

Tramadol and Tapentadol: Clinical and Pharmacologic Review

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KEY POINTS

- Tramadol has 3 distinct mechanisms of analgesia. The parent compound is a norepinephrine reuptake inhibitor and a serotonin reuptake inhibitor.
- Tramadol also is an opioid prodrug and depends on CYP enzymes to be converted to its active form O-desmethyl tramadol for opioid activity, which means some people may have enhanced or reduced opioid therapeutic or side effects from tramadol use due to variable CYP expression or coadministration of CYP enzyme-inhibiting/–inducing medication.
- Many of the adverse effects from tramadol are attributed to serotonin reuptake inhibition. These include nausea, dizziness, a reduction in seizure threshold, and the potential to induce serotonin syndrome.
- Tapentadol is an active drug, not a prodrug, whose mechanism of action is due to moderate mu receptor agonism and a norepinephrine reuptake inhibition. It has a negligible effect on serotonin reuptake.
- Tapentadol has fewer gastrointestinal side effects compared with opioids such as oxycodone, and some authors have suggested it can provide equal analgesia to other strong opioids in an acute pain setting.
- Both tramadol and tapentadol have a lower risk of abuse in comparison with opioids.

INTRODUCTION

Tramadol was first approved for use in humans in Germany in 1977, after being developed in 1962.¹ Tramadol has a unique, triple mechanism of action. The parent compound is a serotonin and norepinephrine reuptake inhibitor. The parent compound has extremely poor affinity for the mu opioid receptor, rendering it without any clinically significant opioid effect; however, demethylation via CYP450 2D6 oxidative mechanisms yields the active M1 metabolite that does have modest mu opioid receptor activity. These pharmacologic properties provide good analgesia while minimizing opioid-related adverse-effects. Unfortunately, these same properties put certain patient populations at risk for serotonin syndrome, lowering of the seizure threshold, and high interindividual variability in common side effects including nausea and dizziness. Therefore, work began to find a serotonin-free version of tramadol, and in the 1980s, tapentadol was created.

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TRAMADOL

Pharmacology

Tramadol is a centrally acting analgesic used for moderate to severe pain. Tramadol acts as both a reuptake inhibitor of the monoamines norepinephrine and serotonin and as a weak opioid agonist effect.¹ The inhibition of serotonin reuptake results in an increased risk of serotonin syndrome in persons taking tramadol with other serotonergic medications.² Tramadol has 2 chiral centres and is a 1:1 racemic mixture of 2 diastereomeric enantiomers, which have differing potencies with respect to monoamine reuptake inhibition.²

Dose and Formulation

Tramadol is produced as an oral formulation, intravenous solution, and a rectal suppository. Local regulations may limit specific formulation availability. Tramadol is available as immediate-release and delayed-release formulations as well as combined with paracetamol (acetaminophen). Various strengths are available, with the most common dosage range between 25 and 300 mg.³⁻⁵

Tramadol is indicated for use in moderate to severe pain. The recommended total daily dosage is 25 to 100 mg every 4 to 6 hours. The recommended maximum daily dose is 400 mg in adults. This is on account of the propensity for problems related to the serotonergic aspects of the molecule as stated above. Because of this dose limitation, tramadol may not be efficacious enough for severe pain situations and typically is used as a weak opioid (ie, step 2 in the World Health Organization acute pain ladder). This may necessitate prescribing a “step 3” opioid such as morphine or hydromorphone to patients where severe pain is present.

Pharmacokinetics

The oral formulation of tramadol is rapidly and almost completely absorbed with a bioavailability of 68% after the first dose and 90% after repeated doses.² Tramadol is converted to active and inactive metabolites in the liver by the cytochrome P450 enzyme system (CYP450).¹ The major metabolite, O-desmethyltramadol (M1), is produced by the CYP 2D6 enzyme and is approximately 400 times more potent than the parent compound.² CYP 2D6 further metabolizes M1 into N,O-didesmethyltramadol (M5), which is also active but less potent than both M1 and the parent compound. When CYP 2D6 becomes saturated, metabolism is carried out by the enzymes CYP 2B6 and CYP 3A4, which are responsible for producing the inactive metabolite N-desmethyltramadol (M2). Both M1 and M2 are further degraded into inactive compounds. Phase 2 metabolism of M1 occurs in the liver to create an inactive compound. Tramadol and its metabolites are renally excreted.²

