PHARMACOLOGY

Tramadol: what have we learned in the last 25 years?

Mark Donaldson, BSP, ACPR, PHARMD, FASHP, FACHE ■ Jason H. Goodchild, DMD

The natural opiate opium was first derived from the poppy plant circa 3400 BC and was used for millennia to produce surgical analgesia and alleviate pain. In 1805, the alkaloid of opium was isolated by Friedrich Sertürner and named *morphine*, after the Greek god of dreams, Morpheus. More than 100 years later, the first fully synthetic opioid, meperidine, was produced and thought to be safer and less addictive than morphine. The drive to synthesize less addictive medications has been a goal for both researchers and marketers, although the results have not always been successful.[1]

Tramadol was first patented in 1963 and launched under the name *Tramal* in 1977 by the West German pharmaceutical company Grünenthal. In March 1995 it was approved by the US Food and Drug Administration, and 10 years later it was approved as an extended-release formulation.[2] While the original US product was named *Ultram*, patent exclusivity was lost in 2014, and most prescribers are familiar with the more common generic name, *tramadol* (Table 1).

According to the original product monograph, tramadol is a centrally acting analgesic agent that is a synthetic analog of codeine but has a relatively low affinity for opiate receptors. For this reason, it was originally marketed as a prescription medication but was not classified as a controlled substance; it did not meet the criteria of the Controlled Substances Act, which assigns all substances into 1 of 5 schedules based on the substance's medical use, potential for abuse, and safety or dependence liability (Table 2).[3]

Shortly after the approval of tramadol, however, diversion and abuse of the drug were reported, leading to changes in the product labeling by the US Food and Drug Administration and the addition of warnings about its abuse potential.[4-7] On July 1, 2014, the US Drug Enforcement Administration Diversion Control Division published a final rule that assigned tramadol to Schedule IV of the Controlled Substances Act.[8] The product monograph now states, "[Tramadol] is an opioid agonist indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."[9]

Not all practitioners were aware of the new labeling and classification of tramadol, and by 2018, against the backdrop of the opioid epidemic, it became the 25th most commonly prescribed medication in the United States, with more than 36.5 million prescriptions written.[7,10]

Another notable driver of tramadol's increased prescribing includes the upregulation of hydrocodone-containing products on October 6, 2014, from Schedule III to Schedule II.[11] Prescriptions for Schedule II controlled substances are generally provided to pharmacies through written prescriptions only, and refills are not permitted.[11] Americans consume more than 99% of the world supply of hydrocodone-containing products, and these were the most commonly prescribed prescription medications in the United States from 2007 through 2011, with more than 131 million prescriptions provided to 47 million patients in 2011 alone.[12] After the upregulation of hydrocodone-containing products to Schedule II status, the number of tramadol prescriptions increased dramatically between 2013 and 2015 for all states.[13] The greatest increase was in California, where the number of tramadol prescriptions per 100 people increased from 0.2 in 2013 to roughly 10 in 2015.[13]

The rescheduling of hydrocodone-containing products, coupled with the additional logistical requirement for written prescriptions only, was intended to help increase safe prescribing practices of these agents and fight the opioid epidemic. An unintended consequence, however, has been the overprescribing of commonly used alternatives to Schedule II medications, such as codeine-containing products and tramadol-containing products, which may be prescribed verbally or electronically in all practice settings and remain the only opioid analgesics for which refills may be issued. The greater numbers of prescriptions have, in turn, contributed to an increased rate of drug overdose deaths involving synthetic opioids such as tramadol. According to the US Centers for Disease Control and Prevention, this rate increased by 10% in a 1-year period, from 9.0 in 2017 to 9.9 in 2018 (data do not include methadone).[14]

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Tramadol has a unique dual mechanism of pain relief.[15] It has central opiate receptor agonist activity and exerts an analgesic

Table 1. Tramadol formulations currently available in the United States.

