Tramadol: Understanding the Risk of Addiction, Serotonin Syndrome and Seizures

Sameer Hassamal M.D; Karen Miotto M.D; William Dale M.D, PH.D; Itai Danovitch, M.D
Disclosure

• The Authors have no proprietary or commercial interest in any materials discussed in this presentation
Objectives

- The pharmacology, epidemiology, and risk factors of Tramadol-related Addiction, Serotonin Syndrome, and Seizures.

- Review evidenced based treatments, and best practices.
Definitions

• Opium is a naturally occurring substance derived from the poppy plant
• Opiates are natural alkaloids derived from opium: morphine, codeine, thebaine
• Opioids are synthetic compounds: heroin, methadone, tramadol
• Narcotics once used to describe soporific agents, now include any substance that alters mood especially illicit opioids.
History

- Tramadol was first developed in Germany in the late 1970s

- Approved by the Food and Drug Administration (FDA) in 1995 for the treatment of moderate to moderately severe pain in adults as the only non-scheduled opioid available

- The expansion of availability of tramadol resulted in an increase in abuse and diversion, and in 2014 tramadol became a schedule IV substance
IS TRAMADOL A NARCOTIC?

10 Reasons to Never Use for You or Your Child

Dr. Axe
FOOD + MEDICINE
Formulations

- Tramadol can be administered orally, parenterally, or rectally; however, only the oral route of administration is FDA-approved in the United States (U.S).

- Formulations include immediate-release tablets, sustained-release tablets, and extended-release capsules.

- The recommended maximum dose of IR is 400 mg/day and the maximum of the ER form is 300 mg per day.

- Brand names in the US include Ultram ©, Ultram ER ©, Ultracet ©, ConZip ©, Ryzolt ©, and Rybix orally dissolving tablet (ODT) ©.
Mechanism of Action

- Tramadol is similar in structure to venlafaxine and codeine.

- Tramadol, a weak agonist at the μ-opioid receptor (MOR) and a serotonin and norepinephrine reuptake inhibitor.

- Commonly prescribed lower risk of constipation, respiratory depression, overdose, and addiction compared to other opioids.
Indications

• Additionally, alleviates pain through modulation of norepinephrine and serotonin descending neuronal inhibitory pathways

• Effective in reducing pain associated with neuropathy, osteoarthritis, rheumatoid arthritis, and low back pain

• Treat a wide range of conditions such as opioid withdrawal, post-operative shivering, premature ejaculation, as well as depressive and anxiety disorders
• Between 2007 and 2011, tramadol prescriptions increased by 65%.

• In 2013, tramadol ranked second in the total U.S. opioid market sales. Tramadol accounted for 14.7%, Hydrocodone 46%, and Oxycodone 13.6%.

• Factors contributing to this increase include the prescribers’ impression that tramadol has low addiction liability and a favorable safety profile.
TRAMADOL MENTIONS BY SUBREDDIT

1 Pill \( \text{AN 627} \) = 100 Mentions

<table>
<thead>
<tr>
<th>Subreddit</th>
<th>Mentions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
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<td>opiates</td>
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<td>Fibromyalgia</td>
<td>278</td>
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<td>explainlikeimfive</td>
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<td>OpiatesRecovery</td>
<td>141</td>
</tr>
<tr>
<td>insects</td>
<td>133</td>
</tr>
</tbody>
</table>

Source: Reddit
Metabolism

- Tramadol is a 1:1 racemic mixture of two enantiomeric diastereomers, the $R,R$-enantiomer (+(+) tramadol) and $S,S$-enantiomer (-(−)-tramadol).

- The (+(+) tramadol enantiomer is the most potent serotonin reuptake inhibitor, while the (−)-tramadol enantiomer is the most potent norepinephrine and serotonin reuptake inhibitor.

- Tramadol is biotransformed by CYP450 2D6 into its major active opioid metabolite (+(+)M1.
M1 Metabolite

• M1 is a high-affinity ligand and produces more potent opioid analgesic effects than the parent compound, which is a low affinity opioid agonist.

• M1 is the main active opioid analgesic metabolite, and is 200-300 times more potent at the MOR compared to the parent compound tramadol.

• 1/4 to 1/10 as potent as morphine
Tramadol

\[ \text{μ-opioid receptor} \rightarrow \text{GABA-ergic neuron} \]

SSRI's (e.g., paroxetine & fluoxetine)

\[ \downarrow \]

CYP2D6

\[ \text{O-desmethyltramadol} \quad \text{(6x more potent at opioid binding only)} \]

\[ \downarrow \]

CYP3A4

\[ \text{N-desmethyltramadol} \quad \text{(inactive)} \]

Conjugation

\[ \text{Glucuronide or Sulfated metabolite} \quad \text{(inactive)} \]

Opioid induced disinhibition on serotonergic neurons further increases 5-HT release

\[ \uparrow \text{Serotonin (5-HT)} \quad \uparrow \text{Norepinephrine (NE)} \]

\[ \downarrow \]

\[ \text{↑Risk for Serotonin Syndrome} \]

- changes in mental status
- changes autonomic function
- neuromuscular changes

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Rapid CYP-450-2D6 metabolizers

• Ultrarapid and extensive metabolizers have approximately a 40% greater serum concentration of the active opioid metabolite M1.

