Tramadol Pharmacology Relevant to Drug Abuse Assessment

Is tramadol an ‘opioid’?

There is no direct answer to this question. The classification of a substance as an ‘opioid’
depends on (1) the substance’s affinity for opioid receptors in vitro and (2) the substance’s
display of morphine-like effects in vivo. The antinociceptive effect of tramadol in animals and
the analgesic effect of tramadol in humans has been demonstrated in multiple studies to be
produced by the combined contribution of both opioid, and non-opioid, analgesic mechanisms
(e.g., Hennies et al., 1988; Raffa et al., 1992; Kayser et al., 1992; Desmeules et al., 1996;
Oliva et al., 2002; Barann et al., 2006; Berrocosco et al., 2006; Ide et al., 2006). Tramadol
itself has very little affinity for opioid receptors. For example, the binding affinity of tramadol
for cloned human µ opioid receptors is 2.4 µM (Gillen et al., 2000) and it is even less for δ or
κ opioid receptors (Raffa et al., 1992). For comparison, the binding affinity of morphine in the
same study was 0.62 nM, more than 2 orders of magnitude greater (400-fold) than tramadol.

Tramadol’s affinity is too low to be considered an opioid by many pharmacologists and, in
fact, is too low to be detected in most modern high-throughput screens for opioids. Further,
tramadol does not produce several characteristic opioid effects (e.g., Preston et al., 1991).
However, tramadol is metabolized (via CYP450-2D6) to O-demethyl tramadol (Lintz et al.,
1981; Paar et al., 1992; Subrahmanyam et al., 2001; Wu et al., 2002), designated the M1
metabolite, which has significant affinity for opioid receptors. For example, the affinity of M1
for cloned human opioid receptors is 5.4 nM and this activity is primarily due to the (R)-(+) enantiomer of M1 (3.4 nM) (Gillen et al., 2000). This is about 1/10th the affinity of morphine
for µ opioid receptors:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Affinity (nM)</th>
<th>Relative Intrinsic Efficacy¹</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>0.62</td>
<td>1.17</td>
</tr>
<tr>
<td>(RS)-(±) Tramadol</td>
<td>&gt; 1,000</td>
<td>0</td>
</tr>
<tr>
<td>(RS)-(±) M1</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>(R)-(+) M1</td>
<td>3.4</td>
<td>1.23</td>
</tr>
<tr>
<td>(S)-(−) M1</td>
<td>240</td>
<td>0</td>
</tr>
</tbody>
</table>

Thus the expression of the opioid component of tramadol requires its metabolic conversion to
M1. The less this metabolic conversion (for example by bypassing the 1st-pass effect) the
less an opioid effect.

¹ Stimulation of [³⁵S]GTPγS binding
Wasn’t tramadol originally thought to be only opioid?

Yes. A modern understanding of the mechanism of action of tramadol evolved with time. The evolution was prompted by two things: (1) advances in technology that allowed elucidation of new analgesic pathways, such as activation of descending inhibitory control (Millan, 2002), and the clinical experience with the use of the drug. Despite some early preclinical studies in the 1970’s and 1980’s that only detected the opioid component to its mechanism, the clinical experience clearly revealed it to be ‘atypical’ of opioid analgesics. In fact, prior to about 1990 there existed an apparent paradox between early preclinical data and the clinical experience, which was viewed as somewhat of a scientific heresy for several years. However, based on the results of subsequent preclinical studies (e.g., Driessen and Reimann, 1989; Reimann et al., 1990; Friderichs et al., 1991; Friderichs et al., 1992; Raffa et al., 1992; Driessen and Reimann, 1992; Raffa et al., 1993; Driessen et al., 1993; Sevcik et al., 1993; Reimann and Hennies, 1994) and clinical studies (Collart et al., 1993 a,b; Desmeules et al., 1994 a,b), it is now clear that the clinical attributes of tramadol result from a dual mechanism of action. The apparent paradox was eliminated by discovery that tramadol’s two enantiomers have different pharmacologies, and neither is opioid. The opioid component of tramadol resides primarily in its M1 metabolite. Thus the history of the evolution of the understanding of the mechanism of action of tramadol can be viewed as divided into three phases. The first phase consisted of the early preclinical investigations (pre-1990) in which the opioid component was detected (e.g., Friderichs et al., 1978; Hennies et al., 1988). However, the low affinity of tramadol for opioid receptors – 60-fold less than $\alpha$-propoxyphene and 10-fold less than codeine (Raffa et al., 1992) – and the minimal withdrawal signs seen in naloxone-precipitation studies (Flohe et al., 1978; Richter et al., 1980) was incongruous with tramadol’s clinical analgesic efficacy in multiple pain conditions (e.g., Bitsch et al., 1980; Flohe et al., 1978; Retting and Kropp, 1980 a,b; Budd, 1990; Bono and Cuffari, 1993; Meszaros et al., 1993; de la Torre et al., 1993) and patient-controlled analgesia (Lehmann et al., 1990). The second historical phase consisted of the demonstration of combined opioid and non-opioid components to tramadol’s analgesic mechanism of action (e.g., Reimann et al., 1990; Kayser et al., 1992; Raffa et al, 1992 and many others). The third historical phase consisted of the elucidation of the two mechanisms in human subjects.

