t is <u>illegal to post this</u> copyrighted PDF on any website Tramadol-Induced Hypomania and Serotonin Syndrome

To the Editor: Tramadol, a centrally acting synthetic opioid analgesic, has at least 2 complementary mechanisms of action. It binds to μ -opioid receptors and is a weak inhibitor of reuptake of norepinephrine and serotonin.¹ Tramadol shares many characteristics with venlafaxine. The drugs are structurally similar, and both cause serotonergic and noradrenergic inhibition.² Tramadol has antidepressant-like properties,³ while venlafaxine on the other hand is efficacious in the long-term treatment of chronic pain with associated major depressive disorder.⁴ Both drugs have been implicated in the induction of mania.^{5–7} This case report describes a woman with bipolar II disorder and comorbid fibromyalgia who developed hypomania and serotonin syndrome 2 days after taking tramadol.

Case report. Ms A was a 63-year-old woman with a history of bipolar II disorder since her early 20s for which she had required several psychiatric hospitalizations. Her mood stabilized on the combination of lithium 600 mg and quetiapine 300 mg, and there were no recurrences of depression or hypomania for at least 15 months prior to the index hypomanic episode (*DSM-5*). However, she continued to struggle with symptoms of fibromyalgia. After failing to respond to pregabalin, she was prescribed tramadol 100 mg daily for fibromyalgia. Within 48 hours of taking tramadol, she began to feel agitated, had twitching of her muscles, and had muscle incoordination. Despite that she was not getting much sleep, she did not feel tired. She felt euphoric and thought her brain was working overtime. She had difficulty expressing herself due to thoughts "popping" into her head.

Within 2 days of stopping tramadol and putting lithium on hold, the symptoms of hypomania (euphoria, decreased sleep requirement, increased energy, and racing thoughts) and serotonin syndrome (agitation, twitching muscles, and muscle incoordination) resolved. When assessed at our clinic a couple days later, she was alert, oriented, and able to provide a detailed and coherent account of the psychiatric and physical symptoms she experienced over the past few days. Ms A confirmed that denied having had any symptoms suggestive of lithium toxicity such as diarrhea, vomiting, stomach pains, dizziness, hand tremor, or slurred speech. Her most recent serum lithium level checked a month before initiation of tramadol was 0.81 mmol/L. When repeated a day after the onset of adverse reactions, her lithium level was <0.4 mmol/L.

Table 1 lists case reports of tramadol-induced mania. Tramadol dose ranged from 100 mg to 400 mg daily. Tramadol was used alone in 4 cases, in combination with an antidepressant in 3 cases, and with lithium in 1 case. Patients developed symptoms of mania and serotonin syndrome within 1 month. Symptoms were severe enough to require psychiatric hospitalization in 5 cases.

Given the timing of symptom onset, improvement following the discontinuation of tramadol, and lack of alternate explanation, it was concluded that tramadol was the probable cause of symptoms of hypomania and serotonin syndrome. A score of 7 on the Naranjo scale also indicated a probable relationship between tramadol and the adverse reactions.¹² Clinical drug information¹³ does not list mania as a side effect of tramadol but acknowledges that 7% to 14% of individuals can have symptoms of central nervous stimulation.

Contrary to reports that lithium provides protection against the occurrence of tramadol-induced mania, our patient experienced hypomania in spite of lithium use for several years. It is highly likely that early recognition of symptoms, correct diagnosis, discontinuation of tramadol, and temporary suspension of lithium¹⁰ played a role in the quick resolution of adverse reactions. Our case highlights the importance of inquiring about personal history of bipolar disorder in individuals with depression and fibromyalgia who are being considered for a trial of tramadol.¹⁴

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Table 1. Case Reports of Tramadol-Induced Mania							
Report	Age, y	Sex	Previous Diagnosis	Adverse Drug Reaction	Tramadol Daily Dose	Time to Symptom Onset	Concomitant Drugs
Gonzalez-Pinto et al ⁸	72	Female	MDD	Mania and serotonin syndrome	150 mg	18 days	Fluoxetine 20 mg
Ansermot et al ⁶	58	Male	MDD	Mania	100 mg or more	1 month	Escitalopram 20 mg, oxazepam 60 mg, sertraline 12.5 mg, quetiapine 300 mg, alprazolam 2 mg
Ceylan et al⁵	28	Male	None	Mania ^a	100 mg		None
Chen et al ⁹	59	Female	BP I	Psychosis	112.5 mg	1 month	Lithium
Oronsky and Martin ¹⁰	26 45 45	Female Male Female	BP BP BP	Mania Mania Mania	200 mg Unknown ^b 200 mg	2 days Unknown ^b Unknown ^b	None None None
John and Koloth ¹¹	53	Female	MDD	Mania and serotonin syndrome	400 mg	Sudden	Paroxetine 20 mg, alprazolam 0.5 mg

^aTwo episodes of mania following 2 separate trials of tramadol. ^bNot specified in report.

Abbreviations: BP = bipolar disorder, MDD = major depressive disorder.

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