

The risk of tramadol abuse and dependence: Findings in two patients

Some say tramadol is no more addicting than NSAIDs, but in these examples, the reliance on tramadol is real. These cases offer guidance on recognizing and treating similar patients.

James D. Stoehr, PhD; Alison C. Essary, MHPE, PA-C; Chrissi Ou; Rob Ashby, MD, PLC; Michel Sucher, MD, FASAM, FACEP

CASE 1

After suffering a seizure, a 38-year-old male who used tramadol frequently was still in denial about his dependence. He experienced brief, intermittent periods of abstinence, then relapsed, and 1 year later had a second seizure. This seizure prompted the man to admit his dependence on tramadol and express a desire to seek treatment. At the peak of his addiction, he was taking 27 tablets (50 mg per tablet) of tramadol daily.

The patient began using tramadol for daily headaches approximately 4 years earlier. He used hydrocodone and oxycodone preparations intermittently but preferred tramadol because of the euphoria and increased energy level he experienced after taking that drug. The patient, who was a physician, obtained the medication through drug samples and Internet purchasing. He attempted to stop the medication several times but ran into difficulty when he experienced physical manifestations, such as rebound headache and mood changes. His medical history was significant for the two seizures and untreated depression. He did not use tobacco products or alcohol. His family history was positive for drug use/abuse. He had no history of physical or sexual abuse. Following completion of a 6-week inpatient detoxification and residential treatment program, the patient presented to the addiction medicine physician for follow-up care.

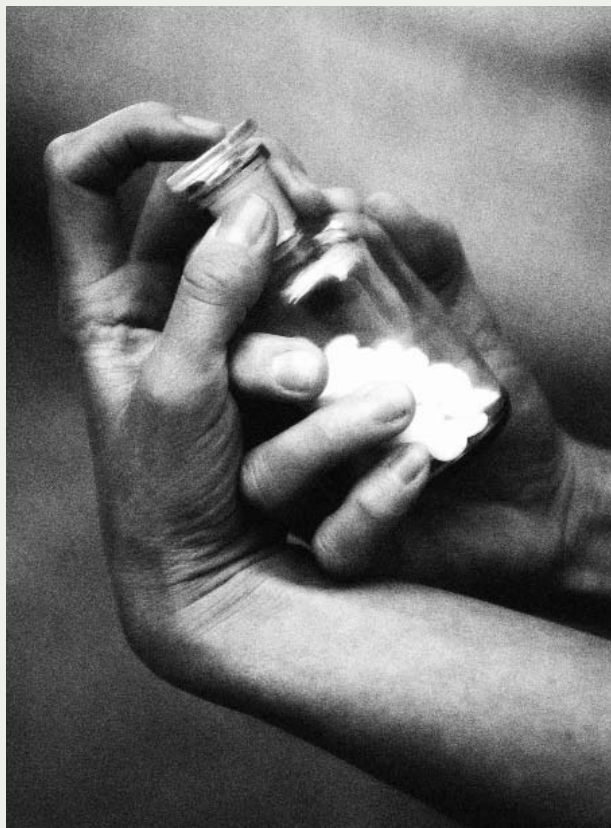
The management plan Because the patient was employed as a physician, his management plan included a voluntary 5-year monitoring program that involved monthly office visits with an addictionist, random urine drug screens (approximately two per month), bimonthly group counseling sessions, and documented participation in 12-step meetings. Medical management included trazodone at bedtime for sleep. The patient was encouraged to seek treatment for depression and daily headaches.

Outcome The patient is under the care of an internist, neurologist, and addictionists. His daily headaches are

well-controlled with modifications to diet, exercise, and as-needed use of sumatriptan and NSAIDs. He has been abstinent for 25 months. He has good family support and involvement in his sobriety, has maintained employment, and is active in the recovery process, which includes 12-step participation, frequent interaction with his sponsor, and bibliotherapy.

CASE 2

A 57-year-old female presented to the addiction medicine physician for a relapse of her addiction. At the time of the visit, she admitted to using tramadol 300 mg five to six



Punchstock

CASE REPORT | Tramadol dependence

times daily for the past 3 months. She expressed a desire to stop taking the tramadol, which she purchased in Mexico, but could not do so without assistance. She complained of rhinorrhea, sweats, myoclonic twitching, and anxiety when stopping the tramadol.

The patient had a 30-year history of intermittent substance abuse, including IV pentazocine, IV meperidine, and oral hydrocodone and oxycodone. Over the past 30 years, she had completed multiple substance abuse treatment programs, including detoxification, inpatient/residential treatment, and intensive outpatient programs. Her medical history was significant for depression requiring two hospitalizations, systemic lupus erythematosus, gastroesophageal reflux disease, menopause, and pancreatitis. Her social history was positive for emotional, physical, and sexual abuse, and her family history was positive for alcohol and drug abuse. She had a 24-pack-year tobacco history and consumed alcohol regularly.

