Tramadol: Relieves Pain, Improves Mood, Induces Mania

To the Editor: Corticosteroids[1] and antidepressants[2] are known to induce manic episodes in predisposed individuals. Manic episodes in bipolar patients triggered by tramadol have also been reported.[3]

Tramadol acts as an opiate agonist by activating the μ-opioid receptor and as a promotor of serotonin and norepinephrine activity by modulating their transport.[4,5] Tramadol overdose, concurrent use with antidepressants, and impaired drug metabolism have been linked to serotonin syndrome.[4]

Case report. Ms A is a 64-year-old woman with a medical history of polycystic kidney disease with secondary chronic kidney disease. She was also diagnosed with breast cancer in 2012 and developed lymphedema and chronic pain after surgery.

She reported a single previous depressive episode following her cancer diagnosis. She was prescribed escitalopram 20 mg/d and amitriptyline 25 mg/d and had maintained that treatment until the current episode, although she reported clinical remission. No manic or hypomanic episodes were detected, and there was no family history of psychiatric disorders.

She presented to the emergency department (ED) on May 1 due to cellulitis and was treated with levofloxacin 500 mg/d and acetaminophen 3,000 mg/d. As the analgesic regimen was insufficient, tramadol 225 mg/d was added on May 5 at the same ED.

Following 2 days of analgesic augmentation, she experienced increased vital energy, restlessness, and insomnia. On May 9, she stopped taking tramadol due to the onset of euphoric mood, increased planning activity, and reduced need for sleep. As these symptoms did not remit, she returned to the ED on May 13, presenting with increased psychomotor activity, euphoric mood with grandiosity and social disinhibition, thought acceleration with flight of ideas, total insomnia of a 48-hour duration, and complex visual hallucinations.

The physical and neurologic examination showed no relevant changes. Analytic evaluation detected an increase of her basal creatinine (2.2–2.9 mg/dL; reference range, 0.5–1.1 mg/dL) and γ-glutamyl transpeptidase levels (350 to 500 U/L, normal < 38 U/L). The toxicology screen was negative. Brain computed tomography and magnetic resonance imaging showed no significant findings.

Ms A was admitted to the psychiatric ward and prescribed olanzapine 15 mg/d. After 5 days, the clinical symptoms had substantially remitted, with the exception of insomnia, which took 2 weeks to normalize. To date, she maintains outpatient follow-up with no recurrence of symptoms.

Reports[3,6,7] in the literature describe patients with known major psychiatric disorders who developed manic episodes secondary to tramadol. Our patient had a single depressive episode at age 60 years following a significant life event.

Tramadol is metabolized by the liver and kidneys, and its metabolites are excreted by the kidneys.[5] As analytic evaluation showed acute-on-chronic renal and hepatic dysfunction, tramadol metabolism could have been compromised. Furthermore, the parent compound is responsible for increasing monoaminergic activity and its metabolites for the μ-opioid agonism.[5] A reduction of the conversion of tramadol into its metabolites could have further enhanced monoaminergic activation.

Antidepressant-related manic episodes usually occur in the first 2 to 3 weeks.[8] Our patient was taking the same antidepressant treatment for the past 4 years without a manic switch, suggesting that escitalopram and amitriptyline had only potential secondary roles. An association between manic episodes and levofloxacin or acetaminophen is not reported in the literature.

Given the chronological development of Ms A's symptoms and the absence of a family or personal psychiatric history, we postulate that a combination of these factors contributed to the manic episode, with tramadol as a key trigger.

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