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 ("doesnt 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; Alprozolam added as pt sounds anxious on phone at 0.5mg prn TID*

QUESTION

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 NEUROTOXOCITY (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- benzodiazeprine,
- Underlying brain disease or cognitive failure
- Dehydration
- Renal failure
- Advanced age
- Prior episode of OIN

Thwaites et al. J Palliat Med 2004.

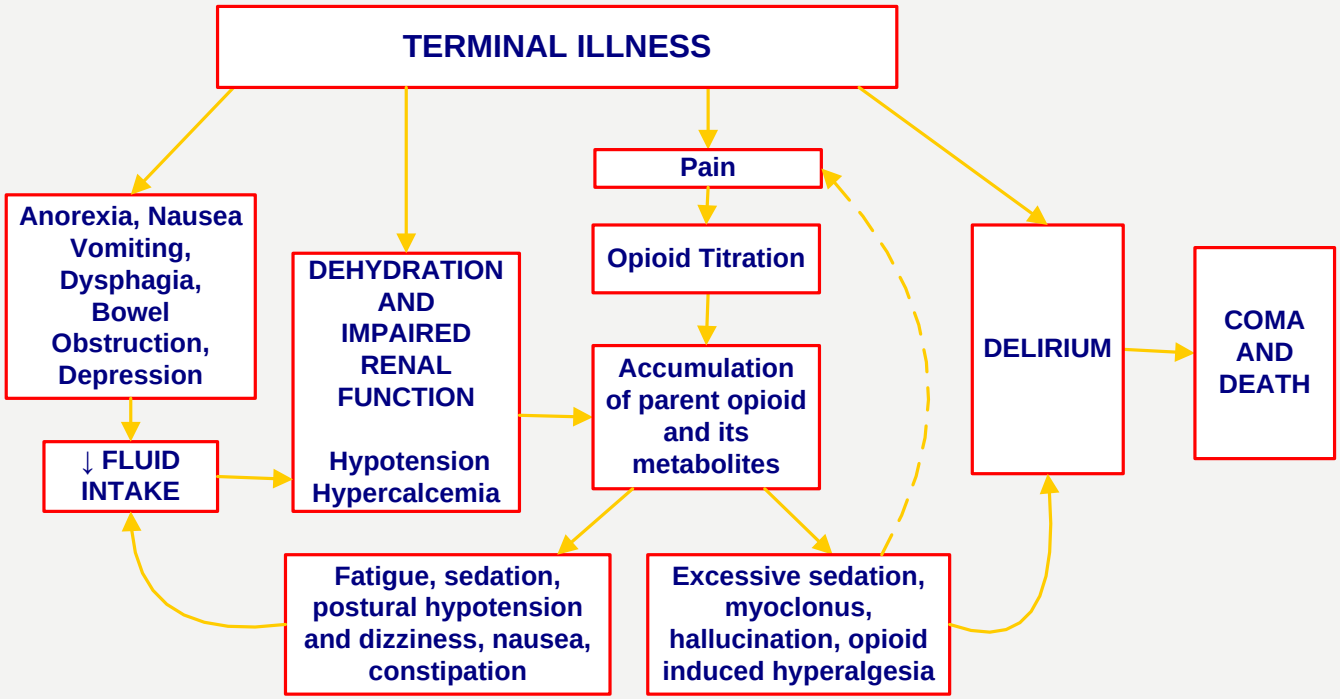
MECHANISM OF OPIOID-INDUCED NEUROTOXICITY

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.



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

Attributed to:

