Treatment of Opioid-Induced Neurotoxicity in End-of-Life Care

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Overview of Presentation
1. Case Scenarios
2. Opioid use in Palliative Care
3. Opioid Analgesic Mechanisms
4. Opioid Side Effects
5. Opioid induced neurotoxicity
6. Predisposing Factors
7. Prevention
8. Management
9. Summary

Patient #1: Mrs Smith, 65 yrs, Metastatic breast cancer to bones
- Discharged from hospital after finishing XRT to T9-11 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, Hydorcodone 10/325mg, 1 tablet q 6 pm;
  - Senna 3 BID and Miralax 17grams; Reglan 10mg every 6 hours; Zolpidem at bedtime

Opioid use in Palliative Care
- Opioids cornerstone of pain management
- Past 2½ decades opioid use ↑↑
  - 1984: WHO’s cancer pain relief program; continued advocacy and educational drive by other organizations (including NCCN, NHPCO, APS)
  - Easing of overly restrictive laws/regulations
  - UN health and International Narcotics Control Board (INCB)
  - Wisconsin Cancer Pain Initiative (WCPI)
  - Morphine consumption globally
    - from < 5 tons in 1985 → 15.5 in 1995 → 39.2 in 2007

Case #2: Mr Jones, 50 years, Metastatic Renal cancer
- Has progressive disease despite multiple therapies in past 2 years. Now on investigational chemo, every 3 weeks via PICC line. No other medical history except for hypertension related to cancer therapy and is on BP meds
- Patient is seen in clinic by palliative care (PC) team. Pain in left flank, and lower extremities related to neuropathy controlled with Oxycontin dose of 80 mg every 12 hours, with oxycodone 15 mg prn (2 tablets using 3-4 times/day), and gabapentin 300mg twice daily and prn senna. No bowel movements for 2 days
- Clinic visit: Oxycontin is increased to 80mg every 8 hours. Senna scheduled to 2 bid
Opioid use in Palliative Care, contd

- Opioids are being prescribed earlier in the disease trajectory and at higher doses.
- Unlike NSAIDs, no ceiling effect

Opioid Analgesic Mechanisms

Pain Signaling Pathways

- Opioid Receptors
  - located in the peripheral nervous and CNS

Dorsal Horn Synapse

Primary Analgesic Effect of Opioid - Receptor Activation

- Opioids decrease neurotransmission by reducing or inhibiting presynaptic neurotransmitter release by
  - ↑ K conductance (hyperpolarization)
  - Inactivation of Ca channels

Mu-opioid Receptor Agonists

- 3 major opioids receptor subtypes
  - mu (μ), kappa (κ), delta (δ)

- Pure mu-receptor agonists most used in palliative care
  - Hydrocodone, codeine, propoxyphene, meperidine
  - Morphine, oxycodone, hydromorphone, fentanyl, oxymorphone, and methadone.

- Morphine, most commonly used worldwide
  - Benchmark "strong" opioid; Used as standard of comparison

Opioid Use for Pain in Terminally Ill

- No uniformly preferred agent

- Opioid Selection typically based on
  - clinical judgment/ comfort, formulary, cost, availability of parenteral formulation
  - patient's past experience/analgesic response

- All opioids have potential for side-effects

- 10-36% of pts may not have a successful outcome
  - ↑ adverse effects or
  - inadequate analgesia or
  - ↑ adverse effects and inadequate analgesia.

Cherny N. J Clin Oncol 2001:19: 264-264
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.

Pasternak GW. Trends in Pharmacological Sciences, 2001; 22: 67-70

Opioid Side-Effects

Commonly recognized side-effects
- Sedation*
- Nausea
- Constipation*
- Urinary retention*
- Respiratory depression*
- Euphoria*
- Pruritis

Constipation requires ongoing management

*Attributed to mu-opioid receptor activation; Reversed by opioid antagonists: Naloxone for severe opioid toxicities; Methylnaltrexone for constipation

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; Xanax added as pt sounds anxious on phone at 0.5mg pm TID

Poll Question

- 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.

↑ reports in the literature of hallucinations, agitation, confusion, myoclonus, seizures, and paradoxical increase in pain after opioid use.

- Collectively referred to as
  - Opioid induced neurotoxicity
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

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)

Delirium in Terminal Illness

- Very common at the end of life
  - In cancer patients: 25–40% of hospitalized patients
  - up to 80% of patients in the terminal stage of disease

- Distressful to patients and/or family
  - 74% remember episode and reported high distress.
  - Distressful decision-making capacity of patients
  - Impairs decision-making capacity of patients
  - Increases hospital stay, falls, and injuries
  - Increases likelihood of death.

- Delirium episode may be reversible in 50% of cases
  - Challenge in whether a particular episode will resolve or not.

