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NARRATIVE REVIEW ARTICLE

Trends in Tramadol: Pharmacology, Metabolism, and Misuse

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Tramadol is a unique analgesic medication, available in variety of formulations, with both monoaminergic reuptake inhibitory and opioid receptor agonist activity increasingly prescribed worldwide as an alternative for high-affinity opioid medication in the treatment of acute and chronic pain. It is a prodrug that is metabolized by cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to its more potent opioid analgesic metabolites, particularly the *O*-demethylation product M1. The opioid analgesic potency of a given dose of tramadol is influenced by an individual's CYP genetics, with poor metabolizers experiencing little conversion to the active M1 opioid metabolite and individuals with a high metabolic profile, or ultra-metabolizers, experiencing the greatest opioid analgesic effects. The importance of the CYP metabolism has led to the adoption of computer clinical decision support with pharmacogenomics tools guiding tramadol treatment in major medical centers. Tramadol's simultaneous opioid agonist action and serotonin (5-HT) and norepinephrine reuptake inhibitory effects result in a unique side effect profile and important drug interactions that must be considered. Abrupt cessation of tramadol increases the risk for both opioid and serotonin–norepinephrine reuptake inhibitor withdrawal syndromes. This review provides updated important information on the pharmacology, pharmacokinetics, CYP genetic polymorphisms, drug interactions, toxicity, withdrawal, and illicit use of tramadol. (Anesth Analg 2017;124:44–51)

Tramadol has been well studied for the treatment of multiple types of chronic moderate to moderately severe pain conditions. Two Cochrane meta-analyses evaluating tramadol concluded that it is efficacious in neuropathic pain[1] and pain related to osteoarthritis.[2] There are also more recent positive Cochrane reviews for the treatment of low back pain and rheumatoid arthritis.[3,4] The evidence for its efficacy in the treatment of acute and postoperative pain is mixed,[5–7] although the analgesic response can be improved in combination with nonopioid analgesics. Most of the studies of acute pain have been done with parenteral preparations that are not available in the United States. In addition to the treatment of pain, there is evidence to support the off-label use of tramadol as on-demand treatment for premature ejaculation (PE).[8–10]

Tramadol was first developed in Germany in the late 1970s, and various formulations such as drops, sustained and extended-release preparations for oral use, suppositories for rectal use, and intramuscular, IV, and subcutaneous solutions have since been launched in more than 100 countries worldwide.[11] It was approved by the US Food and Drug Administration (FDA) in 1995 as the only nonscheduled opioid available. As with other opioids, the expansion of worldwide availability of tramadol has resulted in an increase in abuse and diversion. Consequently, a more restrictive scheduling has been adopted in many countries including the United States, where it became a Schedule IV substance in 2014.

Tramadol is a centrally acting synthetic opioid medication with monoaminergic actions similar to serotonin-norepinephrine reuptake inhibitors (SNRIs). Tramadol, as well as a similar dual-action analgesic, tapentadol, produce analgesia by affecting the nociceptive process and boosting the central modulation of pain.[12] A major difference between the 2 medications is that tapentadol exerts its effects without a pharmacologically active metabolite. In contrast, codeine and tramadol are prodrugs: codeine is metabolized into morphine, and the active metabolite of tramadol is *O*-desmethyltramadol (M1). Tramadol was originally thought to have a lower risk of constipation, respiratory depression, overdose, and addiction compared with other opioids, but CYP metabolic polymorphisms that will be described later in this review contribute to interesting phenotypic differences in the analgesic and side effect profile. The risk factors for serious adverse effects of tramadol, including serotonin syndrome and decreased seizure threshold, will also be discussed.

Use of tramadol for chronic pain or in the perioperative period requires an awareness of its unique pharmacology and special attention to the CYP450 polymorphism status, as well as an understanding of drug–drug interactions, to ensure adequate pain relief and avoidance of adverse drug effects. The emerging use of computer clinical decision support with pharmacogenomics tools guiding

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tramadol treatment is addressed. This review is timely because patients presenting to pain medicine treatment providers and for surgery are increasingly likely to have tramadol among their list of medications.

