WE Jr, Goodwin FK, Murphy DL, et al.: The "switch process" in manic-depressive illness. II. Relationship to catecholamines, REM sleep, and drugs. *Arch Gen Psychiatry.* 1972; 27(3): 304-309.
33. Mundo E, Walker M, Cate T, et al.: The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: Preliminary findings. *Arch Gen Psychiatry.* 2001; 58(6): 539-544.
34. Nemeroff CB, Evans DL, Gyulai L, et al.: Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry.* 2001; 158(6): 906-912.
35. Cohn JB, Collins G, Ashbrook E, et al.: A comparison of fluoxetine imipramine and placebo in patients with bipolar depressive disorder. *Int Clin Psychopharmacol.* 1989; 4(4): 313-322.
36. Himmelhoch JM, Thase ME, Mallinger AG, et al.: Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry.* 1991; 148(7): 910-916.
37. Vieta E, Martinez-Aran A, Goikolea JM, et al.: A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. *J Clin Psychiatry.* 2002; 63(6): 508-512.
38. Beaulieu JM, Sotnikova TD, Yao WD, et al.: Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci USA.* 2004; 101(14): 5099-5104.
39. Viktorin A, Lichtenstein P, Thase ME, et al.: The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. *Am J Psychiatry.* 2014; 171(10): 1067-1073.
40. Ketter TA, Chang KD: Bipolar and related disorders. In Hales RE, Yudofsky SC, Weiss L (eds.): *Textbook of Psychiatry.* 6th ed. Washington, DC: American Psychiatric Publishing, 2014: pp. 311-352.
41. Rellin MV, Giacomini KM: Pharmacogenetics. In Brunton LL, Chabner BA, Knollmann BC (eds.): *Goodman and Gilman's Pharmacological Basis of Therapeutics.* 12th ed. New York: McGraw Hill Medical, 2011: pp. 145-168.