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Drugs of Abuse: A Review of Tramadol Abuse

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**Abstract**

Prescription drug abuse is the fastest growing drug problem in America. Among the different prescription drugs being abused, analgesics are the most commonly abused group of drugs. In the last few years, there is increasing evidence of abuse of tramadol, which is an atypical, centrally acting opioid analgesic. The increasing abuse of tramadol has prompted regulatory authorities to strengthen the product labeling of tramadol with respect to its abuse potential. Furthermore, several states have added tramadol to their controlled substances list. In this article, we will review the pharmacology of tramadol and some of the preclinical and clinical studies that support its abuse liability. In addition, we will focus on the risk factors that may predispose individuals to tramadol abuse and the consequences of tramadol abuse such as tramadol poisoning and tramadol dependence. Lastly, potential strategies with an emphasis on the role of the pharmacist and other health care professionals in controlling tramadol abuse will be discussed.

**Introduction**

Prescription drug abuse is defined as the use of a medication for purposes outside of its original intention.\(^1\) Examples of misuse include abusing a medication without a prescription, using a medication in ways other than prescribed or intending to misuse the medicine for an “experience” or a “feeling.”\(^1\) Prescription drug abuse is the fastest growing problem in the United States with approximately 6,600 new abusers each day.\(^2\) Importantly, the problem affects the country as a whole due to the large societal costs associated with it. The societal cost of prescription drug abuse, including costs to health care, the criminal justice system and lost workplace productivity, was estimated to be $55.7 billion in 2007.\(^2\) Prescription drugs commonly abused include analgesics (pain relievers), tranquilizers, stimulants and sedatives.\(^3\) Among these drugs, analgesics are the most commonly abused prescription drug category. In 2010, 12 million Americans 12 years of age and older reported using prescription analgesics for nonmedical uses for the first time.\(^2\)

Included in this category of prescription analgesics is tramadol [Ultram\(^®\)].\(^1\) Tramadol, approved in the United States in 1995, is a nonscheduled analgesic indicated for the treatment of moderate to moderately-severe pain.\(^3\) For several years after its approval, tramadol was advocated as a unique drug due to its supposed weak narcotic effects.\(^3\) These weak narcotic effects were initially seen as an advantage, as it was thought the drug could be safely used to treat pain in patients with a history of narcotic abuse.\(^3\) However, due to increased reports of overdose and suicides, product labeling of tramadol was revised in July 2010.\(^4\) Revisions included warnings of an increased suicide risk for patients using tranquilizers or antidepressants and patients at risk for addiction.\(^4\) The labeling changes also emphasized the risks of overdose and the abuse potential of the drug.\(^4\)

Despite these warnings, tramadol continued to be widely prescribed. In 2012, 29.8 million prescriptions of tramadol were dispensed.\(^3\) Importantly, there has been increasing evidence of tramadol overdose and abuse.\(^3\) In 2011, poison control centers reported 12,424 cases of tramadol overdose, with 6,361 of these exposures leading to death.\(^3\) In addition to overdose, the 2011 National Survey on Drug Use and Health reported that 2.6 million people ages 12 and older used tramadol for nonmedical uses in the past year, with the most commonly abused dosage form being oral.\(^3,5\) In 2013, the Drug Enforcement Administration (DEA) challenged the previous classification of tramadol\(^3\) and stated in its report that, “Dependence and abuse, including drug seeking behavior and taking illicit actions to obtain tramadol are not limited to those patients with prior history of opioid dependence.”\(^3\) Furthermore, several states, including Arkansas, Kentucky and, most recently, New York, have included tramadol on their controlled substances lists.\(^5,7\) In this review, we will discuss the pharmacology of tramadol and the underlying neural mechanism which facilitates tramadol abuse. We will also explore the factors that increase the risk for tramadol abuse and poisoning, as well as the treatment of tramadol poisoning and withdrawal. Lastly, we will discuss strategies to prevent tramadol abuse.