METHODS

A comprehensive literature search in the Medline electronic database for articles published between January 1980 and January 2016 was conducted for tramadol and the following keywords: pain and meta-analyses or Cochrane review, formulations, epidemiology, pharmacology, metabolism, cytochrome P450 (CYP), pharmacokinetics, drug interaction, clinical decision supports, pharmacodynamics, adverse effects, seizures, ondansetron, withdrawal, legal regulation, illicit use, abuse potential, and evaluation and treatment. Literature reviewed includes original research studies, retrospective case studies, toxicology data, chemical analysis studies, and federal and international regulation documents. Case studies involving individual use were examined and compiled for sections on adverse events. News articles identifying trends in international tramadol use were also included. Two of the authors evaluated the titles and abstracts of all collected publications and then further assessed the full text to be considered for inclusion in the review.

Tramadol Prescription Trends

Although the total number of opioid prescriptions in the United States has increased, the IMS Health National Prescription Audit revealed that between 2007 and 2011, the percent increase for tramadol (65%) was significantly greater than that of oxycodone/acetaminophen (24%) and hydrocodone/acetaminophen (13%) preparations.[13] In 2013, tramadol ranked second in the total US opioid market sales at 14.7%, between hydrocodone/acetaminophen (46%) and oxycodone/acetaminophen (13.6%). Factors contributing to this increase include the prescribers' impression that tramadol has low addiction liability and a favorable safety profile. Indeed, the reports of tramadol overdose are limited, but there are multiple case reports of adverse events because of its unique pharmacology, as discussed below.

Pharmacology

Tramadol was the first medication in its class to produce dual-analgesic effects, acting synergistically as an opioid agonist and monoaminergically as a serotonin and norepinephrine reuptake inhibitor.[11] It acts on the μ-opioid receptor as a weak agonist and acts on serotonergic and noradrenergic nociception. Tramadol has 2 chiral centers and is used as a 1:1 racemic mixture of 2 enantiomeric diastereomers, the *R*,*R*-enantiomer ([+]-tramadol) and *S*,*S*-enantiomer ([–]-tramadol). The (+)-tramadol enantiomer is the most potent serotonin reuptake inhibitor, whereas the (–)-tramadol enantiomer is the most potent norepinephrine and serotonin reuptake inhibitor.[14] By independently enhancing noradrenergic and serotonergic activity, they work together to produce effects of analgesia in the central nervous system (CNS).

Tramadol is converted by CYP450 enzymes 3A4 and 2D6 into 3 major metabolites, 2 of which are active. (+)-Tramadol and (+)-M1 metabolites both bind to the μ-opioid receptor to produce most of its opioid analgesic effects.[15–17] However, (+)-M1 is a high-affinity ligand and produces more potent analgesic effects than the parent compound, which is a low-affinity opioid agonist. There are some enantiomeric differences in analgesic potency of the 2 enantiomers of M1, with the (+)-*O*-desmethyltramadol configuration about 100 times greater than that of the (–) configuration.[15,18,19] The second metabolite, *N*,*O*-desmethyltramadol metabolite (M5), is also active and contributes to the analgesic effects.[15] Because of the high affinity of (+)-M1 for the μ-opioid receptor, its concentration, in combination with that of the M5 metabolite, is primarily responsible for the analgesic effects of tramadol.

