A case of tramadol dependence and successful treatment with buprenorphine/naloxone

Nicole Cupples, PharmD[1]
Troy A. Moore, PharmD, M.S., BCPP[2]

[1] Clinical Pharmacy Specialist, Psychiatry
San Antonio State Supported Living Center
[2] Clinical Pharmacy Specialist, Psychiatry
South Texas Veterans Health Care System
Assistant Professor, Division of Schizophrenia and Related Disorders, Department of Psychiatry
The University of Texas Health Science Center at San Antonio
Adjunct Assistant Professor, Pharmacotherapy Education and Research Center
The University of Texas at Austin College of Pharmacy and The University of Texas Health Science Center at San Antonio

ABSTRACT

Tramadol, a synthetic, centrally acting analgesic with weak mu-opioid agonist activity, is often prescribed as an alternative to opioids due to its negligible abuse potential. Although the potential for the abuse of tramadol appeared low when the medication first became available, findings have demonstrated increased rates of abuse with extended time on the market. This case report details the addiction to tramadol of a 39-year-old female serving in the United States Army. At the height of her addiction, she was consuming an average of 1400mg tramadol daily. Eventually the patient entered into residential inpatient treatment for 28 days at our facility. During this time she was successfully titrated to buprenorphine 8mg/naloxone 2mg daily while maintaining abstinence. Patient care transitioned to the outpatient treatment center during which she maintained sobriety with the continued use of buprenorphine/naloxone. This case adds to previous reports of the increasing abuse of tramadol and the need for quality evidence on successful treatments for this escalating concern.

KEYWORDS

tramadol, buprenorphine/naloxone, substance use disorder

CASE

A 39-year-old female veteran presented for treatment for tramadol dependence as required by Child Protective Services after the birth of her son who suffered from opioid withdrawal. The patient presented to the emergency department for detoxification after reporting that she took 250mg of tramadol the night prior to presentation. On admission, the patient appeared mildly depressed with normal affect and was cooperative with examiner. The patient endorsed depressed mood, decreased sleep, decreased appetite, anhedonia, anergia and increased guilt. She also endorsed increased anxiety and jitteriness that worsened during withdrawal. The patient reported no other abuse of substances other than tramadol. Besides an active prescription for tramadol, the patient stated she was not currently taking other prescription medications except for ibuprofen 800mg as needed for tooth pain.

While undergoing detoxification on the inpatient psychiatric unit, the patient experienced signs and symptoms of both typical opioid withdrawal (tremulousness, hyperhidrosis, lacrimation, agitation, anxiety, diarrhea) and atypical symptoms noted to occur with tramadol withdrawal (electric shock sensations and severe anxiety).[1] A one-time oral dose of lorazepam 1mg was given to the patient as she was becoming increasingly anxious and citalopram 20mg at bedtime was also initiated for mood and possible serotonin withdrawal. Buprenorphine 2mg/naloxone 0.5mg was ordered every 2 hours as needed and a total of 5 doses were given to the patient over the first 24 hours.

The patient reported first being given tramadol for a shoulder injury in January 2009 while serving in the Army. Tramadol use escalated during that time as the patient reported taking four to five 50mg tablets every 3 to 4 hours in order to feel "numb." After the patient reported

her use to her Army medical doctor she was placed on leave and ordered into treatment in March of 2010. The patient was sent to a private psychiatric center for 30 day detoxification treatment where she initially received buprenorphine/naloxone. Upon discharge from the detoxification facility, the patient did not continue the buprenorphine/naloxone as the use of this medication was forbidden at her assigned duty station. Sobriety was maintained for a year until the patient fractured her finger in April of 2011 and was subsequently given tramadol for pain. Of note, the patient had been given oxycodone/acetaminophen tablets a few months prior to relapse for pain related to renal calculi, but the patient stated she disliked the feeling this medication gave her and used it only sparingly. The patient began escalating her dose of tramadol in October of 2011 to six or seven 50mg tablets four times a day (1200-1400mg daily). At the end of October 2011 the patient discovered she was 14 weeks pregnant and asked her obstetrician for help with discontinuing tramadol. The patient was warned to not abruptly stop tramadol due to risk of miscarriage and was advised to gradually reduce her use of tramadol. However, the patient continued to use and received prescriptions from several other providers during her pregnancy. The infant was born premature at less than 35 weeks of gestation and showed signs and symptoms of opioid withdrawal. He was placed in newborn intensive care where he underwent withdrawal treatment for over 4 months.