Are metabolites other than M1 strong opioids?

No. This question was answered using cloned human $\mu$ opioid receptors. The affinity of M5 for opioid receptors is about 30-fold less than that of (R)-(+) M1 and more than 100-fold less than that of morphine. Furthermore, M5 has only low intrinsic activity at opioid receptors, making it a partial agonist. The results of the study are shown below (Gillen et al., 2000):
<table>
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<tr>
<th>Compound</th>
<th>Affinity (µM)</th>
<th>Relative Intrinsic Efficacy</th>
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<tbody>
<tr>
<td>(RS)-(±) M2</td>
<td>&gt; 10,000</td>
<td>0</td>
</tr>
<tr>
<td>(RS)-(±) M3</td>
<td>&gt; 10,000</td>
<td>0</td>
</tr>
<tr>
<td>(RS)-(±) M4</td>
<td>&gt; 10,000</td>
<td>0</td>
</tr>
<tr>
<td>(RS)-(±) M5</td>
<td>100</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Is there a difference in pharmacokinetics of tramadol or M1 in males and females?

No. This question has been examined in several studies. The most recent (Quetglas et al., 2007) confirmed in humans that “No differences between males and females were obtained for the pharmacokinetic parameters of tramadol, M1 and M2 enantiomers ($p > 0.05$ in every comparison.”)

Is tramadol merely a pro-drug of M1?

No. This has been demonstrated in humans in response to the following four questions:

1. **Is tramadol analgesia in humans blocked by an opioid antagonist?**

   No. This question was examined in a randomized, placebo-controlled, double-blind crossover study (Collart et al., 1993 a) in which the opioid antagonist naloxone was administered to volunteers who had taken 100 mg tramadol orally and analgesia was assessed against transcutaneous stimulation of the sural nerve. The analgesia was measured in two ways: by numerical categorical scale (subjective) and by inhibition of R-III synaptic reflex (objective). The results were consistent using both measures: the mean maximal inhibition of tramadol analgesia by naloxone was only 31.3%-34.4%. Thus the contribution of an opioid component was only about a third of the analgesic effect. The small contribution of an opioid component is particularly notable in light of the large dose of tramadol used in the study. These results are similar to results from animal models (e.g., Kayser et al., 1991, Kayser et al., 1992 Raffa et al., 1992) and are consistent with the lack of significant withdrawal signs in naloxone-precipitation studies in human clinical trials (Flohé et al., 1978).

2. **Is tramadol’s analgesia in humans blocked by inhibition of CYP450-2D6?**

   No. This question was addressed in a randomized, placebo-controlled, double-blind crossover study (Collart et al., 1993 a) in which volunteers were co-administered the drug quinidine with tramadol. Quinidine inhibits the metabolism of tramadol to its M1 metabolite (Collart et al., 1993 b; Paar et al., 1992). The results? Quinidine reduced M1 serum concentration to $1/3^{rd} – 1/4^{th}$ the levels of placebo-treated controls, but did not produce statistically significant change in tramadol analgesia by either subjective,
3. Do non-opioid antagonists inhibit tramadol analgesia in humans?

