

Epileptic and depressed

Magdalena Romanowicz, MD, and John Michael Bostwick, MD

Ms. R, age 33, seeks treatment for worsening depression after her epilepsy diagnosis 1 year ago. She has a history of bulimia and ongoing anxiety and chronic pain. How would you manage her?



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CASE New-onset seizures

Ms. R, age 33, is referred by her neurologist for treatment of depressive symptoms that have intensified after she was diagnosed with epilepsy 1 year ago. She has a history of bulimia and ongoing anxiety and depression. She also has long-standing neuropathic pain in her left lateral shin and ankle that started after her foot was amputated in a lawn mower accident at age 5. Ms. R says she didn't take pain medication until age 24, when her pain specialist prescribed tramadol, 300 to 400 mg/d, which she continues to take.

Ms. R's first seizure occurred 1 year ago. Despite trials of several antiepileptics, her seizures persist; she is taking lamotrigine, 200 mg/d, when she presents for treatment. She has no history of brain injuries or strokes to explain her epilepsy. An MRI and 3 electroencephalograms show no signs of focal, potentially epileptogenic lesions.

Ms. R reports worsening depressive symptoms—particularly impaired attention and concentration—over several months that interfere with her housekeeping and ability to finish simple tasks at work. She says she drinks alcohol occasionally, but denies substance abuse. We initiate venlafaxine, titrated to 300 mg/d, because Ms. R has a history of intolerable side effects with fluoxetine (gastrointestinal distress) and citalopram (weight gain).

What is the most likely explanation for Ms. R's worsening depressive symptoms?

- major depressive disorder (MDD) secondary to a general medical condition
- MDD, recurrent
- chronic pain disorder
- somatoform disorder
- substance-induced mood disorder

The authors' observations

Tramadol, a centrally acting synthetic analgesic, consists of 2 enantiomers that act as weak agonists at μ -opioid receptors while also inhibiting serotonin and norepinephrine reuptake.¹ Euphoria associated with μ receptor activation often is considered a "high." Most abused opioids are prototypical μ agonists. When opioids are injected or inhaled, drug levels in the brain rise rapidly, causing a "rush"—a brief, intense, pleasurable sensation—followed by a longer-lasting high. Tolerance and physical dependence occur when opioids are used chronically.

Despite tramadol's μ -opioid activity, the FDA approved it as an unscheduled analgesic in 1994 based on several human studies.² Experience with tramadol has confirmed it has low abuse potential, yet

Dr. Romanowicz is a Child and Adolescent Psychiatry Fellow, Stanford University, Stanford, CA. Dr. Bostwick is Professor of Psychiatry, Mayo Clinic, Rochester, MN.

Table 1

DSM-IV-TR criteria for pain disorder

- | |
|---|
| A) Pain in ≥ 1 anatomical site is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention |
| B) The pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning |
| C) Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain |
| D) The symptom or deficit is not intentionally produced or feigned (as in factitious disorder or malingering) |
| E) The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for dyspareunia |

Source: Reference 17

Clinical Point

At clinically appropriate doses, tramadol slightly suppresses seizure severity, but higher doses can induce seizures

human laboratory data—and some epidemiologic data—show that repeated use can lead to physical dependence. Although tramadol is considered a relatively weak opioid, human studies suggest that it possesses μ -agonist activity. The Drug Abuse Warning Network reported >15,000 emergency department (ED) visits for nonmedical tramadol use in 2009, which was more than the number of ED visits for codeine products (7,958) or propoxyphene products (9,526), but much fewer than visits for hydrocodone (86,258) or oxycodone (148,449) products.³

The recommended tramadol dose is 50 to 100 mg every 4 to 6 hours (maximum 400 mg/d). Adverse effects range from dysphoria, constipation, and nausea to agitation, seizures, respiratory depression, and coma.⁴ Tramadol withdrawal is similar to opioid withdrawal, and is characterized by anxiety, restlessness, insomnia, yawning, rhinorrhea, lacrimation, diaphoresis, tremor, muscle spasms, vomiting, diarrhea, and tachycardia. Rarely, psychomotor agitation and confusion may occur.⁵