**General Pharmacology**

Tramadol is a centrally acting analgesic and is available as both oral immediate-release formulations (50 mg in either capsules, drops, tablets or soluble tablets) and sustained-release tablets. All formulations have a high bioavailability. The plasma protein binding of tramadol is approximately 20 percent.\(^8\) Tramadol is metabolized mainly by hepatic cytochrome P450 isoenzymes 2D6 and 3A4.\(^8,9\) Cytochrome P450 isoenzyme 2D6 (CYP2D6) is primarily responsible for the metabolism of tramadol to its active metabolite O-desmethyl-tramadol.\(^8,10-12\) When CYP2D6 concentrations are low or O-demethylation is inhibited, isoenzymes 2B6 and 3A4 (CYP2B6 and CYP3A4) contribute to metabolism of tramadol into N-desmethyl-tramadol.\(^8,9,11\) Tramadol is excreted via the kidneys and the elimination half-life is approximately six to eight hours.\(^8,9\)

Structurally, tramadol is similar to codeine and morphine.\(^8,11\) It is formulated as a racemic mixture of two enantiomers in its parent form: (+)-tramadol and (-)-tramadol, which play complementary and synergistic roles in mediating its analgesic effects.\(^8,11\) (+)-Tramadol inhibits reuptake of serotonin and (-)-tramadol inhibits the reuptake of norepinephrine. In addition, (+)-tramadol and its active metabolite, (+)-O-desmethyl-tramadol, are mu opioid receptor agonists, which...
further enhance the analgesic efficacy of tramadol.\textsuperscript{8,11} Because of this dual mechanism of action, tramadol is classified as an atypical opioid analgesic. However, despite this dual mechanism of action, the analgesic potency of tramadol is only about 10 percent that of morphine, a potent mu opioid receptor agonist.\textsuperscript{8}

The activation of mu opioid receptors by tramadol and its active metabolite O-desmethyl-tramadol play an important role in the abuse liability of tramadol.\textsuperscript{8-11} In humans, activation of mu opioid receptors results in positive reinforcement and rewarding effects such as euphoria, relaxation and drowsiness. Relaxation and drowsiness can be reinforcing especially in individuals suffering from pain. These positive reinforcing effects thus provide the major motivation for continued use and subsequent abuse of tramadol. When comparing tramadol and its metabolite O-desmethyl-tramadol, the latter is a more potent agonist of the mu opioid receptor. Therefore, both the reinforcing and analgesic effects of tramadol are more dependent on its conversion to its active metabolite. Polymorphisms associated with the CYP450 enzyme CYP2D6 greatly influence the effects of tramadol. Based on the activity of CYP2D6, individuals can be classified as poor metabolizers, normal metabolizers and ultra-rapid metabolizers.\textsuperscript{10,12} Poor metabolizers have reduced or absent activity of CYP2D6 and the analgesic efficacy of tramadol is decreased in these patients as compared to those who have normal CYP2D6 activity.\textsuperscript{10,12} In contrast, ultra-rapid metabolizers of tramadol, who have increased activity of CYP2D6 and rapidly convert tramadol to its active metabolite, are at a higher risk of abusing tramadol. Consistent with this hypothesis, higher rates of tramadol abuse have been reported in individuals from Middle Eastern countries who are commonly ultra-rapid metabolizers of tramadol.\textsuperscript{10,13}