• Up to 28% of the population in North Africa and the Arabian Peninsula are ultrarapid metabolizers

• These geographical areas have experienced higher rates of tramadol addiction and overdose
Poor cytochrome P-450 2D6 metabolizers

• 20% higher serum concentration of tramadol

• Risk for adverse effects related to a hyper-serotonergic state such as serotonin syndrome and seizures

• 20% of Africans, 10% of European Caucasians, and 2% of Asians are poor metabolizers
Epidemiology Tramadol Abuse

• More than 7 million Americans over the age of 12 used tramadol for recreational purposes in 2013

• Abuse rates in CNCP is 2.7%.

• 8.5% of cases reported to the FDA Adverse Events Reporting system involved abuse

• In Iran, lifetime prevalence of tramadol misuse is roughly 4.7%.
Overdose Symptoms and Treatment

- Coma, Central Nervous System Depression, Respiratory Depression, Nausea, Vomiting, Tachycardia, Seizures, Serotonin Syndrome

- Administer activated charcoal within 1-2 hours of ingestion

- Administer Naloxone

- Administer lorazepam for seizures

- Supportive treatments
Tramadol Withdrawal Symptoms

<table>
<thead>
<tr>
<th>Opioid</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonus</td>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>Agitation</td>
<td>Severe anxiety</td>
</tr>
<tr>
<td>Depression</td>
<td>Panic attacks</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Confusion</td>
</tr>
<tr>
<td>Sweating</td>
<td>Delusions</td>
</tr>
<tr>
<td>Goose flesh</td>
<td>Paranoia</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Unusual sensory phenomena</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
</tr>
<tr>
<td>Parasthesias</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>Lacrimation</td>
<td></td>
</tr>
</tbody>
</table>
Withdrawal Management

- Taper Tramadol dose
- Substitution: Buprenorphine/naloxone, Methadone
- Lorazepam
- Clonidine
- NSAIDs
- Loperamide
Etiologies for Serotonin Syndrome and Seizures

- Increases synaptic concentrations of serotonin and norepinephrine at the 5HT-1A and notably 5HT-2A receptors

- The proconvulsant mechanism has not been clearly elucidated; however, possible etiologies include inhibition of monoamine reuptake, and γ-aminobutyric acid (GABA) receptors
Epidemiology of Tramadol-Induced Serotonin Syndrome

- The prevalence of tramadol-related serotonin syndrome is unknown.

- Between 1997 and 2017 there were 968 cases reported to the FDA

- Of the 968 cases, 98 resulted in mortality

- 15% of SSRI overdoses result in serotonin syndrome.
# Signs and Symptoms of Serotonin Syndrome

<table>
<thead>
<tr>
<th>Severity</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>diaphoresis, tremor, irritability, sleep disturbances, mild tachycardia, mild hyperreflexia.</td>
</tr>
<tr>
<td>Moderate</td>
<td>agitation, confusion, diarrhea, hypervigilance, hyperthermia &lt; 41 °C, tachycardia, hypertension, inducible clonus, ocular clonus</td>
</tr>
<tr>
<td>Severe</td>
<td>delirium, hyperthermia &gt; 41 °C, severe hypertension, severe tachycardia, peripheral hypertonicity, trismus, truncal rigidity, spontaneous clonus, myoclonus, severe hyperreflexia.</td>
</tr>
</tbody>
</table>
Complications

- Rhabdomyolysis
- Myoglobinuria
- Renal failure
- Disseminated intravascular coagulation
- Metabolic acidosis
- Acute respiratory distress syndrome
## Diagnosis
### The Hunter Serotonin Toxicity Criteria

The HSTC include the ingestion of a serotonergic agent plus at least one of the following:

- **a)** spontaneous clonus
- **b)** inducible clonus and agitation or diaphoresis
- **c)** ocular clonus and agitation or diaphoresis
- **d)** tremor and hyperreflexia
- **e)** hypertonia, a temperature above 38°C, and ocular or inducible clonus
## Management

