Is Tramadol an Opioid or a Nonopioid Analgesic? Yes!

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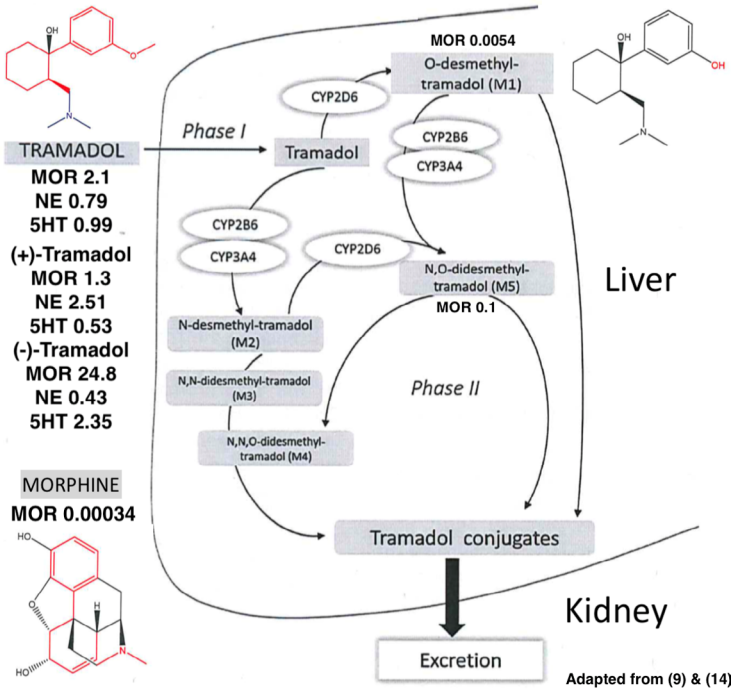
I was sitting in a national conference a few years ago when a prominent pharmacist stood up to speak and talked about the ravages of prescription opioids in the United States. He stated that if anyone in his family ever needed pain medications he would never allow them to have opioids. "They would get Tylenol, Toradol and Tramadol". I was shocked that this respected clinical pharmacologist thought that tramadol was not an opioid. He is not alone. When discussing the dangers of opioids, the tramadol "nonopioid" alternative comes up again and again with students, colleagues and even authors in highly respected medical journals [1, 2, 3]. Tramadol is now available in more than 100 countries and is the most commonly prescribed opioid worldwide [4]. In the US, tramadol prescriptions more than doubled between 2007 and 2015, becoming the second most prescribed opioid. Is it possible that the primary care, and particularly nonphysician, prescribers [5] responsible for the increase in tramadol prescribing in the midst of the "opioid epidemic" are prescribing more tramadol because they don't think tramadol is an opioid? If so, it is important to note that data on opioid use after surgery [6] shows that tramadol is at least as likely as other opioids to be continued long-term; a surrogate measure [7] for abuse and overdose. Indeed, according to the Drug Abuse Warning Network, there was a 250% increase in emergency department visits involving misuse or abuse of tramadol between 2005 and 2011 [8]. In this article I will look at the pharmacology of tramadol with an emphasis on distinguishing its opioid and nonopioid properties.

Regulatory Confusion

Grunenthal first synthesized 2-[(dimethyl amino)-methyl]-1-(3-methoxyphenyl)-cyclo-hexanol in Germany in 1962 and marketed the drug there as tramadol in 1977. It was not until 1995 that the US FDA approved tramadol as a "prescription only" non-controlled substance. Both an immediate release and extended release oral formulation are available in the US. In 2014, the drug was reclassified as Schedule IV; a nod to its abuse potential although still not in the Schedule II category occupied by most opioid analgesics. As a result, tramadol is included today in all state prescription drug monitoring programs (PDMPs) nationwide.

Figure 1 - Schematic of tramadol metabolism pathway. Numbers are Ki affinity constants in micromoles for mu opioid receptor (MOR) binding (morphine shown for comparison) or norepinephrine (NE) or serotonin (5HT) reuptake inhibition.



Pro-drug Pharmacology

Tramadol differs from most other opioids in that it is a prodrug, meaning that the drug itself has very limited affinity at the mu opioid receptor (MOR)[9] (Figure 1). Tramadol is marketed as a racemic mixture of (+) and (-) enantiomers. The (+) configuration has 20 times more MOR affinity than the (-) configuration, though still several thousand times less than morphine. On the other hand, the M1 tramadol metabolite (O-desmethyltramadol) has a MOR affinity only 10 times less than morphine [9] and is probably the mechanism by which tramadol has most of its opioid effect. Thus, it is not tramadol, but it's metabolite, that is most responsible for the drug's opioid analgesic effect. Still, no one would argue that codeine, another pro-drug (metabolized to morphine), is not an opioid. Indeed, like codeine, the opioid effects of tramadol are greatly affected by the pharmacogenetics of the cytochrome P-450 enzyme 2D6 (CYP2D6) which selectively metabolizes tramadol to M1. People with genetic polymorphisms reducing the activity of CYP2D6 ("poor metabolizers"), including 20% of African Americans, 10% of Caucasians and 2% of Asians, will lack significant opioid effect from tramadol [10, 11].

