# Clinical Pharmacology & Toxicology Pearl of the Week

## ~ Tramadol ~

Tramadol inhibits the reuptake of serotonin and norepinephrine from the synaptic cleft; it also inhibits NMDA glutamatergic activity, thereby dampening neuroexcitation.

Tramadol is not actually an opioid. Its metabolite, O-desmethyltramadol (M1), acts as a weak μ-opioid receptor agonist. Tramadol relies on liver metabolism to have any opioid properties.

Metabolism of Tramadol

- Tramadol is a substrate of cytochrome P450 enzymes CYP3A4 and CYP2D6. It is subject to variable metabolism leading to unpredictable clinical effects, and is also commonly affected by drug-drug interactions
- Tramadol induces its own metabolism, as it is both a substrate and inducer of CYP2D6
- Tramadol is variably metabolized into two metabolites: active metabolite O-desmethyltramadol (M1), which occurs via CYP2D6, and inactive N-desmethyltramadol (M2), which occurs via CYP3A4

Serotonergic activity of Tramadol

- Tramadol itself acts as an SNRI and is structurally very similar to venlafaxine
- When combined with other serotonergic medications, serotonin toxicity is possible
- Sudden discontinuation of tramadol can present with antidepressant discontinuation syndrome

Opioid effects of Tramadol Metabolites

- Tramadol is like codeine in that it requires activation into its opioid metabolite to have opioid properties.
- M1 (O-desmethyltramadol) has higher μ-opioid receptor affinity than tramadol itself. M1 is released into circulation following metabolism and acts upon central μ-opioid receptors, providing analgesic and euphoric properties that can lead to physiologic dependence and addiction like all other opioids.
- Another metabolite, M5 (N,O-di-desmethyltramadol), is also active at μ-opioid receptors, but less so than M1.

Genetic Polymorphisms and Variable Metabolism

- Due to different CYP-2D6 genotypes, people variably metabolize tramadol into its active metabolite, M1. M1 is 6 times more potent than the parent compound
- This leads to an unpredictable mix of SNRI and opioid effects in some patients
    - Ultra-rapid metabolizers
        - Some people are ultra-rapid metabolizers of tramadol
        - Death and life-threatening respiratory depression have occurred following a single dose of tramadol in children
    - Poor metabolizers
        - In poor metabolizers, people may experience little, or no analgesic activity as the M1 metabolite cannot be created

Toxicity in overdose:

Common effects in overdose reported from case series include vomiting, drowsiness/lethargy, agitation, seizures, tachycardia, hypertension, respiratory depression, and coma. Symptom onset is usually within 4-6 hours of ingestion.

Summary:

- Tramadol can be likened to a mix of codeine and venlafaxine in unpredictable quantities. It depends on an individual's genetic makeup as to how much SNRI (serotonin norepi reuptake inhibition) vs. opioid effect the drug has.
- It can be dangerous in those with ultra-rapid metabolism and can lead to serotonin syndrome when combined with other serotonergic medications.
- It may also cause hypoglycemia by two main mechanisms:
    - An agonist effect on μ receptors leading to inhibition of hepatic gluconeogenesis, stimulation of muscle glucose utilization and increased expression of GLUT4 transporter genes
    - Inhibition of serotonin reuptake, since administration of serotonin in diabetic rats decreases blood glucose and increases glucose utilization through increased β-endorphin levels

References:

1. Brunton L, Hilal-Dandan R, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Medical; c2018
2. Nelson L, Lewin N, Howland M, Hoffman R, Goldfrank L, Flomenbaum N, editors. Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; 2019.
3. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of Tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007 March;82(1): 41-47
4. Gong L, Stamer U, Tzvetkov M, Altman A, Klein T. PharmGKB summary: tramadol pathway. Pharmacogenet Genom. 2014 July;24(7): 374-380
5. Tramadol. In ToxiNZ. New Zealand Poison Information System. 2025.

**The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.**

**The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.**

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**Created: October 25, 2019**

**Reviewed: May 9, 2025**