Ketorolac, Oxymorphone, Tapentadol, and Tramadol: A Comprehensive Review

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INTRODUCTION

Affecting more than 50 million people in the United States alone, pain remains a tremendous burden not only for patients but also for the health care system as well.1 Uncontrolled pain is the leading cause of disability in the country, and it may also delay patient recovery from surgery, increase the risk of life-threatening events, and increase the risk of developing chronic pain. With the advent of several novel analgesics over recent years, there has been a widespread effort to develop novel drugs.

KEYWORDS

- Ketorolac
- Oxymorphone
- Tapentadol
- Tramadol
- Analgesia
- Pain

KEY POINTS

- Ketorolac is primarily used for the treatment of postoperative pain and has been shown to have opioid-sparing effects and reduces opioid-related side effects.
- Oxymorphone is a powerful opioid used for the treatment of moderate to severe pain in both malignant and nonmalignant-related pain.
- Tapentadol functions as both a weak μ-receptor agonist and a norepinephrine reuptake inhibitor, offering a more favorable side-effect profile compared with pure opioids.
- Tramadol is a μ-receptor agonist, and a serotonin and norepinephrine reuptake inhibitor indicated for management of moderate to severe pain.

INTRODUCTION

Affecting more than 50 million people in the United States alone, pain remains a tremendous burden not only for patients but also for the health care system as well.1 Uncontrolled pain is the leading cause of disability in the country, and it may also delay patient recovery from surgery, increase the risk of life-threatening events, and increase the risk of developing chronic pain. With the advent of several novel analgesics over recent years, there has been a widespread effort to develop novel drugs.

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with differing mechanisms of action in an attempt to best manage the pain epidemic in the United States and worldwide. In this regard, various classes of analgesics currently are available, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioid medications, muscle relaxants, antidepressants, and anticonvulsant medications. This review focuses on 4 medications: ketorolac, oxymorphone, tramadol, and tapentadol, and their role as analgesic agents in different pain states.

**KETOROLAC**

**Background**

Ketorolac tromethamine is the first NSAID approved for parenteral use. It is used for a variety of clinical indications, but is mainly administered for the management of postoperative pain. It can also be used for treatment of cancer-related pain, for pain after cesarean delivery, and in the emergency department for treatment of migraine headaches, renal colic, musculoskeletal pain, and sickle cell crisis. It has been used safely and effectively in select pediatric populations but at present is not recommended for use in children under the age of 17. Ketorolac has strong analgesic properties, with a dose of 30 mg intramuscular (IM) offering similar analgesia as 12 mg of morphine. The strong analgesic properties reduce opioid requirements and thus decrease opioid-related side effects. These side effects can be associated with significant morbidity and mortality, in particular, related to dose-dependent opioid mediated respiratory and CNS depression. Routes of administration include intravenous (IV), IM, oral (PO), ophthalmic, and intranasal (IN).

**Pharmacology**

Ketorolac primarily exerts its effects through inhibition of the cyclo-oxygenase (COX) -1 and -2 isozymes, with a greater affinity for COX-1. COX inhibition decreases the production of prostaglandins, thromboxane, and prostacyclin from arachidonic acid. Prostaglandins are involved in the nociceptive pathway by sensitizing afferent nerves.

All forms of ketorolac are rapidly absorbed with a mean half-life for absorption of 3.8 minutes, and duration of action of approximately 6 to 8 hours. It is the tromethamine moiety that renders the compound hydrophilic, augmenting its solubility and absorption. There is complete bioavailability of both IM and IV administration, and the half-life is approximately 5 hours. Absorption of PO ketorolac is slower than parenteral forms, and the bioavailability is between 80% and 100%. The bioavailability of 15 and 30 mg IN ketorolac is 75% and 67%, respectively. The 30 mg IN dose achieves a plasma level similar to that of 20 mg IM. Maximum plasma concentration is reached on average within 30 to 45 minutes with a terminal half-life of 5 to 7 hours.

Once absorbed, the drug is 99% protein bound in the plasma. Ketorolac is metabolized by the liver into hydroxylated and conjugated forms. The primary route of excretion is renal with 92% of the administered dose being found in the urine. The drug found in the urine is approximately 40% metabolites, and 60% is excreted unchanged. The remaining 6% to 8% of the drug is excreted in the feces.

Ketorolac crosses the placenta and is also excreted into breast milk in small quantities. The hydrophilicity and high protein binding of ketorolac prevents large concentrations of the drug from entering the breast milk. Administrations of ketorolac and other NSAIDs during the third trimester are contraindicated because they can cause premature closure of the ductus arteriosus.

**Adverse Events**

The adverse events associated with ketorolac are similar to those of other NSAIDs, which include gastrointestinal (GI) bleeding, renal impairment, liver dysfunction, and...
possible allergic reactions (Box 1). Use of ketorolac disrupts platelet aggregation through the inhibition of thromboxane A₂. It has been shown to increase bleeding time with no effect on the prothrombin or partial thromboplastin times. The use of ketorolac is associated with a small increased risk of GI and possibly operative site bleeding, and it is advisable to always communicate with the surgeon before administering this drug perioperatively. However, more evidence is accumulating that shows there may be no real increased risk of operative site bleeding with ketorolac. The risks of GI bleed and operative site bleeding increases substantially with higher drug doses, with increased duration of use, and in the elderly. However, there appears to be no significant increased risk of serious operative site bleeding with ketorolac use. Furthermore, death rates from these outcomes were no different compared with those who received opioids alone. Duration of ketorolac use should not exceed 5 days, and dosing should be limited in those over the age of 65.