Nonopioid Analgesic Mechanisms

Tramadol's monoaminergic reuptake blocking activity, causing increases in synaptic norepinephrine (NE) and serotonin (5HT) both *in vitro* and *in vivo* [9], has been highly publicized. Interestingly, tramadol's isomeric differences in MOR affinity

are also seen in its monoaminergic reuptake blocking effects. With the (+) enantiomer (the superior opioid agonist configuration) blocking 5HT uptake more effectively. While the (-) enantiomer blocks NE reuptake more effectively (Figure 1). Increases in NE are well known to mediate endogenous pain inhibitory systems and are responsible for the analgesic effects of SNRI and TCA antidepressants [12] whereas analgesic effects of increases in CNS 5HT are more controversial [12]. Some of tramadol's analgesic effects therefore are due to its increasing synaptic NE where it acts on alpha2 adrenergic receptors [9] completely independent from MOR [13]. Tapentadol, a second dual action (opioid/NE) analgesic (with reduced 5HT reuptake inhibition and no opioid pro-drug activity), was approved by the FDA in 2008 [14].

Side Effect Profile

Tramadol's multi-modal analgesic effects would be expected to reduce opioid needs and thus opioid side effects compared to other opioids. For example, early reports suggested that tramadol, produced less drug reinforcement and respiratory depression in primates [9]. However, like tramadol's opioid analgesic effects, its opioid side effects are also determined by CYP2D6 pharmacogenetics. People with CYP2D6 polymorphisms potentiating metabolism of tramadol to M1 ("Ultra-metabolizers"), up to 20% of Iran, Saudi Arabia, Egypt and Northeast African regions [10], will experience increased opioid effects from tramadol including dangerous opioid side effects [11, 15]. Thus, tramadol, like any other opioid, can cause opioid use disorder and respiratory depression, the latter, particularly when taken with other sedatives [16]. Further, tramadol produces many of the more common opioid-like side effects including constipation (46%), sedation (25%), and pruritus (<11%) although probably less commonly than other opioids [17]. In contrast, tramadol-induced nausea is actually more frequent (40%) than with other opioids. Tolerance and withdrawal were originally thought to be less common with tramadol than with other opioids [9] although analgesic tolerance is not uncommon today [15]. Moreover, withdrawal from both tramadol's opioid effects (Table 1) and SSRI-like effects (e.g., like those with venlafaxine) (Table 1) have been described [15].

Table 1: Common Opioid and Selective Serotonergic Reuptake Inhibitor (SSRI) Like Withdrawal Symptoms Associated with Abrupt Tramadol Discontinuation[15]

Opioid Withdrawal Symptoms		SSRI-Like Withdrawal Symptoms
Abdominal Cramping	Lacrimation	Confusion
Agitation	Myoclonus	Delusions
Anxiety	Nausea	Hallucinations
Depression	Paresthesia	Panic Attacks
Gooseflesh	Rhinorrhea	Paranoia
Hyperkinesia	Sweating	Restless Leg Syndrome
Insomnia	Tremors	Unusual Sensory Phenomena

Other side effects, not normally associated with opioids, occur with tramadol, including headache (32%), dizziness (28%), dyspepsia (13%) and flushing (<15%), perhaps from increases in central NE and 5HT [17]. However, it is the more dangerous nonopioid side effects of seizures and 5HT syndrome that deserve special consideration from the prescriber as the causes of these effects may be unclear. For example, tramadol-induced seizures are more common in patients who already have a history of seizures or are already taking other drugs which lower seizure thresholds, particularly drugs that increase 5HT such as 5HT reuptake inhibitors and serotonergic psychotropics [18]. These drug interactions point to increased 5HT as responsible for the seizures and may explain why the incidence of tapentadol seizures appears to be less than that of tramadol [14]. On the other hand the increase in tramadol seizure risk with CYP2D6 inhibitors [18] suggests that the seizures are due to tramadol itself (or its nonopioid metabolites) and also explains the increased risk of tramadol seizures in patients with renal failure given tramadol's >90% renal excretion [18]. Finally, naloxone, has been reported to increase tramadol seizures [19] suggesting that tramadol's opioid actually raises seizure thresholds.

