Therapeutic Use and Misuse of Tramadol: An Atypical Analgesic

Michelle Lofwall, M.D.
University of KY, Dept. of Psychiatry
Center on Drug and Alcohol Research
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Outline for today’s talk

- Background
- Does tramadol have abuse liability?
- Does an opioid antagonist block tramadol’s effects?
- Is there withdrawal from tramadol?
- Summary
An atypical analgesic

- Indication: moderate-severe pain
- Believed less risk for abuse than full-mu opioid analgesics; unscheduled in USA

Tramadol: \((\pm)-trans-2\)-(dimethylaminomethyl)-1-(m-methoxyphenyl)-cyclohexanol hydrochloride

M1: (+)-O-desmethyltramadol

O-demethylation by CYP2D6
## Tramadol Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Tramadol</th>
<th>Extended release tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum total daily</td>
<td>400 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>recommended dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of dosing</td>
<td>4x/day</td>
<td>1x/day</td>
</tr>
<tr>
<td>Time to Cmax tramadol</td>
<td>1.6-2.3 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Time to Cmax M1</td>
<td>2.5-3.0 hours</td>
<td>15 hours</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>~6 hours</td>
<td>7.9 hours</td>
</tr>
<tr>
<td>tramadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>~7 hours</td>
<td>8.3 hours</td>
</tr>
<tr>
<td>M1</td>
<td></td>
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</tbody>
</table>

Side effects and adverse events

- Common side effects are nausea, headache, constipation

- Case reports of abuse and dependence
  - Health care providers
  - Seizures can be presenting symptom

- Cases of serotonin syndrome when combined with:
  - Other agents that affect serotonin (e.g., SSRIs and TCAs)
  - Inhibitors of CYP2D6 or 3A4
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Abuse potential/liability

- **Definition:** The ability of a CNS drug to produce positive, reinforcing effects that are thought to be predictive of misuse, addiction, diversion, and public health risk.

- **Assessment** affects the FDA screening and DEA scheduling of drugs.
Methods

■ Subjects: Healthy, non-dependent prescription opioid abusers
  - 3 females and 6 males; all Caucasian
  - 33 (± 2.6) years
  - 9.4 (± 1.3) days of prescription opioid use in past 30 days
  - Most common opioid used was oxycodone

■ Design: Within-subject, randomized, double-blind, placebo-controlled design

  ■ 7 paired sample and self-administration sessions to test 7 drug conditions:
    ■ Oral oxycodone (20, 40 mg)
    ■ Tramadol (200, 400 mg)
    ■ Codeine (100, 200 mg)
    ■ Placebo
Sessions

- Sample session: tests subjective and physiologic effects of each drug dose, and subject told this drug is what they will be working for on the following day.

- Self administration session: 7x option to work for either:
  - Portions of the sampled dose (in 1/7th increments) or
  - Money ($21 available, in increments of $3)

- Work requirements: 50, 250, 500, 1000, 1500, 2000 and 2500 clicks (a total of 7800 clicks to earn all drug or $)

- Self administration outcomes:
  - number of ratios completed
  - breakpoint
Time course of drug effect

“Do you feel any drug effect?”

Oxycodone
- 40 mg
- 20 mg
- 0 mg

Tramadol
- 400 mg
- 200 mg
- 0 mg

Codeine
- 200 mg
- 100 mg
- 0 mg

Babalonis et al. Abuse liability and reinforcing efficacy of oral tramadol in humans, under review
Peak liking and high

“How much do you LIKE the drug?”

“How HIGH are you?”

Babalonis et al. Abuse liability and reinforcing efficacy of oral tramadol in humans, under review
Physiologic outcomes

End Tidal CO2

Pupils

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Self-administration

Babalonis et al. Abuse liability and reinforcing efficacy of oral tramadol in humans, under review
How much will they work?

Babalonis et al. Abuse liability and reinforcing efficacy of oral tramadol in humans, under review
How much will they work?