Pharmacokinetics

As CYP450-mediated phase I metabolic reactions are slower than phase II conjugation reactions, they become rate limiting in the overall metabolic disposition of CYP substrate drugs. The phase I metabolism of tramadol, shown in Figure 1, is catalyzed by CYP2D6 and CYP3A4, with the *O*-demethylation reaction to the active M1 metabolite catalyzed by CYP2D6. Approximately 80% of tramadol is metabolized by CYP2D6, an easily saturated, low-capacity, high-affinity enzyme that represents only 1% to 5% of the liver CYP content. Because the metabolizing capacity of patients with hepatic impairment may be significantly reduced, toxicity at the recommended dose may occur, but this has not yet been studied in patients with liver disease.[20] Although metabolized in the liver, unchanged tramadol and its metabolites are mainly excreted in urine.[21] In renal impairment, there are reports of decreased clearance and a 2-fold increase in the half-life of tramadol and the M1 metabolite.[21,22] Because only 7% of an administered dose is removed by dialysis, patients may receive their regular dose of tramadol.

The *N*-demethylation to the inactive metabolite, *N*-desmethyltramadol (M2), is catalyzed by CYP2B6 and CYP3A4. CYP3A4 is responsible for the metabolism of 50% of all drugs;[16] although it exhibits polymorphisms and is subject to induction and inhibition by other substrates, few significant drug interactions between tramadol and CYP3A4 substrates have been reported.[23–25]

CYP Genetic Polymorphisms

Tramadol is bioactivated to M1, the main opioid metabolite, by CYP2D6, and there is a significant variability in the efficiency and amount of CYP2D6 enzymes among individuals. The large phenotypic variation affects the speed of metabolism and the rate of accumulation or elimination. There is increasing widespread clinical use in grouping people based on their CYP2D6 profile as follows: very low (PM or poor metabolizers) with little or no CYP2D6 function; intermediate metabolizers (IM) between poor and extensive enzymatic activity; extensive metabolizers (EM), defined as the most common level of activity; and very high (UM or ultra-metabolizers) that express multiple functional copies of the CYP2D6 gene.[26] The effect of the CYP2D6 group activity on the opioid analgesic potency and side effect profile of tramadol was demonstrated in a pharmacokinetics study by Kirchheiner et al.[17] The CYP2D6 gene duplication was evaluated following an 100-mg oral dose of tramadol.[17] The bioavailability of the active M1 metabolite was found to be

