TRAMADOL

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ABSTRACT

Tramadol is a synthetic, schedule IV opioid. Tramadol is called a weak opioid because it was initially compared to hydromorphone and morphine. Although it began as a non-controlled analgesic when first marketed in the US, reports of misuse and diversion led to a change in labeling. By 2014, tramadol became a schedule IV drug. It is now known that tramadol can lead to a substance use disorder and cause serious morbidities and death. It should be used cautiously because tramadol can cause sedation and other physical side effects. Abrupt cessation of tramadol can lead to withdrawal symptoms like other opioids. Dosing adjustments should be made for patients with hepatic and renal conditions with ongoing monitoring of the patient's response and progress. Tramadol should be avoided or used with caution in patients with a history of mental illness and a history or risk of a substance use disorder. Although said to be a weak opioid, tramadol use disorder is a real risk, and it can be a dangerous drug when taken in excess of therapeutic levels.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From August 25, 2022, through August 25, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
2) Study the section entitled "educational activity;" and
3) Complete the Post-test and Evaluation form. The Post-test will be graded automatically. Following successful completion of the Post-test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the basic pharmacological profile, use, and clinical outcomes of tramadol treatment.
2. **Identify** the dosing for tramadol for the treatment of acute and long-term pain.
3. **Compare** the benefits and risks of tramadol compared to other drugs used to treat acute and long-term pain.
4. **Identify** the contraindications and potential side effects of tramadol.

Disclosures

The following individuals were involved in the development of this activity: Susan DePasquale, MSN, PMHNP-BC, Amanda Mayer, PharmD, and Jeff Goldberg, PharmD. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Tramadol is a synthetic, schedule IV opioid that is used for the treatment of acute and long-term pain, and as an analgesic agent in perioperative clinical settings. Tramadol is widely prescribed in the US and worldwide. Its historical popularity was partly due to its perceived favorable side effects profile and safety, and the perception that it was less likely to be misused than other short-acting opioids; however, tramadol may be just as misused as other opioids. Tramadol remains a popular drug to prescribe, and it does provide positive patient outcomes when it is used properly; however, it is not indicated for all patient populations, and for some patients dosing should be adjusted. Because of tramadol's pharmacodynamics, it can cause an accidental overdose. In these cases, tramadol can cause serious morbidities and death.

Natural and Synthetic Opioids

Opiates are derived from resin that is found in the opium poppy plant, *Papaver somniferum*.[1] The two naturally occurring, primary alkaloids are codeine and morphine.[1] In addition to naturally occurring opiates, other opioids exist and are categorized as either semi-synthetic or synthetic. A semi-synthetic opioid is a derivative of a natural opiate. For example, heroin is a semi-synthetic opioid that is derived from morphine.[1] Synthetic opioids are not derived from opiates, but instead are made in a laboratory and designed to mimic natural opioids.[2] Tramadol is an example of a synthetic opioid that mimics naturally occurring codeine and produces opioid-like effects.[3]

The synthetic, semi-synthetic and natural forms of opioids bind to specific opioid receptors to produce their effects. All types of opioids will produce this effect in varying duration and magnitude depending on their pharmacokinetic and pharmacodynamic profile.

History of Tramadol

Tramadol was initially developed in Germany in the 1970s. In 1995, it was approved in the United States by the Food and Drug Administration (FDA)

as a non-controlled analgesic.[4] After its introduction into the US, tramadol rose quickly in popularity because of its perceived favorable side effects profile and safety, along with the perception that it was less likely to be misused than other short-acting opioids.[4] In fact, several studies exploring the risks associated with opioid use have failed to include tramadol due to these perceptions. The perceptions of tramadol's favorable side effect profile led to it becoming one of the most prescribed opioids in the US.[4]

As the opioid crisis grew and attracted more attention, tramadol was revisited by the FDA. In 2014, the control status of tramadol was increased to a schedule IV controlled substance in the US.[4,5] The reason for tramadol's control status change was due to a re-evaluation of its probability for misuse.[5] As a schedule IV drug, tramadol is said to have legitimate medical use, with a low potential for the development of a substance use disorder.[6] Other countries have also classified tramadol as a controlled substance. The United Kingdom did so in 2014, and Canada added tramadol to its list of controlled substances as of April 30, 2021.[7]

Some clinicians have raised the question of why tramadol is a schedule IV drug while other opioids, *e.g.*, morphine and oxycodone, are schedule II drugs.[4,6] This appears to be the result of tramadol's reputation as a drug that has a lower propensity of leading to a substance use disorder than other opioids. This reputation was reflected in a 2018 randomized clinical trial that grouped tramadol with other "non-opioid medications."[8,9] The view that tramadol is less problematic than other controlled substances is evidenced by its continuing popularity as a prescription drug. Reports from the Drug Enforcement Administration (DEA) imply this as well: after tramadol's classification as a controlled substance, prescriptions of the drug within the US have not dropped significantly.[5]

Pharmacologic Profile

Tramadol is categorized as an analgesic and a synthetic opioid. It has unique characteristics when compared to other conventional opioids causing some medical researchers and clinicians to refer to tramadol as an "atypical"

opioid with milder, opioid-like results. An opioid's potency is typically determined by its relation to morphine's potency and is described with the term "morphine milliequivalents," or MMEs. Tramadol is considered a mild opioid partially due to a 50mg tablet of tramadol being equivalent to 5mg of morphine or having 5 MMEs.[10-12] Tramadol's uniqueness begins with its mechanism of action described below.[9] Because of the perceived safety of its pharmacologic profile, tramadol is widely used. It may be prescribed in different forms, and there are dosing recommendations and adjustments that guide clinicians who prescribe and administer the drug. Clinicians must also consider the warnings and adverse events that may be associated with tramadol's use.[9]

