HHS Public Access

Author manuscript

Psychosomatics. Author manuscript; available in PMC 2017 July 10.

Published in final edited form as:

Psychosomatics. 2014 ; 55(1): 98–100. doi:10.1016/j.psym.2013.06.008.

Acute Mania Associated with Levetiracetam Treatment

Eliza M Park, MD[1], **Jordan A Holmes, MD**[2], and **Katherine E Reeder-Hayes, MD, MBA**[2]

[1]Department of Psychiatry, University of North Carolina, Chapel Hill, NC

[2]Department of Medicine, University of North Carolina, Chapel Hill, NC

Introduction

Levetiracetam is a novel antiepileptic used for treatment of partial and generalized epilepsy. Its mechanism of action is unclear though it is thought to bind to a presynaptic vesicle protein that ultimately reduces the synaptic release of glutamate, impeding conduction of epileptic action potentials across the synapse.[1] Levetiracetam is frequently used due to its ease of oral administration, excellent bioavailability and low rate of drug interactions as it is not metabolized by the liver or bound significantly to serum proteins.[2, 3] Adverse cognitive effects are atypical; however, central nervous system adverse effects are relatively common, with behavioral symptoms occurring in up to 16% of patients in randomized controlled trials.[4] Frequently reported behavioral symptoms include depression, hostility, agitation, emotional lability, anger, nervousness, and depersonalization. Non-behavioral central nervous system effects include sedation, headache, and asthenia.[5] Psychosis is infrequently associated with levetiracetam, occurring in approximately 1% of patients, but well described in multiple case reports.[6, 7] Researchers have explored the use of levetiracetam as a mood stabilizer for treatment of both depressive and manic phases of bipolar disorder with mixed results.[8–10] Despite the known association between levetiracetam and aggression and irritability, there are no reported cases in the literature of levetiracetam precipitating manic symptoms. In the case we report, we describe the acute onset of mania following levetiracetam therapy in a woman with no prior history of mania or hypomania.

Case report

Ms. B was a 58-year-old woman with stage IV inflammatory breast cancer and a remote history of postpartum depression who was admitted to the cancer hospital for evaluation of brief stuttering spells. Upon admission to the hospital, her vital signs were unremarkable with the exception of tachycardia (pulse 120). She did not exhibit any abnormal movements

Address and phone number for correspondence and reprint requests: Eliza M Park, MD, University of North Carolina, Department of Psychiatry, Comprehensive Cancer Support Program, Campus Box 7305, Chapel Hill, NC 27599, Phone: (919) 966-4772, Fax: (919) 966-6735, leeza_park@med.unc.edu.

Disclosures: The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.

or tremor and she was no longer experiencing stuttering spells. A comprehensive neurologic assessment, including neurology consultation, brain MRI with and without contrast, laboratory work-up and video electroencephalogram did not reveal any explanatory etiology for her symptoms. Her hospital course was unremarkable and she was discharged home with a new prescription for levetiracetam 750mg twice daily as prophylaxis for possible seizures. She did not receive any doses of steroids, antihistamines, or antidepressants during her hospital stay. Two weeks prior, she had received oral dexamethasone as an anti-emetic without incident. She continued to take lorazepam 1mg at night as previously prescribed. She was originally provided this medication three months earlier for chemotherapy-associated nausea.

Two weeks later, she presented to the outpatient oncology clinic with symptoms of acute mania. During the previous one and a half weeks, she reported racing thoughts, erratic and impulsive behavior, decreased need for sleep (requiring less than 3 hours of sleep per night), and emotional lability with irritability. She was paranoid and had called the police to her home due to her belief that her son was trying to harm her and wanted her dead. She was verbally aggressive with strangers and was escorted from local stores by security. She gave away all of her available spending money to strangers. Upon examination, her speech was rapid and hyper-verbal. Her affect was expansive and she described her mood as “great.” She was restless and unable to sit for longer than a few minutes. Her thought process was tangential with loosened associations. She denied suicidality, homicidality or abnormal perceptions, though she continued to express paranoia toward her son and desire to pursue large purchases such as a vacation home. She denied any misuse of alcohol or illicit substances during this period. Drugs of abuse were not tested though Ms. B had no previous history of substance misuse.

Ms. B and her adult son indicated that she had discontinued the levetiracetam three days prior to her evaluation due to concern that it precipitated her symptoms. Both the patient and her son confirmed that she had no prior history of mania or hypomania prior to starting levetiracetam therapy. There was no known family history of bipolar illness.

Due to the severity of her symptoms, her levetiracetam was held and scheduled daytime lorazepam 1mg daily and olanzapine 5mg at night were added to her medication regimen. She continued her previously prescribed nighttime lorazepam and no additional medications were used for management of insomnia. Within two weeks, her behavior had improved and she resumed her scheduled chemotherapy. During the following month, her olanzapine was discontinued and lorazepam tapered to her previous dosage without incident. She was periodically followed by the psycho-oncology service for six subsequent months and no further episodes of mania or hypomania were noted.

Discussion

Levetiracetam is an antiepileptic with known neuropsychiatric adverse effects. To our knowledge, this is the first known report of levetiracetam-induced mania. While the mechanism of this adverse effect remains unknown, the temporal relationship between emergence and subsequent resolution of symptoms with initiation and cessation of treatment

with her antiepileptic medication is compelling. Notably, she was not treated with concomitant medications like steroids that can precipitate symptoms of mania and it appears unlikely that her psychiatric symptoms were due to primary seizure etiology given the negative neurologic work-up.