Tramadol and seizures

At clinically appropriate doses, tramadol slightly suppresses seizure severity,⁶ but higher doses can induce seizures.⁷⁻¹² This paradox is explained by tramadol's effect on γ -aminobutyric acid (GABA) receptors. Although at clinical doses tramadol does not affect GABA, which could precipitate seizures, at higher doses it has been shown to have an inhibitory effect on GABA receptors.^{13,14} No prospective studies have assessed how often tramadol-induced seizures occur. Case reports^{12,15} suggest that seizures are more likely with acute tramadol intoxication, in patients with a history of alcohol abuse, or with pharmacologic regimens that include other medications that may cause seizures. Tramadol-induced seizures are generalized tonic-clonic in nature, and typically occur within 24 hours of the last dose.¹⁶

HISTORY Worsening seizures

Two months after she presents for psychiatric evaluation, Ms. R experiences 6 generalized convulsions lasting from 15 minutes to 1 hour with no identifiable precipitant. Because oxcarbazepine and lamotrigine have failed to suppress her seizures, her neurologist adds phenytoin, 200 mg/d, and increases lamotrigine from 200 to 300 mg/d. Her depression continues to worsen. She reports severe insomnia, anhedonia, restlessness, and hopelessness, so we add sertraline, 50 mg/d, to venlafaxine. Ms. R says the seizures are terrifying and she cannot work. She moves in with her parents because she is unable to care for herself.

During a psychiatric appointment, Ms. R confesses that for 2 years her pain has been so unbearable that she has been buying extra tramadol from Internet retailers and taking 600 to 800 mg/d in addition to the prescribed 400 mg/d.

How would you manage Ms. R?

- ask for her permission to discuss her tramadol abuse with her neurologist



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Table 2

Tramadol: Major drug-drug interactions

Drug	Symptoms
Selegiline	Nausea, vomiting, cardiovascular collapse, respiratory depression, seizures, or serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes); use of the transdermal formulation with tramadol is contraindicated
Carbamazepine	Decreased tramadol efficacy and increased seizure risk
Venlafaxine	Increased risk of serotonin syndrome
Linezolid	Increased risk of serotonin syndrome
Fluoxetine	Increased risk of seizures and serotonin syndrome; increased concentrations of tramadol and decreased concentrations of tramadol active metabolite, O-desmethyltramadol (M1)
Olanzapine	Increased risk of serotonin syndrome
Mirtazapine	Increased risk of serotonin syndrome
Haloperidol	Increased risk of seizures
Escitalopram	Increased risk of seizures and serotonin syndrome
Clomipramine	Increased risk of seizures
Risperidone	Increased risk of seizures
Ketamine	Increased risk of respiratory depression and excessive CNS depression
Imipramine	Increased risk of seizures
Duloxetine	Increased risk of serotonin syndrome
Nortriptyline	Increased risk of seizures
Clozapine	Increased risk of seizures
Sertraline	Increased risk of seizures and serotonin syndrome
Paroxetine	Increased risk of seizures and serotonin syndrome; decrease in the analgesic effect of tramadol
Amitriptyline	Increased risk of seizures; increased concentrations of tramadol and decreased concentrations of tramadol active metabolite, M1
Desipramine	Increased risk of seizures
Doxepin	Increased risk of seizures
Citalopram	Increased risk of seizures and serotonin syndrome
Fluvoxamine	Increased risk of seizures and serotonin syndrome

Source: Reference 19

- b) try to manage her condition on your own
- c) report her to her employer and ask preventive health services to follow up on her treatment
- d) none of the above

The authors' observations

Ms. R had a history of chronic pain (*Table 1*)¹⁷ and developed seizures after escalating her tramadol use. After her first epilepsy attack, she did not tell her physicians she was taking additional tramadol nor did she stop taking it. Treatment with several

antiepileptics was unsuccessful. Her seizures persisted as long as her tramadol addiction continued.

Spiller et al¹⁸ reported the lowest daily tramadol dose associated with seizures is 500 mg/d, although Talaie et al¹⁶ observed seizures at doses as low as 100 mg/d. Additionally, seizure risk may increase through tramadol's interactions with several medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines, fluoroquinolone antibiotics, meperidine, clozapine,

Clinical Point

Seizures have been observed with tramadol doses as low as 100 mg/d

Clinical Point

Seizure risk may increase through tramadol's interactions with several medications, including some antidepressants

Related Resource

• Clark MR, Treisman GJ. Chronic pain and addiction. Basel, Switzerland: Karger; 2011.