Drug Abuse Potential: Evidence from Clinical and Preclinical Studies

Preclinically, the positive reinforcing effects of drugs can be assessed using the conditioned place preference (CPP) model.\textsuperscript{14} Conditioned place preference is conducted using an apparatus that has two chambers, which are distinct with respect to their texture and/or color. The drug of interest is administered to the animal and the animal is placed in one of the chambers. This pairing of the drug to a particular chamber is done repeatedly over several days. This process is known as conditioning and allows the animals to associate the reinforcing effects of the drug (if any) with the specific environment. Along with this pairing of the drug to one of the chambers, the animal is also conditioned to a distinct chamber in the apparatus using a vehicle (control). On the test day, the animal is allowed to explore both the drug- and vehicle-associated chambers in a drug-free state. The time spent by the animal in the drug-associated compartment is compared to the time spent by the animal in the vehicle-associated compartment. If a drug is reinforcing, the animal will spend significantly more time in the drug-associated compartment compared to the vehicle-associated compartment.\textsuperscript{14} Several preclinical studies showed that tramadol-administration induced CPP in rats.\textsuperscript{15,16} Additionally, tramadol enhanced morphine-induced CPP. Importantly, pretreatment with mu receptor antagonist naloxone attenuated tramadol-induced CPP. Together these data suggest that tramadol has positive reinforcing effects, which are mediated by the mu opioid receptor. Furthermore, drugs with high abuse liability increase the activity of the mesolimbic dopaminergic neurons in the brain. These mesolimbic dopaminergic neurons originate in the ventral tegmental area in the midbrain and project to several limbic sites including the nucleus accumbens (NAcc). The increase in activity of these mesolimbic dopaminergic neurons is determined by measuring the increase in levels of the neurotransmitter dopamine in the NAcc using a procedure called in vivo microdialysis. Tramadol administration in rats increased NAcc dopamine levels.\textsuperscript{15} In summary, these preclinical studies suggest that tramadol has positive reinforcing effects and support the abuse liability of tramadol.

Clinical Studies

A within-subject, randomized, double-blind, placebo-controlled study evaluated the reinforcing effects of different doses of tramadol (200 and 400 mg), oxycodone (20 and 40 mg) and codeine (100 and 200 mg) by allowing subjects to self-administer the different drugs and placebo. The highest self-administration was observed when subjects received the 400 mg tramadol compared to 200 mg of tramadol, placebo and both doses of oxycodone and codeine. The high rates of self-administration suggest that 400 mg of tramadol has strong reinforcing effects. In addition, the study also reported that 400 mg of tramadol increased mu opioid receptor agonist-like measures such as itchy skin and pupillary constriction. Lastly, the study reported that all drugs (except low doses of codeine) increased subjective measures of abuse liability such as "liking" or "high" for the drug. Taken together, these data suggested that tramadol has a high abuse potential.\textsuperscript{17} Several other clinical studies also reported findings that support the abuse potential of tramadol.\textsuperscript{8,11,13,15,17}

In contrast to the above studies, some clinical studies conducted immediately after the approval of tramadol reported that tramadol may not have abuse potential.\textsuperscript{16} It is not entirely clear why these studies suggested that tramadol is not linked with the possibility of abuse. One possible reason could be that these studies were conducted in individuals with a history of opioid drug abuse, who generally develop tolerance to the reinforcing effects of weaker reinforcers. The relatively weak reinforcing effects of tramadol were, therefore, not detected in these subjects. Another possible reason could be that in most of these studies, tramadol was administered intramuscularly rather than orally. As described above, the active metabolite of tramadol is mainly responsible for its reinforcing effects. The conversion of tramadol to this specific active metabolite is maximal when it is administered orally, due to hepatic first pass effect via CYP isoenzymes. The results of the studies described above contributed to the misguided perception of low abuse potential of tramadol, and to its continued use and abuse.\textsuperscript{1,4}

Tramadol Abuse and Overdose

One potentially fatal consequence of tramadol abuse is
Tramadol overdose and poisoning. A review of 114 studies of tramadol-intoxicated subjects suggests that 80 percent of the patients poisoned themselves with the intent of suicide. These data therefore suggest that physicians and pharmacists must be very careful in prescribing tramadol for patients with a history of suicidal ideation, previous suicide attempts or depression. Furthermore, patients suffering from depression are at an increased risk of tramadol poisoning. Clinical reports suggest that there is extensive comorbidity in patients suffering from depression and pain. Patients with chronic pain have decreased serotonin and tryptophan concentrations in the hippocampus, which may predispose them to depression. In addition, depressed patients may be more likely to develop chronic pain due to an alteration in the utilization of tryptophan. It is logical to recognize that some patients on tramadol, who may also have chronic pain, may be diagnosed with, or be at an increased risk for, depression. Furthermore, taking tramadol concomitantly with a benzodiazepine (a class of drugs used to treat central nervous system (CNS) disorders, including depression) predisposes individuals to cardiopulmonary arrest. The pharmacodynamic interaction of tramadol and a comorbid psychiatric disorder, like depression, along with the pharmacokinetic interactions between tramadol and depression medications may predispose individuals to tramadol poisoning. In addition to depression medications, risk of tramadol poisoning is increased following concomitant administration of tramadol with other CNS-depressant medications/substances including alcohol, tranquilizers, sedatives and muscle relaxants. In summary, patient groups prone to tramadol-related poisonings and deaths include patients with a previous history of depression or suicidal ideation and attempts as well as a history of misuse of alcohol and other CNS-depressant medications.