Mechanism of Action

Tramadol acts centrally as a weak μ-opioid receptor agonist. It acts to inhibit ascending pain pathways.[9,13] Tramadol is demethylated by the liver to the active metabolite O-desmethyltramadol (M1), which is a μ-opioid receptor agonist.[9] The cytochrome P450 pathways, particularly the CYP2D6 enzymes, are the primary actors in this process.[9] The affinity of the MI metabolite for the μ-opiate receptors in the central nervous system (CNS) may be as great as 700 times that of the parent drug.[9]

In addition to tramadol's effect on μ-opioid receptors, tramadol differs from other short-acting opioids through its action on the CNS. Tramadol blocks the reuptake of serotonin and norepinephrine, two neurotransmitters directly involved in the inhibitory pain pathway.[9,11]It is this modulation of norepinephrine and serotonin that makes tramadol distinct from classic opioids.[9,14] Tramadol can cause unwanted side effects such as sedation, euphoria, and respiratory depression. However, since tramadol's affinity for μ-opioid receptors is relatively low compared to other opioids, the incidence of unwanted side effects is relatively low as well when used appropriately.[15]

Labeled Uses

Tramadol is indicated for use in the management of moderate to severe pain in adults who require an opioid analgesic.[4] This includes its use for perioperative pain relief, and the treatment of chronic pain, such as chronic cancer pain.[4,17] In cases of persistent postoperative pain relief, tramadol may be coadministered with a non-opioid analgesic, *e.g.*, acetaminophen.[16] Treatment with tramadol has also been used to manage pain from chronic, non-cancer conditions such as osteoarthritis, rheumatoid arthritis, musculoskeletal injuries, and chronic back pain;[16,18] however, long-term use of tramadol to treat these conditions is not well understood.[4]

Tramadol has been used as a first-line treatment for musculoskeletal pain, relief from persistent postoperative pain, and other chronic pain conditions,[16] but some medical scientists and clinicians do not recommend it as a first-line treatment for chronic, non-cancer pain.[4,16] They maintain that any benefit tramadol may provide appears to be offset by the risk of misuse and dependence.[4,9] If a medical condition does require long-term treatment for pain, an extended-release form can be used. Extended-release formulations can provide pain relief for patients who require around-the-clock pain treatment for an extended period of time.[18,19]

Off-label Uses

Tramadol is also used off-label to treat refractory restless legs syndrome and premature ejaculation.[9]

Future Trends in Tramadol Use

Medical scientists are evaluating the use of tramadol to treat depression and fibromyalgia since there appears to be evidence in support of tramadol's use in these disease states.[20] There is also evidence supporting the efficacy of tramadol as a treatment for opioid withdrawal.[21]

Available Forms

Tramadol is available in immediate-release and extended-release formulations and is also manufactured as a combination pill with acetaminophen. The specific formulation strengths and brand names for tramadol are as follows:[22]

- Immediate release: 50 mg, generic and brand name Ultram®.
- Extended-release tablet: 100 mg, generic and as Ultram ER®.
- Extended-release capsule: 100 mg, 150 mg, 200 mg, and 300 mg. Available as the brand name ConZip®, 100 mg, 200 mg, and 300 mg.
- External cream: 8% cream, generic. Also available as the brand name EnovaRx-Tramadol®, 5%.
- Suspension: 10 mg/mL.
- Tramadol and acetaminophen: 37.5mg/325mg respectively, generic and under the brand name Ultracet®. The maximum daily limit of single ingredient acetaminophen is 4,000 mg per day for a healthy adult.

Dosing for Tramadol

Tramadol immediate-release formulation is used for the treatment of pain for less than a week in duration, and it should not be used as an as-needed medication.[22] For pain lasting more than a week, tramadol extended-release is the preferred therapeutic choice. The indication for extended-release is for pain control requiring 24-hour coverage or for an extended period. As with other medications, the lowest effective dose should be used for the shortest effective period. If the patient is taking tramadol for an extended period of time, the dose should be decreased by 25% - 50% every two to four days, and during this taper, the patient should be closely observed for signs and symptoms of withdrawal. Therapy with tramadol should not be abruptly discontinued.[22]

Immediate-Release Formula

The immediate-release formulation may be prescribed as 50 mg to 100 mg every four to six hours, not to exceed 400 mg in a 24-hour period.[22] For patients with moderate acute pain, some clinicians recommend an initial dose of 25 mg, three times a day, which may be adjusted as needed.[22]

Extended-Release Formula

If the patient is not using the immediate-release formulation of tramadol, then the extended-release can be started at 100 mg a day, increasing by 100 mg every five days until the maximum daily dosage of 300 mg is reached, while also remembering to use the lowest effective dose.[22] If, however, the patient is taking the immediate-release formulation, before prescribing the extended-release form, the 24-hour dose being taken should first be determined. The clinician should start the extended-release tramadol at a dose rounded down to the next lowest 100 mg increment, then increase as needed. The therapeutic dose of tramadol considered effective is serum concentrations of 0.1-0.3 mg/L.[22] The topical form of tramadol may be used as needed.[22]

Dosing Adjustments for Certain Patient Groups

Certain patient groups require dosing adjustments. These groups include geriatric patients and patients with renal or hepatic impairment. For these patients, tramadol use and dosing should be evaluated and prescribed cautiously.[22]

