25 Respondents

- Tramadol = 12
- Anticoagulation = 9
- Pain Management = 5
- Other = 4
- Antibiotics = 3
<table>
<thead>
<tr>
<th>Question</th>
<th>Number of correct responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would be concerned if a patient with Parkinson’s Disease was prescribed Tramadol on discharge.</td>
<td>9/25 = 36%</td>
</tr>
<tr>
<td>I would be concerned if a patient with cost concerns was prescribed Tramadol on discharge.</td>
<td>16/25 = 64%</td>
</tr>
<tr>
<td>I would be concerned if a patient with a history of seizures was prescribed Tramadol on discharge.</td>
<td>18/25 = 72%</td>
</tr>
</tbody>
</table>
WHAT PEOPLE WANT TO KNOW

- Difference between tramacet and tramadol
- Dosage
- Mechanism
- Contraindications
- Interactions
- Monitoring
- Withdrawal concerns, how to discontinue therapy
- Patient teaching and nursing intervention
- Coverage issues
- Information needed before starting tramadol
LEARNING OBJECTIVES

• Mechanism of action of tramadol
• Effectiveness of Tramadol
• Identify patients who are at risk of adverse effects from tramadol
• Describe symptoms of Serotonin Syndrome
LEARNING OBJECTIVES

• Be able to provide tramadol patient counseling
• Describe symptoms of tramadol withdrawal
• Identify patients who are at risk of tramadol withdrawal
• Recognize the cost associated with tramadol prescriptions
PATIENT SCENARIO 1: WHAT WOULD YOU DO?

49 y/o woman post THA
PMHx: Osteoarthritis
Home meds:
Acetaminophen 1000 mg qid
In hospital:
Pain well controlled
Hydromorphone 1-3 mg q3h prn
2 mg X 3 doses in last 24 h

Ishtpreet Virk
DOB: Jan 18, 1967

Tramadol 50-100 mg po qid prn
X 100 tablets

ASA 160 mg po daily
X 35 days

Dr. Smith
PATIENT SCENARIO 2: WHAT WOULD YOU DO?

43 y/o man post TKA
PMHx: Treatment Resistant Depression, Seizure Disorder
Home Meds:
Bupropion 300 mg ER once daily
Sertraline 100 mg daily
Phenytoin 300 mg po qhs
In hospital:
Hydromorphone 1-3 mg q3h prn
2 mg X 5 doses in last 24 hours

Charles Montgomery
DOB: Feb 28, 1974

Hydromorphone 1-2 mg q3h prn (90 tablets)
(on narcotic script)

Tramadol 50-100 mg po qid prn
X 100 tablets

ASA 160 mg po daily
X 28 days

Dr. Smith
PATIENT SCENARIO 3: WHAT WOULD YOU DO?

37 year old woman post THA
PMHx: Rheumatoid arthritis
Home meds:
Methotrexate once weekly
Folic acid 5 mg daily
Celebrex 200 mg daily
Tramadol 300 mg ER q24h (last dose yesterday morning)

In hospital:
Pain management orders
Tramadol discontinued
TRAMADOL AND TRAMACET

• Tramadol brand names: Ultram(IR), Durela (LA), Ralivia(LA), Tridural (LA), Zytram XL
• Dosing: Tramadol 50-100 mg q4-6h prn
• Max: 400 mg per day (max 300mg per day in elderly)

• Tramacet ➔ Tramadol 37.5 mg + Acetaminophen 325 mg
• Dosing: Tramacet 1-2 tablets q4h prn (max 8 tabs/day)
MECHANISM OF ACTION

- Bind to μ-opioid receptors in CNS
- Inhibits the reuptake of norepinephrine and serotonin
**ORAL DOSE EQUIVALENCIES?**

*** PLEASE NOTE NURSES WERE NOT GIVEN THIS SLIDE IN HANDOUT → IT WAS MERELY DISCUSSED

*****Rough estimates only*****

Morphine dose equivalence not reliably established

Some references stated:

Tramadol 100 mg ≈ Morphine 10-20 mg

Other references stated:

Tramadol 100 mg ≈ Morphine 10 mg (oral)

And

Morphine 10-15 mg ≈ Hydromorphone 2 mg ≈ Codeine 100 mg

*For patient specific dose conversion ask Pharmacist *
# TRAMADOL IN CHRONIC OA PAIN


| Inclusion: | 17 Randomized controlled trials, 2000–2015  
Predominantly knee OA patients  
At least 8 weeks in duration |
| Assessment: | Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale |
| Results: | Mean improvement in WOMAC score comparable between all therapies  
• NSAIDs (18 points)  
• Potent opioids (19 points)  
• Less potent opioids (18 points) |

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Randomized double-blind trial, 4 week duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>462 subjects with low back pain (24%) or OA pain (35%) or both (41%)</td>
</tr>
<tr>
<td>Intervention</td>
<td>309 subjects, Tramadol 37.5 mg/Acetaminophen 325 mg 1-2 tablets q4-6 h prn (max 8 per day)</td>
</tr>
<tr>
<td>Control</td>
<td>153 subjects, Codeine 30 mg/ Acetaminophen 300 mg 1-2 capsules q4-6 h prn (max 8 per day)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Similar pain control in both groups</td>
</tr>
</tbody>
</table>
### TRAMACET IN CHRONIC PAIN


<table>
<thead>
<tr>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tramacet group</strong></td>
</tr>
<tr>
<td>71% of reported side effects (S/E)</td>
</tr>
<tr>
<td>17% somnolence</td>
</tr>
<tr>
<td>11% constipation</td>
</tr>
<tr>
<td><strong>Codeine/Acetaminophen</strong></td>
</tr>
<tr>
<td>76% reported side effects (S/E)</td>
</tr>
<tr>
<td>24% somnolence</td>
</tr>
<tr>
<td>21% constipation</td>
</tr>
</tbody>
</table>
SAFETY QUESTIONS

• Would you be concerned if a patient with Parkinson’s disease was prescribed Tramadol on discharge?

• Would you be concerned if a patient with a history of seizures was prescribed Tramadol on discharge?
SAFETY: ADVERSE EFFECTS AND PRECAUTIONS

• Standard opioid adverse effects:
  • Drowsiness
  • Dizziness
  • Nausea
  • Vomiting
  • Constipation
  • Allergic reaction
• Increases risk of seizures
• Serotonin Syndrome
• Impact on blood glucose
• Avoid in kidney and liver dysfunction
SEROTONIN SYNDROME

- GI symptoms
  - Nausea and vomiting
  - Diarrhea
- Mental status changes
  - Agitation
  - Hallucinations
  - Coma

- Autonomic instability
  - Tachycardia
  - Labile blood pressure
  - Hyperthermia
- Neuromuscular changes
  - Hyperreflexia
  - Incoordination
SWITCHING OPIOIDS DUE TO ADVERSE EFFECTS

• No opioid is optimal for all patients

• Tolerance to sedation, nausea and vomiting generally occurs in 3-5 days
TRAMADOL PHARMACOKINETICS

• Immediate release
  • Onset: Within 1 hour
  • Peak effect: 2 to 3 hours

• Half life
  • Immediate release:
    • ~ 6.3 hours; active metabolite (M1) ~ 7.4 hours
  • Extended-release:
    • ~7.9-10 hours; active metabolite (M1): ~8.8- 11 hours
TRAMADOL WITHDRAWAL SYNDROMES

• 422 patients with tramadol withdrawal (April 1995-March 2000)
• 367 had typical withdrawal symptoms
• 55 had atypical withdrawal symptoms

TYPICAL OPIOID WITHDRAWAL

- Anxiety, depression, insomnia, and restlessness
- Rhinorhea (runny nose) and mydriasis (tearing)
- Nausea, vomiting, abdominal cramping, diarrhea
- Bone pain and muscle aches
- Gooseflesh and sweating
ATYPICAL WITHDRAWAL:

- Documented “Atypical” withdrawal signs and symptoms:
  - Extreme anxiety, panic attacks, CNS (Confusion, delusions, paranoia) unusual sensory experiences (numbness, tingling, parathesia, tinnitus), hallucinations (tactile, auditory, visual)