Yes. This question was addressed in a double-blind, placebo-controlled, crossover study (Desmeules et al., 1994 a,b). Tramadol analgesia (assessed by subjective and objective measures) was reduced 89% by an adrenergic receptor antagonist, which is consistent with tramadol's inhibition of neuronal reuptake of norepinephrine.

4. Does tramadol display morphine-like effects in humans?

This question was addressed in a study of non-dependent opiate abusers (Preston et al., 1991; see also recent review by Epstein et al. (2006)). Tramadol, morphine, and placebo were given intramuscularly. Subjective, behavioral, and pupil diameter effects were assessed prior to dosing and intermittently for 12 hours following administration. Morphine produced typical subjective effects, opiate identifications, and pupil miosis. The authors reported that “Tramadol 75 and 150 mg were not different from placebo. Although tramadol 300 mg was identified as an opiate, it produced no other morphine-like effects.”

What about studies in CYP450-2D6 poor metabolizers?

The extent to which the analgesic effect of tramadol depends upon the production of M1 is a function of the dose of tramadol, which in turn is a function of the type and level of pain. For mild to moderate pain, the opioid and non-opioid components both contribute; whereas for more severe pain, a higher dose of tramadol is required and M1 is presumed to contribute to a greater extent. Particularly in the latter group, the analgesic effect of tramadol would be expected to be less in patients with low CYP450-2D6 enzymatic activity (CYP450-2D6 ‘poor metabolizers’). The serum concentration of M1 has been shown to be considerably less in poor metabolizer genotype (PMs) than in extensive metabolizers (EMs) (e.g., Paar et al., 1997). The impact of genetic polymorphism of CYP450-2D6 (PMs) on tramadol-induced analgesia has been investigated in several studies, three of which are summarized below.

In the first study (Poulsen et al., 1996), using two parallel, randomized, double-blind, placebo-controlled crossover designs, the analgesic effect of tramadol (2 mg/kg, oral) was assessed in 27 volunteers (15 EMs and 12 PMs) using several experimental pain models. Sufficient differences were noted between the EMs and PMs to suggest that M1 is important for some of the analgesic effect of tramadol on experimental pain. However, the dose that was used in this study was 2 mg/kg. This translates into 140 mg (70 kg patient), an amount far in excess of the approved dose of only 50 mg. In the second study (Stamer et al., 2003), the effect of
genetic CYP450-2D6 polymorphism on tramadol analgesia was assessed in 300 Caucasian patients undergoing major abdominal surgery. Genotyping revealed that 35 patients were PMs (the most common genotype was CYP450-2D6*4/*4). Patients who had at least one functional allele were classified as EMs. Compared to the EMs, the PMs displayed a higher incidence of non-response and required more tramadol or rescue medication. Again, though, the tramadol dose was greater than 100 mg. In the third study (Wang et al., 2006), the effect of CYP450-2D6 polymorphism (specifically CYP450-2D6*10, a SNP that results in Pro34 → Ser substitution and reduced CYP450-2D6 metabolic activity) on tramadol-induced analgesia (administered via PCA) was assessed in 63 Chinese patients who underwent gastrectomy for gastric cancer. The patients were classified as EMs (n = 17) or either heterozygous (n = 26) or homozygous (n = 20) for CYP2D6*10. Compared to the other groups, the homozygous group required more tramadol. Again, however, the patients received a very large dose: 135 to 140 mg in only two hours.

Could tramadol be ground up and ‘snorted’ (insufflated)?

Although it is technically possible to grind up and to ‘snort’ (insufflate) tramadol as a powder, this route of administration is not desirable to drug abusers. Administration of tramadol by this route results in less conversion to M1 by CYP450-2D6, because it bypasses the 1st-pass effect, leaving little in the way of euphoric effect, as evidenced by the following quotes from the Internet (http://www.tokeup.com/forums/showthread.php?t=5430):