Brand name	Formulation	Manufacturer
Ultram	Tramadol hydrochloride, 50 mg tablet	Janssen Pharmaceuticals
Multiple generics	Tramadol hydrochloride, 50 mg tablet	Multiple generics
Generic	Tramadol hydrochloride, 100 mg tablet	TruPharma
ConZip	Tramadol hydrochloride, 100 mg, 200 mg, or 300 mg ER capsule	Vertical Pharmaceuticals
Generic	Tramadol hydrochloride, 100 mg, 200 mg, or 300 mg ER capsule	Trigen Laboratories
Multiple generics	Tramadol hydrochloride, 100 mg, 200 mg, or 300 mg ER tablet	Multiple generics
Generic	Tramadol hydrochloride, 150 mg ER capsule	SA3 Pharma
Ultracet	Tramadol hydrochloride/acetaminophen, 37.5 mg/325.0 mg tablet	Janssen Pharmaceuticals
Multiple generics	Tramadol hydrochloride/acetaminophen 37.5 mg/325.0 mg tablet	Multiple generics

Abbreviation: ER, extended release.

Table 2. Definitions and examples of US Drug Enforcement Administration controlled substance scheduling.[3]

Schedule	Definition	Examples
I	Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.	Heroin, lysergic acid diethylamide (LSD); marijuana (cannabis); peyote; methaqualone; and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
II	Substances in this schedule have a high potential for abuse which may lead to severe psychological or physical dependence.	Codeine; hydrocodone; fentanyl (Sublimaze; Duragesic); hydromorphone (Dilaudid); methadone (Dolophine); meperidine (Demerol); morphine; opium; and oxycodone (OxyContin, Percocet)
III	Substances in this schedule have less potential for abuse than substances in Schedules I or II, and abuse may lead to moderate or low physical dependence or high psychological dependence.	Buprenorphine (Suboxone); ketamine; and products containing ≥ 90 mg of codeine per dosage unit (acetaminophen with codeine)
IV	Substances in this schedule have less potential for abuse than substances in Schedule III.	Alprazolam (Xanax); carisoprodol (Soma); clonazepam (Klonopin); clorazepate (Tranxene); diazepam (Valium); lorazepam (Ativan); midazolam (Versed); temazepam (Restoril); triazolam (Halcion); and tramadol-containing products
V	Substances in this schedule have less potential for abuse than substances in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.	Cough preparations containing ≥ 200 mg of codeine per 100 mL or per 100 g (Robitussin Ac, Phenergan-Codeine); ezogabine

effect through binding of the parent drug and the O-desmethyltramadol metabolite (M1) to μ receptors.[15-17] The relative contribution of tramadol and M1 to human analgesia is dependent on the plasma concentrations of each compound. The affinity of tramadol for μ receptors is 10 times less than that of codeine, 60 times less than that of propoxyphene, and 6000 times less than that of morphine. The M1 metabolite has 4 to 200 times greater affinity for the μ receptor than tramadol.[15-17]

Tramadol also inhibits the reuptake of norepinephrine and serotonin, thus increasing the concentrations of these 2 neurotransmitters in the central nervous system.[18] Since endogenous norepinephrine and serotonin are involved in pain modulation, they may also mediate the analgesic effect of tramadol.

The hepatic microsomal CYP2D6 enzyme is responsible for breaking down tramadol into the active metabolite M1.[19] Some individuals carry more than 2 copies of the enzyme, and these ultrarapid metabolizers break down tramadol into M1 quickly; thus, individuals who take even normal doses of tramadol may develop opioid toxicity.[20] Tramadol-induced analgesia is only partially antagonized by the opiate-competitive antagonist naloxone. Regardless, if it is known that a patient has overdosed on tramadol, administration of naloxone is recommended, and most people require repeated doses or a continuous intravenous infusion.[21]

Box. Potentially significant drug-drug interactions with tramadol.

Drugs that may cause additive central nervous system depression

- Alprazolam (Xanax)
- Buspirone (Buspar)
- Clonazepam (Klonopin)
- Codeine
- Cyclobenzaprine (Flexeril)
- Diazepam (Valium)
- Eszopiclone (Lunesta)
- Gabapentin (Neurontin)
- Hydrocodone (Vicodin)
- Hydroxyzine (Atarax)
- Lorazepam (Lorazepam)
- Meperidine (Demerol)
- Metaxalone (Skelaxin)
- Midazolam (Versed)
- Oxycodone (OxyContin)
- Ramelteon (Rozerem)
- Risperidone (Risperdal)
- Temazepam (Restoril)
- Triazolam (Halcion)
- Zaleplon (Sonata)
- Zolpidem (Ambien)