Ketorolac is contraindicated in patients with recent history of GI bleed, peptic ulcer disease, intracranial bleed, renal failure, and those with allergies to NSAIDs and/or aspirin.

There is also a theoretic risk for impedance of bone healing following surgeries involving orthopedic bone manipulation or hardware placement. However, one study showed no difference in outcomes for patients receiving ketorolac versus those that did after a spinal fusion with pedicle screw insertion.

**Drug Interactions**

Ketorolac should not be administered with other NSAIDs, because this can increase the risk for GI bleeding and renal impairment. Coadministration with aspirin is not recommended, because it decreases protein binding, resulting in increased free drug concentrations. However, the clinical significance of this is unknown. Concurrent use of diuretics especially with angiotensin converting enzyme inhibitors and angiotensin II receptor blocking drugs can increase the risk of renal impairment and should be used cautiously.

**Routes of Administration**

**Intramuscular/Intravenous**

Ketorolac has been approved for 60 mg IM or 30 mg IV initial dose followed by 15 to 30 mg every 6 to 8 hours. Maximum daily doses should not exceed 120 mg. Doses

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should be altered for age greater than 65, for body mass less than 50 kg, and for patients with renal impairment. Doses in these populations should not exceed 60 mg per day.

**Oral**

PO administration is not recommended as an initial dose. A dose of IV or IM ketorolac can be given followed by 10 PO mg every 6 hours. Food in the stomach can delay but will not reduce absorption. The half-life for PO preparations is similar to that of IV and IM (5 hours).

**Intranasal**

IN ketorolac is approved for short-term management of moderate to severe pain. The IN formulation is generally well tolerated. The standard adult dose is one 15.75-mg spray in each nostril for a total dose of 31.5 mg. Maintenance doses are given every 6 to 8 hours with a maximum daily dose of 126 mg. In those over the age of 65, those less than 50 kg, or those with underlying renal impairment, the dose should be halved to one 15.75-mg spray every 6 to 8 hours to a maximum daily dose of 63 mg. Adverse events occur in less than 2% of patients, with the most common being local nasal symptoms, including rhinalgia and rhinitis.

**Subcutaneous**

The subcutaneous route is currently not approved by the US Food and Drug Administration (FDA). Optimal doses are unknown; the pharmacokinetics and pharmacodynamics are not completely defined, and the safety and efficacy are yet to be established. However, subcutaneous administration of ketorolac maybe useful in patients with no IV access or low muscle mass. It may also have some benefit in pain control due to its lower rate of absorption. Dosing is usually by slow continuous infusion of 30 to 120 mg over 24 hours.

**OXYMORPHONE**

**Background**

Oxymorphone (oxymorphone hydrochloride, 14-hydroxy-dihydromorphinone) is a semisynthetic μ-opioid receptor agonist, which was introduced to the pharmacologic market in the United States in 1959 in parenteral and rectal formulations. In June 2006, the FDA approved PO formulations of oxymorphone as extended-release (ER) and immediate-release (IR) tablets. Before this, oxymorphone was predominantly used in suppository form and occasionally given parenterally for long-term therapy, with no PO option. The development of the ER and IR formulations of oxymorphone has provided new options for managing moderate to severe pain. Trials studying nonmalignant and malignant pain support the drug’s ability to serve as a step-3 option. Oxymorphone is effective and well tolerated for the management of pain and has been used in the presurgical, postsurgical, labor and delivery, and patient-controlled analgesia (PCA) setting.

**Pharmacology**

Oxymorphone is a pyidine-ring unsubstituted pyridomorphinan that can be distinguished from morphine by the 7,8 double bond and the ketone-group substituent in the C6 position. Its ketone-group substituent increases the molecule’s lipid solubility and likens it structurally to hydromorphone. Its lipophilic properties enable the transport of oxymorphone across the blood-brain barrier with greater ease than less lipophilic opioids. Furthermore, once the drug enters the CNS, it tends to remain in the aqueous phase, where receptor sites are concentrated, rather than...
redistributing throughout the lipid membrane. It is available in the freely water-soluble hydrochloride (HCl) salt form, which is an odorless powder in white or off-white color. The HCl salt form of oxymorphone has a molecular weight of 337.80 and is marginally soluble in ether and alcohol. Its octanol/water partition coefficient is 0.98 at pH 7.4 and 37°C.