<table>
<thead>
<tr>
<th>Severity</th>
<th>Management</th>
</tr>
</thead>
</table>
| Mild      | - Can be managed in an urgent care facility. Observe for at least four to six hours.  
- Discontinue serotonergic medications, and administer benzodiazepines for sedation.                                               |
| Moderate  | - Admit to the inpatient setting  
- Discontinue serotonergic agents, and provide supportive care.  
- Administer benzodiazepines for sedation, AND cyproheptadine.                                                                                       |
| Severe    | - Admit to the Intensive Care Unit (ICU).  
- Discontinue serotonergic agents, and provide supportive care.  
- Administer benzodiazepines for sedation, AND cyproheptadine.  
- Administer esmolol or sodium nitroprusside for severe hypertension and tachycardia.  
- Intubate, sedate, and induce paralysis with a nondepolarizing agent such as vecuronium bromide for hyperthermic patients ( >41 °C). |
Treatment Pearls

- Discontinuing tramadol and other serotonergic agents
- Life-saving treatments: I.V. fluids, cardiac monitoring, cooling blankets, and oxygen therapy.
- Benzodiazepines are preferred over antipsychotics and restraints for agitation.
- Antipyretics are not indicated for hyperthermia.
- Cyproheptadine, an antidote for serotonin syndrome, should be administered to patients with moderate to severe symptoms or who fail to respond to supportive treatments alone.
Risk Factors

1) Serotonergic psychotropic agents. Dose of tramadol ranged from 50-400 mg
2) Serotonergic antidepressants (i.e. paroxetine, fluoxetine) inhibit cytochrome P-450 2D6
3) Tramadol is specifically contraindicated with monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuing a MAOI
4) Mono-ingestion at doses greater than 1000 mg
5) Abusing supratherapeutic doses of Tramadol
6) Decreased hepatic metabolism and renal clearance
Common drug combinations with Tramadol that may increase the risk for Serotonin Syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Common Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotropics</td>
<td>MAOIs, TCAs, SSRIs, SNRIs, buspirone, trazodone, nefazodone, mirtazapine, maprotiline, amphetamines and derivatives, second generation antipsychotics, bupropion, divalproex sodium, carbamazepine, lithium</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Herbal supplements</td>
<td>St. John’s Wort (Hypericum perforatum), Yohimbe, Ginseng, L-Tryptophan</td>
</tr>
<tr>
<td>Appetite Suppressants</td>
<td>sibutramine</td>
</tr>
<tr>
<td>Antimigraine agents</td>
<td>triptans, ergot alkaloids</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>linezolid</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>ritonavir</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>setrons i.e. ondansetron, metoclopramide,</td>
</tr>
<tr>
<td>Analgesics</td>
<td>pethidine, tapentadol, fentanyl, hydrocodone, oxycodone, methadone, cyclobenzaprine</td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>cocaine, MDMA, LSD, DXM, cathinones</td>
</tr>
</tbody>
</table>
Tramadol-induced Seizures

- Typically occur within the first 4-6 hours after excessive tramadol ingestion.
- The seizures usually present as a single generalized tonic-clonic episode.
- No aura
Epidemiology

- The prevalence of tramadol-related seizures in population-based studies ranges from 0.15% to 0.86%.

- Between 1997 and 2017, there were 2019 tramadol-related seizure cases reported to the FDA. Of the 2019 cases, 145 resulted in mortality.
Risk Factors

• Higher mono-ingestion tramadol doses >3.2 grams
• Younger adults abusing tramadol at doses greater than 1,000 mg.
• 8-14% of tramadol mono-ingestion overdoses
• Serotonergic psychotropic cytochrome P-450 2D6 inhibitors. 5.0 to 9.4 increased risk
• Epilepsy, Renal disease, Stroke, and Traumatic Brain Injury
• Chronic tramadol use-4 x increased risk
• > 10 tramadol prescriptions were 6 times more likely to experience a seizure compared to patients not prescribed tramadol
Diagnosis and Management

• The most common adverse sequelae is physical injury to the head area
  ≈1% of patients
• Benzodiazepines, supportive treatments, and discontinuing tramadol and
  other proconvulsant serotonergic agents
• 40% of patients will have non-specific electroencephalography
• 96-97% of patients will have a normal brain magnetic resonance imaging
  and head computed tomography scan
• Prophylactic antiepileptic drug administration is not indicated or
  necessary
Conclusion

• The prevalence of tramadol-induced serotonin syndrome and seizures appears to be modest in the general population.

• Seizures have shared risk factors with serotonin syndrome, and are a result of excessive serotonergic activity.

• Rapid cytochrome P-450 2D6 metabolizers, experience a stronger tramadol opioid response and are more likely to abuse and overdose on higher doses of tramadol.

• Patients having a tramadol addiction liability are at a particularly high risk.
Conclusion

• Serotonin syndrome and seizures can be effectively treated by and administering benzodiazepines, providing supportive treatments, and discontinuing tramadol and other contributing agents.

• Clinicians should consider utilizing pharmacogenetic testing to predict an individual’s analgesic response to tramadol, addiction lability, and the risk of developing serotonin syndrome and seizures.
References