Physical examination demonstrated a talkative female with scattered thoughts; the remainder of her examination was benign. A urine drug screen was positive for opiates, benzodiazepines, and amphetamines.

The management plan The patient was prescribed trazodone at bedtime for sleep and a daily dose of a sublingual combination of buprenorphine plus naloxone. She was referred to a counselor to address her history of abuse and encouraged to participate in 12-step meetings (ie, Pills Anonymous).

Outcome The patient continues to struggle with her sobriety and has intermittent positive urine screens for amphetamines, barbiturates, benzodiazepines, and opiates. She has chronic pain and headaches and has undergone surgery, all requiring pain control. She has difficulty with sleep and controlling depressive symptoms. Yet she is compliant with her appointments with the addiction medicine specialist and seems to have good family support.

DISCUSSION

The medical literature is mixed with respect to the abuse potential of tramadol. Physical dependence and withdrawal have been associated with abuse of tramadol and tramadol/acetaminophen in several reports, including published case series, medical watch reports, and retrospective reviews.¹⁻⁶ However, the significance of this abuse potential has been questioned,⁷ and the rates of abuse have been reported to

be no different than those for NSAIDs.⁸ Nonetheless, authors generally agree that tramadol abuse and physical dependence can occur, and caution should be used before prescribing tramadol to patients at high risk of addiction, such as those with previous personal or family histories of alcohol and/or drug abuse.¹⁻¹¹ This caveat is supported by the cases presented here: Both patients had positive family histories for substance abuse, and the patient in Case 2 had a positive personal history of opiate abuse. Both patients exhibited significant physical dependence; withdrawal symptoms; and extensive social, financial, and occupational consequences of their addictive behaviors.

“As an unscheduled medication, tramadol can be obtained online, diverted from clinical settings, and bought outside the United States.”

Tramadol was approved by the FDA in 1995 as an unscheduled medication to treat mild to moderate pain. Weak opioid activity as a μ -receptor agonist presumably underlies the ability of tramadol to cause analgesia as well as euphoria. The analgesia associated with tramadol is also believed to result from its ability to block the reuptake of synaptic norepinephrine and serotonin in the CNS.¹² Consequently, the abuse of tramadol has been associated with a reduction in seizure threshold. Notably, the first symptom of substance abuse in the patient in Case 1 was seizure. Significant caution is also warranted when prescribing tramadol in conjunction with selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors. Patients who are taking antidepressants should be carefully monitored while on tramadol to avoid drug-drug interactions.

An easy-to-obtain drug As an unscheduled medication, tramadol can be obtained online, diverted from clinical settings, and purchased outside the United States. In both of the cases presented, the patients reported the ease with which they obtained and used very high doses of tramadol. These patients exhibited significant tolerance and were reportedly taking tramadol at three to five times the recom-

TEACHING POINTS

- Physical dependence and withdrawal are possible with tramadol misuse and abuse.
- Elicit a patient's drug/alcohol history before prescribing tramadol or any controlled substance.
- Be aware of drug-drug interactions with tramadol (selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, monoamine oxidase inhibitors).
- Taper the dose of tramadol following chronic use, or consult with pain management/addiction specialists. Treatment may then include drug detoxification, inpatient rehabilitation, outpatient care, and alternative forms of pain management.
- Be aware of the widespread availability of tramadol and the side effects associated with its abuse.

CASE REPORT | Tramadol dependence

mended maximum daily dose of 400 mg. The surreptitious acquisition and availability of tramadol for diversion has been documented in other cases.^{4,6} Some case reports have documented the financial problems that can result when dependent patients purchase tramadol over the Internet. Such monetary problems may be the first sign of drug dependence.⁴

Abuse or dependence The clinical signs and symptoms associated with abuse, dependence, and withdrawal associated with tramadol are very similar to those of opiates. While intoxication is accompanied by euphoria, sedation and/or excitation, nausea, and miosis, behavioral withdrawal symptoms are typically the opposite and are associated with depressed mood, craving, and drug-seeking. According to the American Psychiatric Association (APA),

TABLE 1. Terminology of addiction

Addiction	A psychological construct that defines the compulsive physiologic need for and use of a habit-forming substance characterized by tolerance and by well-defined physiologic symptoms upon withdrawal. The persistent, compulsive use of a substance known by the user to be physically, psychologically, or socially harmful.
Drug diversion	Situation in which the legal supply chain of prescription analgesic drugs is broken and drugs are transferred from a licit to an illicit channel of distribution or use.
Physical dependence	Chronic and/or long-term use of a drug that results in unpleasant physical symptoms if the drug is suddenly stopped or taken in smaller doses.
Pseudoaddiction	A circumstance in which a chronic condition is undertreated (eg, chronic pain), and the legitimate pain patient seeks further medication management.
Substance abuse	Persistent use despite health, social, and legal consequences. Can be associated with increased frequency or dosing of substance. Usually precedes physical dependence.
Tolerance	The capacity of the body to endure or become less responsive to a substance (ie, a drug) with repeated use or exposure. Develops quickly to the euphoric effects of certain opiates.
Withdrawal	Symptoms that appear after discontinuing or decreasing the dosage of a drug that causes physical dependence.