Oxymorphone is more potent than morphine by approximately 10-fold following IV administration and more lipid-soluble than oxycodone and morphine. The drug undergoes extensive liver metabolism by conjugating with glucuronic acid in order to produce oxymorphone-3-glucuronide, its primary metabolite. Glucuronidation at the 3-position is catalyzed by uridine diphosphate glucuronyltransferase subtype B27. Of note, the 6-ketone group is also reduced to 6-hydroxy (OH)-oxymorphone. Although oxymorphone-3-glucuronide possibly has some analgesic activity, the pharmacologic significance has not been sufficiently investigated.

Oxymorphone has, therefore, been considered to have relatively clinically inert metabolites. Studies have not shown any clinically significant drug-drug interactions mediated by cytochrome (CYP) CYP3A4, CYP2C9, or CYP2D6 with oxymorphone. Thus, there is minimal risk for clinically significant drug-drug interactions.

The mean volume of distribution for oxymorphone is about 3 L/kg, and the median PO clearance varies from 18 to 26 L/min. The drug is predominantly eliminated by the liver, and only 2% of it is excreted unaltered by the kidney. Of note, there is a significant variability between individuals.

Given that oxymorphone is not significantly protein-bound relative to other opioids, advantages to oxymorphone may include administering it in hypoalbuminemic patients, and in patients receiving numerous highly protein-bound drugs, although these clinical trials are yet to be conducted.

The pharmacokinetics of oxymorphone are dose-dependent and linear for doses between 5 and 40 mg. It should be taken on an empty stomach and should not be taken in conjunction with alcohol.

### Oxymorphone Immediate Release

In single- and multiple-dose trials of oxymorphone IR, absorption of the drug is rapid, and the time of maximum plasma concentration (t_{max}) following PO administration was 0.5 hours. In a study using single or multiple doses of oxymorphone IR 20 to 30 mg, this observed t_{max} was consistent with the rapid onset of analgesia in 0.5 to 0.75 hours. The half-life of elimination for one dose of oxymorphone IR ranges from around 7.2 hours for 5 mg to 9.4 hours for 20 mg.

A randomized crossover study of oxymorphone IR in healthy subjects demonstrated that the single-dose and steady-state pharmacokinetic profiles were dose dependent and linear for a dose of 5 to 20 mg. The drug did not demonstrate any significant effects on safety or laboratory variables.

### Oxymorphone Extended Release

The mechanism for the ER in oxymorphone ER is based on the embedment of the drug in an agglomerated hydrophilic matrix of dextrose and 2 naturally occurring gums. As water enters the matrix, the 2 gums produce a semiporous gel barrier, which permits the diffusive passage and release of oxymorphone. This leads to continuous plasma levels of oxymorphone throughout a 12-hour dosing interval and low peak-to-trough fluctuations. As a result, the formulation for oxymorphone ER provides numerous benefits, including improved patient compliance and quality of life, and decreased dosing frequency.
Postoperative Pain

Numerous studies have been conducted investigating the efficacy of pain relief with various medications. Gimbel and Ahdieh\(^{33}\) conducted a parallel-group, double-blind study in patients undergoing total hip or knee replacement surgery. These patients were given a single dose of placebo; oxymorphone 10, 20, 30 mg; or oxycodone IR 10 mg, and pain relief was measured for 8 hours. The study found that any opioid-related adverse events were similar across all study groups, and that administration of oxymorphone IR 10, 20, or 30 mg provided substantial dose-associated pain relief relative to placebo. This pain relief was successfully sustained over several days with a safety profile similar to that of oxycodone IR. In a separate parallel-group, double-blind, multicenter study,\(^{35}\) the analgesic efficacy of PCA, opioid, and dose-sparing practice was studied, using placebo or oxymorphone ER. The study found that oxymorphone ER provided significant improvements compared with the placebo in regards to delivering single-dose total pain relief over 12 hours (\(P = .0056\)). Furthermore, patients who received oxymorphone were found to use significantly lower amounts of rescue PCA than those who were given placebo (\(P<.02\)).

Multimodal Analgesia

The use of multimodal analgesia incorporates the administration of local anesthetics, anticonvulsants, tricyclic antidepressants, and NSAIDs alongside opioids. The broad range of benefits associated with the utilization of adjunctive therapy includes delayed development of hyperalgesia and tolerance,\(^{36}\) and a decrease in opiate requirements by 25% to 50%, and reduced adverse effects.\(^{24}\)

Contraindications/Adverse Events

Adverse effects

In general, the adverse effects caused by oxymorphone are comparable to those seen with potent \(\mu\)-agonists. A study conducted by Beaver and colleagues\(^{37}\) found that the rate adverse effects were quantitatively and qualitatively comparable between IM morphine and oxymorphone, and IM morphine and PO oxymorphone. When oxymorphone was administered through PCA, it was found to cause less sedation relative to morphine, but more events of nausea and vomiting.\(^{38}\) Sloan and colleagues\(^{17}\) found that there was no significant difference in sedation or nausea between the groups receiving oxymorphone, oxycodone ER, and morphine.