As in the epileptogenic effects of tramadol, increased 5HT levels are responsible for its most dangerous nonopioid side effect – 5HT syndrome. 5HT syndrome is a clinical diagnosis lacking any definitive diagnostic tests. It can present with the classic symptom cluster of neuromuscular hyperactivity, autonomic hyperactivity and altered mental status (Table 2) but frequently involves more mild nonspecific symptoms such as sweating, tremors and hyperreflexia (Table 2). Nonetheless, a high index of suspicion must be maintained as severe cases of 5HT syndrome (Table 2) can cause dangerous complications including rhabdomyolysis, renal failure, disseminated intravascular coagulation and acute respiratory distress syndrome and even death [18]. This syndrome must be treated as an emergency, with oxygen, cooling blankets, intravenous fluids, cardiac monitoring and the 5HT antagonist cyproheptadine [18].

Table 2 - Severity and Signs and Symptoms of Serotonin (5HT) Syndrome [18].

Severity	Signs and Symptoms
Mild	Diaphoresis, Tremor, Diarrhea, Irritability, Sleep Disturbances, Tachycardia and Hyperreflexia
Moderate	Agitation, Hypervigilance, Hyperthermia (<41 degrees C), Tachycardia, Hypertension and Myoclonus (Inducible Clonus and Occular Clonus)
Severe	Delirium, Hyperthermia (>41 degrees C), Severe hypertension, Severe Tachycardia, Peripheral Hypertonicity, Trismus, Truncal rigidity and Spontaneous clonus

High dose (2-3 times the recommended maximum dose of 400 mg/day tramadol alone) is occasionally responsible for 5HT syndrome but, as with seizures, tramadol more commonly combines with other drugs which increase 5HT to produce the syndrome [15]. Antidepressants, antiemetics, and headache therapy have all been reported to elicit 5HT syndrome when paired with even normal tramadol doses [18] (Table 3). These are important interactions to keep in mind given the common co-prescribing of antidepressants for pain and the common nausea and headache side effects of tramadol [cf., 20].

Table 3 – Drugs Known to Produce Serotonin (5HT) Syndrome in Patients Also Taking Tramadol [18]

Antirrhythmic agents	Quinidine
Antibiotics	Linezolid
Antiemetics (controversial)	Setrons (e.g., ondansetron), metoclopramide
Antimigraine Agents	Ergot alkaloids, Triptans (e.g., sumatriptan – also are controversial)
Antiretrovirals	Ritonavir
Appetite Suppressants	Sibutramine
Cold and Allergy Agents	Dextromethorphan and chlorpheniramine
Herbal Supplements	St. John's wort (*Hypericum perforatum*), yohimbe, ginseng, L-tryptophan
Illicit Drugs	Ecstacy (MDMA), amphetamines and cocaine
Opioid Analgesics	Fentanyl and methadone (morphine and oxycodone are controversial)
Psychotropics	MAO inhibitors, Tricyclic Antidepressants, SSRIs, SNRIs, nefazodone, maprotiline, amphetamines, second-generation antipsychotics, buproprion, divalproex, and carbamazepine

Patients at risk for noncompliance - including histories of drug abuse and drug overdoses - have been found to have an increased risk of tramadol seizures [18]. Similarly, the most frequent abusers of tramadol are those with a history of prior substance abuse, in addition to a history of chronic pain and those with easy access to the drug including health professionals [15]. In 2004, a review of physician health programs reported that tramadol was the third most frequently reported drug of abuse (outpacing fentanyl and oxycodone)[21].

Sounds Like Toradol – But Isn't

Thus, I am frequently surprised when I see patients with a long history of alcohol or drug abuse coming to surgery on tramadol for their chronic pain. Of course, I do not really think that this is because tramadol (approved in 1995) is being confused with the NSAID Toradol (ketorolac - approved in 1989). Tramadol, unlike Toradol, is an opioid analgesic with a complex pharmacokinetic and pharmacodynamic profile which can produce dangerous and diagnostically challenging opioid and nonopioid side effects. Further, although approved by the FDA for moderate to severe pain like other opioids, tramadol's analgesic efficacy is controversial [e.g., 22] and the WHO recommends tramadol on step 2 of its 3 step analgesic ladder [23,24], below most other opioids. Indeed, in a network meta-analysis of trials evaluating the morphine-sparing effects of a variety of "nonopioid" analgesics in the post-operative period, tramadol was found to have similar morphine-sparing effects to acetaminophen and less than that caused by NSAIDs or alpha2 adrenergic receptor agonists [2]. Further, unlike acetaminophen, adding tramadol to morphine did not provide a significant analgesic benefit [2, 25]. This should factor strongly into a prescriber's risk/benefit analysis given the generally safer profile for truly nonopioid drugs like acetaminophen and NSAIDs in most patients.

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