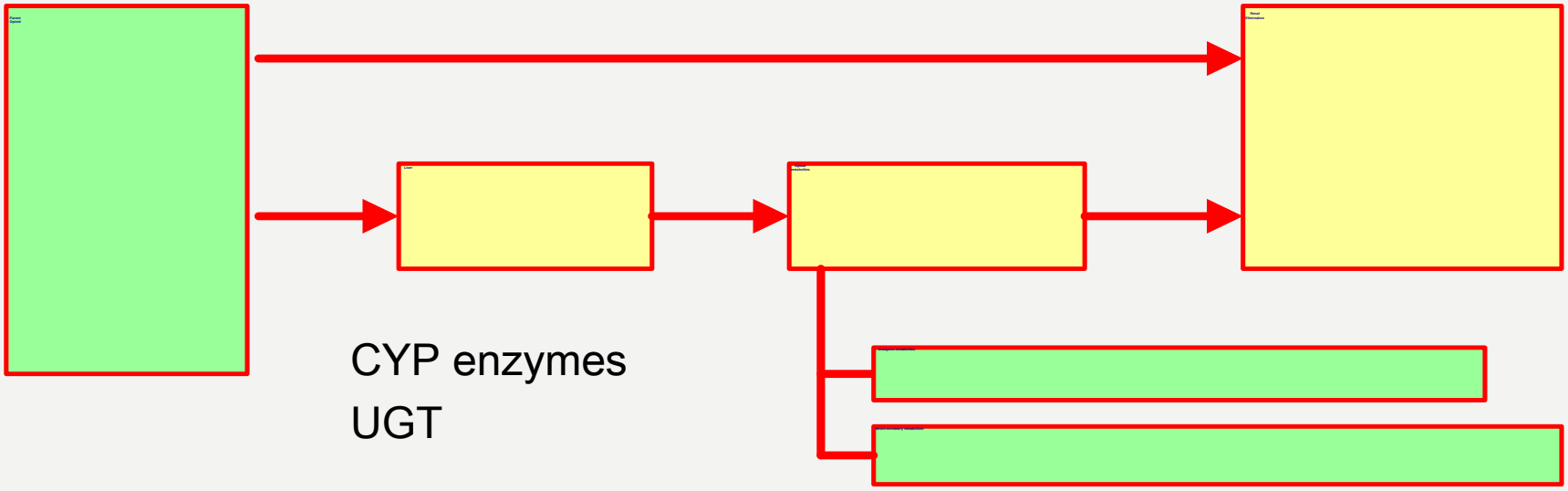
- Several opioid receptor subtypes
  - Mu-receptor has many (~7) subtypes
- Subtle differences between opioids in binding to these various subtypes
- Genetic differences between pts in receptor sensitivity

➢ 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.



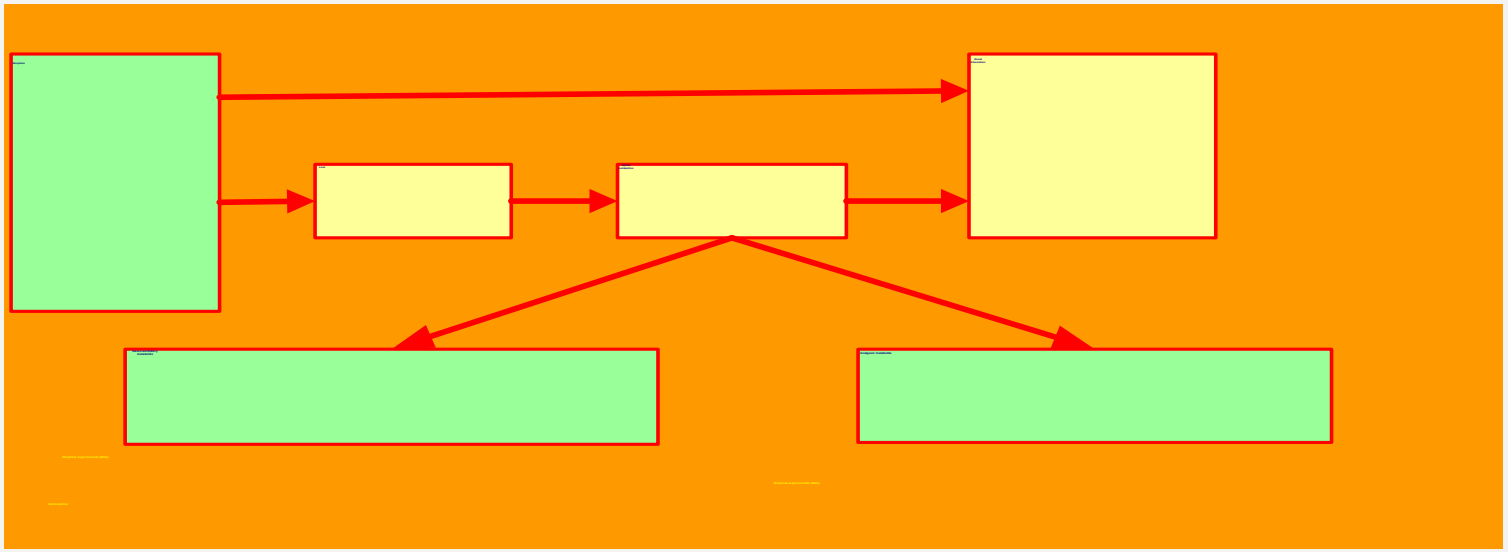
- ↑ accumulation of parent opioid and its metabolites
  - with high opioid doses; dehydration; renal failure.
  - metabolites may cause toxicity via non mu-receptor actions