LITERATURE REVIEW

Tramadol is a synthetic, centrally acting analgesic with a mixed mechanism of action. Tramadol acts as a weak μ-opioid receptor agonist as well as a serotonin and norepinephrine reuptake inhibitor.[2] In the United States, tramadol was approved as a non-controlled substance in 1995 due to studies showing its negligible abuse potential and limited evidence of diversion and abuse.[3] An independent post-marketing surveillance group funded by Ortho-McNeil Pharmaceutical, the makers of Ultram®, reviewed reports of abuse and dependence over a three-year time period (1995-1998). Results showed a low rate of abuse with a peak occurring the first 18 months after introduction to the market and a steady decline to less than one case per 100,000 patients at the end of the three years.[3] In addition to the early post-marketing surveillance, a large randomized trial conducted in 2006 by Adams et al. found that the abuse of tramadol was comparable to non-steroidal anti-inflammatory drugs (NSAIDS).[4] An algorithm called the "Abuse Index" was developed by the researchers as a relative scale to provide comparative outcomes among medications. Four dimensions were identified and included inappropriate use, use for purposes other than intended, an inability to stop use and evidence of opioid withdrawal.[4] Results found that the percentage of subjects who scored positive for abuse in a 12-month period were 2.5% for NSAIDS, 2.7% for tramadol and 4.9% for hydrocodone.[4]

Although the potential for abuse of tramadol is low, the MedWatch program of the Food and Drug Administration (FDA) reported 766 cases of abuse and 482 cases of withdrawal from tramadol over the period of 1995 through 2004.[5] Due to increasing reports of abuse, the FDA issued a safety warning in May of 2010 advising prescribers of the potential for tramadol abuse and overdose.[6] Recent federal data on tramadol abuse has been compiled by the U.S. Department of Health and Human Services' Drug Abuse Warning Network (DAWN) which collects data regarding emergency department (ED) visits related to illicit and prescription medication abuse. The most recent report detailing tramadol abuse in 2009 illustrated that tramadol accounted for 15,349 out of 1,079,683 visits, or 1.4% of total ED visits involving nonmedical use of pharmaceuticals. Hydrocodone products in comparison were estimated at 86,258 visits or 8.0%.[7]

Lanier et al have discovered that physical dependence on tramadol does occur among human subjects.[8] The subjects in the randomized, placebo-controlled, crossover study underwent phases consisting of 60mg daily morphine administration and 200mg or 800mg daily tramadol dosing. Results showed that overall, naloxone-precipitated withdrawal occurred and that effects were similar for subjects taking 60mg daily morphine doses and 800mg daily tramadol doses. Results also suggested that physical dependence can occur at typically prescribed doses for pain of 200mg/day (maximum dose 400 mg per day). Tramadol physical dependence appears to be dose related and sustained dosing regimens may lead to development of neural adaptations similar to those seen from use of other mu-agonists.[8] Withdrawal symptoms have been reported to mimic symptoms of opioid withdrawal including abdominal cramps, anxiety, goose flesh, lacrimation, rhinorrhea, sweating and depression. However, atypical symptoms of withdrawal, often combined with typical opioid withdrawal signs and symptoms are also known to occur. These symptoms include severe anxiety and panic, derealization, delusions, paranoia, numbness, tingling and hallucinations that may be auditory, tactile and/or visual in nature.[1]