Babalonis et al. Abuse liablity and reinforcing efficacy of oral tramadol in humans, under review
Results and Conclusions

- Placebo was never self-administered, but both oxycodone and tramadol were dose-dependently self-administered.
- High dose tramadol was self-administered to a similar degree as high dose oxycodone, an opioid with known abuse liability.
- Tramadol produced positive subjective effects (e.g., like drug effect, high) indicative of abuse liability, although the magnitude of these effects was less than those produced by oxycodone.
- These results suggest that oral tramadol does have abuse liability.
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Methods

- Subjects: Healthy, non-dependent prescription opioid abusers
  - 4 females, 6 males (9 Caucasian, 1 mixed Asian/Caucasian)
  - Mean age of 37 (± 8) years
  - 9 (± 2) days of prescription opioid use, past 30 days
- Design: 6 week inpatient, within-subject, randomized, double-blind, placebo-controlled design
- 12 sessions with 2 oral drug administrations each session:
  - At 9:00 AM, placebo or naltrexone 50 mg
  - At 10:00 AM, one of the following:
    - Placebo
    - Tramadol: 87.5, 175 or 350 mg
    - Hydromorphone: 4 or 16 mg; positive control
Pupil Diameter: Hydromorphone

Subjective effects

“How Much Do You LIKE the Drug?”

Subjective effects

Subjective effects

Summary & Conclusions

- Hydromorphone (16 mg) produced prototypic opioid effects that were completely blocked by naltrexone.

- High dose tramadol produced miosis that occurred later than hydromorphone, consistent with pharmacokinetics of M1 (i.e., $T_{max}$ is approximately 2 hours after dosing).

- Naltrexone pretreatment blocked tramadol induced miosis, but also unveiled tramadol-induced mydriasis.

- Subjective effects of tramadol were evident within 1 hour of dosing, consistent with the pharmacokinetics of the parent drug (i.e., $T_{max}$ is approximately 1 hour after dosing).
High dose tramadol produced modest positive subjective effects, which were not completely blocked by naltrexone; negative subjective effects were enhanced by naltrexone:

- ? a non-opioid mechanism contributing to subjective effects
- Higher naltrexone doses may be necessary to completely block positive subjective effects of tramadol

Mu and non-mu systems likely play a role in tramadol’s pharmacodynamic profile, however more work needs to be done to determine which receptor systems contribute to its positive subjective effects.
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- Subjects: Healthy, prescription (rx) opioid dependent adults willing to undergo medically-assisted withdrawal
  - 14 females, 22 males (34 Caucasian, 2 African American)
  - Mean age of 30 years
  - 29 days of short-acting rx opioid use, past 30 days
- Design: 2 wk inpt, randomized, double-blind, placebo-controlled
  - Phase 1 (days 1-7) randomized to twice daily: placebo, ER tramadol 100 mg, ER tramadol 300 mg
  - Phase 2 (days 8-13) double-blind cross-over to placebo
- All had access to breakthrough withdrawal medications:
  - Acetaminophen
  - Alumina, magnesia, simethicone,
  - Bismuth subsalicylate
  - Zolpidem
Total breakthrough doses

<table>
<thead>
<tr>
<th>Phase 1 Days</th>
<th>Phase 2 Days</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
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</tbody>
</table>

Mean # of Doses per Day

- Placebo
- Tramadol 100 mg BID
- Tramadol 300 mg BID
Acetaminophen

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<th>Phase 1 Days</th>
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<tbody>
<tr>
<td>1 2 3 4 5 6 7</td>
<td>8 9 10 11 12 13</td>
</tr>
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- **Placebo**
- **Tramadol 100 mg BID**
- **Tramadol 300 mg BID**

Mean # of Doses per Day
Opioid withdrawal

Observer-rated Withdrawal Adjective Scale

Placebo
○ Tramadol 100mg BID
△ Tramadol 300mg BID

Himmelsbach

Phase 1 Days
Phase 2 Days

Phase 1 Days
Phase 2 Days
Summary

- Acute dosing cessation of ER tramadol 600 mg daily, a suprathereapeutic dose, produced withdrawal as evidenced primarily by an increase in use of breakthrough withdrawal medications, particularly acetaminophen.

- There was no clear evidence of withdrawal from 200 mg of ER tramadol daily, which is a recommended therapeutic daily dose.
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