Patients who have abused or intentionally overdosed on tramadol may present with adverse effects such as nausea, vomiting, central nervous system depression, tachycardia, seizures and apnea. Some patients may present with symptoms characteristic to serotonin syndrome, which include altered mental state, neuromuscular hyperactivity and autonomic dysfunction. Management of tramadol poisoning involves treatment of symptoms of overdose as they arise and providing supportive care to ensure patient comfort and safety. Naloxone, an opioid antagonist, is used as an antidote to treat tramadol poisoning. However, a much larger dose of naloxone is required for tramadol poisoning in comparison to the dose needed to treat poisoning of other opioids. However, the use of naloxone as an antidote to treat tramadol poisoning is controversial as an increased risk of seizures has been reported with its use.

Tramadol Withdrawal and Treatment
Another major problem with tramadol abuse is tramadol dependence. In tramadol-dependent patients, withdrawal from tramadol results in symptoms such as abdominal cramps, anxiety, bone pain, diarrhea, goose flesh, insomnia, lacrimation, nausea, restlessness, rhinorrhea and sweating. These withdrawal symptoms are similar to those seen in opioid dependent patients. Some patients report atypical withdrawal symptoms including severe anxiety, panic attacks, unusual CNS symptoms, sensory symptoms and hallucinations. These latter symptoms are similar to those observed in patients who withdraw from selective serotonin reuptake inhibitors (SSRIs). This parallel may be due to the ability of tramadol to block the reuptake of serotonin, similar to SSRIs.

Treatment of tramadol withdrawal is patient specific. In most cases, a gradual reduction of the patient's tramadol dose, rather than stopping suddenly, yields the least withdrawal symptoms. Unfortunately, there is no standardized protocol for reducing tramadol administration; patients should work with their doctor and pharmacist to set a schedule that works for them. Tramadol withdrawal symptoms are generally managed through supportive care in a way that is most comforting to the patient. Treatment of these symptoms is critical as the symptoms can lead to relapse among abstinent tramadol-dependent patients.

In addition to treatment of the withdrawal symptoms, it is necessary to address any underlying factors that may have facilitated tramadol abuse. For example, if the patient continues to experience pain and needs an analgesic, switching to a nonopioid analgesic may be an option. If that is not possible, another option would be the creation of a detailed monitoring strategy, in which both prescribers and pharmacists are deeply involved, in order to ensure that the therapeutic effects of tramadol outweigh negative consequences. This may include extensive laboratory testing of the cardiovascular, pulmonary and central nervous systems for objective data, as well as meeting with the patient to gain subjective data. Due to the possible link between tramadol abuse and depression, as discussed above, pharmacological treatment of depressive symptoms may help facilitate the reduction of tramadol abuse and prevent relapse in dependent patients. In addition to this pharmacological treatment, psychological support in the form of psychotherapy and support groups may help prevent relapse in abstinent tramadol-dependent patients.

Prevention of Tramadol Abuse and Poisoning
Counseling and educating the patient is the first step to preventing tramadol abuse. Both prescribers and pharmacists have a duty to educate patients on tramadol toxicity, overdose and abuse potential, as well as a duty to formulate abuse prevention and treatment strategies individualized to each patient.