Kidney disease

Oxymorphone has been found to build up in patients suffering from renal failure. The bioavailability of oxymorphone was found to increase by 26%, 57%, and 65% in patients with creatinine clearance rates of 51 to 80 mL/min, 30 to 50 mL/min, and less than 30 mL/min, respectively, relative to healthy controls.\(^{22}\) A pharmacokinetic study investigating the pharmacokinetics of oxycodone and the excretion of this drug and its metabolites oxymorphone and noroxycodone in 10 uremic patients undergoing renal transplantation found the mean elimination half-life of oxymorphone to be prolonged.\(^{39}\) As a result, it is essential for clinicians to consider an increase in dosing intervals in patients with kidney disease.\(^{40}\)

Liver disease

Studies have suggested that there may be significant effects of liver disease on the pharmacokinetics of oxymorphone. Its bioavailability was found to increase by 1.6-fold and 3.7-fold in subjects with Child-Pugh class A and Child-Pugh class B
hepatic impairment, respectively, relative to healthy controls. There is no dosage adjustment that is required in mild liver disease, but initiating treatment at a low dose and gradually titrating upwards is crucial. In patients with moderate to severe hepatic impairment, oxymorphone is relatively contraindicated.25

TAPENTADOL

Background

Classically considered a centrally acting opioid analgesic, tapentadol was recently developed by Gruenthal, a pharmaceutical company in Germany, alongside Johnson & Johnson Pharmaceutical Research and Development, in an attempt to reduce the tolerability issues associated with opioids, while providing comparable analgesia.41 Tapentadol has a dual mechanism of action that was initially designed to treat moderate to severe acute pain. An IR formulation approved by the FDA in 2009 is available in 50-, 75-, and 100-mg dosages and provides approximately 4 to 6 hours of analgesia. Over time, an ER formulation was developed and approved by the FDA in 2011 for the management of moderate to severe chronic pain. Studies have shown that tapentadol is comparable in its efficacy to oxycodone in the management of pain control in studied patient populations.42–47 An unexpected beneficial effect of tapentadol was observed in many patients, who reported lower incidence of GI side effects normally associated with opiates.

Pharmacology

Tapentadol exerts its analgesic effects via a dual mechanism of action.48–50 It functions as both a weak μ-receptor agonist and a norepinephrine reuptake inhibitor. Its weak μ-receptor affinity allows the drug to exert its effects with fewer common side effects associated with opioid use and is thought to decrease abuse potential, and its inhibition of norepinephrine reuptake contributes to its analgesic effects. Although these 2 distinct mechanisms produce analgesia individually, when they are combined, they act synergistically to produce an even greater level of analgesia at both the spinal and the supraspinal levels. The synergistic effect due to the dual mechanism of action helps explain why, despite tapentadol having 50 times less affinity for μ-receptors than morphine, it is only 2 to 3 times less potent.51

Norepinephrine will physiologically inhibit the transmission of nociceptive impulses by activating alpha-adrenergic receptors located on pain fibers in the CNS. By blocking the reuptake of norepinephrine, tapentadol thereby prolongs the effects of norepinephrine at the terminal endings of interneurons and descending inhibitory fibers, which suppress the transmission of pain.52,53 When combining this increase in norepinephrine levels at the nerve terminal with its μ-agonistic effects, tapentadol is able to achieve a high level of analgesia.

Tapentadol exists as a single active enantiomer and is metabolized primarily by O-glucuronidation (phase II metabolism) mediated by UGT1A9 and UGT2B7.54–58 As opposed to some other PO analgesics such as codeine and tramadol, tapentadol does not require enzymatic activation. This is particularly beneficial in the ~5% to 15% of the patient population that has CYP P450 variants resulting in poor drug metabolism and consequently less analgesia. Its principal metabolite is inactive, with no affinity for the μ-receptor or the norepinephrine transporter. Nearly 99% of tapentadol and its inactive conjugated metabolites are excreted via the kidneys following PO administration (69% in conjugated form, 27% as other metabolites, and 3% as unchanged drug). This prompted its manufacturer to suggest that
tapentadol be avoided in patients who have severe hepatic or renal failure; however, no formal studies have been conducted in these populations. Peak plasma concentrations are reached ~1.5 hours following PO intake, and the elimination half-life of IR tapentadol is 4 hours, whereas that of ER tapentadol is extended to 5 to 6 hours. As a result of extensive first pass metabolism, the bioavailability of PO tapentadol is approximately 32%, which is comparable to orally administered morphine, but less than oxycodone (60%–87%), methadone (41%–99%), and tramadol (75%).

Several studies have demonstrated that body weight has a statistically significant effect on clearance and maximum concentration values of orally administered tapentadol. However, it was also found that although body weight influences the pharmacokinetics of tapentadol, it is not necessary to adjust doses accordingly.

**Indications/Benefits**

Initially, tapentadol was formulated as an IR preparation to treat acute pain. Eventually, an ER formulation was developed to aid in the treatment of chronic pain as well. Many trials have since been conducted to evaluate the efficacy of tapentadol compared with traditional PO opioids, primarily oxycodone and morphine.