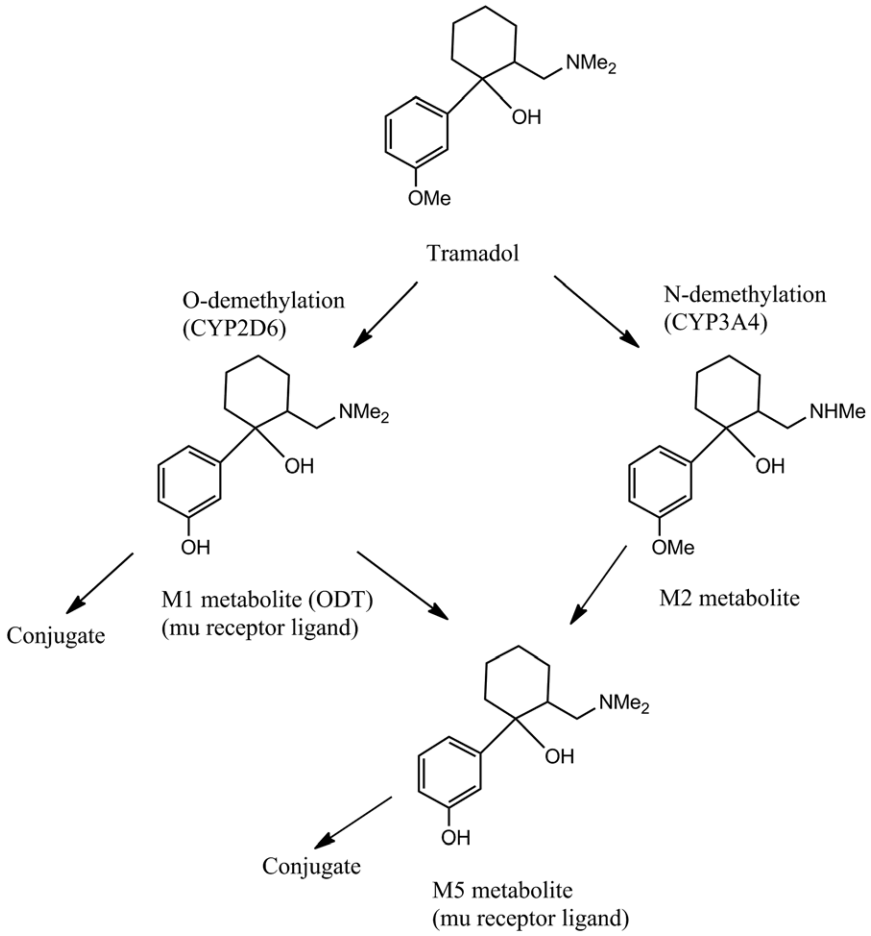

Figure 1. Key phase I metabolites of tramadol.

about 3% of the administered dose in PMs. Notably in the PM group, assays identified the highest concentrations of the parent tramadol compound.[27] In contrast, bioavailability of the M1 metabolite was 63% in EMs and 86% in UMs. Consistent with these pharmacokinetic differences, UMs exhibited a stronger opioid response including increased pain tolerance, greater miosis, and a higher frequency of nausea compared with EMs. Pharmacogenetic testing for tramadol has historically been used to explain inefficacy or toxicity. The goal of personalized medicine is advancing with the increase in availability of commercial pharmacogenetics testing kits. Drug-metabolizing enzymes represent a major target for research and testing, and panels are available to analyze the metabolism of psychotrophic and opioid medications.

Testing has identified notable racial, ethnic, and regional patterns in the prevalence of CYP genetic polymorphisms. The PM phenotype is more frequently found in African Americans, followed by 6% to 10% in the Caucasian populations with the smallest percentage found in Asian populations (1% to 2%). Conversely, UMs are concentrated in Egypt, Iran, Saudi Arabia, and Northeast Africa where tramadol-related opioid analgesic effects, addiction, nausea, and respiratory depression are more frequently reported.[26,28–30]

Tramadol Formulations

Tramadol is available in the United States only as an oral preparation. Outside the United States, it is also available in a suppository and parenteral form. Formulations include immediate-release (IR) tablets (50 mg), sustained-release (SR) tablets (100, 200, and 300 mg), and extended-release (ER) capsules (100, 200, and 300 mg). A tramadol hydrochloride/acetaminophen tablet preparation (37.5 mg tramadol HCl and 325 mg acetaminophen) is also available. The recommended maximum dose of IR is 400 mg/day and the maximum dose of the ER form is 300 mg/day. Brand names in the United States include Ultram, Ultram ER, Ultracet, ConZip, Ryzolt, and Rybix orally dissolving tablet (ODT).

For the IR preparations, the effects peak at about 3 hours after administration, but can persist for 5 to 7 hours. Mean bioavailability of IR tramadol is about 70% with a half-life of about 6 hours. The SR and ER formulations increase the bioavailability and offer more stable plasma concentrations. The tablets provide a peak concentration at about 12 hours with an elimination half-life of about 9 hours. The ConZip® ER capsules contain an IR tablet with multiple SR pellets. This preparation has biphasic release: 25% within the first 2 hours, and 75% gradually released over 24 hours with a peak plasma level at 9 hours.[31]

Drug Interactions

CYP2D6 enzymes contribute to the metabolism of approximately 25% of all medications, many of which are commonly administered to hospitalized patients receiving tramadol such as antiarrhythmics, antiemetics, antidepressants,

antipsychotics, analgesics, and tamoxifen.[32] The nature of certain tramadol drug–drug interactions involve overlapping pharmacodynamic, pharmacokinetic, and pharmacogenetic risk factors that require an appreciation of the possible interactions with certain classes of medications.