In general, psychiatric disorders in patients with epilepsy are common and multifactorial in origin. Patients with history of psychiatric disorders may demonstrate an increased susceptibility to the behavioral adverse effects of antiepileptics suggesting an underlying vulnerability to antiepileptic central nervous system toxicity.[4, 11] However, the development of manic symptoms with antiepileptic treatment is unusual. Many, if not most, antiepileptic medications are also used for their mood-stabilizing properties. There are several reports that have specifically used levetiracetam for treatment of mania.[12, 13] Levetiracetam, though, is an antiepileptic with unique mechanism of action and known association with aggression, hostility, and psychosis. The cause of these behavioral effects with levetiracetam remains unknown.

In one prospective study of 553 patients treated with levetiracetam, behavioral abnormalities were the most frequently cited reason for premature medication discontinuation.[14] Known risk factors for the development of behavioral disturbance with levetiracetam include rapid dosage titration, having a learning disability, prior psychiatric history or symptomatic generalized epilepsy.[14] Other studies on the relationship between dosage and risk of aggression with levetiracetam are conflicting.[15] In the case we have presented, the rapid dosage escalation of levetiracetam as well as her previous psychiatric history may have contributed to her symptomatology.

More research is needed on the mechanisms of behavioral disorders with levetiracetam as well as more specific predictors of which patient populations are most susceptible to these symptoms. Prospective studies of levetiracetam that use formal psychiatric assessments and measurement of irritability and aggression would help with elucidating this complex relationship. It is possible that these two symptoms may be reflective of an underlying hypomania, mixed mania, or acute mania in patients who develop levetiracetam associated adverse effects.

Given the increasingly widespread use of this newer anti-epileptic,[16, 17] clinicians should consider close monitoring of patients for treatment-emergent mood and psychotic symptoms, including the possibility of mania. In addition, slower titration rates of levetiracetam, particularly in patients with previous psychiatric histories, should be considered.

References

1. Rogawski MA. Diverse mechanisms of antiepileptic drugs in the development pipeline. Epilepsy Res. 2006; 69(3):273–94. [PubMed: 16621450]
2. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacol Ther. 2000; 85(2):77–85. [PubMed: 10722121]
3. Patsalos PN, Ghattaura S, Ratnaraj N, Sander JW. In situ metabolism of levetiracetam in blood of patients with epilepsy. Epilepsia. 2006; 47(11):1818–21. [PubMed: 17116020]

4. Cramer JA, De Rue K, Devinsky O, Edrich P, Trimble MR. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. Epilepsy & behavior : E&B. 2003; 4(2):124–32.
5. Lyseng-Williamson KA. Levetiracetam: a review of its use in epilepsy. Drugs. 2011; 71(4):489–514. [PubMed: 21395360]
6. Youroukos S, Lazopoulou D, Michelakou D, Karagianni J. Acute psychosis associated with levetiracetam. Epileptic disorders : international epilepsy journal with videotape. 2003; 5(2):117–9. [PubMed: 12875956]
7. Aggarwal A, Sharma DD, Sharma RC, Kumar R. Probable psychosis associated with levetiracetam: a case report. Progress in neuro-psychopharmacology & biological psychiatry. 2011; 35(1):274–5. [PubMed: 20854866]
8. Saricicek A, Maloney K, Muralidharan A, Ruf B, Blumberg HP, Sanacora G, et al. Levetiracetam in the management of bipolar depression: a randomized, double-blind, placebo-controlled trial. The Journal of clinical psychiatry. 2011; 72(6):744–50. [PubMed: 21034692]
9. Kruger S, Sarkar R, Pietsch R, Hasenclever D, Braunig P. Levetiracetam as monotherapy or add-on to valproate in the treatment of acute mania-a randomized open-label study. Psychopharmacology. 2008; 198(2):297–9. [PubMed: 18369598]
10. Kaufman KR. Monotherapy treatment of bipolar disorder with levetiracetam. Epilepsy & behavior: E&B. 2004; 5(6):1017–20.
11. Kanner AM. Can antiepileptic drugs unmask a susceptibility to psychiatric disorders? Nature clinical practice Neurology. 2009; 5(3):132–3.
12. Grunze H, Langosch J, Born C, Schaub G, Walden J. Levetiracetam in the treatment of acute mania: an open add-on study with an on-off-on design. The Journal of clinical psychiatry. 2003; 64(7):781–4. [PubMed: 12934978]
13. Goldberg JF, Burdick KE. Levetiracetam for acute mania. Am J Psychiatry. 2002; 159(1):148.
14. White JR, Walczak TS, Leppik IE, Rarick J, Tran T, Beniak TE, et al. Discontinuation of levetiracetam because of behavioral side effects: a case-control study. Neurology. 2003; 61(9): 1218–21. [PubMed: 14610123]
15. Dinkelacker V, Dietl T, Widman G, Lengler U, Elger CE. Aggressive behavior of epilepsy patients in the course of levetiracetam add-on therapy: report of 33 mild to severe cases. Epilepsy & behavior : E&B. 2003; 4(5):537–47.
16. Hollingworth SA, Eadie MJ. Antiepileptic drugs in Australia: 2002–2007. Pharmacoepidemiol Drug Saf. 2010; 19(1):82–9. [PubMed: 19802824]
17. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993–2008: cohort study using the General Practice Research Database. Seizure. 2012; 21(6):466–70. [PubMed: 22608976]