Tapentadol Therapy to Manage Moderate-to-Severe Pain: Key Considerations for Nursing
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Objectives

• Describe the place of opioid therapy in the treatment of pain
• Distinguish the properties of tapentadol from those of other opioids
• Design a comprehensive pain management plan

Pain affects the whole person
Severe or persistent pain sends ripples through the nervous system, invading the person’s whole life…personality…& relationship with the world
Duty to relieve pain & suffering

- Health professionals have an ethical duty
  - To alleviate suffering
  - To provide competent & humane services
- Uncontrolled acute pain hurts….
  - Impairs immune function (post-op infection)
  - Impairs metabolism (weight loss, hyperglycemia)
  - Impairs respirations (atelectasis, PNA)
  - Exposes to hazards of immobility
  - Changes nervous system sensitivity (development of chronic pain)

Harmful Effects of Chronic Pain

- CNS remodeling with 5-10% gray matter loss
  - Reversible with better pain control
- Long-term exposure to potential risky drugs
- Health care expenditures average $10,000/patient/year
- Increase in all-cause mortality in 10 years
  - 50% higher risk; (3x if pain severe)
- Chronic pain is a common reason for:
  - Seeking health care,
  - Specialist consultation
  - Risk of developing depression

Potential Harm from Analgesics

- Leading cause of drug-related hospitalization
  - 25% involving older adults related NSAID toxicity
  - >1 million opioid-related hospitalizations (CMS)
- 1 million older adults/year go to ED for ADEs
  - 9% involve opioids and 8% nonopioid analgesics
- Opioids leading cause of overdose deaths
  - 2012 Rx opioid overdose deaths 16,007 (38% of all overdoses)
  - 77% Benzodiazepine deaths – also had opioids
  - 65% antiepileptic/anti-parkinson deaths w/ opioids

JAMA, 309(7):657-659
Young (2014) CQ Healthbeat. Medicare Sees Most Growth in Opioid-Related Hospitalizations


Expected opioid effects

- Analgesia
- Side effects
- Tolerance
  - Diminution of one or more opioid effects
- Physical dependence
  - Abstinence syndrome

Undesirable Opioid Effects

- Respiratory depression, bronchospasm
- Sedation, dizziness, ataxia, visual disturbances
- Nausea / vomiting, constipation
- Urinary retention, sexual dysfunction
- Itching, skin rash
- Immune, hormonal or neurological problems
- Psychosocial problems
- Behavioral / existential problems

Rx Analgesic Sales & Deaths

![Graph showing trends in Rx Analgesic sales and deaths from 1999 to 2013.](image)
Are opioids indicated?

- Indicated
  - Moderate-severe acute pain (<15-30 days)
  - Cancer pain / severe pain at end of life
  - Chronic non-cancer pain benefits/risks (controversial)
- Not Indicated
  - True allergy
  - Untreated addiction disorder (relative contraindication)
  - Unmonitored environment if IV/Neuraxial route
  - Drug diversion confirmed

Avoiding Overdose

- Patient selection based on risk
- Lower risk by drug selection (highest to lowest risk:Rx)
  - Methadone, morphine, hydrocodone, fentanyl, hydromorphone, oxycodone, buprenorphine
  - Tramadol and Tapentadol
- General & tailored dosing
  - Most overdose deaths include >1 drug
  - Rx poisonings 8% non-opioids; 9% opioids

1. CDC (2012) MMWR July 12 61(26);493-497

WHO 3-Step Approach to Relief

1. Non-opioid for mild to moderate pain
2. Opioids for moderate to severe pain ± Adjunct
3. Stronger, higher dose opioids for severe pain ± Non-opioid ± Adjunct

Adjuvant examples

Drugs
- Gabapentin
- Duloxetine
Interventions
- Nerve blocks
- Neuroablation
- Non-drug
- Heat or cold
- Distraction
- Acupuncture

*Originally published by the World Health Organization (WHO) for cancer pain
2015 Cancer Pain Guideline Update

• Greater use of adjuvants before opioid escalation
• Added assessment of risk factors for opioid abuse
• Avoid certain drugs in renal compromised patient
  – Morphine, Codeine, Hydrocodone, Hydromorphone, Oxymorphone
• Added indications for opioid rotation
  – Physical factors including route of administration
  – Insurance coverage, formulary & cost impact
• Added monitoring of aberrant drug behaviors
  – Monitor both patient and family
• Added information on ER/LA REMS