Tramadol–Ondansetron Interactions. Nausea is a prominent adverse event associated with the initial oral or IV tramadol treatment; therefore, it is important to elucidate the potential interaction between tramadol and antiemetics. In addition, most antiemetic medications that are used to prevent postoperative- and chemotherapy-induced nausea and vomiting are 5-HT_3 receptor antagonists, whereas tramadol decreases serotonin reuptake. These opposing serotonergic effects increase the risk of a pharmacodynamic interaction. In addition, the "setrons," including ondansetron, dolasetron, and palonosetron (with the exception of granisetron), are partially metabolized by CYP2D6, increasing the concern for a pharmacokinetic interaction. A review of the literature suggests that the concurrent use results in a common reduced response: tramadol is a less potent analgesic, and ondansetron is less effective as an antiemetic.[18,33–40] A recent systematic review by Stevens et al[37] supports the presence of a drug interaction with ondansetron in the early postoperative period that potentially decreases the effectiveness of tramadol; however, this likely to be less problematic in the United States where IV tramadol is not used postoperatively.

Serotonin Syndrome

Coadministration of tramadol with proserotonergic medications can result in a hyperserotonergic state that develops soon after initiation or dosage changes of the offending agent. Serotonin syndrome (SS) can be subacute or chronic and range from mild to severe. In mild cases, patients are afebrile and may report symptoms of diarrhea, tremor, tachycardia, and autonomic findings such as shivering, diaphoresis, or mydriasis.[41]

In severe cases, neuromuscular hyperactivity, autonomic hyperactivity, altered mental state, gastrointestinal symptoms, and even death have been reported.[42] Serotonergic medications that can interact with tramadol include SSRIs, SNRIs, tricyclic antidepressants (TCAs), and triptans (eg, sumatriptan), antipsychotics, anticonvulsants, antiparkinsonian agents, cough and cold medications containing dextromethorphan, herbal products containing St. John's wort, and medications that inhibit the metabolism of serotonin, such as monoamine oxidase inhibitors (MAOIs).[43]

Although we were unable to find anesthesia literature discussing SS in tramadol-treated patients, there are reports from medical, psychiatric, and emergency medicine journals. In summary, the risk for SS increases with higher dosages of both tramadol and the proserotonergic medication. Inhibition of CYP2D6 enzymes by SSRIs prevents the hepatic metabolism of tramadol. This elevates the concentration of the parent compound and increases its serotonergic effects in the brain (Table 2).[1] SSRIs that are strong inhibitors of CYP2D6, such as sertraline,[44,45] paroxetine,[46,47] and fluoxetine,[48] increase the risk of serotonin syndrome when taken with tramadol. CYP2D6 plays a secondary role in the metabolism of citalopram, and 2 case reports describe tramadol–citalopram-associated serotonin syndrome.[48,49] A review of the literature by Nelson and Philbrick[50] confirms that the risk is enhanced in CYP2D6 PMs, as would be expected because they have the greatest concentration of the parent compound. In terms of treatment of serotonin syndrome, all serotonergic agents should be discontinued. Supportive care aimed at normalizing vital signs should be administered, such as oxygen given to normalize oxygen levels and IV fluids to hydrate and treat hyperthermia. If temperatures are higher than 41°, the patient should be intubated with induced neuromuscular paralysis. Muscle relaxants such as benzodiazepines (valium, lorazepam, or diazepam) may be administered to control seizures, agitation, and muscle stiffness. In extreme cases, serotonin-production blocking agents like cyproheptadine may be given. Excellent reviews of the treatment of serotonin syndrome are provided by Sporer and Frank.[48,49]