Dosing Adjustments for Geriatric Patients

Pain-related medical conditions tend to increase as people age, and so pain is more prevalent in the elderly.[14] Older adults also experience physiological changes that magnify their susceptibility to the adverse effects of medications such as analgesics.[14] Tramadol offers a potential pain relief

medication for elderly patients, but it comes with risks, and it should be used cautiously.[14,19]

The AGS Beers Criteria®

In 2019, the American Geriatric Society (AGS) issued new recommendations in its AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults.[23] With respect to the use of tramadol for elderly patients, the 2019 update restated some of the 2015 criteria and made recommendations for changes related to the use of tramadol.[23]

The 2019 AGS Beers Criteria® continued the warning from its 2015 criteria that tramadol should be avoided in older adults due to its potential effects on the CNS.[14,23,24] If tramadol were to be used, it should be used with caution.[14,23] In addition, in patients with creatinine clearance levels of mL/min <30, the dosage of immediate-release tramadol should be reduced, and the extended-release form should be avoided.[23,24]

The changes in the 2019 AGS Beers Criteria® were material. Tramadol was added to the list of drugs associated with hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion (SIADH); and, The AGS removed chronic seizures and epilepsy associated with tramadol because these conditions were not unique to older adults.[23,24] As far as SIADH and hyponatremia were concerned, the criteria stated that tramadol may cause or aggravate SIADH or hyponatremia in elderly patients.[23] Hyponatremia is characterized by abnormally low sodium in the blood. Syndrome of inappropriate antidiuretic hormone occurs when an excessive amount of antidiuretic hormone is released, resulting in water retention and a low sodium level.[25] This syndrome has symptoms similar to hyponatremia: central nervous system dysfunction due to plasma osmolality of < 240 mOsm/kg (< 240 mmol/kg), which can lead to confusion or other cognitive disorder.[25] The 2019 criteria strongly recommend that a patient's sodium levels be carefully monitored when an older patient is first prescribed tramadol, or when the dose is changed.[23]

Side Effects of Tramadol in Older Adults

Clinical trials of tramadol found that CNS effects such as dizziness, orthostatic hypotension, and somnolence were associated with use in older adults.[4,19,26] These CNS effects can increase an elderly patient's risk of falling, and, subsequently, injuries associated with falls.[26] Falls, or injuries from falling, are adverse events generally associated with opioid use and not just tramadol use.[27] The risk appears to be greatest when opioids are started, and the risk tends to wane over time.[27] Musich, *et al.* (2021) found that the rate of injuries in older adults from falls associated with tramadol was similar to other opioids.[27] Hunnicutt (2018) found a lower fracture risk for short-acting tramadol among older adults in a community setting compared to other opioids, *hydrocodone, for example*, especially during the first 30 days of using the drug.[28]

There is data that indicates that the pharmacokinetics of extended-release tramadol are different for elderly patients. For example, the volume of distribution is significantly higher, while the renal clearance, elimination half-life, and the terminal elimination rate are significantly lower.[29] As such, older adults should have doses at the lower end of the dosing range with close monitoring, and the extended formula should rarely be used. If extended-release formulations are to be used, they should be used at the lowest effective dose and only with extreme caution.[14,22]

Hepatic Impairment

The Child-Pugh classification system may be used to determine the severity of liver disease. Table 1, below, recites the Child-Pugh Classification System.

In patients with *hepatic impairment,* Child-Pugh classes A and B may be prescribed tramadol with caution. Patients in class C should not use tramadol at all.[22]

Table 1: Child-Pugh Classification System

The Child-Pugh measures albumin, bilirubin, and prothrombin time and assesses the severity of ascites and hepatic encephalopathy, a point score is assigned to each of these, depending on the result (for example, a PT 4-6 seconds beyond the control is given a score of 2), and the total score can be used to determine the one-year survival rate in patients who have cirrhosis.

The score ranges from 5 to 15. Patients with a score of 5 or 6 have Child-Pugh class A cirrhosis (well-compensated cirrhosis); a score of 7 to 9 is Child-Pugh class B cirrhosis (significant functional compromise), and a score of 10-15 is Child-Pugh class C cirrhosis (decompensated cirrhosis).

There is little, documented clinical experience about the consequences of using tramadol in patients who have hepatic disease, but the information that is available about liver impairment in patients who take opioids, including tramadol, clearly suggests that administering tramadol to anyone who has hepatic disease requires close monitoring and special considerations.[9,30] The M1 metabolite is an important part of the analgesic effect of tramadol, and it is produced by metabolic activity of the liver; and, the opioids are extensively metabolized by the liver, and the clearance of opioids is decreased in patients who have hepatic insufficiency.[9,30] For dosing in patients with hepatic impairment, Roulet, *et al.* (2021) states: "An increase in the bioavailability and elimination half-life of tramadol is expected in cirrhosis due to decreased hepatic clearance. In patients with hepatic impairment, a doubling of the dosing interval is therefore recommended to avoid tramadol accumulation."[4]

Renal Impairment

Tramadol is not recommended for patients with severe renal impairment because tramadol's half-life elimination is increased in these patients.[4] If tramadol is used by a renally impaired patient, evaluation of their creatinine clearance (CrCl) is needed prior to use. If the CrCl is <30 mL/minute, extended-release tramadol should not be used at all; otherwise, "immediate-release tramadol should be selected in doses of 50 mg and not exceeding 200 mg per day for patients with a glomerular filtration rate (GFR) between 10 and 30 mL/min, and 100 mg per day for patients with a GFR of less than 10 mL/min or who are on dialysis."[4]