Drugs that may increase the risk of seizures

- Bupropion (Wellbutrin)
- Ciprofloxacin (Cipro)
- Levofloxacin (Levaquin)
- Lithium
- Moxifloxacin (Avelox)

Drugs that may increase the risk of serotonin syndrome

- Citalopram (Celexa)
- Duloxetine (Cymbalta)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac)
- Ondansetron (Zofran)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Sumatriptan (Imitrex)
- St. John's wort
- Trazodone (Desyrel)
- Venlafaxine (Effexor)
- Vortioxetine (Trintellix)
- Zolmitriptan (Zomig)

Table 3. Analgesic use according to pain level.[23-26]

Anticipated pain level	Oral analgesic options
Mild	Ibuprofen, 200-400 mg, as needed every 4-6 h
Mild to moderate	Ibuprofen, 400-600 mg, at fixed intervals of every 6 h for 24 h *then* Ibuprofen, 400 mg, as needed every 4-6 h
Moderate to severe	Ibuprofen, 400-600 mg, plus acetaminophen, 500 mg, at fixed intervals of every 6 h for 24 h *then* Ibuprofen, 400 mg, plus acetaminophen, 500 mg, as needed every 6 h
Severe	Ibuprofen, 400-600 mg, plus acetaminophen/hydrocodone, 650 mg/10 mg, at fixed intervals of every 6 h for 24-48 h *then* Ibuprofen, 400-600 mg, plus acetaminophen, 500 mg, as needed every 6 h

Tramadol has a comparatively long duration of action—5 to 6 hours—and an elimination half-life of 7 hours. For moderate to severe pain, most adults require 25 mg once daily as a starting dose, which may be titrated to 100 mg/d by increasing it by 25 mg/d as separate doses every 3 days (25 mg 4 times daily). Usual doses are 50 to 100 mg every 4 to 6 hours as needed, with a maximum recommended total daily dose of 400 mg.[22]

As an opioid, tramadol exposes users to the risks of addiction, abuse, and misuse. It is contraindicated in patients who have suicidal ideation or are addiction-prone, and it should be used with caution in patients who are taking central nervous system–active drugs (including tranquilizers, antidepressants, or alcohol in excess) and patients who suffer from emotional disturbance or depression.[22] Seizures have been reported in patients receiving tramadol within the recommended dosage range, and tramadol should be avoided in patients with known or suspected gastrointestinal obstruction, significant respiratory depression, acute asthma, or severe asthma. Tramadol is contraindicated in pregnant patients and is incompatible with breastfeeding.[22] Prescribers should be aware of potential interactions between tramadol and other commonly used drugs (Box).

Pain management in dentistry

A flexible analgesic strategy for the management of acute orofacial pain was developed in 1995 by the American Association of Endodontists and has been updated by others (Table 3).[23-26] Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be more effective at reducing acute dental pain than opioid analgesics and are therefore recommended as the preferred therapy for pain management. In fact, the American Dental Association House of Delegates adopted a statement that reads, "Dentists should consider nonsteroidal anti-inflammatory analgesics as the first-line therapy for acute pain management."[26] For situations in which NSAIDs alone are not effective, the combination of an NSAID with acetaminophen is recommended.[27] The American Dental Association has never advocated that tramadol be used for the management of dental pain.

Evidence-based use

The question becomes, does tramadol have a role in treating acute pain? In a study of 400 outpatients with moderate or severe pain after dental surgery, tramadol, in doses of 50, 75, or 100 mg, provided better analgesia than placebo ($P < 0.05$).[28] Since the completion of this early trial to show efficacy versus placebo, tramadol has been compared with many active drugs for pain associated with dental surgery. Mehlisch et al compared single doses of oral tramadol hydrochloride (75 or 150 mg), codeine (60 mg), and acetaminophen/propoxyphene hydrochloride (650 mg/65 mg) in 239 patients with pain after tooth extraction, and tramadol was found to be more effective than codeine.[29]