<table>
<thead>
<tr>
<th>Name</th>
<th>Postings in response to question about snorting tramadol</th>
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<tr>
<td>sexualhealing</td>
<td>“don’t snort it and it makes u feel kinda like codeine, not that great but I guess if you wanna get fuct [sic] up its alright to take a few .. but its known to cause seizures at higher doses. be safe”</td>
</tr>
<tr>
<td>LorTab</td>
<td>“… Definitely don’t snort tramadol. That stuff is pretty much worthless imo [in my opinion]. You may get a small buzz, but that’s about it. If you’re going to take tramadol, don’t snort it. Just take it like a normal pill. Tramadol has been known to cause seizures in high doses, and doesn’t give you a good buzz …”</td>
</tr>
<tr>
<td>RXNMAN</td>
<td>“Yep tramadol blows …”</td>
</tr>
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A similar description of lack of effect – and unpleasant “taste/smell/feeling” – is described at the website http://www.erowid.org/experiences/exp.php?id=19002, an excerpt of which is:

“… one night when we couldn’t get any mdma or cannabis we decided to take lots of tramadol and see if I could get anything from the experience. So male friend had four 50 mg tablets, as did I and female had two. We washed them down with a little red wine and sat about and listened to music and chatted, which was nice but really I couldn’t say whether the tramadol did anything I could notice. After explaining to them that I wasn’t really feeling much we decided to supplement by smoking some, hoping that this would do something. We sliced open the capsules and put about 75 mg in to a two kingsize skin joint. Smoke was pretty unpleasant plasticky and harsh on the throat but none of us
really felt much nausea from it. However keeping the joint lit was hard, it kept on going out which was a pain in the ass. We tried playing about with the way we rolled it. We mixed 100mg with a couple of drops of brandy to make a dryish paste which we mixed with the tobacco and then rolled. That smoked a little better but I certainly didn't feel any real hit off of it. Since then it has occurred to me that we might need to convert it to the freebase to smoke it properly and maybe purify it to get rid of any fillers or shit that are in the capsules, luckily female friend studies pharmacology so we're going to look into that. We smoked six joints in total but I think that was mainly because I enjoy smoking a lot and the whole rigmarole of skinning up. Male friend and I also snorted two tablets each. Again it was fairly unpleasant but we generally dip our thumb and forefinger in brandy and snort a drop of that after each line to try and get rid of the taste/smell/feeling and hopefully help its uptake into the body. We also do that when we snort mdma. Since none of us were really getting any effect except drowsiness we decide to knock it on the head and go to sleep. I was a bit worried because we had all taken quite a lot more than we had before, but the only problem was pretty bad constipation for that night and most of the next day. I had a pretty good sleep and felt pretty relaxed. … Since then we haven't really taken tramadol in that way again."

It is difficult to find any other mention of snorting tramadol on the Internet. The DEA site does not list tramadol (http://www.usdoj.gov/dea/concern/concern.htm).

**Could tramadol be ‘smoked’?**

This would be counterproductive – it would completely preclude the conversion of tramadol to its metabolite M1.

**Isn’t the non-opioid mechanism of action too weak to explain tramadol’s analgesia?**

No. That a non-opioid mechanism of tramadol produces analgesia was demonstrated in a double-blind, placebo-controlled, crossover study (Desmeules et al., 1994 a,b). The reason the non-opioid mechanism is strong enough has to do with the fact that the enantiomers of tramadol interact in a synergistic manner to produce analgesia (Raffa et al., 1993).

Racemic tramadol inhibits the neuronal reuptake of norepinephrine (NE) and serotonin (5-HT) with equivalent potencies, but the enantiomers differ in their selectivities for the two reuptake sites. Specifically, the (R)-(+) enantiomer is about 5-fold more potent in inhibiting 5-HT than NE reuptake, whereas the (S)-(−) enantiomer is about 5- to 10-fold more potent than the (R)-(+) enantiomer in inhibiting neuronal NE reuptake (Driessen et al., 1993; Raffa et al., 1993). Individually, the inhibitory activities of the two enantiomers at monoamine reuptake sites are probably insufficient to account for the antinociceptive and analgesic potency and efficacy of tramadol. Critically, however, when the two enantiomers are combined, as is the case with racemic tramadol, synergistic analgesic interaction occurs, producing greater pain relief than simple additivity. That is, the ED50 value and associated variance for tramadol is significantly
smaller\(^2\) than the ED\(_{50}\) value and variance expected if the contribution of each enantiomer were simply additive (Raffa et al., 1993). This synergy magnifies the analgesic effect of the non-opioid component of tramadol.