Multiple randomized, double-blind trials were conducted investigating the efficacy and tolerability of IR-tapentadol compared with IR-oxycodone and placebo for post-operative pain control on patients who underwent unilateral bunionectomy. These studies all concluded that IR-tapentadol provided similar analgesic efficacy compared with IR-oxycodone in a dose-dependent manner. Most studies demonstrated a statistically significant difference in the rates of nausea, dizziness, vomiting, and constipation between tapentadol and oxycodone. All findings supported lower rates of these adverse effects in the tapentadol treatment group (nausea rates were 46%–53% and 70%–72% for tapentadol and oxycodone, respectively; vomiting rates were 16% and 39% for tapentadol and oxycodone, respectively; constipation rates were 6% and 18% for tapentadol and oxycodone, respectively). Similar results were obtained in another study in patients with moderate to severe chronic pain from chronic osteoarthritis of the knee awaiting primary joint replacement surgery for end-stage joint disease—GI disorders occurred in 30%, 49%, and 56% of patients treated with ER-tapentadol 100 mg, ER-tapentadol 200 mg, and ER-oxycodone, respectively. These findings were validated in yet another trial looking at patients with acute low back pain and associated radicular leg pain. Pain improvement was similar in both tapentadol and oxycodone groups, whereas oxycodone had more GI adverse events, such as nausea/vomiting (15.9% vs 24.7%) and constipation (2.2% vs 7.2%). Similarly, in patients suffering from chronic low back pain, it was documented that ER-tapentadol had equivalent efficacy compared with ER-oxycodone, but with significantly fewer adverse GI side effects.

In addition to treating nociceptive pain, the effectiveness of ER-tapentadol in managing moderate to severe diabetic neuropathic pain has also been evaluated. Results revealed a statistically significant decrease in pain intensity with the use of tapentadol compared with placebo (decreasing in intensity from 7.3 to 3.5).

Another favorable profile of tapentadol compared with standard opiates is its effect on the development of tolerance. Tolerance, defined as the loss of antinociceptive effect, has been shown to be delayed with the use of tapentadol compared with morphine. One study assessed tolerance following administration of equi-analgesic doses of tapentadol and morphine in rat models. Complete tolerance developed in 51 days for tapentadol and in 21 days for morphine.
Based on these studies, the advantages of tapentadol over traditional PO opioid analgesics are clear. Tapentadol has been proven to provide exceptional analgesia, similar to oxycodone, but with lower incidences of adverse GI events. The lower incidence of adverse effects is likely attributed to the decreased affinity of tapentadol for \( \mu \)-receptors, but because of its synergistic dual mechanisms of action, it is capable of producing a relatively potent level of analgesia. Furthermore, by also inhibiting the reuptake of norepinephrine, tapentadol provides a broader spectrum of efficacy than conventional opioids and is able to treat neuropathic pain in a similar mechanism as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors.

Contraindications/Adverse Events

Despite tapentadol having a more favorable side-effect profile than pure \( \mu \)-agonists, patients still report suffering from adverse CNS and GI symptoms when taking tapentadol. These symptoms include nausea, vomiting, dizziness, somnolence, dry mouth, and headache—with nausea being the most common (30%), followed by dizziness (24%), vomiting (18%), and somnolence (15%). These effects also appear to be dose related, with patients reporting higher incidences of adverse effects following intake of higher doses.

Existing norepinephrine reuptake inhibitors have the potential for cardiovascular effects. However, more research needs to be done in order to explore whether similar effects would be experienced by patients taking tapentadol. Tapentadol causing vision-related symptoms have also not been encountered in the current literature. However, because tapentadol may activate \( \mu \)-receptors in the Edinger-Westphal nucleus of the midbrain resulting in an increase in parasympathetic tone, there is the risk of resultant blurry vision related to miosis and the loss of accommodation from the use of tapentadol.

As discussed previously, it is recommended that patients with severe renal or hepatic failure not use tapentadol. However, no dosage adjustment is necessary in patients with mild or moderate renal insufficiency.

Although studies have not observed significant respiratory depression in patients receiving tapentadol, it is still advised that tapentadol be avoided in patients with acute or severe bronchial asthma or hypercapnia. Tapentadol should also be used cautiously in patients at risk of developing serotonin syndrome. Although tapentadol has limited interaction with serotonin transporter proteins, it still has the potential to precipitate serotonin syndrome. Thus, those that are taking serotonergic drugs should be monitored carefully for any changes in autonomic function, mental status, and neuromuscular function. However, one should also realize that patients may experience a monoamine syndrome of poorly characterized irritability and agitation, which resembles serotonin syndrome but is not associated with any major complications.

TRAMADOL

Background

Tramadol is an opioid pain medication used to help relieve moderate to moderately severe pain, acute and chronic. Tramadol is commonly prescribed for postoperative, dental, cancer, and acute musculoskeletal pain and also as an adjuvant to NSAID therapy in patients with osteoarthritis. Tramadol, structurally related to codeine and morphine, belongs to the opiate agonist class. It has 2 different mechanisms of action: it binds to the \( \mu \)-opioid receptor and it inhibits the reuptake of serotonin and norepinephrine. Tramadol is a fully synthetic opioid and does not occur naturally in nature.
Tramadol is in contrast to morphine and codeine, which are naturally occurring opiates derived from the opium poppy. It differs from the other opioid derivatives hydromorphone, hydrocodone, and oxycodone, although also semisynthetic and made in the laboratory, in that they still retain some natural qualities. In 1962, tramadol was formulated by a German drug company, Grünenthal GmbH, a family-owned company specializing in pain medications and focusing on treatment of pain. The medication was tested for 15 years in Germany before successful approval. In 1977, the medication was available to the foreign market under the name Tramal. However, it was not until 1995 that the drug became available in the United States.