Moore et al compared tramadol (50 or 100 mg), codeine (60 mg), aspirin (650 mg) with codeine (60 mg), and a placebo

in a study using the third molar extraction model.[30] Over the first 3 hours postoperatively, total pain relief scores were highest for the patients receiving aspirin with codeine. After 6 hours postoperatively, there was no significant difference in pain intensity between patients who received aspirin with codeine and either tramadol dose. Tramadol, in doses of 100 or 50 mg, was superior to codeine, and no difference was observed between codeine and the placebo. Within the 6-hour study period, a high rate of subjects received the rescue medication (85.2%), and the authors concluded that that none of the agents used in the study was appropriate for 6-hour therapy.[30]

In a subsequent literature review, Moore stated that tramadol may have limited utility for management of acute pain in dentistry; however, there may be some therapeutic advantage if tramadol is combined with a peripherally acting analgesic such as acetaminophen or an NSAID.[31] Possible indications for use in dentistry can include cases where the potential for gastrointestinal adverse events contraindicate NSAIDs or where aspirin with codeine combinations are poorly tolerated or contraindicated.[31]

In a 2016 systematic review of randomized controlled trials, Aminoshariae et al reported on studies that investigated the effect of opioids versus NSAIDs.[27] They found that NSAIDs were more effective than tramadol or acetaminophen combined with codeine in reducing endodontic pain.[27,32,33] Another analysis of active comparators found tramadol to be the least effective analgesic versus ibuprofen and celecoxib.[34]

The objective of a 2019 cohort study by Thiels et al was to determine the risk of prolonged opioid use in patients receiving tramadol compared with other short-acting opioids.[35] Despite tramadol being the third most prescribed medication behind hydrocodone and short-acting oxycodone, the authors noted a 6% increase in the risk of additional opioid use and a 47% increase in the risk of persistent opioid use, defined as any span of opioid use starting in the 180 days after surgery and lasting at least 90 days. The authors concluded, "…clinicians prescribing tramadol for acute pain should exercise a level of caution similar to that surrounding the prescribing of other short acting opioids, including those on higher Drug Enforcement Administration schedules."[35]

Conclusion

Tramadol is an opioid analgesic, and opioid activity is the overriding contributor to its pharmacologic effects. Abuse of and adverse events related to tramadol are similar to those of other opioid analgesics, and this safety-versus-efficacy profile fails to justify its consideration as a first- or even second-line agent for postoperative dental pain ahead of acetaminophen and NSAIDs.

Author affiliations

Vizient Pharmacy Advisory Solutions, Irving, Texas (Donaldson); Skaggs School of Pharmacy, University of Montana, Missoula (Donaldson); School of Dentistry, Oregon Health & Sciences University, Portland (Donaldson); Faculty of Dentistry, University of British Columbia, Vancouver (Donaldson); Premier Dental Products Company, Plymouth Meeting, Pennsylvania (Goodchild); Department of Oral and Maxillofacial Surgery, Creighton University School of Dentistry, Omaha, Nebraska (Goodchild); Division of Oral Diagnosis, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Newark, New Jersey (Goodchild).

