OPIOID-INDUCED NEUROTOXICITY*

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*Slide Deck courtesy Dept PRIM MDACC
PATIENT #1: MRS SMITH, 65 YRS, METASTATIC BREAST CANCER TO BONES

- Discharged from hospital after finishing XRT to T 9-11 spine (pain, epidural disease), and left hip (pathological #)
- Pain located in left hip and mid-lower back
- Not candidate for surgery or further cancer therapies. Hospice advised but declined by patient/family

Discharge medications:

- Morphine ER 60mg q 8h; Morphine IR 15mg, 2 tablets q 4 hrs prn; Hydorocodone 10/325mg, 1 tablet q 6 prn;
- Senna 3 BID; Metaclopramide 10mg every 6 hours; Zolpidem at bedtime
PATIENT #1: MRS SMITH, MET BREAST CANCER, CONTD.

- 1 week after discharge home:
  - ↑ pain, despite scheduled + 8 PRN 15mg daily (“doesn’t work”);

- Calls MD for ↑ pain meds. Pt does not want to come to the hospital as more fatigued, issues with mobility and long waits in EC/clinic

- Prescriptions mailed out:
  - Morphine ER ↑ from 60mg to 120mg q 8 hrs; morphine IR 30-45mg as needed; Alprazolam added as pt sounds anxious on phone at 0.5mg prn TID
Q. What is the most likely reason for uncontrolled pain?

A. Progressive disease
B. Tolerance to opioid analgesic effects
C. Opioid toxicity
D. Combination of events
PATIENT #1: MRS SMITH, MET BREAST CANCER, CONTD.

3 days later:
- Has pain now in both legs, further reduction in mobility and transfers; Patient increases morphine ER 120 to every 6 hours

Next day:
- ↑ nausea, ↓ oral intake, spending all day in bed, but not able to sleep more than 1 hour at time. Very restless. Family is very upset. Husband calls for referral to hospice

Following day:
- Hospice nurse arrives, patient has “pain all over,” 10” out of 10, has muscle jerking (1-2 every hour or so), more at night; Husband reports she is asking for her brother (deceased) who she says was in her room.
OPIOID INDUCED NEUROTOXICITY (OIN)

A syndrome of neuropsychiatric toxicity

- Cognitive impairment
- Delirium
- Severe sedation
- Hallucinations
- Delirium
- Myoclonus
- Seizures
- Hyperalgesia (paradoxical pain)

- Each can occur alone, in combination, in any order
- Suspect OIN if any present in a patient taking opioids
PREDISPOSING FACTORS FOR OIN

- High opioid doses
- Prolonged opioid use
- Recent rapid dose escalation
- Use of other psychoactive drugs - benzodiazepine,
- Underlying brain disease or cognitive failure
- Dehydration
- Renal failure
- Advanced age
- Prior episode of OIN

MECHANISM OF OPIOID-INDUCED NEUROTOXICITY
MECHANISM OF OPIOID INDUCED NEUROTOXICITY

Not fully understood

• Accumulation of excitatory non-analgesic opioid metabolites
• Accumulation of the parent opioid
• NMDA activation
POTENTIAL CONTRIBUTORS FOR OIN IN A TERMINAL ILL PATIENT.

- Anorexia, Nausea Vomiting, Dysphagia, Bowel Obstruction, Depression
- ↓ FLUID INTAKE
- DEHYDRATION AND IMPAIRED RENAL FUNCTION
  - Hypotension
  - Hypercalcemia
  - Fatigue, sedation, postural hypotension, and dizziness, nausea, constipation

- Pain
- Opioid Titration
  - Accumulation of parent opioid and its metabolites
  - Excessive sedation, myoclonus, hallucination, opioid induced hyperalgesia

TERMINAL ILLNESS

DELIRIUM

COMA AND DEATH
INTER-INDIVIDUAL VARIABILITY IN OPIOID ANALGESIC AND SIDE-EFFECT RESPONSE

Attributed to:

- Several opioid receptor subtypes
  - Mu-receptor has many (~7) subtypes
- Subtle differences between opioids in binding to these various subtypes
- Genetic differences between pts in receptor sensitivity

 Trials of several opioids are often needed before finding one that provides an acceptable balance of analgesia and tolerability for an individual patient.

Pasternal GW Trends in Pharmacological Sciences, 2001;22: 67-70
OPIOID METABOLISM

- Most opioids metabolized in the liver, and renally excreted.