**Mechanism of Action**

Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of 2 enantiomers, both of which contribute to analgesic activity via different mechanisms. Of note, a dextrorotary compound (+) is an optically active compound that rotates the plane of polarized light to the right (clockwise), whereas a levorotatory compound (−) rotates the plane of polarized light to the left (counterclockwise). (+) Tramadol and the metabolite (+) O-desmethyltramadol (M1) are μ-opioid agonists. The μ activity of tramadol is one-tenth less than that of codeine and M1 metabolite, 300 times affinity for μ receptor compared with the parent compound.

In addition, (+) tramadol inhibits serotonin reuptake and (−) tramadol inhibits norepinephrine reuptake, therefore enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the 2 enantiomers improve the analgesic efficacy and tolerability profile of the racemic mixture.

Furthermore, tramadol is also a noncompetitive NMDA receptor antagonist, contributing to the antinociceptive effect at relatively large concentrations.

**Pharmacokinetics**

Tramadol may be administered orally, rectally, sustained release, and parenterally IV/IM.

In healthy adults, after PO administration, it is rapidly and almost completely absorbed. The mean absolute bioavailability of a 100 mg PO dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at 2 and 3 hours, respectively. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours, and have a bioavailability of 87% to 95% compared with capsules.

Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours. Tramadol may pass through the placental barrier with minimal amounts of the parent compound and its metabolites detected in breast milk.

Tramadol undergoes hepatic metabolism by O- and N-demethylation via the CYP P450 isozymes CYP2B6, CYP2D6, and CYP3A4. The O-demethylation of tramadol to M1 (O-desmethyltramadol), the main analgesic effective metabolite, is catalyzed by CYP P450 2D6, whereas N-demethylation to M2 (N-desmethyltramadol) is catalyzed by CYP2B6 and CYP3A4.

The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. As with codeine, in 10% of the population that have reduced CYP2D6 activity (therefore reduced metabolism), there is decreased M1 metabolite levels with subsequent reduced analgesic effect. Those with decreased CYP2D6 activity require a dose increase of 30% of the racemic tramadol to achieve the same degree of pain relief compared with those with a normal level of CYP2D6 activity. Those with renal and hepatic impairment require reduced dose adjustment.
Dosage

Adult

Dosage forms:
- Tablet: Schedule IV
  - 50 mg
- Suspension reconstituted
  - 10 mg/mL
- Capsule, ER: Schedule IV
  - 100 mg (ConZip, Ultram ER)
  - 150 mg (ConZip)
  - 200 mg (ConZip, Ultram ER)
  - 300 mg (ConZip, Ultram ER)

Immediate release
- Chronic pain: 25 mg PO every morning initially; increased by 25 to 50 mg/d every 3 days up to 50 to 100 mg PO every 4 to 6 hours as needed; not to exceed 400 mg/d
- Acute pain: 50 to 100 mg PO every 4 to 6 hours as needed; not to exceed 400 mg/d

Extended release
- 100 mg PO once daily initially; increased by 100 mg/d every 5 days; not to exceed 300 mg/d

Conversion from IR to ER: Round total daily dose down to nearest 100 mg

Dosing modifications
- Severe renal impairment (CrCl < 30 mL/min): Immediate release, 50 to 100 mg PO every 12 hours; ER not recommended
- Severe hepatic impairment: Immediate release, 50 mg PO every 12 hours; ER not recommended

Pediatric

Dosage forms:
- Tablet: Schedule IV
  - 50 mg
- Suspension reconstituted
  - 10 mg/mL

Immediate release
- Less than 17 years: Safety and efficacy not established.
- ≥17 years (acute): 50 to 100 mg PO every 4 to 6 hours as needed; not to exceed 400 mg/d
- ≥17 years (chronic): 25 mg PO every morning initially; increased by 25 to 50 mg/d every 3 days as separate doses up to 50 to 100 mg PO every 4 to 6 hours as needed; not to exceed 400 mg/d

Geriatric
- Greater than 65 years: Initiate at lower end of dosing range; not to exceed 300 mg/d
- Greater than 75 years: Not to exceed 300 mg/d IR; use great caution with ER

Adverse Effects

The most commonly observed side effects with tramadol include nausea, vomiting, dizziness, dry mouth, indigestion, constipation, and sedation. In general, tramadol is well tolerated and does not require dose modification. However, the severity of these side effects may require dose adjustment if necessary. Tramadol is commonly preferred because of its relatively lower risk of addiction and better safety profile in
comparison with other opiates. Of note, there are several significant adverse reactions that may occur. They are as follows.