ATYPICAL WITHDRAWAL:

• Could potentially also experience:
  • Depression, aggressiveness, insomnia, vivid dreams/nightmares, headache, sneezing,
  • Palpitations, tremors, sweating, restless legs syndrome and electric shock-like sensations
TRAMADOL WITHDRAWAL

Typical Withdrawal (Info from 63% of cases)
Dose range: 50-2000 mg, 92% of cases occurred on doses below 400 mg/day
Withdrawal usually resolved in 2-3 days

Atypical Withdrawal (Info from 78% of cases)
Dose range: 50-1300 mg per day, 25% of cases occurred in patients more than 400 mg/day
Withdrawal lasted longer

NON-FORMULARY USE IN HOSPITAL

• Options: Tramacet or Tramadol 50 mg IR

• Restricted to those who were on tramadol/tramacet regularly at home and are at risk of withdrawal

• Restricted to patients who have not tolerated at least 2 other opioids
PATIENT SCENARIO 1: WHAT WOULD YOU DO?

49 y/o woman post THA
PMHx: Osteoarthritis
Home meds:
Acetaminophen 1000 mg qid
In hospital:
Pain well controlled
Hydromorphone 1-3 mg q3h prn
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Folic acid 5 mg daily
Celebrex 200 mg daily
Tramadol 300 mg ER q24h (last dose yesterday morning)

In hospital:
Pain management orders
Tramadol discontinued
COST AND COVERAGE OF TRAMADOL
COST QUESTIONS

Would up be concerned if a patient with cost concerns was prescribed Tramadol on discharge?
COST IN HOSPITAL

- Tramadol 50 mg = $0.17
- Morphine 5 mg = $0.11
- Hydromorphone 1 mg = $0.14
- Hydromorphone 2 mg = $0.21
- Tramacet = $0.16 (in blister)
- Tylenol #3 = $0.13 (in blister)
- Codeine 30 mg = $0.05
OUTPATIENT COST

• Hydromorphone 1 mg (100 tablets)= $27.91*
• Tramadol 50 mg (100 tablets)= $90.15*
• Tylenol #3 (30 tablets)= $14.50*
• Tramacet (30 tablets)= $31.35*

*Includes $11.60 dispensing fee
OUTPATIENT COST: PHARMACARE COVERAGE

Morphine, Codeine, Hydromorphone IR, Oxycodone and Tylenol#3: Yes

Hydromorphone LA: Requires special authority

Tramadol: No

Tramacet: No
## Prices for tramadol — Canada

<table>
<thead>
<tr>
<th>Price</th>
<th>Date</th>
<th>Location</th>
<th>Product</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2</td>
<td>May 29, 2017</td>
<td>Ontario</td>
<td>tramadol, 50mg pill</td>
<td>$</td>
</tr>
<tr>
<td>$1</td>
<td>Jan 23, 2017</td>
<td>Alberta</td>
<td>tramadol, 50mg pill</td>
<td>$</td>
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<tr>
<td>$0.50</td>
<td>Dec 28, 2016</td>
<td>Alberta</td>
<td>tramadol, 50mg pill</td>
<td>$</td>
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</table>
## COST OF STREET MEDICATIONS