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 occurs in normal individuals and is worse in patients with renal dysfunction
- Meperidine should NOT be used in treating chronic pain

Pond SM, Clin Pharmacol Ther. 1981;30:183–188.

MAJOR MORPHINE METABOLITES



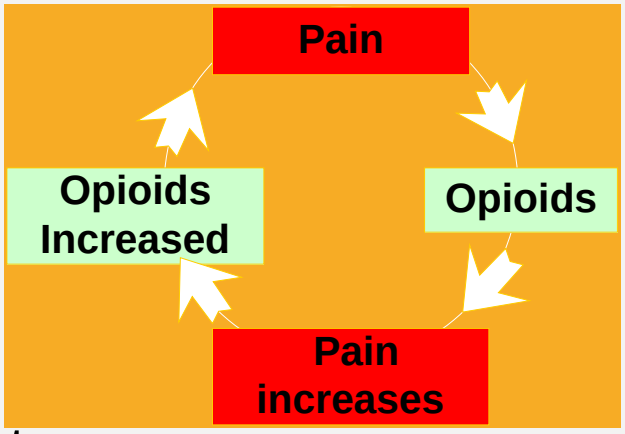
- Neuro-excitatory effects
- Hallucinations, delirium, allodynia, hyperalgesia, myclonus, seizures.
- Is not a mu-agonist;
- Naloxone does not reverse effects

- is a potent mu-agonist
  - ↑ analgesic effects
  - ↑ mu-receptor side-effects

SUMMARY OF OPIOID METABOLITES

Opioid	Key Enzyme	Major metabolites
Morphine	UGT2B7	M3G and M6G
Hydromorphone	UGT1A3, 2B7	H3G
Oxycodone	CYP3A4, 2D6	Noroxycodone, oxymorphone
Oxymorphone	UGT2B7	6-OH-oxymorphone, oxymorphone-3-glucuronide
Fentanyl	CYP3A4	Norfentanyl
Codeine	CYP3A4, 2D6	Morphine, C6G
Hydrocodone	CYP3A4, 2D6	Hydromorphone, norhydrocodone
Propoxyphene	CYP3A4	Norpropoxyphene
Meperidine	CYP3A4, 2B6,2C19	Normeperidine
Tramadol	CYP2D6	O-desmethyl tramadol

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

Fountain A. Visual hallucinations: A prevalence study among hospice inpatients. Palliat Med 2001;15:19–25

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 OPIOID INDUCED NEUROTOXICITY

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, 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
  - ? 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

OPIOID ROTATION, CONT'D

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

Opioid	Oral Dose	Parenteral (IV/SC) Dose	Conversion Factor	
			From IV/SC opioid to oral opioid	From oral opioid to oral morphine
Morphine	15 mg	6 mg	2.5	1
Oxycodone	10 mg	NA	NA	1.5
Oxymorphone	5 mg	0.5 mg	10	3
Hydromorphone	3 mg	1.5 mg	2	5

- 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

Morphine equivalent Daily Dose (mg/d)	Initial dose ration (MSO4 : Methadone)
<30	2:1
30-99	4:1
100-299	8:1
300-499	12:1
500-999	15:1
≥ 1000	20:1

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.