**Serotonin syndrome**
Serotonin syndrome is a potentially lethal event that is caused by excessive serotonin at the serotonin receptors in the central and peripheral nervous system. Serotonin syndrome may develop as a result of increased serotonin synthesis, increased serotonin release, decreased serotonin metabolism, inhibition of serotonin reuptake, and/or direct agonist activity on serotonin receptors. The syndrome is most often the result of a prescription drug, overdose of causative drugs, and/or complex interactions among several drugs. Three key clinical features of this syndrome are

1. Neuromuscular hyperactivity (eg, tremor, clonus, myoclonus, hyperreflexia, rigidity);
2. Autonomic hyperactivity (eg, diaphoresis, fever, tachycardia, tachypnea);
3. Altered mental status (eg, agitation, confusion).81

Serotonin syndrome may occur with tramadol monotherapy (+ tramadol inhibits serotonin reuptake) but appears more commonly following either excessive use or with coadministration of other medications, particularly antidepressants. For patients with impaired metabolism of tramadol and/or deficient serotonin reuptake, there is a potential risk for elevated (+) tramadol levels with concomitant use of nonspecific serotonin reuptake inhibitors, for example, cocaine, chlorpheniramine, selective serotonin reuptake inhibitor (SSRI), for example, fluoxetine, sertraline, paroxetine, citalopram, Serotonin-Norepinephrine Reuptake inhibitors, for example, venlafaxine, duloxetine, tricyclic antidepressants, and monoamine oxidase inhibitor, for example, selegeline, phenelzine, tranylcypromine. The use of SSRIs with tramadol induces serotonin syndrome through synergistic serotonergic action, along with the inhibition of CYP2D6, resulting in higher levels of (+) tramadol levels.81

There is no designated laboratory study for the diagnosis of serotonin syndrome. Management consists of discontinuing the offending agent and instituting supportive care. Signs and symptoms typically resolve within 24 hours after the discontinuation of the causative medication. In patients exposed to drugs with long elimination half-lives, symptom resolution may be prolonged.81

**Seizures**
Seizures may occur with tramadol, when high doses are used or with concurrent use of medications that lower seizure threshold. The coadministration of antidepressants with tramadol heightens the risk for seizures. Regarding abuse and/or overdose, tramadol’s neurotoxicity is related to its inhibition of reuptake of serotonin and norepinephrine, rather than its opioid effects. Patients with a history of seizures appear to be more at risk for adverse effects.82

**Respiratory depression**
Tramadol may produce respiratory depression, but less compared with morphine at the recommended dosages. Respiratory depression occurs when tramadol is given in high dosages in combination with anesthetic medications, alcohol, or other sedatives.83 Tramadol may also increase airway resistance, resulting in dyspnea. In general, at therapeutic analgesic dosages, the respiratory effects are not clinically significant except in patients with pre-existing pulmonary abnormality. Therefore, tramadol should be administered cautiously in patients with underlying central nervous system (CNS) and respiratory depression. Of note, Naloxone may be administered when clinically significant respiratory depression occurs, but will only partially antagonize the symptom while increasing the risk of tramadol-associated seizures.83
**Hyperalgesia**

Opioid-induced hyperalgesia is a known side effect with chronic opioid therapy. Patients receiving opioids for pain control may paradoxically become more sensitive to pain as a consequence of opioid therapy. If opioid-induced hyperalgesia is suspected, opioid switching is an acceptable treatment option.84

**Psychiatric**

CNS stimulation has been reported as a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability, and hallucinations. During clinical trials, tolerance development was mild, and reports of withdrawal syndrome were rare. Symptoms of a withdrawal syndrome have included panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms (ie, confusion, delusions, personalization, derealization, and paranoia).

- Very common (10% or more): CNS stimulation (up to 14%)
- Common (1% to 10%): Anxiety, euphoria, nervousness, sleep disorder, insomnia, depression, agitation, apathy, depersonalization
- Uncommon (0.1% to 1%): Emotional lability
- Rare (less than 0.1%): Hallucinations, nightmares, dependency
- Very rare (less than 0.01%): Withdrawal syndrome85

**Hypersensitivity**

- Rare (less than 0.1%): Anaphylaxis, allergic reactions, such as dyspnea, bronchospasm, wheezing, angioneurotic edema, swollen skin85

**Gastrointestinal**

- Very common (10% or more): Nausea (up to 40%), constipation (up to 46%), vomiting (up to 17%), dyspepsia (up to 13%)
- Common (1% to 10%): Dry mouth, diarrhea, abdominal pain, flatulence, sore throat, gastroenteritis viral
- Uncommon (0.1% to 1%): Toothache, appendicitis, pancreatitis85

**Nervous system**

- Very common (10% or more): Dizziness (up to 28%), somnolence (up to 25%), headache (up to 32%)
- Common (1% to 10%): Confusion, coordination disturbance, tremor, paresthesia, hypoesthesia
- Uncommon (0.1% to 1%): Migraine, sedation, syncope, disturbance in attention
- Rare (less than 0.1%): Epileptiform seizures

Epileptiform seizures primarily occurred following administration of high doses or following concomitant treatment with drugs that lower the seizure threshold or trigger seizures.85