Tramadol and tramadol metabolites are primarily excreted by the kidneys. Case reports have documented adverse effects (renal complications) caused by tramadol when the drug is given to patients who have seizures induced by tramadol toxicity.[31] Moreover, authoritative reviews affirm the need for decreased doses of opioids in patients who have renal impairment.[4]

Table 2: Creatinine Clearance (CrCL)

Creatinine clearance (CrCl)is a test that estimates glomerular filtration rate, GFR. The GFR is a highly accurate reflection of kidney function but directly measuring GFR is complex and invasive and using the CrCl is an acceptable and widely used substitute method of estimating GFR. Creatinine clearance is determined by measuring serum creatinine and measuring the amount of creatinine in a 24-hour urine collection. The patient's age and body weight and the results of the tests are used with standard formulas like the Cockcroft-Gault equation or the Modification of Diet in Renal Disease equation to establish a CrCl value. A CrCl of < 30 mL/minute is very low and indicates the presence of impaired renal function.

Side Effects and Warnings for Tramadol Use

Tramadol can be associated with multiple side effects, and in some cases, they can cause serious morbidities and death. Misuse of tramadol is well-documented, and clinicians must be cognizant of the abuse potential, and that a patient may develop a tramadol substance use disorder.

US Boxed Warning

Boxed warnings used to be referred to as "black box warning," and it is a designation by the Food and Drug Administration as the strongest drug safety action that they can implement, often warning of serious risks.[22] Tramadol has a boxed warning as its use can lead to opioid misuse and an opioid use disorder, with the potential for overdose and death.[22]

The risk of respiratory depression is increased by the improper use of the medication, so patients should be told to swallow the immediate release and extended-release forms. The drug should not be chewed, crushed, or dissolved in water. Serious and life-threatening respiratory depression, which can result in death, is more likely when the patient is starting therapy with tramadol or when the dose is increased.[22]

Accidental ingestion of tramadol can cause an overdose, and an overdose may be fatal. Children are particularly vulnerable to this danger.[22] Life-threatening respiratory depression and death have been documented with tramadol. For example, respiratory depression occurred after a tonsillectomy and adenoidectomy in which tramadol was used.[22]

Children who are "ultra-rapid metabolizers" are especially at risk. Ultra-rapid metabolization may be caused by a cytochrome P450 enzyme polymorphism. This can cause an increase in the production of the active metabolites of tramadol, which can lead to oversedation, respiratory depression, and death.[22] In 2015, the FDA issued a warning for the use of tramadol in children who were ultra-rapid metabolizers. The FDA warned that

these children were at risk for severe respiratory depression from tramadol based on documented cases confirming this adverse event.[32]

In 2017, the FDA updated the warning regarding tramadol use in the pediatric population, making it contraindicated in patients under the age of 12 years, in children who are obese, in children who have obstructive sleep apnea, or in children with severe lung disease.[33,34] Tramadol's use is also contraindicated after tonsillectomy or adenoidectomy in pediatric patients < 18 years old. Before giving tramadol to patients 12 – 18 years of age, there should be a careful assessment to ensure there is no sensitivity to the respiratory depressant effects of tramadol or opioids.[34]

Concomitant use of tramadol and drugs that induce or inhibit cytochrome P450 enzymes P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors), or discontinuation of these drugs may cause harmful drug-drug interactions. Concomitant use of tramadol and other drugs that cause CNS depression like alcohol and benzodiazepines can cause coma, respiratory depression, sedation, and death.[22] Moreover, in neonates, prolonged use of tramadol during pregnancy can lead to symptoms of withdrawal.[22]

Contraindications

In addition to the cautionary dosing for certain populations and the boxed warnings, there are some other contraindications for the use of tramadol. Its contraindication in children under the age of 12 years, and its use in children 12-18 in ear, nose, and throat procedures, have already been discussed. Any hypersensitivity to tramadol or any of its components would also make it a contraindication for use. Tramadol is precluded in patients who have significant respiratory depression, or acute or severe bronchial asthma (unless they can be closely monitored). Patients with a gastrointestinal (GI) obstruction, including paralytic ileus are also precluded.[22] Tramadol should not be used concomitantly with an MAO inhibitor or within 14 days of treatment with an MAO inhibitor.[22]

Warnings

Anaphylactoid Reactions

Serious anaphylactoid reactions and fatalities have been reported after tramadol use.[35] A previous anaphylactoid reaction to an opioid may increase the risk of anaphylaxis happening from tramadol. Anaphylaxis caused by tramadol appears to be rare; the prescribing information notes that anaphylactoid reactions were reported as an adverse effect in <1% of post-marketing studies and/or case reports about tramadol.

Cardiac Side Effects

In therapeutic doses, cardiovascular side effects are not likely with tramadol.[37] Tramadol can lead to hypotension and/or orthostatic hypotension with syncope in older adults, but it is not generally regarded as a concern when it comes to cardiac side effects.[37]

A rare case of tramadol-associated pericarditis was reported by Krantz, *et al.* (2005).[38] An 88-year-old male presented with acute pericarditis two days following the initiation of tramadol. His symptoms resolved upon discontinuation of the drug.[38] Mladěnka, *et al.* (2018) list pericarditis as a potential side effect of tramadol but refers to it as a rare, mild side effect.[39] They also refer to the difficulty in linking pericarditis to a particular drug due to the significant number of variables that can lead to pericarditis, but it is a side effect clinicians should be aware of in patients taking tramadol.[39]

Tramadol may be associated with QTc prolongation due to a potassium channel blockade effect.[37] Keller, *et al.* (2016) showed a significant increase in the QT interval after treatment with tramadol.[40] Clinicians should consider monitoring QT intervals regularly in patients with concurrent risk factors for QT prolongation, such as other medications or cardiovascular conditions while taking tramadol.[37,40]