Seizurogenic Activity

Many clinicians are unaware that tramadol can increase a patient's risk for seizure via lowering the seizure threshold.[42] A comparison of tramadol and tapentadol exposures reported to the Data System of the American Association of Poison Control Centers between 2009 and 2014 revealed that individuals exposed to tramadol (8566 cases) identified significantly higher rates of seizures and vomiting, whereas tapentadol was associated with more classical opioid agonist reports such as respiratory depression.[51,52] Generalized seizures may occur within the first 24 hours after administration. Notably, seizures occurred both at therapeutic and supratherapeutic ranges in individuals with and without the history of a seizure disorder.[53] Risk factors for seizures compiled from case reports include the history of traumatic brain injury and seizure activity secondary to hypoxia; administration with other medications that lower seizure threshold such as antipsychotic medications; high-dose ingestion; and coingestion with substances likely to cause drug–drug interactions.[54–56] To decrease the risk of seizure occurrence, an alternative analgesic for pain management should be selected for seizure-prone patients, and those being administered combinations of multiple medications

Table 1. Common Opioid and SSRI-Like Withdrawal Symptoms Associated With Abrupt Tramadol Cessation[2,68,69] (Table 2)

Opioid	SSRI
Myoclonus	Restless leg syndrome
Agitation	Severe anxiety
Depression	Panic attacks
Anxiety	Confusion
Sweating	Delusions
Goose flesh	Paranoia
Insomnia	Unusual sensory phenomena
Hyperkinesia	Hallucinations
Tremor	
Paresthesias	
Gastrointestinal symptoms	
Nausea	
Rhinorrhea	
Lacrimation	

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.

Table 2. Online References

1. The mechanism for Tramadol (Ultram)-induced risk of serotonin syndrome in patients taking SSRI antidepressants. Available at: http://www.ebmconsult.com/articles/tramadol-interaction-ssri-serotonin-syndrome-mechanism. Accessed November 17, 2015.
2. WHO Tramadol Update Review Report: Agenda item 6.1. Available at: http://www.who.int/medicines/areas/quality_safety/6_1_Update.pdf. Accessed February 9, 2015.
3. Tramadol therapy and *CYP2D6* genotype. Available at: http://www.ncbi.nlm.nih.gov/books/NBK315950. Accessed December 8, 2015.

that lower the seizure threshold should be carefully monitored. In addition, those undergoing simultaneous withdrawal from tramadol and other substances should be monitored, with gradual decreases in tramadol dosage to reduce the likelihood of a withdrawal seizure.

Withdrawal

Tramadol has been reported to have distinctive opioid and SNRI-associated withdrawal symptoms that can occur as a result of abrupt cessation of IR and ER formulations in both abusers and patients receiving therapeutic doses for pain management. Common opioid and atypical SNRI-like withdrawal symptoms are presented in Table 1. Clinically these atypical discontinuation features have been considered similar to those of the SNRI venlafaxine and have been reported in sensitive individuals irrespective of the dosage, but generally remit with gradual dose reduction. High doses of tramadol may be tapered in the preoperative period if time permits. Although there is no literature supporting a particular tapering schedule, it is important to monitor for both typical opioid and atypical withdrawal symptoms. A case report suggested the use of lorazepam and clonidine for symptomatic relief of withdrawal symptoms.[57]

Illicit Use of Tramadol

Despite previous assumptions that tramadol did not have an addiction liability, various English- and Arabic-language studies concluded that tramadol produces desirable euphoric, stimulant, and relaxing effects that increase its abuse potential.[58–63] The most frequent abusers of tramadol are those with easy access and history of substance abuse, patients with chronic pain, and health professionals. Although rarely a primary drug of choice, a review of physician health program records showed that tramadol was the third most frequently mentioned opioid and it exceeded the abuse liability of fentanyl, oxycodone, and hydromorphone in this group of physicians.[64] Increased monitoring is necessary in patients with a history of tramadol abuse or dependence because they are more likely to exhibit toxidromes and continue use to avoid opioid and SNRI withdrawal.