ASA Guidelines: Acute Pain

• Assess potential risks/benefits of therapy options
• Select lowest risk approach
  – Peripheral Nerve Blocks
  – Neuromax Analgesia
  – PCA / Opioids
• Use Multimodal opioid-sparing approaches
  – Non-opioid analgesics
  – Local Anesthetics
  – Adjuvant therapies

Risks & Benefits of Acute Opioids

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factor</th>
<th>Appropriateness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Low risk</td>
<td>High benefit, low risk, not appropriate</td>
</tr>
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</table>
**Teach Patients**

- Medication ~ necessary but alone is insufficient
- Use right drug for right discomforts in right way
  - Analgesics: lowest dose, shortest time
  - Adjuvants, Give adequate trial
- Avoid interactions;
  - 1 prescriber – 1 pharmacy
  - Know foods, drugs, herbs, alcohol that can interact
  - [http://healthtools.aarp.org/drug-interaction](http://healthtools.aarp.org/drug-interaction)
- With opioids
  - Always use opioid sparing methods
  - Always be concerned about safe storage/disposal
  - Never sell or give opioids to another person

**Balance Opioid Benefits / Risks**

**AHRQ report on chronic opioid therapy efficacy & risks**

- 39 of 4,209 studies met quality standards
  - Differences in definitions & measures preclude the ability to deduce comparative effectiveness & risks
  - Strength of evidence was rated no higher than low
- Lack evidence to know benefits & harms
- Most patients do not develop drug problems
  - opioid abuse 0.6% to 8%
  - Rates of dependence were 3.1 % to 26%
  - aberrant drug-related behaviors 5.7% to 37.1%

Initiating Opioids for Chronic Pain

Initial treatment as a therapeutic trial

- May last from several weeks to several months
- Decision to proceed w/ long-term treatment should be intentional & based on careful consideration of outcomes during the trial

<table>
<thead>
<tr>
<th>Progress toward meeting therapeutic goals</th>
<th>Presence of opioid-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in underlying pain condition</td>
<td>Changes in psychiatric or medical comorbidities</td>
</tr>
<tr>
<td>Identification of aberrant drug-related behavior, addiction, or diversion</td>
<td></td>
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</tbody>
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Universal precautions for chronic opioid therapy

- Make a diagnosis with appropriate differential
- Psychological assessment (including risk of addiction)
- Informed consent & treatment agreement
- Pre-treatment assessment of pain level & function
- Trial of opioid therapy with adjunctive therapy
- Reassessment of pain score and level of function
- Regularly assess the four A’s of pain medicine
- Periodically review pain diagnosis & comorbidity
- Documentation

Monitor Adherence & Behavior

- Recognize & document aberrant behavior
  - In addition to patient self-report also use:
    - State PDMPs, where available
    - UDT
      - Positive for nonprescribed drugs
      - Positive for illicit substance
      - Negative for prescribed opioid
    - Family member or caregiver interviews
    - Monitoring tools such as the COMM, or PDUQ
    - Medication reconciliation (e.g., pill counts)
**Interpretation of UDT Results**

<table>
<thead>
<tr>
<th>Positive Result</th>
<th>Negative Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrates recent use</td>
<td>Does not diagnose diversion</td>
</tr>
<tr>
<td>- Most drugs in urine have detection times of 1-3 d</td>
<td>- More than presence or absence of drug in urine</td>
</tr>
<tr>
<td>- Chronic use of lipid-soluble drugs: test positive for ≥ 1 wk</td>
<td>- May be maladaptive drug-taking behavior</td>
</tr>
<tr>
<td>Does not provide enough info to determine</td>
<td>- Bingeing, running out early</td>
</tr>
<tr>
<td>- Exposure time, dose, or frequency of use</td>
<td>- Cessation of insurance, financial difficulties, etc.</td>
</tr>
</tbody>
</table>

**How Worried are You?**

Patient is prescribed Hydrocodone 20mg/day; Buprenorphine patch 20mg/week; Alpraxolam 0.5mg TID; Venlafaxine 225mg Daily