Coadministration of tramadol with CYP450 enzyme inhibitors or inducers should be avoided as these will alter the metabolism, produce variable clinical effects, and potentially increase adverse effects. Examples of strong CYP 2D6 inhibitors that may cause less opioid effect for a given dose of tramadol include paroxetine, fluoxetine, bupropion, quinidine, and terbinafine. CYP 2D6 inducers, which cause a greater opioid effect for a given dose of tramadol, are less common. Examples include rifampicin, dexamethasone, and haloperidol.⁶ A comprehensive list of CYP inducers and inhibitors can be found at the SuperCYP comprehensive database of cytochrome P450 enzymes.⁷

Genetic variation in CYP 2D6 enzyme activity is well characterized, and individuals can be categorized into 4 groups: (1) poor metabolizers, (2) intermediate metabolizers, (3) extensive metabolizers, or (4) ultra-rapid metabolizers.⁸ Extensive and ultra-rapid metabolizers will have more opioid effect from an equivalent dose of tramadol.⁹ Genetic testing has shown regional and racial variability in the prevalence of the above 4 phenotypes. Of note, high concentrations of extensive and ultra-rapid metabolizers have been found in Southern Europe, the Middle East, and Northeast Africa.^{10,11}

After ingestion of an immediate-release formulation, peak plasma levels are observed after 3 hours and are sustained for 5 to 7 hours. Delayed-release formulations have peak plasma levels around 12 hours, with an approximately 4-fold increase in duration compared with the immediate-release formulation.^{3,12}

Special Groups

Dosage adjustment is necessary in patients with impaired renal function,² and only 7% of a given tramadol dose is removed by dialysis.¹¹

Tramadol is labelled as US Food and Drug Administration (FDA) pregnancy category C, which means there may be risk but it has not been adequately studied in this population.

There is controversy over the use of tramadol during breast-feeding. In 2017, the US FDA released a “strengthened warning” (their second strongest warning) against the use of tramadol while breast-feeding.¹³ The rationale given is that tramadol is metabolized to an active metabolite by the CYP2D6 enzyme, similarly to how codeine is metabolized to morphine. There have been many reports of infant morbidity and mortality related to codeine use in breast-feeding mothers due to the genetic

variation in CYP2D6 activity resulting in infants receiving a much larger dose of the active metabolite, morphine, than anticipated.^{13,14} There have been no reports of adverse events in infants breast-fed by mothers who are receiving tramadol for analgesic purposes. There is 1 case report of suspected opioid-related toxicity in a breast-fed infant whose mother was abusing tramadol.¹⁵ Pharmacokinetic studies have found a relative infant dose (RID) of 2.24% for tramadol and 0.64% for the M1 metabolite.¹⁶ Poor metabolizers are estimated to receive an RID of 2.6% for tramadol and 0.47% for M1, compared with extensive metabolizers, which are estimated to receive an RID of 2.2% for tramadol and 0.93% for M1.¹⁷ The combined RID is well below 10%, which is the threshold of concern for transfer of drugs to breast milk. Both the UK Drugs in Lactation Advisory Service and the Society for Pediatric Anesthesia in New Zealand and Australia have published statements recommending the continued use of tramadol in breast-feeding patients, despite the US FDA warning, based on a review of the same evidence.^{18,19} Any breast-feeding infant whose mother is taking opioid-based medications, including tramadol, should be closely observed for any signs of respiratory distress, lethargy, or poor feeding.

Cautions

Tramadol has been found to lower the seizure threshold in both patients with and without a preexisting seizure disorder.³ The phenomenon is likely due to serotonergic activity and can occur in patients taking therapeutic and supratherapeutic doses. The risk appears to be greater with supratherapeutic doses or with co-ingestion of other medications that lower the seizure threshold, such as bupropion.^{3,5} Caution should be used if co-prescribing these types of medications.

Tramadol is thought to be a drug of abuse because of its weak opioid activity; however, rates of abuse have not been well characterized.^{5,20} However, chronic use of the medication may lead to physical dependence.²¹

A recent World Health Organization (WHO) report indicates that abuse may be prevalent throughout North America, the Middle East, Asia, and West Africa.⁵ Formal studies in humans are scarce.²⁰ To date, 1 study in humans has evaluated tramadol dependence. The study patients received up to 400 mg/d of tramadol for the treatment of severe pain. After 3 weeks of treatment, patients were randomized to intramuscular naloxone or placebo 3 hours after the last tramadol ingestion. Three of 54 patients receiving naloxone and 1 of 52 patients receiving placebo reported signs of opioid withdrawal, which may indicate a low potential for dependence.²² Deaths have been reported in association with tramadol use. In Northern Ireland, there has been an increase of 10% in the number of tramadol-related deaths between 1996 and 2012.²³

The euphoric effects of tramadol may be dose dependent, as evidenced by the ability of blinded nondependent tramadol users to identify 300-mg tablets but not lower doses after ingestion.²⁴ In a separate study, nondependent volunteers were able to discern between the opioid properties and stimulant properties of tramadol at varying doses. Doses below 100 mg were identified as placebo, doses between 200 and 400 mg were noted to produce similar effects to hydromorphone, and doses greater than 400 mg were noted to have stimulant-like effects.²⁵ Despite the similar effects of tramadol to other known drugs of abuse (opioids and stimulants), it is important to note that there is currently no high-quality evidence directly linking these effects with drug-seeking behaviour in humans.