DISCUSSION

Tramadol has a unique mechanism of action. It inhibits the reuptake of norepinephrine and serotonin, resulting in antinociceptive activity similar to the SNRIs venlafaxine or duloxetine. In the United States, tramadol is available as an oral formulation generally prescribed for the treatment of chronic musculoskeletal and neuropathic pain, but it is also utilized off-label for on-demand therapy for erectile dysfunction. A growing number of patients will present with tramadol on their medication list as prescribers are moving away from chronic prototypic opioid treatment for nonmalignant pain. This review summarizes the essential knowledge on tramadol pharmacology, pharmacogenetics, drug interactions, and possible adverse events for the anesthesiologist. Key clinically significant findings are summarized in Table 3.

Genetic polymorphisms modulating CYP enzyme activities are the main source of variability in a patient's analgesic response to tramadol. CYP2D6 dependent and, to a lesser extent, CYP3A4 metabolic activation, are required for the full opioid analgesic effects. The clinical studies reviewed demonstrate that the opioid analgesic response rates to tramadol are significantly lower in PM compared with the other 3 phenotypic groups, IM, EM, and UM. Of clinical significance, patients who are PMs may report tramadol as ineffective for pain relief and request a stronger opioid. It is important to appreciate that this does not constitute drug seeking, rather an inability to convert tramadol to the active M1 opioid metabolite.

In addition to the metabolic activation of medication, the CYP2D6 enzyme families are inhibited or induced by drugs, resulting in clinically significant interactions that can cause unanticipated adverse reactions or therapeutic failures. One example is administering tramadol with medications that strongly inhibit CYP2D6, including the antidepressants fluoxetine or paroxetine, the antiemetic metoclopramide, or the antiarrhythmic and antiparasitic quinidine, which results in a net effect of changing an individual's apparent phenotype from an EM to a PM.[65]

A perioperative consideration is drug interactions with tramadol, particularly the number, types, and dosages of coadministered serotonergic medications. The risk of SS is increased with the concomitant use of medications that increase serotonin levels in the CNS or that inhibit the metabolism of tramadol (strong CYP2D6 inhibitors), as discussed. Drug classes implicated in SS include a long list of medications that are common in hospitalized patients, including antimigraine agents; triptans, antidepressants, buspirone, TCAs, MAOIs, antipsychotics; anticonvulsants; antiparkinsonian agents; and analgesics such as meperidine. The most notable risk is with the combinations of medications that increase serotonin by different mechanisms.[66] The manifestations of SS range from mild diarrhea and tremor to lethal symptoms of hyperpyrexia, muscle rigidity, and multiorgan failure. Monitoring for and counseling a patient about SS is prudent when starting a new serotonergic agent or when doses are increased.[40] In general, treatment of SS first involves supportive care and discontinuing the offending medications. Patients presenting with severe symptoms may need sedation, intubation, and paralyzation. Despite many antiemetic medications being serotonin antagonists, coadministration with tramadol does not increase the risk of SS because of the opposing effects; however, this interaction may decrease the effectiveness of the antiemetic.

An appreciation of the possibility of withdrawal is an early consideration when evaluating a patient taking tramadol. Withdrawal states are more frequent with abrupt

Table 3. Summary of Key Clinically Significant Findings

Summary
Tramadol is an analgesic medication with monoaminergic reuptake inhibitory and opioid receptor agonist activity recommended for ambulatory surgical patients and treatment of chronic pain.
Tramadol sales and distribution are increasing worldwide.
Tramadol has a complex pharmacology; the effects of the active metabolites are dependent upon a patient's CYP2D6 profile, and the analgesic efficacy varies depending on the rate of metabolism.
Genotyping for cytochrome P450 polymorphisms to identify specific genetic variations that may be linked to reduced/enhanced response or severe side effects of opioid analgesics, antipsychotic medications, and antidepressants are increasingly being utilized in academic medical centers.
Risk for drug interactions is greatest in PMs when combined with strong inhibitors of CYP2D6, including SSRIs and MAOIs.
Symptoms of serotonergic and norepinephrine withdrawal are possible upon abrupt cessation of tramadol. Gradual tapering or symptomatic support decreases the symptoms.
Patient education needs to include the importance of reporting all serotonergic medications because of the risk of serotonin syndrome.
Patients should be screened for seizure risks and medications that lower the seizure threshold as tramadol lowers the seizure threshold.
Tramadol carries a greater opioid addiction liability in CYP2D6 UMs..