Endocrine

Adrenocortical Insufficiency

Extended use of an opioid can cause secondary hypogonadism, which can cause infertility, mood disorders, osteoporosis, and sexual dysfunction.[41] In a biochemical, genetic experimental study by Abdelaleem, *et al.* (2017), it was confirmed that long-term use of tramadol can induce severe adrenal insufficiency through the use of immunohistochemical studies, electron microscopic examinations, and biochemical studies.[42] Thus, tramadol should be used cautiously if a patient has adrenal insufficiency.[42]

Hypogonadism

A study performed by Darweesh, *et al.* (2020) investigated testosterone suppression in patients dependent on tramadol. There was a statistically significant correlation between the severity of testosterone reduction with the duration and doses of tramadol intake, and this correlated with a high addiction severity scale. This correlation suggests that opioid use, including tramadol, could have inhibitory effects on the hypothalamic-pituitary-gonadal axis via GnRH secretion in the hypothalamus, which could significantly reduce the levels of testosterone. The results provide evidence for the association between testosterone suppression in patients with tramadol dependence with high Addiction Severity scores.[43]

Hypoglycemia

Hypoglycemia is a rare side effect that can occur within the first few weeks of starting therapy with tramadol and is potentially fatal.[44,45] A retrospective review and a case-control analysis of tramadol and hypoglycemia were undertaken by Fournier, *et al.* (2015) to determine if tramadol use when compared with the use of codeine, was associated with an increased risk of hypoglycemia requiring hospitalization.[46] They concluded that the initiation of tramadol therapy is associated with an increased risk of hypoglycemia, especially during the first 30 days of treatment, requiring

hospitalization.[46] Most patients who developed hypoglycemia were elderly and/or had a risk factor predisposing them to hypoglycemia. Clinicians should remain alert to this possible etiology of otherwise unexplained hypoglycemia, especially after starting a patient on tramadol.[45] The mechanism of action of tramadol-associated hypoglycemia is not completely understood, but it may be from a possible effect the drug has on serotonergic control of serum glucose.[44] Hypoglycemia may occur after an overdose with tramadol, either intentional or not.[46]

Thyroid Dysfunction

Tramadol should be used cautiously in patients who have thyroid dysfunction, who may concurrently have treated or untreated cardiac dysfunction, sleep disorders, or obesity, since all of which have been shown to have potential risks with to tramadol use and could exacerbate the underlying issues.[47] Clearance of opioids is decreased in patients who have hypothyroidism, so tramadol should be used cautiously in this situation.[48]

Obesity

Morbid obesity is defined as a Body Mass Index(BMI) of 40 or higher.[49] Tramadol should be used cautiously in patients who are morbidly obese because of risk factors and conditions associated with obesity, such as obstructive sleep apnea, risk of diabetes, chronic obstructive airway disease, and/or other pulmonary conditions.[50,51] Patients with these conditions should also use tramadol cautiously because opioids may exacerbate these conditions, or exacerbate their risk of developing these conditions.[51]

This being said, Porażka, *et al.* (2019) found no clinically relevant change in the pharmacokinetics of tramadol and its active metabolite O-desmethyltramadol when comparing a non-overweight control group to a group made up of patients who were overweight, obese, and obese with diabetes.[52] This study found that "tramadol can be administered to overweight, obese and type 2 diabetes mellitus patients without dose adjustment."[52] Moreover, in a study looking at provider preferences for

postoperative analgesia in obese and non-obese patients, several providers indicated tramadol over other opiates to be the pain management preferred drug for obese patients experiencing moderate pain.[53]

Gastrointestinal Disorders

The μ-opioid receptors are found throughout the CNS;[54] and, as mentioned above, tramadol has an affinity for the MI metabolite of the μ-opiate receptors in the CNS. The μ-opiate receptors are also found in the intestinal tract.[55] Opioids can have an undesirable effect on gastrointestinal function such as nausea, emesis, crampy abdominal pain, and constipation.[4] Tramadol may only pose a minor interference with gastrointestinal motility compared to other opioids.[56]

Nausea and Vomiting

Like other opioids, tramadol may cause nausea and vomiting.[4] Tramadol may have a higher incidence rate than other opioids, *e.g.*, codeine.[4] This may be explained by tramadol's unique actions on dopaminergic and serotonergic receptors.[4] The extent of these effects may be greater depending on the dose. Gradually introducing a patient to tramadol may minimize nausea and vomiting.[4]

Constipation

Constipation is a significant issue for patients who take opioids for chronic pain, especially among elderly patients.[4] For most patients, constipation does not subside over time, so because of this, patients on opioid treatment for chronic pain usually continue taking laxatives for the duration of opioid treatment.[4] With that said, tramadol is associated with a low incidence of constipation compared to other opioids.[4]

GI Obstruction, Including Paralytic Ileus

Stimulation of the opioid receptors in the gut decreases peristalsis, slowing GI transit time and increasing fluid reabsorption from the bowels and the feces. These effects would clearly be harmful to a patient who has a GI obstruction, and opioids themselves can cause GI obstructions like paralytic ileus.[57] Paralytic ileus is often associated with postoperative motility problems that may be due in part to the use of opioid analgesics.[57]

Hepatic Impairment

As previously discussed, use tramadol cautiously if the patient has hepatic impairment, and do not use the extended-release form of the drug if the patient has severe hepatic impairment, Child-Pugh class C.