- Patient’s UDT (IA) results:
  - Negative for opiates
  - Negative for benzodiazepines

- Confirm (GC/MS) because:
  - IA doesn’t reliably identify non-opiate opioids
  - IA doesn’t identify Alpraxolam
  - Venlafaxine → give false + PCP
  - Omeprazole → give false + for cannabinoids

1st Minute: Write down … What finding is least worrisome for Aberrant Behaviors?  
2nd Minute: Compare notes with neighbor

**Switching to an ER/LA Opioid?**

- Reason for switching to ER/LA Opioids:
  - Continuous, around-the-clock opioid analgesic is needed for an extended period of time
  - No alternative therapy is likely to pose as favorable a balance of benefits to harms

- May be used in lowest dose for non-tolerant:
  - Extended release morphine, oxycodone, hydrocodone:
  - Tapentadol ER; Buprenorphine transdermal system

- Only for opioid-tolerant patients (any dose):
  - Fentanyl, methadone, oxymorphone, hydromorphone
### Abuse Deterrent Formula Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/Chemical Barrier</td>
<td>Prevents chewing or crushing, prevents ability to extract drug chemically</td>
</tr>
<tr>
<td>Agonist/Antagonist</td>
<td>Combination (e.g., naloxone) added to prevent euphoria</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Sequestered antagonist released if altered</td>
</tr>
<tr>
<td>Aversion</td>
<td>Sequestered substances (irritant) combined to produce an unpleasant effect if altered</td>
</tr>
<tr>
<td>Delivery systems that resist abuse</td>
<td>Delivery system difficult to manipulate, (e.g., ER - IM injections; SubQ implants)</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Converts to active form in GI Tract</td>
</tr>
</tbody>
</table>

United States Food and Drug Administration. (2013) FDA’s Efforts to Address the Misuse and Abuse of Opioids. Available online.

### Case Study

- **EW 64 y.o. man** with hypertension and insulin dependent diabetes mellitus
- Chronic pain conditions: Severe low back pain with radicular symptoms, diabetic peripheral neuropathic pain, severe osteoarthritis right knee planning for total knee replacement
- Poor response to acetaminophen, nonsteroidal anti-inflammatory drugs, topical analgesics, corticosteroid injections, physical therapy, and exercise
- Tricyclic antidepressant contraindicated, had side effects from SNRIs and gabapentinoids

Would tapentadol be an appropriate analgesic option for both acute and chronic pain?

### Tapentadol Mechanism of Action

- **Exact mechanism of action unknown**
- **Centrally acting synthetic analgesic**
- **Dual mechanisms of action**
  - Mu-opioid receptor agonist
  - Norepinephrine reuptake inhibitor
- **Synergistic action for pain reduction**
- **Dual mechanism may affect tolerance development**

Mechanism of Action (2)

- Tapentadol similar binding to norepinephrine reuptake inhibitor as venlafaxine (SNRI)
- Tapentadol dose escalation show minimal increase in serotonin levels

Take away: May have less serotonergic effects


Indications

- Tapentadol IR
  - Moderate to severe acute pain in adults
- Tapentadol ER
  - Management of pain severe enough to require daily around the clock opioid therapy
  - Painful diabetic peripheral neuropathy in adults that is unresponsive to alternative treatment
  - Only opioid in US approved for this indication

NUCYNTE. Janssen Pharmaceuticals, Inc. 2011; NUCYNTE ER. Janssen Pharmaceuticals, Inc. 2014

Postoperative Pain

- Bunionectomy
  - All doses of tapentadol (50 mg, 75 mg and 100 mg) or oxycodone 15 mg significantly improved pain intensity (p<0.001) compared with placebo at 48 hours
  - Incidence of nausea and/or vomiting was significantly less with tapentadol IR 75 mg (41%) when compared with oxycodone IR 15 mg (70%)

### Postoperative Pain

- **Bunionectomy**
  - No significant differences in pain relief between oxycodone 10 mg and tapentadol IR 50 mg
  - Significant difference in nausea/vomiting between tapentadol 50 mg (35%) and oxycodone 10 mg (59%) but no significant differences seen with tapentadol 75 mg and oxycodone 10 mg