“Atypical withdrawal symptoms from tramadol dependence include delusions, paranoia, peripheral numbness, and hallucinations.”

substance abuse exists when, over a 12-month period, recurrent use

- Results in inability to meet necessary obligations at work, school, or home
- Persists despite the potential for physical harm
- Causes legal problems
- Continues despite persistent or exacerbated social problems.¹³

Both of the patients presented here exhibited physical, psychological, and social consequences of use that meet the definition of substance abuse. However, one of the requirements of substance abuse is that patients not fulfill the criteria for dependence. In these cases, both patients exhibited signs of tramadol dependence. According to APA criteria, dependence requires three or more of the following during a 12-month period:

- Tolerance—a need for higher amounts of the substance to achieve the usual effect or a lesser effect from the amount customarily taken
- Withdrawal—evidenced by a typical withdrawal syndrome or the substitution of another substance to avoid withdrawal symptoms
- Greater substance use (in amount or duration) than intended
- Inability to control substance use
- Excessive amounts of time lost in obtaining the substance, using it, and recovering from its use
- Altered participation (ranging from a decrease to complete cessation) in social, work-related, or recreational activities
- Continued substance abuse despite awareness that the substance is causing persistent or exacerbated physical and psychological problems.¹³

Atypical withdrawal symptoms have also been reported from tramadol dependence, including confusion, delusions, paranoia, peripheral numbness, and hallucinations.¹¹ These atypical symptoms were noted in the second patient presented. Clinicians who note signs of abuse, dependence, or withdrawal are urged to consult with an addictionist or pain management specialist.⁵ The treatment plan may then include drug detoxification, inpatient rehabilitation, outpatient care, and alternative forms of pain management.

A prudent approach Prior to prescribing any controlled substance, the prudent approach is to obtain a personal and family history profile regarding substance abuse or other compulsive behavioral disorders.¹³ Given the cases presented, this advice may also apply to prescribing tramadol. Furthermore, Case 2 reinforces the notion that physical or emotional abuse can prime the person for substance abuse at a later

CASE REPORT

“Treatment may include outpatient care, drug detoxification, inpatient rehabilitation, and alternative forms of pain management.”

time. This patient had a previous history of substance abuse, emotional and physical abuse, and possible mental illness, all of which manifested in her chronic relapses. Primary care clinicians should be aware of the clinical differences between substance abuse, dependence, tolerance, and withdrawal (see Table 1, page 34) and should be comfortable in consulting with pain management and addiction specialists on the care of their patients. [JAAPA](#)

James D. Stoehr is a professor in the PA Program at Midwestern University, Glendale, Arizona. **Alison Essary** is an associate professor in the same program. **Chrissi Ou** is a fourth-year medical student at Arizona College of Osteopathic Medicine, Midwestern University. **Rob Ashby** specializes in addiction medicine and pain management in Scottsdale, Arizona. **Michel Sucher** is an addiction medicine specialist and president of Greenberg and Sucher, LLC, in Scottsdale. The authors have indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Buprenorphine plus naloxone (Suboxone)
Hydrocodone
Meperidine (Demerol, generics)
Oxycodone (OxyContin, Oxydose)
Pentazocine (Talwin)
Sumatriptan (Imitrex, generics)
Tramadol (Ultram, Ryzolt, generics)
Tramadol/acetaminophen (Ultracet, generics)
Trazodone

REFERENCES

1. Skipper GE, Fletcher C, Rocha-Judd R, Brase D. Tramadol abuse and dependence among physicians. *JAMA*. 2004;292(15):1818-1819.
2. Yates WR, Nguyen MH, Warnock JK. Tramadol dependence with no history of substance abuse. *Am J Psychiatry*. 2001;158(6):964.
3. Ehrenreich H, Poser W. Dependence on tramadol. *Clin Investig*. 1993;72(1):76.
4. Ritvo JI, Koonce R, Thurstone CC, Causey HL 3rd. Tramadol dependence: treatment with buprenorphine/naloxone. *Am J Addict*. 2007;16(1):67-68.
5. Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study. *Eur J Pain*. 2000;4(3):307-311.
6. Leo RJ, Narendran MB, DeGuiseppe B. Methadone detoxification of tramadol dependence. *J Subst Abuse Treat*. 2000;19(3):297-299.
7. Adams EH, Dart RC, Knisely JS, Schnoll SH. Tramadol abuse and dependence among physicians. *JAMA*. 2005;293(16):1977-1978.
8. Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage*. 2006;31(5):465-476.
9. Cicero TJ, Inciardi JA, Adams EH, et al. Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol Drug Saf*. 2005;14(12):851-859.
10. Cicero TJ, Adams EH, Geller A, et al. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend*. 1999;57(1):7-22.
11. Senay EC, Adams EH, Geller A, et al. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend*. 2003;69(3):233-241.
12. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:569-619.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.