**Does more M1 in the bloodstream translate to an equivalent amount more in the brain?**

No. It would seem reasonable to assume that a larger amount of tramadol in a formulation would lead to an equivalent amount more M1 in the brain and, therefore, more morphine-like subjective effects. However, this assumption turns out not to be the case. The ratio of M1 in the brain to M1 in the plasma has been measured as a function of the administered oral dose of tramadol (Tao et al., 2002). Following oral administration to mice or rats, tramadol and M1 plasma levels peak at the same time. However, brain levels peak at different times. Brain levels of tramadol peak at 10 minutes, whereas M1 brain levels are delayed till 20-60 minutes after dosing. This delay in M1 corresponds to negative comments made by drug abusers about the undesirable wait for subjective effect of (Epstein et al., 2006). Equally revealing is that M1 does not penetrate the brain to the same extent as does tramadol. Specifically, the ratio of tramadol to M1 in brain increases with increasing dose of tramadol (Fig 1). In fact, in rats the amount of M1 in brain hardly increases with increasing dose of tramadol (Fig 1B).

![A. Mice](image1)

![B. Rats](image2)

**Fig 1.** Comparison of peak tramadol and M1 levels (mean ± s.e.m.) in plasma and brains of mice and rats administered tramadol orally. From Tao et al. (2002).

These results demonstrate that a larger dose of tramadol does not result in a correspondingly greater amount of M1 in the brain. This phenomenon helps explain the fact that in humans tramadol is only about 1/20th as potent as morphine in producing subjective effects (Preston et al., 1991; Epstein et al., 2006), whereas it is about 1/10th as potent in producing analgesia (Gutstein and Akil, 2001).

What would happen to M1 $C_{\text{max}}$ and $T_{\text{max}}$ if someone were to grind and dissolve a CR or IR formulation and inject it i.v.?

Not much. A recent study compared the plasma levels of tramadol and M1 following oral or i.v. administration of tramadol to rats (Parasrampuria et al., 2007). The $C_{\text{max}}$ of M1 in plasma was a bit higher following i.v. than oral administration of tramadol (about 225 vs 153 ng/ml). The $T_{\text{max}}$ was of course shorter, but not by much (about 30 vs 40 min). Importantly, tramadol plasma level following oral dosing was only 363 ng/ml compared to about 4,500 ng/ml –more than 10-fold greater– than following i.v. dosing. Hence, injecting tramadol offers little in the way of increasing M1 blood levels, but exposes the abuser to a very large increase in the amount of tramadol. The concomitant increase in potential adverse effects results in an undesirable increase in the risk:benefit ratio.

A similar finding was recently reported in a PK study of 100 mg tramadol in human volunteers (Quetglas et al., 2007). Despite higher plasma levels of tramadol following i.v. compared to oral administration, there was virtually no increase in M1 when tramadol was administered i.v. rather than orally.

Even though plasma levels of M1 are about the same following i.v. compared to oral administration of tramadol, wouldn't the more rapid kinetics of the i.v. route enhance the subjective effects of tramadol?

No. The subjective effects of i.v. tramadol were extensively studied in a crossover study of experienced opiate drug abusers who were given placebo, morphine, and tramadol (100 and 200 mg) according to a balanced Latin square design under double-blind conditions (this and related studies on are summarized in Epstein et al. (2006)). Morphine significantly increased the abusers’ subjective ratings on a standardized ‘liking’ scale. What did the abusers think about i.v. tramadol? The authors report that: “In contrast, neither dose of tramadol [i.e., 100 or 200 mg] increased ratings on the liking … or on any other subjective measure of opiate-like effects.”
What if abusers went to even higher doses of tramadol i.v. (e.g., by injecting 300 – 400 mg from a crushed CR formulation?)

As summarized by Epstein et al. (2006), in an initial dose-ranging study in experienced opiate drug abusers 700 mg i.v. tramadol produced a seizure, as did 300 mg i.v. This seizure risk is well known in the drug-abusing population (multiple Internet ‘hits’).

Then what if abusers went to even higher doses of tramadol orally (e.g., 300 – 400 mg from a crushed CR formulation?)

The amount of M1 in brain does not increase at the same rate as tramadol oral dose (Fig 1A and 1B). The increase in potential adverse effects due to the parent drug would result in an undesirable increase in the risk:benefit ratio.

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