**Dermatologic**

- Very common (10% or more): Pruritus (up to 11%)
- Common (1% to 10%): Sweating, rash, dermatitis
- Uncommon (0.1% to 1%): Cellulitis, piloerection, clamminess, urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, hair disorder, skin disorder85
Genitourinary
- Common (1% to 10%): Menopausal symptoms, urinary frequency, urinary retention, urinary tract infection
- Uncommon (0.1% to 1%): Difficulty in micturition, hematuria, dysuria, cystitis, sexual function abnormality\(^{85}\)

Cardiovascular
- Very common (10% or more): Flushing (up to 15.8%)
- Common (1% to 10%): Vasodilation, postural hypotension, chest pain
- Uncommon (0.1% to 1%): Palpitations, myocardial infarction, lower limb edema, peripheral swelling, hypertension, peripheral ischemia, electrocardiogram abnormality, hypotension, tachycardia
- Rare (less than 0.1%): Bradycardia\(^{85}\)

Other
- Very common (10% or more): Asthenia (up to 12%)
- Common (1% to 10%): Malaise, weakness, pain, feeling hot, influenza like illness, rigors, lethargy, pyrexia
- Uncommon (0.1% to 1%): Tinnitus, vertigo, ear infection\(^{79}\)

Metabolic
- Common (1% to 10%): Anorexia, decreased weight, increased blood glucose
- Uncommon (0.1% to 1%): Gout
- Rare (less than 0.1%): Changes in appetite\(^{85}\)

Endocrine
- Very rare (less than 0.01%): Syndrome of inappropriate antidiuretic hormone secretion\(^{85}\)

Hematologic
- Uncommon (0.1% to 1%): Anemia, ecchymosis\(^{85}\)

Hepatic
- Uncommon (0.1% to 1%): Cholelithiasis, cholecystitis, alanine aminotransferase and aspartate aminotransferase increased, abnormal liver function tests\(^{85}\)

Ocular
- Common (1% to 10%): Miosis, visual disturbance, blurred vision
- Uncommon (0.1% to 1%): Lacrimation disorder
- Frequency not reported: Mydriasis\(^{85}\)

Renal
- Uncommon (0.1% to 1%): blood urea nitrogen increased\(^{85}\)

Musculoskeletal
- Common (1% to 10%): Hypertonia, arthralgia, back pain, limb pain, neck pain, muscle cramps, muscle spasms, joint stiffness, muscle twitching, myalgia, aggravated osteoarthritis
- Uncommon (0.1% to 1%): Joint swelling, joint sprain, muscle injury, leg cramps
- Rare (less than 0.1%): Involuntary muscle contractions\(^{85}\)
Contraindications

Tramadol is not advised for those deficient in CYP2D6 enzymes accounting for about 6% to 10% of Caucasians and 1% to 2% of Asians. This subgroup of the population has impaired metabolism of the drug with subsequent decrease of M1, O-desmethyl-tramadol, the active metabolite of tramadol.86 Tramadol also should not be given to patients who have previously demonstrated hypersensitivity to tramadol, any other component of the product, or opioids. Tramadol is also contraindicated in situations where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, sedatives, centrally acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen CNS symptoms and respiratory depression in these patients.

Tramadol’s use in pregnancy is generally avoided because it may cause reversible withdrawal effects in the newborn. Previous studies suggest possible teratogenicity, but the increased risk is moderate.87 Its use during lactation is also not advised. A small trial by Bloor and colleagues88 noted that infants breastfed by mothers taking tramadol were exposed to about 2.88% of the maternal consumption. At this dose level, there was no evidence of a harmful effect on the newborn.

Overdose

Fatalities with tramadol overdose have been reported and are increasing in frequency. Most of the overdoses involved a combination of other drugs, including alcohol.89 Recognized risk factors for tramadol overdose include depression, addiction, and seizures. Naloxone, a pure opioid antagonist, only partially reverses the toxic effects of tramadol overdose but increases the risk of seizures. Even though naloxone has been available for many years, there is still uncertainty and confusion over the appropriate dose and route of administration as well as the overall effectiveness.90

Physical Dependence and Withdrawal

The main concern for clinicians when prescribing long-term tramadol is the potential for physical dependence.91 Opioids activate addiction pathways in the brain with need for increasing dose to achieve the same degree of pain relief.92 Abrupt discontinuation of Tramadol, or even dose reduction, may precipitate withdrawal symptoms.93 They are 2 major types: symptoms classical of opioid withdrawal and atypical symptoms of agitation, hallucinations, paranoia, extreme anxiety, panic attacks, headaches, nausea, vomiting, confusion, and abnormal sensory numbness and tingling of extremities.93 The atypical withdrawal symptoms occur in 1 in 8 cases of tramadol withdrawal. If the drug is not consumed in a timely manner, acute withdrawal symptoms set in in 12 to 20 hours with symptom duration longer than that of other opioid withdrawal: 7 or more days for acute withdrawal compared with 3 or 4 days for other codeine analogues. To minimize or prevent tramadol withdrawal symptoms, a slow taper is recommended. A safe taper is a 10% reduction every week and then a 20% reduction every 3 to 5 days.94

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