Evidence for Use

Tramadol has evidence for use in a variety of conditions, including osteoarthritis, neuropathic pain, and cancer pain.

A meta-analysis of 11 randomized controlled trials with a combined total of 1019 participants found that participants who received tramadol had a 12% reduction in pain intensity on a visual analogue scale (VAS) between 0 and 100 compared with participants who used placebo (95% confidence interval [CI]: -12.0 to -5.0 units less). However, persons using tramadol were more than 2 times more likely to report any adverse event compared with persons using placebo.²⁶

A second meta-analysis found that tramadol may be beneficial in some people with moderate or severe neuropathic pain. This study included 6 randomized controlled trials with a combined 438 participants. Although the included studies were judged to be of poor quality, the authors report a risk ratio of 2.2 (95% CI: 1.02-4.6) and a number needed to treat of 4.4 (95% CI: 2.9-8.8), indicating that 5 persons need to be treated with tramadol for 1 to experience at least a 50% reduction in neuropathic pain intensity. Once again, there were more adverse events in the tramadol-treated participants.²⁷

Tramadol may not be useful for chronic tumour-related pain. A meta-analysis of 10 studies including 958 participants was attempted, but all located studies were judged to be of poor quality. Despite this, the located studies seemed to indicate that tramadol may be less effective than morphine for treating chronic cancer pain.²⁸

TAPENTADOL

Tapentadol is a novel analgesic with multiple mechanisms of action. It was developed in the 1980s to address the adverse effects associated with tramadol's serotonin reuptake inhibition. Tapentadol was approved by the FDA in 2008 and approved in Europe in 2010.

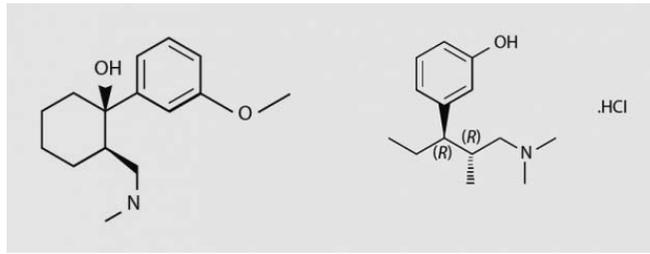


Figure. Chemical structure of tramadol (left) and tapentadol (right).³⁰

Pharmacology

Tapentadol is a unique, centrally acting opioid of the aromatic hydrocarbon benzenoid class²⁹ (Figure).

Tapentadol is a nonracemic molecule and, unlike tramadol, is not a prodrug. Its analgesic effect is produced through moderate opioid receptor agonism and norepinephrine reuptake inhibition. Clinical trials have shown that the analgesic potency of tapentadol is quite good; tapentadol 50 mg has an analgesia equivalent to 10 mg of oxycodone. When used in the patient able to take oral analgesics, a WHO acute pain ladder step 3 opioid is usually not required. This provides added convenience, as tapentadol is able to fulfil the role of weak and strong opioid in the acute pain ladder by simply adjusting the dose. Tapentadol at 600 mg per day provides 3 times the analgesic efficacy of tramadol 400 mg. Tapentadol is a weak serotonin reuptake inhibitor that is not considered clinically relevant.

Dose and Formulation

Tapentadol is available as 25-, 50-, 75-, and 100-mg tablets. The recommended maximum dose is 600 to 700 mg daily for an adult without significant contraindications. The immediate-release and extended release formulations are equipotent. At present, there is no commercially available intravenous preparation. It has been suggested that tapentadol 50 to 100 mg every 4 to 6 hours has equal analgesic effect to oxycodone, 10 to 15 mg every 4 to 6 hours for moderate to severe acute pain.

Pharmacokinetics

The oral bioavailability of tapentadol is 32%. The volume of distribution is approximately 540 ± 98 L, and 20% of the drug is protein bound. Because of low protein binding, there is a low potential for interactions with other medications.