  - ↑ accumulation of parent opioid and its metabolites
    - with high opioid doses; dehydration; renal failure.
    - metabolites may cause toxicity via non mu-receptor actions
MEPERIDINE (DEMEROL)

• Meperidine metabolized to Normeperidine
  – highly neurotoxic, and has half of analgesic potency as parent drug

• Normeperidine accumulation
  – irritability, seizures, myoclonus, tremors, and prolonged lethargy
  – may occur in normal individuals and is worse in patients with renal dysfunction

• Meperidine should NOT be used in treating chronic pain

MORPHINE
Liver
Opioid metabolites
Renal Elimination
Analgesic metabolite
Neuro-excitatory metabolite

- Neuro-excitatory effects
- Hallucinations, delirium, alldynia, hyperalgesia, myclonus, seizures.
- Is not a mu-agonist;
- Naloxone does not reverse effects

- is a potent mu-agonist
  - ↑ analgesic effects
  - ↑ mu-receptor side-effects
### SUMMARY OF OPIOID METABOLITES

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Key Enzyme</th>
<th>Major metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>UGT2B7</td>
<td>M3G and M6G</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>UGT1A3, 2B7</td>
<td>H3G</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP3A4, 2D6</td>
<td>Noroxycodone, oxymorphone</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>UGT2B7</td>
<td>6-OH-oxymorphone, oxymorphone-3-glucuronide</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A4</td>
<td>Norfentanyl</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP3A4, 2D6</td>
<td>Morphine, C6G</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP3A4, 2D6</td>
<td>Hydromorphone, norhydrocodone</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>CYP3A4</td>
<td>Norpropoxyphene</td>
</tr>
<tr>
<td>Meperidine</td>
<td>CYP3A4, 2B6,2C19</td>
<td>Normeperidine</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6</td>
<td>O-desmethyl tramadol</td>
</tr>
</tbody>
</table>
PARADOXICAL PAIN WITH OPIOID USE

• Opioids implicated to paradoxically ↑ pain

➢ Allodynia:
Painful response to a stimulus that is normally not painful (such as light touch)

➢ Hyperalgesia:
Severe pain response to a stimulus that normally produces only mild pain response.
OPIOID-INDUCED HYPERALGESIA (OIH)

• Pain is usually
  – more severe than pre-existing pain
  – More diffuse
  – extends to other areas of distribution from the preexisting pain.
  – less defined in quality

  – *Gets worse with increasing the opioid dose*

*Most of these present in patient example # 1*
OPIOID-INDUCED HYPERALGESIA (OIH)

Differentiate from

- ↑ pain due to disease progression
- Opioid tolerance

Opioids usually increased in above two and associated with improvement, but would worsen OIH

- Not always easy to distinguish OIH from above two
  - If a trial of increasing opioids worsens pain, need to consider OIH
OPIOID TOLERANCE VS HYPERALGESIA

• Opioid Tolerance to analgesic effects
  – manifested by ↑ opioid dose requirements to achieve the same degree of pain relief.
  – *Decreased sensitivity of opioids*

• Opioid induced Hyperalgesia:
  – ↑ sensitivity to pain from painful and normal stimuli
  – *increased sensitivity to pain*

• May share similar mechanisms, but treatment different!
  – changes in NMDA receptors or descending modulatory pathways by mediators (such as CCK)
HALLUCINATIONS

• Usually Visual or tactile
• A study found 47% of hospice inpatients had visual hallucination within the prior month.
  – Hallucinators were more likely to be on opioids
  – Hallucinations of a person standing by the bedside was the commonest type

TREATMENT OF OPIOID INDUCED NEUROTOXICITY
MANAGEMENT OF OPIOID INDUCED NEUROTOXICITY (OIN)

A. Prevention

B. Treatment
  – Elimination of contributing etiology of OIN
  – Management of Pain in presence of OIN
  – Symptomatic management of OIN features
PREVENTION OF OIN

1. Evaluate and treat risk factors, as appropriate

2. Initiate and titrate opioids cautiously

3. Frequent Re-assessment for analgesic and adverse effects of opioids
PREVENTION OF OIN:
EVALUATE FOR PRESENCE OF RISK FACTORS

– Able to maintain hydration?
  • ? Nausea, bowel obstruction, anorexia, depression
– Underlying renal and liver function?
– Does patient have underlying brain disease, sepsis, or hypoxia
– Is patient on sedating medications
– Screening for cognitive impairment or delirium
  • Mini-mental State Examination (MMSE)
  • Memorial Delirium Assessment Scale (MDAS)
  • Nursing Delirium Screening Scale (NuDESC)
DELIRIUM SCREENING

Nursing Delirium Screening Scale (NuDESC)

- Validated observational
- 5-item scale (each scored from 0-2, max score 10)
  - Disorientation
  - Inappropriate behavior
  - Inappropriate communication
  - Illusions, or hallucinations
  - Psychomotor retardation

- Takes < 2 minutes to complete
- Can be used for screening & monitoring delirium severity.
PREVENTION OIN: MANAGEMENT OF RISK FACTORS FOR OIN

– Discontinue sedating medications
– Treatment of nausea, constipation, anorexia, depression, as appropriate
  \(\rightarrow\) to ↑ fluid intake
– Treatment of hypoxia, infections, depending on clinical setting
– Hydration
  – Will patient benefit from parenteral hydration?
PREVENTION OIN: INITIATE AND TITRATE OPIOIDS CAUTIOUSLY

In opioid naïve patients:

- First start as needed low dose, short acting opioids every 2-4 hours
- In some, extended release opioids can be considered
- Fentanyl patches not recommended in opioid-naïve
- If renal failure, chose agents without active metabolites (methadone), or space out doses.
PREVENTION OIN: FREQUENT ASSESSMENT OF PAIN/SIDE-EFFECTS