The use of multiple physicians and pharmacies by patients often makes it difficult for a health care professional to know every medication the patient is taking and the effects of each of these medications. One way to prevent toxic effects and fatalities in patients using tramadol, or any other opioid, is monitoring what drugs are being prescribed, dispensed and administered by one or more doctors using medication lists and patient profiles. Medication lists and patient profiles allow the pharmacist to identify potentially harmful and fatal drug interactions before they occur. For example, patient profiles increase pharmacists' ability to see if a patient taking
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a CNS depressant prescribed by one doctor is prescribed tramadol by a different or the same doctor. Furthermore, it gives pharmacists an opportunity to discuss with prescribers possible alternatives to tramadol and/or other interacting medications. Thus, pharmacists have the unique ability to catch and rectify a problem before it occurs.

As stated previously, there is evidence of increased tramadol abuse in certain groups of patients, such as those with a previous or current history of emotional disturbances, depression, suicidal ideation, suicidal attempts, as well as previous or current use of tranquilizers, alcohol and other CNS-active drug abuse. Therefore, another useful approach to decrease tramadol abuse would be to screen such patients after careful review of their medical histories. In these patients, it may be necessary to either avoid prescribing tramadol or prescribe tramadol with careful and rigorous monitoring as described above. Additionally, ultra-rapid metabolizers of tramadol may be at greater risk for tramadol abuse compared to poor and normal metabolizers of tramadol. Thus, in the current era of personalized medicine, it may be possible to identify patients who may be at greater risk of tramadol abuse based on CYP2D6 polymorphisms. Although no such test currently exists, it is not inconceivable that such a test may be developed in the near future. The test may perhaps only require a simple cheek swab from a potential patient. Regardless of the challenges, it is critical for every healthcare professional to be alert to identify and prevent tramadol abuse among the different patient populations.

Regulatory mechanisms can also help in reducing and preventing tramadol abuse. The use of automated prescription reporting systems such as the Ohio Automated Rx Reporting System (OARRS) can also play an important role in controlling prescription drug abuse. The OARRS requires outpatient pharmacies to report every dispensed prescription of controlled substances, tramadol and carisoprodol. Because tramadol prescriptions have to be reported to OARRS, and because tramadol either is currently or is anticipated to be a controlled substance in many states, pharmacists have the ability to track patients’ tramadol use, as well as the use of any other opioids that may increase tramadol abuse and poisoning. Additionally, OARRS provides pharmacists the opportunity to cut down on inappropriate opioid use and to work with prescribers and patients to find an alternate therapy. However, OARRS is not a perfect system. One major limitation is the system’s dependence on the compliance of pharmacies. If pharmacies are not properly reporting each tramadol prescription within eight days of dispensing, as required by OARRS, the system cannot work to its full potential. Although OARRS generates a report identifying pharmacies which have “failed to report” in an eight-day period, it may not necessarily be a comprehensive list to identify all errant pharmacies. Furthermore, as with almost any rule, there are exceptions to reporting to OARRS. For example, inpatient pharmacies, including federal Veterans Affairs (VA) hospitals and nursing homes, as well as doctors who dispense out of their office, are not required to report to OARRS, making the system less reliable. While there are flaws in how tramadol use is monitored, important measures are being taken to rectify the deficiencies. The effort on part of some states (such as Arkansas, Kentucky and New York) to make tramadol a controlled substance is a welcome step and will help greatly in controlling the menace of tramadol drug abuse.

Conclusion

The abuse of prescription analgesics like tramadol is a growing problem in the United States. In fact, the number of tramadol poisoning cases over the last few years has increased despite improvements in label warnings. Tramadol abuse can be confronted through patient education, increased regulatory surveillance and identifying patient groups who may be predisposed to tramadol abuse/poisoning. In addition, increasing awareness among physicians and pharmacists regarding the high abuse potential of tramadol is warranted. This awareness, along with the resources described above (such as OARRS, medication lists and patient profiles), will allow pharmacists and prescribers to flag potential abuse before it occurs and step in with alternative therapies. As for patients who are already abusing tramadol or have experienced tramadol poisoning, management strategies for both toxicity and withdrawal symptoms are available in order to prevent further abuse and relapse.

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