Tapentadol is 97% metabolized to inactive metabolites, primarily via glucuronidation.³¹ Unlike tramadol, tapentadol is not affected by CYP activity.³² Tapentadol is 99% renally eliminated and follows first-order kinetics. The clearance is 1530 ± 177 mL/min. The extended-release formulation has a mean terminal half-life shown to range between 4.4 and 5.9 hours.³³

Special Groups

Tapentadol is not recommended in severe renal or hepatic impairment. It can be used with caution in moderate hepatic impairment. This does not contraindicate its use in geriatric patients, although caution should be used in this population.

Tapentadol is labelled as FDA pregnancy category C, which is similar to tramadol and oxycodone. It is not recommended by the FDA for use during breast-feeding.³⁴ Animal studies show tapentadol is excreted in breast milk.³⁵ There are no human studies available at this time. Use during breast-feeding is not recommended by either the FDA or the UK Specialty Pharmacy Service.³⁶

Cautions

Contraindications to tapentadol include impaired pulmonary function in an unmonitored setting (for example acute, severe asthma), monoamine oxidase inhibitor use in the past 14 days, and paralytic ileus.

There may be a lower incidence of abuse with tapentadol compared with other opioids; however, since FDA approval, tapentadol has been consistently shown to have a low, but present, event rate for abuse.³⁷ In fact, the US FDA has classified tapentadol in the same drug grouping as hydromorphone and morphine.³⁸

Evidence for Use

The analgesic benefit of tapentadol has been clinically demonstrated in the context of acute pain, such as in orthopaedic and cardiac surgery, as well as in nonoperative settings such as chronic low-back pain and cancer-related pain.

In 2009, a randomized, double-blinded, placebo- and active-controlled trial of patients who underwent bunionectomy (N = 603) compared pain scores over 48 hours in patients treated with tapentadol or oxycodone. Researchers found a comparable analgesic effect between immediate-release tapentadol 100 mg with immediate-release oxycodone 15 mg and less nausea and vomiting in the tapentadol group.³⁹

In 2015, a randomized, single-centre trial compared oral tapentadol with tramadol poststernotomy for a variety of cardiac procedures, including mitral valve replacement and coronary artery bypass grafting.⁴⁰ Patients who received tapentadol reported significantly lower VAS pain scores and less nausea, vomiting, and drowsiness compared with those receiving tramadol.

Tapentadol has also been studied in chronic pain. A meta-analysis of 4 randomized control trials found that 3 of 10 people treated with tapentadol for low-back pain had 50% or more pain relief, while only 2 of 10 people treated with oxycodone demonstrated similar pain relief.⁴¹

SUMMARY

- Tramadol and tapentadol are analgesic agents with multiple mechanisms of action. They are both norepinephrine reuptake inhibitors with weak opioid agonist activity.
- Tramadol also has serotonin reuptake inhibiting properties that may be associated with some of its prominent side effects, including nausea and seizures.
- Studies have shown tapentadol and tramadol to be effective analgesics. Tapentadol may be associated with fewer adverse effects and low rates of abuse.

REFERENCES

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43(13):879-923.
2. Gong L, Stamer UM, Tzvetkov MV, Altman RB, Klein TE. PharmGKB summary: tramadol pathway. *Pharmacogenet Genomics*. 2014;24(7):374-380.
3. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. *Anesth Analg*. 2017;124(1):44-51.
4. US Food and Drug Administration. ULTRAM (tramadol hydrochlorid) tablets. Highlights of prescribing information. 2009. Revised May 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022370s000lbl.pdf.
5. World Health Organization, Expert Committee on Drug Dependence. Tramadol: update review report. June 2014. https://www.who.int/medicines/areas/quality_safety/6_1_Update.pdf.
6. US Food and Drug Administration, Center for Drug Evaluation and Research. Drug development and drug interactions: table of substrates, inhibitors and inducers. November 2017. <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1>.
7. Preissner S, Kroll K, Dunkel M, et al. SuperCYP: a comprehensive database on cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. *Nucleic Acids Res*. 2010;38:D237-D243.
8. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. *PLoS One*. 2013;8(12):e82562.
9. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin Pharmacol Ther*. 2007;82(1):41-47.
10. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics J*. 2005;5(1):6-13.
11. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol. *Anesth Analg*. 2017;124(1):44-51.
12. McCarberg B. Tramadol extended-release in the management of chronic pain. *Ther Clin Risk Manag*. 2007;3(3):401-410.
13. US Food and Drug Administration. FDA drug safety communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2017. <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM553814.pdf>. Accessed November 18, 2018.
14. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368(9536):704.
15. Hussien R. Tramadol intoxication in an 8-months-old infant through breastfeeding: a case report. *J Clin Toxicol*. 2017;7(1):1-3.
16. Ilett KF, Paech MJ, Page-Sharp M, et al. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. *Br J Clin Pharmacol*. 2008;65(5):661-666.
17. Salman S, Sy SKB, Ilett KF, Page-Sharp M, Paech MJ. Population pharmacokinetic modeling of tramadol and its O-desmethyl metabolite in plasma and breast milk. *Eur J Clin Pharmacol*. 2011;67(9):899-908.
18. Society for Paediatric Anaesthesia in New Zealand and Australia. SPANZA advisory on tramadol - use of tramadol during breastfeeding and in the neonate. 2017. http://www.anzca.edu.au/documents/policy_spanza-tramadol_20170624.pdf. Accessed November 18, 2018.