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


Etiology of Delirium in Terminally Ill

- Underlying Brain disease
- Uremic or Hepatic encephalopathy
- Dehydration
- Hypercalcemia,
- Hypernatremia
- Hypoxemia
- Sepsis
- Opioids and other psychoactive medications
- "Terminal Delirium"

Opioids & dehydration top 2 causes of reversible delirium

Rafter J, Cancer 1997;79:835–842

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

Not fully understood

- Accumulation of excitatory non-analgesic opioid metabolites
- Accumulation of the parent opioid
- NMDA activation

Potential contributors for delirium/OIN in a Terminal ill patient.

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
**Major Morphine Metabolites**

- **Morphine**
  - Liver
  - Opioid metabolites
  - Renal Elimination
  - Neuroexcitatory metabolite
    - Morphine-3-glucuronide (M3G)
    - Morphine-6-glucuronide (M6G)
  - Analgesic metabolite
    - Morphine-glucuronide (MG)

- **Neuroexcitatory effects**
  - Hallucinations, delirium, allodynia, myoclonus, seizures.
  - Is not a mu-agonist.
  - Naloxone does not reverse effects.

- **Hydromorphone and its metabolites**
  - Major metabolite
    - Hydromorphone-3-glucuronide (H3G).
  - No analgesic activity
  - Neuroexcitatory
    - Allodynia, myoclonus, seizures, chewing, ataxia, and convulsions.
  - H3G may accumulate with renal failure.

- **Codeine and Hydrocodone**
  - **Codeine**: Metabolized in liver by CYP2D6 enzymes
    - To morphine (10%), codeine-6-glucuronide (C6G) and norcodeine.
    - C6G and M3G accumulate in renal failure → neurotoxicity.
  - **Hydrocodone**: Metabolized by
    - CYP2D6 → hydromorphone
    - CYP3A4 → norhydrocodone
    - H6G accumulates in renal failure → neurotoxicity.
  - **Poor metabolizers of CYP2D6**
    - Little to no analgesia with codeine and hydrocodone (as less conversion to morphine/hydromorphone).
  - **Ultra-rapid metabolizers of CYP2D6**
    - Amplified analgesic and adverse effects.

- **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.

- **Propoxyphene**
  - Propoxyphene metabolized to in the liver to norpropoxyphene.
  - Norpropoxyphene has a much longer half-life than the parent drug.
  - Risk for cardiotoxicity.
  - Not recommended for chronic use.

- **Fentanyl**
  - Fentanyl metabolized by the liver
    - Mostly into norfentanyl by the CYP3A4.
    - Other minor metabolites: despropionylfentanyl, hydroxyfentanyl, hydroxynorfentanyl, and N-phenylproprionamide.
  - Fentanyl metabolites not considered to be active.
  - But several reports of fentanyl associated neurotoxicities reported: myoclonus, sedation, and hyperalgesia.
**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>Oxycodeone</td>
<td>CYP3A4, 2D6</td>
<td>Noroxycodone, oxymorphone</td>
</tr>
<tr>
<td>Oxycodeone</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>Morphone, CSG</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>CYP3A4, 2D6</td>
<td>Hydromorphone, norhydrocodeine</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>CYP3A4</td>
<td>Norpropoxyphene</td>
</tr>
<tr>
<td>Meperidine</td>
<td>CYP3A4, 2B6, 2C19</td>
<td>Norperidone</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP2D6</td>
<td>O-desmethyl tramadol</td>
</tr>
</tbody>
</table>

**Methadone**

- Synthetic mu-opioid receptor agonist
- N-methyl-D-aspartate (NMDA) receptor antagonism
- Useful in:
  - Neuropathic pain
  - Opioid tolerance:
  - Lower need for opioid escalation when used in treating cancer pain, as compared to other opioids.
- Has mainly been used as second line opioid
- Preliminary evidence supports use of methadone as first-line strong opioid.


**Methadone**

- Oral bioavailability, ~ 80%.
- Highly lipophilic
- Rapidly absorbed and taken up by tissues, from where it is slowly released
- Metabolized in liver to inactive metabolites
- Elimination mainly via fecal route
  - Does not require dose adjustment in pts with renal failure.
- However, half life is (elimination phase) variable 15-60 hours; higher reported.
- Accumulation can result in prolonged sedation and/or difficulties in managing pain fluctuations.
- QT interval prolongation can occur with methadone.

**Opioid Use for Pain Management**

A balancing act?