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References

1. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health.* 2009;99(2):1-7.
2. *Physicians' Desk Reference*. 50th ed. Medical Economics Company; 1996.
3. Drug Enforcement Administration Diversion Control Division. Controlled substance schedules. Accessed April 18, 2021. https://www.deadiversion.usdoj.gov/schedules/
4. Goeringer KE, Logan BK, Christian GD. Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers. *J Anal Toxicol.* 1997;21 (7):529-537.
5. Lusthof KJ, Zweipfenning PG. Suicide by tramadol overdose. Letter. *J Anal Toxicol*. 1998;22(3):260.
6. Liu ZM, Zhou WH, Lian Z, et al. Drug dependence and abuse potential of tramadol. *Zhongguo Yao Li Xue Bao*. 1999;20(1):52-54.
7. Drug Enforcement Administration, Department of Justice. Schedule of controlled substances: placement of tramadol into schedule IV. Final rule. *Fed Regist*. 2014;79(127): 37623-37630.
8. Drug Enforcement Administration Diversion Control Division, Drug & Chemical Evaluation Section. Tramadol. March 2020. Accessed April 18, 2021. https://www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf
9. Janssen Pharmaceuticals. Ultram. Highlights of prescribing information. Updated March 2021. Accessed April 18, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020281s048lbl.pdf
10. ClinCalc DrugStats Database. The top 300 of 2021. ClinCalc.com. Accessed April 18, 2021. https://clincalc.com/DrugStats/Top300Drugs.aspx
11. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: rescheduling of hydrocodone combination products from schedule III to schedule II. Final rule. *Fed Regist*. 2014;79(163):49661-49682.
12. Traynor K. FDA advisers support rescheduling of hydrocodone products. *Am J Health Syst Pharm*. 2013;70(5):383-384.
13. Harrison ML, Walsh TL. The effect of a more strict 2014 DEA schedule designation for hydrocodone products on opioid prescription rates in the United States. *Clin Toxicol (Phila)*. 2019;57(11):1064-1072.
14. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999-2018. Centers for Disease Control and Prevention National Center for Health Statistics. NCHS Data Brief No. 356. January 2020. Accessed April 18, 2021. https://www.cdc.gov/nchs/products/databriefs/db356.htm
15. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther*. 1992;260(1):275-285.
16. Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittelforschung*. 1988;38(7):877-880.
17. Dayer P, Collart L, Desmeules J. The pharmacology of tramadol. *Drugs*. 1994;47(Suppl 1):3-7.
18. Kayser V, Besson JM, Guilbaud G. Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. *Eur J Pharmacol*. 1992;224(1):83-88.
19. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993;46(2):313-340.
20. Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. Clin *Pharmacol Ther*. 1996;60(6):636-644.
21. Schiller EY, Goyal A, Mechanic OJ. Opioid overdose. StatPearls. Updated Nov 20, 2020. Accessed April 18, 2021. https://www.statpearls.com/ArticleLibrary/viewarticle/26226
22. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43(13):879-923.
23. American Association of Endodontists. Management of acute pain. *Endodontics: Colleagues for Excellence*. Newsletter. Spring/Summer 1995:1-4.
24. Hersh EV, Kane WT, O'Neil MG, et al. Prescribing recommendations for the treatment of acute pain in dentistry. *Compend Contin Educ Dent*. 2011;32(3):22, 24-30.
25. Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. *J Am Dent Assoc*. 2013;144(8):898-908.

26. American Dental Association. Oral analgesics for acute dental pain. Updated September 15, 2020. Accessed April 27, 2021. https://www.ada.org/en/member-center/oral-health-topics/oral-analgesics-for-acute-dental-pain
27. Aminoshariae A, Kulild JC, Donaldson M, Hersh EV. Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: a systematic review of randomized controlled trials. *J Am Dent Assoc*. 2016;147 (10):826-839.
28. Sunshine A. New clinical experience with tramadol. *Drugs*. 1994;47(Suppl 1):8-18.
29. Mehlisch DR, Minn F, Brown P. Tramadol hydrochloride: efficacy compared to codeine sulfate, acetaminophen with dextropropoxyphene, and placebo in dental extraction pain. *Clin Pharmacol Ther*. 1990;47:187.
30. Moore PA, Crout RJ, Jackson DL, Schnieder LG, Graves RW, Bakos L. Tramadol hydrocholoride: analgesic efficacy compared with codeine, aspirin with codeine, and placebo after dental extraction. *J Clin Pharmacol*. 1998;38(6): 554-560.
31. Moore PA. Pain management in dental practice: tramadol vs. codeine combinations. *J Am Dent Assoc*. 1999;130 (7):175-179.
32. Sadeghein A, Shahidi N, Dehpour AR. A comparison of ketorolac tromethamine and acetaminophen codeine in the management of acute apical periodontitis. *J Endod*. 1999;25(4):257-259.
33. Mehrvarzfar P, Abbott P, Saghiri M, et al. Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial. *Int Endod J*. 2012;45 (1):76-82.
34. Akinbade AO, Ndukwe KC, Owotade FJ. Comparative analgesic effects of ibuprofen, celecoxib and tramadol after third molar surgery: a randomized double blind controlled trial. *J Contemp Dent Pract*. 2018;19(11):1334-1340.
35. Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. *BMJ*. 2019;365:l1849. doi:10.1136/bmj.l1849