Information regarding the treatment of tramadol dependence is unfortunately scarce. Case reports have detailed inpatient detoxification regimens using benzodiazepines, clonidine, and methadone and successful maintenance of abstinence has been reported with the use of naltrexone and mirtazapine.[9,10] Ritvo et al, in 2006, described two case reports where buprenorphine/naloxone was used to treat tramadol dependence.[11] Patient A, a 34-year-old female with a four year history of tramadol abuse was titrated to buprenorphine 32mg/naloxone 8mg daily after withdrawal. The patient reported significant improvement in mood and energy with this treatment regimen and at a four-month follow-up had continued tramadol sobriety and was eventually able to return to work full-time. Patient B, a 44-year old female with a three year history of tramadol abuse and current nicotine dependence, was titrated to buprenorphine 32mg/naloxone 8mg daily. Over the next year, the patient reported improvement in mood and alertness and began to wean her dose to 8mg buprenorphine/2mg naloxone daily. A 28-month follow-up appointment found the patient had continued tramadol abstinence.[11]

CONCLUSION

The 39-year-old female in this present case successfully completed 28 days of inpatient treatment at our center from May to June 2012. During this time, the patient was titrated to buprenorphine 8mg/naloxone 2mg daily and was also switched from citalopram to sertraline 150mg daily due to QTc prolongation. After discharge, the patient transitioned to the outpatient treatment center and continued to be maintained on the same buprenorphine/naloxone dose with negative urine drug screens and self-reports of abstinence. The patient's son was discharged from the hospital and is now in her and the father's care. She attended parenting classes and family therapy sessions.

In conclusion, the reported potential for tramadol abuse appears lower than that for other opioid agonists however trends in addiction and abuse of tramadol are growing. As the rise in prescription opioid abuse continues, a corresponding increase in risk of abuse for tramadol may occur as many prescribers turn to tramadol as an alternative treatment for pain. In order to implement successful treatment programs, randomized, controlled trials on treatment of tramadol dependence with opioid replacements such as buprenorphine/naloxone would add significant value to clinicians and provide data for the development of evidence-based guidelines.

REFERENCES

1. Senay EC, Adams EH, Geller A, Inciardi JA, Muñoz A, Schnoll SH, et al.. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. Drug Alcohol Depend. 2003;69(3):233-41. PubMed PMID: 12633909.
2. Duke AN, Bigelow GE, Lanier RK, Strain EC. Discriminative stimulus effects of tramadol in humans. J Pharmacol Exp Ther. 2011;338(1):255-62. doi: 10.1124/jpet.111.181131. PubMed PMID: 21467190.
3. Cicero TJ, Adams EH, Geller A, Inciardi JA, Muñoz A, Schnoll SH, et al.. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend. 1999;57(1):7-22. PubMed PMID: 10617309.
4. Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, 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):465-76. doi: 10.1016/j.jpainsymman.2005.10.006. PubMed PMID: 16716877.
5. McDiarmid T, Mackler L. What is the addiction risk associated with tramadol? J Fam Pract 2005;54:72-73.
6. PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., ***Ultram: Dear Healthcare Professional Letter.*** Retrieved from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm
7. Substance Abuse and Mental Health Services Administration, ***Drug Abuse Warning Network 2009: National Estimates of Drug-Related Emergency Department Visits.*** HHS Publication No.(SMA) 11-4656, DAWN Series D-35. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011.
8. Lanier RK, Lofwall MR, Mintzer MZ, Bigelow GE, Strain EC. Physical dependence potential of daily tramadol dosing in humans. Psychopharmacology (Berl). 2010;211(4):457-66. doi: 10.1007/s00213-010-1919-3. PubMed PMID: 20589494; PubMed Central PMCID: PMC3028382.
9. Leo RJ, Narendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. Journal of Substance Abuse Treatment. 2000;19(3):297- 299. doi: 10.1016/S0740-5472(00)00098-2.
10. Prakash J, Saini R. Tramadol dependence: A case Report. Medical Journal Armed Forces India. 2010;66(1):90. doi: 10.1016/S0377-1237(10)80112-1.
11. Ritvo JI, Koonce R, Thurstone CC, Causey HL. Tramadol dependence: treatment with buprenorphine/naloxone. Am J Addict. 2007;16(1):67-8. doi: 10.1080/10550490601080118. PubMed PMID: 17364425.

How to cite:
Cupples N, Moore TA. A case of tramadol dependence and successful treatment with buprenorphine/naloxone. Ment Health Clin [Internet]. 2013;3(6):283-5. Available from: http://dx.doi.org/10.9740/mhc.n183348