

Tramadol Induced Rapid-Cycling Bipolar Disorder

Cheryl Willsie MD; Joel Lamoure RPh, DD, FASCP;
Volker Hocke MD; Jessica Stovel RPh, HonBSc, BScPhm, ACPR

Rationale

- Depression is one of the most commonly reported and treated disorders in psychiatry
- Many mental health patients also suffer from concurrent chronic pain requiring pharmacological treatment and may be at increased risk of addiction
- Tramacet** (*acetaminophen 325 mg/tramadol 37.5 mg*) is used to treat acute and chronic pain with less potential for physiological and psychological dependence
- Tramadol** is an atypical, centrally-acting opioid analgesic with highest affinity for the μ -opioid receptor
 - Also weakly inhibits the reuptake of serotonin (5-HT) & norepinephrine (NE), acting like a weak serotonin-norepinephrine reuptake inhibitor (SNRI)
 - Exhibits greater SNRI effects at higher doses
 - Prodrug requiring CYP 2D6 to convert tramadol to its active (+) o-desmethyltramadol or 'M1' metabolite
 - Therefore, susceptible to genetic polymorphisms
 - Renally excreted (30% unchanged; 60% as metabolite)
- Serotonergic medications have been documented as potential inducers of activation, hypomania, and rapid-cycling Bipolar Disorder

Case Description

- A 55-year-old Caucasian male presented to an outpatient psychiatric clinic with a long history of depression and anxiety
- Both patient and spouse describe:
 - Abrupt onset of rapid mood cycling with daily periods of irritability/emotional lability
 - Episodes consistent with hypomania interspersed with longer depressive periods
- Past Medical History:** Crohn's Disease with ileostomy, Ménière's Disease, DM-II, HTN, chronic renal failure, OSA, OA, and avascular hip necrosis
- Current medications:** ramipril 2.5 mg daily, gliclazide MR 120 mg daily, lansoprazole 30 mg daily, insulin glargine, Tramacet 1-2 tabs q 4-6 hours PRN
- Previous medication trials/exposure:** duloxetine 30 mg daily, quetiapine 12.5 mg daily, desvenlafaxine 50 mg daily, clonazepam 0.5 mg at bedtime, and past steroid use

Interpretations of Causality

- +1** SSRIs and SNRIs have been documented to induce rapid-cycling mood states
- +2** Temporal link between initiation of tramadol and onset of mood cycling was established using patient and collateral history, as well as pharmacy records
- +2** No alternative causes could, on their own, have caused this mood cycling
- +1** There was some improvement of symptoms when taking tramadol less often
- 0** Previous SNRI trials were at low doses or short trials, but did not cause ADR
- +1** Pharmacy records confirmed tramadol was started < 1 month before ADR

Naranjo Probability Score

Assessment	Yes	No	Don't Know	Score
Are there previous conclusive reports of this reaction?	+ 1	0	0	1
Did the ADR appear after the suspected drug was administered?	+ 2	- 1	0	2
Did the ADR improve when the drug was discontinued?	+ 1	0	0	0
Did the ADR reappear when the drug was re-administered?	+ 2	- 1	0	0
Are there alternative causes that could, on their own, have caused the ADR?	- 1	+ 2	0	2
Did the ADR reappear when a placebo was given?	- 1	+ 1	0	0
Was the drug detected in the blood or other fluids in known toxic concentrations?	+ 1	0	0	0
Was the ADR more severe with increased doses or less severe with decreased doses?	+ 1	0	0	1
Did the patient have a similar reaction to the same or similar drugs in previous exposures?	+ 1	0	0	0
Was the ADR confirmed by any objective evidence?	+ 1	0	0	1
TOTAL SCORE				7

Score:

9 = Highly Probable; 5-8 = Probable;
1-4 = Possible; 0 = Doubtful

Evaluation of the Literature

- Serotonergic drugs have been well documented as potential inducers of mania and rapid-cycling Bipolar Disorder
- Several case reports have described mania or mood alterations attributable to the combined use of Tramadol and an SSRI
- One case report of tramadol-induced mania (200 mg/day) in a patient with a history of Bipolar Disorder
 - A temporal link was established

Relevance to Clinicians

- Pain and depression have a strong interface, and are often used as marketing strategies for some SNRIs
- Tramacet-induced rapid cycling Bipolar Disorder in the absence of other serotonergic medications is not discussed in the product monograph and has yet to be documented in medical literature
- Psychiatrists seeing patients with rapid mood cycling or manic symptoms should consider including tramadol on Axis III as a potential contributor to Axis I presentation
- Inter-professional collaboration may help identify some answers where unusual responses are noted by psychiatrists
- All prescribers of tramadol should be aware that it has the potential to induce rapid-cycling Bipolar Disorder

References

- Biernacka JM, et al. 2012. Pharmacogenomics of antidepressant-induced mania: A review and meta-analysis of the serotonin transporter gene (5HTTLPR) association. *Journal of affective disorders* 136, (1-2): e21-e29.
- Calabrese JR, Fatemi SH, and Woysville MJ. 1996. Antidepressant effects of lamotrigine in rapid cycling bipolar disorder. *The American Journal of Psychiatry* 153, (9): 1236-1236.
- Hurwitz GI, and Liebowitz MR. 1993. Antidepressant-induced rapid cycling: Six case reports. *Journal of clinical psychopharmacology* 13, (1): 52-56.
- John AP, and Koloth R. 2007. Severe serotonin toxicity and manic switch induced by combined use of tramadol and paroxetine (letter; comment). *Australian and New Zealand Journal of Psychiatry*, 192-193.
- Kirchheiner J, Jan-Tobias HA, Keulen MS, et al. 2008. Effects of the CYP2D6 Gene Duplication on the Pharmacokinetics and Pharmacodynamics of Tramadol. *Journal of Clinical Psychopharmacology* 28, (1):78-83.
- Lamoure J, and Stovel J. 2011. Serotonin Syndrome: The Perfect Storm. How to prevent, recognize and manage Serotonin Syndrome. *Pharmacy Practice* 27, (2): 22-26,30-31.
- Marangell LB, et al. 2004. Lamotrigine treatment of bipolar disorder: Data from the first 500 patients in STEP-BD. *Bipolar disorders* 6, (2): 139-143.
- Mustafa FA, Almoshosh N, Al-Robb H, and AbuKmeil S. 2010. A case of possible duloxetine-induced mania. *German Journal of Psychiatry* 13, (1): 54-56.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239-45.
- Pinto A, Imaz H, de Heredia JLP, Gutierrez M, and Mico JA. 2001. Mania and tramadol-fluoxetine combination. *American Journal of Psychiatry* 158:964-5.
- Simpson HB, Hurwitz GI, and Liebowitz MR. 1997. General principles in the pharmacotherapy of antidepressant-induced rapid cycling: A case series. *Journal of Clinical Psychopharmacology* 17, (6): 460-466.
- Thomson Healthcare. Micromedex Healthcare Series, Volume 133. "Tramadol." <http://www.thomsonhc.com/home/dispatch>. Accessed June 10th, 2012
- Watts BV, and Grady, TA. 2012. Tramadol-induced mania. *American Journal of Psychiatry* 154:1624.