Drug Brand Names

Acetaminophen, butalbital, and caffeine • Fioricet	Linezolid • Zyvox
Amitriptyline • Elavil	Meperidine • Demerol
Bupropion • Wellbutrin	Mirtazapine • Remeron
Buspirone • Buspar	Nortriptyline • Aventyl
Carbamazepine • Tegretol, Carbatrol	Olanzapine • Zyprexa
Citalopram • Celexa	Oxcarbazepine • Trileptal
Clomipramine • Anafranil	Oxycodone • Percolone, OxyContin
Clozapine • Clozaril	Paroxetine • Paxil
Desipramine • Norpramin	Phenylephrine • Lusonal
Doxepin • Adapin, Silenor	Phenytoin • Dilantin
Duloxetine • Cymbalta	Propoxyphene • Darvon
Escitalopram • Lexapro	Risperidone • Risperdal
Fluoxetine • Prozac	Selegiline • Eldepryl, EMSAM
Fluvoxamine • Luvox	Sertraline • Zoloft
Guaifenesin • Tenex	Theophylline • Aerolate
Haloperidol • Haldol	Thioridazine • Mellaril
Imipramine • Tofranil	Tramadol • Ultram
Ketamine • Ketalar	Tripelennamine •
Lamotrigine • Lamictal	Pyribenzamine •
	Venlafaxine • Effexor

Disclosure

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buspirone, bupropion, phenylephrine, guaifenesin, tripelennamine, thioridazine, theophylline, and acetaminophen, butalbital, and caffeine combination (*Table 2, page 47*).¹⁹ Transdermal selegiline is contraindicated with tramadol. For Ms. R, the sertraline and venlafaxine she was taking may have augmented tramadol's seizure potential.

It is important to avoid polypharmacy in patients taking tramadol.²⁰ Most psychiatrists are aware of the risk of serotonin syndrome with antidepressants, but may be less likely to attribute serotonergic additive effects from other medication classes such as analgesics. Recognizing tramadol's potential to contribute to serotonin syndrome—especially in light of concomitant usage with other serotonergic medications such as antidepressants—is essential.

Tramadol toxicity appears to be caused by monoamine uptake inhibition rather

than its opioid effects.²¹ The most frequent pharmacokinetic drug-drug interactions that lead to side effects such as serotonin syndrome or seizures involve several isoenzymes of the hepatic cytochrome P450 (CYP). The isoenzymes CYP2D6 (substrates—eg, amitriptyline, tramadol, and venlafaxine; inhibitors—eg, fluoxetine and duloxetine) and CYP3A4 (substrates—eg, carbamazepine, oxycodone, and venlafaxine; inductors—eg, carbamazepine; inhibitors, eg—grapefruit juice) are most important clinically.²²

Ms. R readily obtained tramadol from Internet retailers. In a 2004 report, a Google search yielded 2,150,000 sources for acquiring tramadol, most of which did not require a prescription.²³ Chronic pain patients have a higher prevalence of substance abuse than the general population.²⁴ Because Ms. R did not have a documented substance abuse history, none of her physicians screened her for drug abuse, although toxicology screening wouldn't have helped because the tramadol had been prescribed. We didn't think to directly ask Ms. R about medication misuse, but if we had, she might have revealed it sooner.

OUTCOME Seizure free

With Ms. R's permission, we speak to her neurologist, who agrees that excess tramadol likely induced her seizures. The seizures stop after Ms. R discontinues tramadol. After 3 months without seizures, phenytoin is discontinued and lamotrigine is tapered to 200 mg/d. Ms. R participates in a pain rehabilitation program and continues to take venlafaxine, 300 mg/d, and sertraline, 50 mg/d. Her mood improves and she returns to work. Her pain is managed by nonsteroidal anti-inflammatory drugs because she decides to decrease her activity level. Ms. R also is trying alternative medicine modalities such as acupuncture and acupressure.

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Clinical Point

Chronic pain patients have a higher prevalence of substance abuse than the general population

Bottom Line

Patients with a history of chronic pain who present with new-onset seizures or other unexplained symptoms should be evaluated for possible substance abuse. At indicated doses, tramadol may suppress seizures, but higher doses may cause seizures. Drug-drug interactions between tramadol and antidepressants also may contribute to seizures.