### Acute Pain

- **Osteoarthritis pain in end-stage joint disease**
  - Tapentadol 50 mg or 75 mg significant pain reduction when compared to placebo, no significant difference in efficacy when compared to oxycodone 10 mg
  - Nausea, vomiting, constipation significantly less (p<0.001) when compared to oxycodone 10 mg


### Chronic Pain

- **Osteoarthritis of knee\(^1\) and chronic low back pain\(^2\)**
  - Tapentadol ER 100 mg-250 mg BID produced significant reductions in pain intensity and overall impression of change at 12 weeks
  - Less nausea, vomiting and constipation when compared to oxycodone ER

## Diabetic Peripheral Neuropathic Pain

- Two RCT studies Tapentadol ER\(^1,2\)
  - 53.6%\(^1\) and 55.4%\(^2\) with greater than 30% improvement in pain at week 12.
  - 37.8%\(^1\) and 40.4%\(^2\) with greater than 50% improvement in pain at week 12.
- Pooled analysis 100-250 mg BID effective-meaningful reductions pain intensity\(^3\)


## Chronic Cancer Pain

- Tapentadol ER - No significant difference in efficacy when compared to Morphine ER 40-100 mg BID\(^1\)
  - Tapentadol ER- Morphine CR dose ratio was 2.5:1
  - Tapentadol ER 25-200 mg bid similar in efficacy oxycodone CR 5-40 mg bid\(^2\)
  - Tapentadol (mean daily dose 190 mg) significant reductions pain intensity\(^3\)


## Dosing

- Tapentadol IR
  - 50 mg, 75 mg or 100 mg q4h – max dose 700 mg day one, 600 mg subsequent days
- Tapentadol ER
  - 50 mg q12h – opioid naïve; titrate by 50 mg every 3 days
  - Maximum dose 500 mg daily
### Equianalgesia

- **Osteoarthritis Pain or Low Back Pain**
  - Morphine
  - Tapentadol ER (start)
  - ≤ 100 mg/d: 50 mg BID
  - 101 to 160 mg/d: 100 mg BID
  - > 160 mg/d: 150 mg BID


- **Chronic pain**
  - Morphine Equivalent
  - Tapentadol ER (start)
  - < 80 mg/d: 50 mg BID
  - 80 to < 120 mg/d: 100 mg BID
  - 120 to < 160 mg/d: 150 mg BID
  - 160 to < 200 mg/d: 200 mg BID
  - ≥ 200 mg/d: 250 mg BID


- **Cancer pain**
  - Morphine
  - Tapentadol ER
  - 20 to 30 mg/d: 50 mg BID
  - > 30 to 40 mg/d: 75 mg BID
  - > 40 to 60 mg/d: 100 mg BID
  - > 60 to 90 mg/d: 150 mg BID
  - > 90 to 120 mg/d: 200 mg BID


- **Morphine to tapentadol switch 1:4.5**


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## Side effects
- Gastrointestinal: Nausea, Vomiting, Constipation
- Nervous System: Dizziness, Somnolence
- Skin: Pruritis
- In studies chronic low back pain and osteoarthritis Tapentadol ER less incidence of above side effects when compared to Oxycodeone CR

## Limitations
- Dose limits
  - Daily ceiling dose 500 mg ER and 600 mg IR
- Risk for serotonin syndrome
  - Although mostly norepinephrine reuptake, some serotonergic effects – caution when using with serotonergic agents
- Contraindicated with use of monoamine oxidase inhibitors in last 14 days
- Avoid when history of seizures

**DESIGNING A COMPREHENSIVE TREATMENT PLAN**

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Case Study (cont.)

- EW undergoes a total knee replacement and receives a regional nerve block prior to surgery, IV acetaminophen and as needed opioid analgesics
- When transitioning to oral agents EW starts tapentadol IR therapy at a dose of 50 mg every 4 as needed for pain
- Physical therapy is initiated
- He attends a session on cognitive behavioral therapy

Multimodal Therapy

- Guidelines for postoperative pain and chronic pain recommend multimodal therapy
- The use of opioids are only one part of the comprehensive plan for both acute and chronic pain
  - risks must be balanced with benefits

Selected References

References