19. Kearney L, Fenner S. UKDILAS REVIEW: FDA warning regarding tramadol use during breastfeeding. 2017. <https://www.sps.nhs.uk/articles/ukdilas-review-fda-warning-regarding-tramadol-use-during-breastfeeding/>
20. Epstein DH, Preston KL, Jasinski DR. Abuse liability, behavioral pharmacology, and physical-dependence potential of opioids in humans and laboratory animals: lessons from tramadol. *Biol Psychol.* 2006;73(1):90-99.
21. 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. <http://www.ncbi.nlm.nih.gov/pubmed/20589494>.
22. Richter W, Barth H, Flohé L, Giertz H. Clinical investigation on the development of dependence during oral therapy with tramadol. *Arzneimittelforschung.* 1985;35(11):1742-1744.
23. Randall C, Crane J. Tramadol deaths in Northern Ireland: a review of cases from 1996 to 2012. *J Forensic Leg Med.* 2014;23:32-36.
24. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug Alcohol Depend.* 1991;27(1):7-17.
25. Duke AN, Bigelow GE, Lanier RK, Strain EC. Discriminative stimulus effects of tramadol in humans. *J Pharmacol Exp Ther.* 2011;338(1):255-262.
26. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database Syst Rev.* 2006;19(3):CD005522.
27. Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. *Cochrane Database Syst Rev.* 2017;(6):CD003726.
28. Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. *Cochrane Database Syst Rev.* 2017;(5):CD012508.
29. Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: a novel analgesic. *Saudi J Anaesth.* 2013;7(3):322-326.
30. Fudin J, PharmD, DAIPM, FCCP, FASHP, Boglish P. et al. Ask The Expert: Is Tapentadol a Glorified Tramadol? [Internet]. Practical Pain Management. [cited 2019 Jul 16]. Available from: <https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/tapentadol-glorified-tramadol>.
31. Terlinden R, Ossig J, Fliegert F, Lange C, Göhler K. Absorption, metabolism, and excretion of 14C-labeled tapentadol HCl in healthy male subjects. *Eur J Drug Metab Pharmacokinet.* 2007;32(3):163-169.
32. Kneip C, Terlinden R, Beier H, Chen G. Investigations into the drug-drug interaction potential of tapentadol in human liver microsomes and fresh human hepatocytes. *Drug Metab Lett.* 2008;2(1):67-75.
33. Zannikos PN, Smit JW, Stahlberg H-J, Wenge B, Hillewaert VM, Etropolski MS. Pharmacokinetic evaluation of tapentadol extended-release tablets in healthy subjects. *J Opioid Manag.* 2013;9(4):291-300.
34. Nucynta (tapentadol hydrochloride) tablets label - FDA. October 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022304s003lbl.pdf
35. Australian public assessment report for tapentadol. 2011. <https://www.tga.gov.au/sites/default/files/auspar-palexia.pdf>.
36. Specialist Pharmacy Service. Tapentadol lactation safety information. 2015. <https://www.sps.nhs.uk/medicines/tapentadol/>
37. Vosburg SK, Severtson SG, Dart RC, et al. Assessment of tapentadol API abuse liability with the researched abuse, diversion and addiction-related surveillance system. *J Pain Off J Am Pain Soc.* 2018;19(4):439-453.
38. Gabay M. The federal controlled substances act: schedules and pharmacy registration. *Hosp Pharm.* 2013;48(6):473-474. <http://www.ncbi.nlm.nih.gov/pubmed/24421507>.
39. Daniels SE, Upmalis D, Okamoto A, Lange C, Häeussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin.* 2009;25(3):765-776.
40. Iyer SK, Mohan G, Ramakrishnan S, Theodore S. Comparison of tapentadol with tramadol for analgesia after cardiac surgery. *Ann Card Anaesth.* 2015;18(3):352.
41. Santos J, Alarcão J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2015;(5):CD009923.



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