Mental Health

Patients who have chronic pain and a mental health condition like depression or anxiety should be given tramadol only if they can be closely monitored for opioid use disorder and/or intentional overdose. Tramadol should not be prescribed for patients who are suicidal.[58] Tramadol should be used cautiously in the presence of toxic psychosis, also known as substance-induced psychosis. This is a psychotic disorder caused by exposure, intoxication, or withdrawal from a drug or substance. Adverse effects of tramadol like confusion, drowsiness, and insomnia would certainly exacerbate the condition of substance-induced psychosis, and psychosis is a rarely reported adverse effect of tramadol.[59,60]

Neurologic

Central Nervous System Depression

Tramadol can cause central nervous system (CNS) depression, and this can potentially affect a patient's safety.[61] Tramadol can increase CO_2 retention, so tramadol should be used cautiously in patients who have

impaired consciousness or are comatose since high levels of CO_2 can be particularly harmful to these patients. A retrospective chart review by Marquardt, *et al.* in 2005, had shown that overdoses with tramadol frequently caused CNS depression, nausea/vomiting, tachycardia, and seizures. Symptoms were seen to generally resolve within 24 hours if medically observed or given activated charcoal. However, seven patients in the study were given naloxone, and rapid improvement was observed.[62]

Delirium Tremens

Delirium tremens is a serious medical condition that is characterized by delirium, shaking, and hallucinations, typically occurring with severe alcohol withdrawal.[63] Benzodiazepines are typically used as a treatment for alcohol withdrawal, and because of the CNS depressant effects of both tramadol and benzodiazepines, concurrent use is not recommended. Tramadol can also induce delirium so use with alcohol intake is not recommended, especially if the patient is elderly with alcohol use.[63-65] These factors indicate that tramadol should be used cautiously if a patient has delirium tremens or is at a high risk of developing delirium or delirium tremens.

Craniotomy and Head Trauma

Opioid analgesics are used to control pain for patients having cranial surgery.[66,67] Opioids may increase intracranial pressure and may also interfere with a postoperative neurologic examination, which could lead to respiratory depression, nausea, and over sedation.[67] Tramadol shares many of these adverse effects but is less likely to cause respiratory depression when compared to other opioids.[67] Tramadol's effectiveness is considered less than morphine in the context of craniotomies.[67]

A concern with tramadol, discussed next, is the possibility of tramadol-induced seizures. The incidence of seizures is low, but the risk rises in head injury and stroke patients.[67] These are all concerns when considering tramadol for a craniotomy candidate.

Seizures

Seizures are a well-documented adverse effect of tramadol. The prescribing information for tramadol states that seizures occurred in <1% of post-marketing and/or case reports; however, the prevalence is potentially impacted by other risk factors for seizures.[68] Risk factors for seizures include a preexisting seizure disorder, and the situation where a patient is taking a drug that lowers the patient's seizure threshold, such as antipsychotics/antidepressants, muscle relaxers, and other opioids. Seizure risk may also increase due to alcohol withdrawal, CNS infection, head trauma, malignancy, or metabolic disorders.[68]

Seizures after tramadol ingestion usually occur with a tramadol overdose or in the context of misuse of the drug.[69] This factor is important because the risk of seizure should be lower for those taking tramadol legitimately.[69]

Serotonin Syndrome

Serotonin syndrome is a potentially fatal condition that is caused by the accumulation of serotonin at 5-HT receptors in the CNS.[70] Patients who have slower rates CYP2D6 function and those with deficient serotonin (5-HT) uptake, are at risk for serotonin syndrome when taking tramadol.[69] Serotonin syndrome will be evident within 24 hours of a patient initiating a 5-HT reuptake inhibitor or CYP2D6 inhibitor, or when the dose of an existing 5-HT reuptake inhibitor or CYP2D6 inhibitor has been increased.[69]

Pulmonary Disease

Tramadol, as previously discussed, can cause respiratory depression and retention of CO_2, so it should be used cautiously in patients who have chronic obstructive pulmonary disease (COPD), cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or respiratory depression. Adverse respiratory effects are more likely to occur when therapy with tramadol is being started or when the dose is increased. Opioids cause respiratory

depression by decreasing the sensitivity of the central chemoreceptors to carbon dioxide and by depressing the ventilatory response to hypoxia, but if opioids are administered correctly, respiratory depression is an unusual adverse effect and is preventable.[71]

Tramadol may be less likely than other opioids to cause respiratory depression,[68,72,73] but the studies are limited, and the prescribing information states that tramadol may cause serious and life-threatening respiratory depression.[22,72]

Renal Disease

As described earlier, the extended-release form of tramadol should not be given to patients who have severe renal impairment, and the dose of immediate-release tramadol should be in the lower end of the range if the patient has severe renal impairment.

Urologic

Prostatic hyperplasia, urinary stricture, and urinary retention are conditions that may be aggravated by drugs, including opioids.[74-76] Patients with these conditions should use tramadol cautiously.