Abbreviations: MAOIs, monoamine oxidase inhibitors; PMs, poor metabolizers; SSRIs, selective serotonin reuptake inhibitors; UMs, ultra-metabolizers.

cessation of high-dose, long-term use or in polysubstance users; however, symptoms have been reported in sensitive individuals at therapeutic dosages. In addition, in the preoperative period, tramadol and a serotonergic antidepressant may both need to be stopped, increasing the likelihood of a combined tramadol and antidepressant discontinuation syndrome. The antidepressants that carry the greatest risk for a discontinuation reaction in rank order include venlafaxine, paroxetine, sertraline, and fluvoxamine. In the cases where these medications cannot be tapered preoperatively, monitor patients for withdrawal and provide symptomatic treatment. If the withdrawal symptoms shown in Table 1 are present, they will subside once the patient is no longer nothing by mouth and can resume tramadol and the antidepressant.

Tramadol should also be considered for postoperative analgesia in surgical patients in which respiratory depression must be avoided, such as those with respiratory or cardiopulmonary compromise, obesity hypoventilation syndrome, smokers, or the elderly. The best candidates for tramadol treatment are those taking few serotonergic medications, perhaps have had a positive analgesic response to tramadol in the past, or are identified as UMs. In the practice of personalized medicine, several academic medical centers have developed clinical support services to assist health care providers in identifying CYP genotypes likely to have an optimal analgesic response to tramadol and alerting clinicians in the electronic medical records of significant drug-drug interactions. Pharmacogenomics testing offers better therapeutic outcomes, choice of treatment, and dose adjustments based on the patient's genotype. The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy has developed tramadol dosing recommendations based on CYP profiles (Table 2).[3]

One review in the anesthesia literature suggests multimodal-action medications that block the reuptake of norepinephrine and/or serotonin may be effective in improving analgesia and functional outcome of postoperative pain in ambulatory surgery. Tramadol is often compared with another multimodal analgesic, tapentadol. Pharmacologically, tapentadol does not require metabolic activation, has greater affinity for μ-opioid receptors, and blocks reuptake of norepinephrine with limited serotonergic effects. In addition, as a weaker serotonin reuptake inhibitor, tapentadol carries less risk of precipitating SS. Although there are no head-to-head comparisons between the 2 medications, in a meta-analysis extracting data from historical studies, tapentadol was associated with slightly lower risks of constipation and nausea than tramadol.[67] The Poison Control Study data discussed determined that tramadol was associated with a higher rate of seizures and vomiting, whereas tapentadol was associated with reports more of respiratory depression, coma, and sedation. A limitation of this review is that the data on adverse effects, seizures, drug interactions, withdrawal, and abuse are compiled from case reports, many of which are not from the anesthesia literature and do not address oral tramadol in use for perioperative treatment of pain.

In conclusion, tramadol use is increasing worldwide. It is anticipated that clinical decision support systems will soon be available that draw on data from genetic analysis of opioid metabolism to assist clinicians in patient selection. A greater understanding of patient's metabolic profile and tramadol pharmacology will ensure the patient's optimal analgesic outcome. Finally, awareness that tramadol has an addiction liability is important for clinicians because abuse is prevalent among health care professionals and in geographic regions with high availability such as the Middle East. ■

DISCLOSURES

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Contribution: This author contributed the pharmacology and pharmacokinetics sections of the manuscript.
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