<table>
<thead>
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<tbody>
<tr>
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<td>hydromorphone, 2mg pill</td>
<td>London, Ontario</td>
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<tr>
<td>$2</td>
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<td>Ontario</td>
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<tr>
<td>$20</td>
<td>Jun 14 2017</td>
<td>hydromorphone, 8mg pill</td>
<td>Toronto, Ontario</td>
</tr>
<tr>
<td>$6</td>
<td>May 10 2017</td>
<td>hydromorphone, 4mg pill</td>
<td>Ontario</td>
</tr>
<tr>
<td>$2</td>
<td>Apr 19 2017</td>
<td>hydromorphone, 2mg pill</td>
<td>Ottawa, Ontario</td>
</tr>
<tr>
<td>$10</td>
<td>Apr 6 2017</td>
<td>hydromorphone, 1mg pill</td>
<td>Ontario</td>
</tr>
<tr>
<td>$10</td>
<td>Feb 22 2017</td>
<td>hydromorphone, 8mg pill</td>
<td>Moncton, New Brunswick</td>
</tr>
<tr>
<td>$21</td>
<td>Jan 27 2017</td>
<td>hydromorphone, 64mg pill</td>
<td>Winnipeg, Manitoba</td>
</tr>
<tr>
<td>$10</td>
<td>Jan 4 2017</td>
<td>hydromorphone, 4mg pill</td>
<td>Ontario</td>
</tr>
<tr>
<td>$5</td>
<td>Nov 10 2016</td>
<td>hydromorphone, 2mg pill</td>
<td>Prince Albert, Saskatchewan</td>
</tr>
<tr>
<td>$5</td>
<td>Nov 5 2016</td>
<td>hydromorphone, 1mg pill</td>
<td>Quebec</td>
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<tr>
<td>$20</td>
<td>Oct 31 2016</td>
<td>hydromorphone, 8mg pill</td>
<td>Alberta</td>
</tr>
<tr>
<td>$20</td>
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<td>hydromorphone, 8mg pill</td>
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<td>Alberta</td>
</tr>
</tbody>
</table>
TRAMADOL IN REVIEW

• What was the most important thing that you learned today?

• What was the most difficult point?
THANK YOU!

ADDITIONAL QUESTIONS?
REFERENCES


Up-to-date. Tramadol monograph

RX-files


REFERENCES


Lanier R, Lofwall, Mintzer M, Bigelow G, Strain E, Physical Dependence potential of daily tramadol dosing in humans


El-Hadidy MA, Helaly AMN. Medical and Psychiatric Effects of Long-term Dependence on High Dose tramadol. Substance Use and Misuse. 2015
DRUG ABUSE

• Centers for Disease Control
  • Prescription drug abuse fastest growing drug problem in the United States

• From 1999 to 2013
  • Number of deaths from pain killer overdose in the US quadrupled
  • 16000 deaths in 2013

• From 1997 to 2007
  • Total amount of opioid medication prescribed and distributed through the pharmaceutical system in the United States increased by 600%
# Examples of Medications Which Raise Tramadol Levels

<table>
<thead>
<tr>
<th>CYP 3A4 Inhibitors</th>
<th>CYP 2D6 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>Antidepressants (bupropion)</td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
</tr>
<tr>
<td>HIV medications</td>
<td>HIV medications</td>
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</table>
TRAMADOL IN ACUTE PAIN


<table>
<thead>
<tr>
<th>Trial type</th>
<th>Randomized double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Trauma patients in pre-hospital setting</td>
</tr>
<tr>
<td>Intervention</td>
<td>Tramadol group: 53 patients (severe pain in 56%) Initially received iv tramadol 100 mg X 1 dose iv then, a further dose of 50 mg tramadol q5min to a max of 200 mg</td>
</tr>
<tr>
<td>Comparator</td>
<td>Morphine group: 48 patients (severe pain in 49%) Initially received iv morphine 5 mg (body weight 70 kg) or 10 mg morphine (body weight 70 kg), then morphine 5 mg q5min to a max morphine 15 mg (body weight 70 kg) or 20 mg (weight 70 kg)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Similar mean decrease in pain score between baseline and 40 min mark</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Nausea: 9 patients (17%) on tramadol and 7 patients (15%) on morphine experienced at least one episode of nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting: Three patients on tramadol experienced at least one episode of vomiting, no patient on morphine vomited</td>
</tr>
</tbody>
</table>
EXAMPLES OF MEDICATIONS WHICH RAISE TRAMADOL LEVELS

**CYP 3A4 INHIBITORS**
- Clarithromycin
- Antifungals
- HIV medications

**CYP 2D6 INHIBITORS**
- Antidepressants
  - (bupropion)
- HIV medications

**CYP 3A4 INDUCERS**
- Phenytoin
- Rifampin
- Carbamazepine
- St. John’s Wart

**CYP 2D6 INDUCERS**
- Genetic polymorphisms