Stimulation of opioid receptors can inhibit micturition.[75] Urinary retention has been reported as an adverse effect of tramadol.[76,77] Urinary incontinence has also been associated with tramadol.[78]

Use During Pregnancy and Breastfeeding

Studies are limited but some have found an association of severe congenital malformations, cardiovascular defects, and clubfoot with opioids, including tramadol.[79] Prolonged use of tramadol during pregnancy can cause neonatal abstinence syndrome (NAS), a potentially serious, life-threatening condition. Neonatal abstinence syndrome is the condition of opioid withdrawal in a neonate that occurs in the immediate postnatal period.[80] This occurs

because opioids easily cross the placenta during pregnancy; moreover, tramadol, as a lipophilic opioid, also freely crosses the placenta.[81-83] The prevalence of newborns affected by NAS (because the mother used an illicit or prescribed opioid drug during pregnancy) has reportedly ranged from 27%–94%.[82]

Opioid withdrawal is rarely life-threatening, but it may be associated with weight loss, fever, or seizures in newborns.[84] Other concerns associated with prenatal opioid exposure are spontaneous abortion, premature rupture of membranes, preeclampsia, abruption placentae, and fetal death.[82] There can be long-term cognitive and behavioral effects caused by NAS as well,[85] and NAS are associated with longer hospital stays and considerable medical costs.[83]

A pregnant woman should be screened for substance use at the first prenatal visit. The American College of Obstetrics and Gynecology recommends universal screening to avoid cases that may be missed because a pregnant woman who is misusing substances does not exhibit the stereotypical characteristics of someone who is misusing substances.[86]

Tramadol was listed as a category C pregnancy risk drug under the prior pregnancy risk system. This system has been replaced by the FDA's Pregnancy and Lactation Labeling Rule (PLLR). A clinician should consult the PLLR at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450636.pdf

In January 2018, the FDA issued a Drug Safety Communication which recommended that tramadol should not be used during breastfeeding,[87] summarizing its position by stating: "In our review of the medical literature for data regarding codeine use during breastfeeding, we found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in

breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine."[87]

Tramadol Use Disorder

As discussed above, when tramadol was first marketed, the interpretation by regulatory agencies and the medical community of the data from clinical trials was that tramadol had a low potential for addiction, and the drug did not need to be categorized as a controlled substance. The subsequent experience made it clear that tramadol use disorder is possible and is occurring.[9] Some clinicians are also calling for tramadol to be rescheduled with other opioids. Thiels, *et al.* (2019) wrote:" We found that tramadol, a drug that is scheduled at a lower risk level than other common short-acting opioids (schedule IV versus schedule II for hydrocodone and oxycodone), has a similar or somewhat greater risk of prolonged opioid use after surgery. Although all factors related to the safety of a drug must be considered, from the standpoint of opioid dependence, the Drug Enforcement Administration and FDA should consider rescheduling tramadol to a level that better reflects its risks of prolonged use."[9]

The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for the diagnosis of opioid use disorder states that opioid use disorder is present if opioid use is causing significant impairment and if two of 11 specific behaviors are present within a 12-month period. Those behaviors include tolerance, withdrawal, and taking the opioid in larger amounts or over a longer period than was intended.[88] The published information about tramadol use disorder is not as extensive as it is for other opioids and the incidences of tramadol use disorder are not known, but there is enough clinical experience to confirm that tramadol misuse is not unusual, and it can devolve to opioid use disorder.[2,11]

Tramadol Overdose

Tramadol is an opioid, and patients who overdose on tramadol can experience adverse effects, such as nausea and vomiting, hypertension,

tachycardia, CNS depression, respiratory depression, agitation, and seizure.[37,89] A tramadol overdose differs from other opioids in two ways: 1) serotonin syndrome may occur, and 2) seizures are relatively common after a tramadol overdose, and this may be due to the drug itself, not from complications like hypoxemia that can happen in any case of opioid poisoning.[4,9] The Hunter Serotonin Toxicity Criteria is used to diagnose patients with serotonin syndrome.

Table 3: Hunter Serotonin Toxicity Criteria

A patient has serotonin syndrome if in the context of exposure to a serotonergic drug any of the following exist:

1) **Inducible clonus plus agitation and diaphoresis**
2) **Ocular clonus plus agitation and diaphoresis**
3) **Inducible clonus or ocular clonus plus hypertonia and hyperthermia**
4) **Spontaneous clonus**
5) **Tremor plus hyperreflexia**

Several cases of cardiogenic shock have been reported but this is a very unusual event after tramadol overdose.[90,91] Death from tramadol overdose alone is rare: most patients who die after taking an overdose of tramadol had one or several co-ingestants. The toxic dose of tramadol is not known. Toxicity more commonly occurs when a person ingests tramadol deliberately to overdose, with the intent to cause self-harm, or when pediatric exploratory exposure occurs.[92,93]

Treatment of Overdose

Any patient who has taken an overdose of tramadol with the intent to cause self-harm should be referred to a hospital, and a child who has ingested any amount of tramadol (apart from a small taste) should be referred to a hospital. Symptomatic patients should be admitted; asymptomatic patients should be observed for six to eight hours unless an extended-release product

was ingested, and then 12 hours of observation is advised.[94] The recommended treatment for the central nervous system (CNS), cardiovascular, and pulmonary signs of tramadol poisoning is supportive care.[94] The two exceptions would be the use of naloxone to correct hypoventilation and the use of cyproheptadine to treat patients who have serotonin syndrome.