**Analgesia**

Benefits of analgesia should clearly outweigh treatment-related adverse effects

**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
  → 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, choose 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
  - 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 Opioid Induced Neurotoxicity

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

OIN: Opioid Dose Reduction or Rotation?
- Dose reduction may be considered
  - if OIN is mild and pain is well controlled.
  - balance between analgesia and side-effects can be a challenge.
  - Eventually most patients may need rotation
- Opioid Rotation preferred

Hydration
- Rationale:
  - Facilitates elimination of accumulated opioid and neuro-excitatory metabolites.
- Consider Pros and Cons
- Subcutaneous route an option if oral not available
  - Simple, low cost, less need for supervision
  - 25 or 27 gauge butterfly needle is used, use 5-7 days
  - Continuous versus bolus infusions
  - Can be used to administer other medications, including opioids

Opioid Rotation
Rationale:
- OIN attributed to accumulation of offending opioid and its metabolite, so the treatment is stopping offending opioid
- 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

Opioid Rotation, contd
Which opioid is best to switch to?
- OIN 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>
<th>From IV/SC opioid to oral opioid</th>
<th>From oral opioid to oral morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>15 mg</td>
<td>6 mg</td>
<td>2.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 mg</td>
<td>NA</td>
<td>NA</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>5 mg</td>
<td>0.5 mg</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 mg</td>
<td>1.5 mg</td>
<td>2</td>
<td>5</td>
<td></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.

Morphine to Methadone Conversion

<table>
<thead>
<tr>
<th>Oral morphine equivalent daily dose (MEDD) in milligrams</th>
<th>Conversion ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>3:1</td>
</tr>
<tr>
<td>&gt; 100 – 300</td>
<td>5:1</td>
</tr>
<tr>
<td>&gt; 300 – 600</td>
<td>10:1</td>
</tr>
<tr>
<td>&gt; 600 – 800</td>
<td>12:1</td>
</tr>
<tr>
<td>&gt; 800 – 1000</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>20:1</td>
</tr>
</tbody>
</table>

* Dose of methadone is calculated by dividing the MEDD by the conversion ratio. This dose should be decreased by 25-50% to accommodate for lack of incomplete tolerance.

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 2-4 hours as needed.
Step 5: Titrate new opioid until adequate analgesia is achieved.

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

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

Patient #1: Mrs Smith, 65 yrs, Metastatic breast cancer

- Summary: escalation of morphine with no improvement in pain. New areas of pain, "pain all over", muscle jerks, hallucinations, confusion.
- What should be done: Poll Question
  a. Increase morphine dose
  b. Stop all opioids. Start lorazepam
  c. Opioid rotation
**Treatment: Opioid Rotation**

- Discontinue offending opioid (morphine)
- Calculate dose from oral morphine to oral methadone from morphine to methadone conversion chart.
- Daily (24 hr) morphine dose =120mg X3, plus 3 doses of 30 mg (breakthrough doses)= 450 mg
- Corresponds to 45 mg oral methadone
- May start patient on 7.5mg every 8 hours ATC
- Use another opioid such as hydromorphone or oxycodone for breakthrough pain.

**What else can be done?**

- Haloperidol at bedtime and prn added orally to help with restlessness and agitation.
- Hydration via subcutaneous route offered, but patient’s family declines
- Xanax discontinued
- Family education and counseling

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**Case # 2: Mr Jones, 50 years, Metastatic Renal cancer**

- Summary: Pain well controlled when seen in the clinic, was using prn doses of about 90 mg/day, so at visit Oxycontin was increased to 80mg every 8 hours.
- 6 days later, patient arrives via ambulance to the Emergency Room
- 2 days vomiting, minimal oral intake, cramping in abdomen, and is extremely lethargic and disoriented. Oxygen saturations are 93%, RR is 24/min, BP 90/60. Pupils are pinpoint
- Workup reveals renal failure. BUN is 55, creatinine 2.8

**Poll Question: Should Naloxone (Narcan) be given to patient?**

- **Yes**
- **NO**

---

**Why didn’t Naloxone help patient?**

Delirium with excessive sedation related to a combination of events:
1. Sepsis
2. Dehydration
3. Renal failure
4. Accumulation of non-analgesic neuroexcitatory opioid metabolites which act via non-mu-opioid receptor mechanisms.
Case # 2: Mr Jones, 50 years, Metastatic Renal cancer. contd

- 24 hours later patient calls hospice team that he is having excruciating pain, and hydrocodone not helping

**Best option? Poll Question**

A. Offer lorazepam as patient is anxious
B. Resume Oxycodone that patient was at same dose
C. Resume Oxycodone at lower dose
D. Switch to any other new opioid
E. Switch to methadone

Case # 2: Mr Jones, 50 years, Metastatic Renal cancer. contd

- Delirium was multifactoral and patient received IV fluids, and Antibiotics, and opioids were stopped. All opioid toxic metabolites were excreted, so patient improved. However lack of opioids has precipitated a pain crisis
- Best option during hospitalization;
  - Oxycodone stopped
  - Start low dose alternate opioid via IV/SC route such as fentanyl (lack of active metabolites)
  - Titrate during admission.
  - Discharge on oral methadone

Case # 2: Mr Jones, 50 years, Metastatic Renal cancer. contd

- What should be done now
- Start on oral methadone
- Patient risk for renal failure, renal functions not known now as in hospice care.
- Short acting hydromorphone or morphine can be given as needed.

**In Summary...**

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.

Thank You!