• Monitor opioid use
  – Use of scheduled and as needed opioids. Compliance

• Monitor pain and its characteristics
  – Does pain features the same, improved or worse after opioids
  – Is there diffuse “all over pain”, does pain medication make the pain worse? Suspect opioid induced hyperalgesia

• Monitor side-effects in a systematic fashion
  – GI side-effects may interfere with fluid status; Rx as appropriate
  – CNS side-effects: Sedation, cognitive decline, delirium

(delirium scales: eg. NuDESC)
TREATMENT OF OIN

• Treat underlying etiology of OIN
  – Elimination of offending opioid and/or metabolites
  – Hydration to help elimination
  – May consider dose reduction if symptoms mild, and pain controlled

• Manage the pain
  – Patient still needs opioid for pain management
  – Chose alternate opioid should be selected
  – Alternatives options to decrease need for opioids

• Symptomatic management of OIN
  – Such as for agitated delirium
TREATMENT OF SPECIFIC OIN FEATURES

MYOCLONUS

• If mild:
  – Observation alone may be appropriate. Opioid rotation if myoclonus more frequent, or if associated with other features of OIN

• If severe/frequent:
  – After opioid rotation, the following have been used: Baclofen, clonazepam, & anticonvulsants.
  – However, do not address the etiology of the problem
  – Risk for polypharmacy and new issues
TREATMENT OF SPECIFIC OIN FEATURES. DELIRIUM

Neuroleptics:
• Haloperidol most commonly used for agitation or mixed delirium
• Less sedating and fewer anti-cholinergic effects
• Atypical antipsychotics, such as olanzapine, risperidone, and quetiapine have been used for delirium
• Chlorpromazine if above not options/refractory; frequently causes hypotension

Benzodiazepines: not generally recommended (unless seizures) due to excessive sedation, increased confusion, and increased disinhibition with use
SUMMARY

• All opioids have potential of side-effects
• Recognize the syndrome of Opioid Induced Neurotoxicity
  – Myoclonus, Agitation Confusion
  – Pain “everywhere” not relieved/ exacerbated by opioids
• Recognize risk factors for OIN
  – High opioid dose, rapid escalation of opioid
  – Underlying renal, liver and brain impairments
  – Dehydration
• Screen regularly for Opioid side-effects including OIN
• Treatment:
  – Usually opioid rotation, treatment of contributing factors, hydration if feasible and consistent with care goals.
  – Opioid reduction if none of above possible.
OPIOID ROTATION

Rationale:

- Uncontrolled pain
- Toxicity attributed to accumulation of offending opioid and its metabolite, so the treatment is stopping offending opioid
- Change in route
- Drug Interactions
  -- New opioid is used to control pain

*de Stoutz et al. JPSM; 1995
  - Retrospective study of 80 patients with OIN (Cognitive deterioration, hallucinations, myoclonus)
  - Opioid rotation significantly improved symptoms and pain control in vast majority of patients
  - New opioid dose was significantly lower than that thought to be equianalgesic
Which opioid is best to switch to?

- Toxicity is not believed to be a class effect so any alternate opioid may be chosen.
- Dose of new opioid calculated from Equianalgesic Table.
- Meperidine or propoxyphene NOT appropriate for chronic pain.

- Switch to methadone may have advantages:
  - No neuro-excitatory or active metabolites.
  - Good oral bioavailability.
  - Does not depend on renal excretion, so safer in presence of renal failure.
INITIAL EQUIANALGESIC OPIOID DOSE CONVERSION TABLE

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Oral Dose</th>
<th>Parenteral (IV/SC) Dose</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>From IV/SC opioid to oral opioid</td>
</tr>
<tr>
<td>Morphine</td>
<td>15 mg</td>
<td>6 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 mg</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>5 mg</td>
<td>0.5 mg</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 mg</td>
<td>1.5 mg</td>
<td>2</td>
</tr>
</tbody>
</table>

• Helps select the initial dose avoiding over- or under-dosing
• Comparative values are approximate. Opioid dose should be further titrated based on the patient’s response.
**Equianalgesic Ratio**

**Morphine to Methadone**

<table>
<thead>
<tr>
<th>Morphine equivalent Daily Dose (mg/d)</th>
<th>Initial dose ration (MSO4 : Methadone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>2:1</td>
</tr>
<tr>
<td>30-99</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999</td>
<td>15:1</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>20:1</td>
</tr>
</tbody>
</table>
OPIOID ROTATION RECOMMENDED STEPS

**Step 1**
- Calculate total daily (24 hr) dose of the offending opioid

**Step 2:**
- Calculate new opioid daily dose using Equianalgesic conversion table.

**Step 3:**
- Decrease above new opioid dose by 25-50% for incomplete tolerance between opioids

**Step 4:**
- Divide by number of scheduled doses/day. Breakthrough dose ~ 10-15% of daily dose every 1-2 hours as needed.

**Step 5:**
- Titrate new opioid until adequate analgesia is achieved.