Naloxone is an opioid antagonist that displaces opioids from opioid receptors and prevents opioid-opioid receptor binding. Naloxone is the antidote for opioid poisoning, it has an excellent safety profile, and it has been used successfully to treat tramadol overdose but there is some evidence - which could reasonably be called inconclusive - that the use of naloxone in the context of a tramadol overdose may cause seizures.[93,95] An experimental investigation was performed using a rat model by Lagard, *et al.* (2018) which demonstrated that naloxone used to treat tramadol toxicity reversed respiratory depression but caused a significantly higher incidence of seizures.[95] There are differing outcomes regarding the outcome of the use of naloxone, where some literature points to a 91% improvement in abnormal brain activity after naloxone injection, other studies show an increase in seizures, after injection, and some report a lack of any response of the patient after injection. Some reports list the naloxone seizurogenic effect as that which puts the patient at risk for seizure due to tramadol injection. A study by Eizadi-Mood, *et al.* (2014) investigated a preventative naloxone injection for the aversion of seizure initiation in tramadol toxicity, comparing seizure incidence in those who received naloxone injection for tramadol toxicity against those who did not.[93] Their conclusion was that "although the seizure incidence was lower in patients with tramadol poisoning who received naloxone, the logistic regression did not support the preventive effect of naloxone on seizure in tramadol poisoning cases. Most guidelines recommend naloxone as the first step of treatment in opioid overdose, there are some controversies between studies regarding using naloxone in tramadol poisoning due to possible risk factors for seizure."[93] Clinicians treating a patient who has taken an overdose of tramadol would need to consider the risks (causing a seizure and for a person with opioid use disorder, precipitating withdrawal)

and benefits (reversing apnea and restoring adequate ventilation) of naloxone.

Cyproheptadine is a 5-HT2A antagonist that prevents the binding of serotonin to serotonin receptors. Cyproheptadine has been successfully used to treat cases of serotonin syndrome, but the evidence for its effectiveness as a treatment for serotonin syndrome is limited. In a non-interventional, retrospective chart review by Frye, *et al.* (2019), the effectiveness of cyproheptadine treatment for serotonin syndrome was evaluated.[96] The recommended dosage is initially 12 mg, followed by 2 mg every 2 hours until the symptoms resolve. Most received the initial dose between 1-2 days of admission and were treated for the most part in the ICU (78.6%), with the remainder receiving treatment in the emergency department (21.4%). The authors concluded that those diagnosed with serotonin syndrome and who were administered cyproheptadine had a resolution of their symptoms within 48 hours. There was also a lower mortality rate than in previous studies, with a 96.4% survival rate. There was a recommendation for additional prospective studies.[96] Additional prescribing information not provided in this article lists a maintenance dose of 8 mg every 6 hours until stabilized. A total daily dose is not to exceed 0.5mg/kg/day, and is only available in an oral dose, but can be crushed if needed, to administer through a nasogastric tube.[97] There would be little risk of harm from giving cyproheptadine to a patient who had serotonin syndrome, but the cornerstone of treatment for this clinical situation is symptomatic and supportive care.

Summary

Tramadol is a centrally acting synthetic opioid analgesic used for the treatment of short-term and long-term pain. It is available in immediate-release and extended-release tablets. The analgesic effect of tramadol is mediated by how the drug binds to opioid receptors and by inhibition of the reuptake of norepinephrine and serotonin. It is the latter mechanism of action that makes tramadol unique from the typical opioids. Tramadol is categorized as a schedule IV drug, which means it has legitimate medical uses and a low potential for a substance use disorder.

Cautious use of tramadol in certain populations, such as the elderly and those with hepatic and renal impairment, is needed because of an increased risk of adverse effects. The typical adverse effects of tramadol are common to all opioids. Prescribing tramadol in children and pregnant or nursing women carries risks. Tramadol should not be used for patients at risk or with a history of substance use disorder. If it is chosen as a treatment for this population group, it should be used very cautiously. It should also be used with caution for patients with a history of psychiatric illness.

Tramadol was considered an atypical opioid that is not likely to be misused as other opioids, but tramadol use disorder is a real risk, and it can be a dangerous drug when taken in overdose.

Course Test

1. **Tramadol is a synthetic opioid, which means it was**

    a. derived from opiates.
    b. made from the resin of the opium poppy plant.
    c. made in a laboratory and mimics natural opioids.
    d. designed to block opioid-like effects of other drugs.

2. **How is tramadol's mechanism of action different from other short-acting opioids?**

    a. It does not cause euphoria.
    b. It inhibits the reuptake inhibitors norepinephrine and serotonin.
    c. It is much more powerful than other opioids.
    d. It does not cause respiratory depression.

3. **Tramadol has a recognized use for the treatment of**

    a. minor pain, on an as-needed basis.
    b. chronic cancer pain.
    c. anxiety in children.
    d. All of the above

4. **Tramadol is principally demethylated by the _____ to the active metabolite O-desmethyltramadol (M1), which is a μ-opioid receptor agonist.**

    a. kidneys
    b. pancreas
    c. liver
    d. spleen

5. **For pain lasting more than a week, tramadol**

    a. should not be used.
    b. immediate-release formula must be used.
    c. must be coadministered with another pain reliever.
    d. extended-release is the therapeutic choice.

6. **If a patient is taking the tramadol immediate-release formulation and is being prescribed the extended-release form, the immediate-release dose would first need to be**

    a. stopped.
    b. determined, *i.e.*, the dose amount.
    c. reduced by at least 50%.
    d. increased to its maximum dosage.

7. **Patients with creatinine clearance levels of mL/min <30**

    a. must not be prescribed tramadol.
    b. may take tramadol without reducing the recommended dose.
    c. should not take the extended-release form of tramadol.
    d. must take dabigatran with tramadol.

8. **True or False: Patients who have slow functioning CYP2D6 enzymes, and those with deficient serotonin (5-HT) uptake are at risk for serotonin syndrome when taking tramadol.**

    a. True
    b. False

9. **The FDA recommends that mothers who take tramadol**

    a. should not breastfeed.
    b. may breastfeed because tramadol is not present in breast milk.
    c. should continue the drug but at a reduced dose.
    d. may only take the oral form of tramadol.

10. **People who overdose on tramadol can experience adverse effects such as**

    a. hypertension.
    b. respiratory depression.
    c. agitation and seizure.
    d. All of the above

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