Opioid Induced Neurotoxicity (OIN)

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Objectives

By the end of the activity, learners will be able to:

- **Define** opioid-induced neurotoxicity (OIN) and its clinical significance
- Identify the **pathophysiology and risk factors** underlying OIN.
- Briefly identify and differentiate **Opioid Induced Hyperalgesia, Opioid Tolerance**
- Apply evidence-based guidelines for the **management and treatment** of OIN

Case Presentation: Mr. N

History

- 74 y/o male **metastatic colorectal cancer** & **malignant bowel obstruction (MBO)**
- Localized cancer dx 2014
    - requiring resection, developed recurrence, left ureteral metastasis with ureteral obstruction requiring stent, eventual APR and end ostomy.
- MBO in late 2023 and in mid-2024, resolved with **conservative management**.

Admission

- Presented to hospital late 2024 with worsening abdominal pain, nausea
    - **Noted recurrence of malignant SBO.**
- Reported **chronic cancer pain** in abdomen
    - **fentanyl 50 mcg/hr every 72 hours, oxycodone 5 mg every 6 hours prn, gabapentin 600mg BID**
- NGT placed for conservative medical management.
- Palliative care was consulted for **pain control on HD 2.**

Pain Description

Baseline pain: focal left sided abdominal pain 4-5/10 in severity.

Additional complaint of diffuse colicky abdominal pain

Pain constant ~7/10 in severity
Bursts of worsening pain at 9/10 in severity.

Reports pain somewhat improved with IV Dilaudid

- However pain relief is not sustained

Timeline

-despite return of bowel function with ostomy output and imaging improvement
-ongoing uncontrolled pain (never <7)
-other potential sources of acute pain mitigated with additional means (next slide)

Concern for worsening obstruction on imaging and decreased output

HD 2	HD 3-5	HD 6	HD 7-9	*	HD 10-12	HD 13-15	*	HD 16-19
initiated on Dilaudid PCA basal 0, PCA 0.3mg q10 min, add'l PRN of 1.5mg IV q1h PRN 15mg IV total previous 24 hours	**Increased->Added** basal rate 0.5mg/hr cont PCA 0.3mg q10 min, **increase** add'l PRN to 2mg IV q1h PRN 21 mg IV total prev 24h	21mg IV dilaudid total from PCA; additional 16mg IV dilaudid given in prns 37 mg IV total prev 24h	PCA+ prns at same rate ~28-30 mg IV total prev 24h		**PCA stopped; concern for PCA overuse; wanted to monitor with nurse driven** ~25 mg IV total prev 24h	**Uncontrolled pain PCA resumed** ~30mg IV total prev 24h		**PCA continues** ~30mg IV total prev 24h

Fentanyl 50mcg patch.

Of Importance

- Difficult to discern exact pain
- **Pain description** initially with left sided or diffuse abdominal pain but progressed to include, **“pain all over”, could not discern further**
- Assumed primarily from SBO however on objective improvement continued with subjective pain: **did not always corroborate with increased pain** medicine usage
- Adjuncts and Multimodal pain approach
    - Ureteral stent spasm?- Sanctura
    - OIC; miralax, lactulose, naloxegol, suppositories, enema through stoma
    - MBO: octreotide. Steroids deferred
    - Did not have significant nausea or vomiting: reglan was used when noted to be partial obstruction. Zofran prn
- Appeared to have **increased anxiety** during course and query of medicating with opiates for this. PCA overuse?

Obstructed?

HD 20

50 mg IV dilaudid total prev 24h

from both PCA and PRN pushes

HD 21 **Concern for oversedation, no overt delirium**

PCA same dose from both PCA and PRN pushes

55 mg IV total prev 24h

PCA STOPPED, changed to nurse driven **standing dilaudid 3mg every 3 hours (approx 50% decrease)**

HD 22 **Moderate myoclonus, confusion, fever**

Approx 24mg IV dilaudid total from standing dilaudid and only 1 dose of prn given

25 mg IV total prev 24h

Physical Exam, pertinent positives

Patient extremely somnolent, briefly awakens to verbal stimuli and able to follow minimal commands before falling asleep again

Nonsensical speech, delirious

Pupils constricted, sluggish

Dry oral mucosa

Normal respiratory rate

Moderate generalized myoclonus, noted both whilst awake and asleep

Full neuro exam could not be performed to determine any further focal neuro deficits

Labs/ Vital Signs

Pertinent positives
• +one time fever 101 • + UA

Pertinent negatives
• Normal ammonia • Normal Co2 level • No electrolyte disturbance • Normal Renal Function • Normal BP

Active Medications

- Acetaminophen (TYLENOL) 1000 mg ever 8 hours
- FentaNYL (DURAGESIC) 50 mcg/hr TD PT72
- **Gabapentin 600 mg BID**
- Trospium (SANCTURA) 20 mg PO BID

- senna-docusate (SENOKOT-S) 8.6-50 mg PO TABS
- promethazine (PHENERGAN) 12.5 mg PO TABS
- polyethylene glycol (MIRALAX) 17 gram PO daily
- Naloxegel

- carvediloL (COREG) 3.125 mg BID
- digoxin (LANOXIN) 125 mcg (0.125 mg) PO TABS daily
- INSULIN LISPRO PROTAMINE-LISPRO 20 units BID
- melatonin 3 mg PO TABS
- simvastatin (ZOCOR) 20 mg PO TABS

- On TPN

Treatment

- **Standing Dilaudid STOPPED**
- **PRNS only continued. Later in the day, patient did have times when he awakened and reported pain**
- Given fever and fentanyl dose being possibly potentiated as well as severe AMS, **patch STOPPED**.
- Started on **aggressive IV hydration**
- **Started on abx for UTI**

36 hours

HD 20

PCA decreased by 25%

50 mg IV dilaudid total from both PCA and PRN pushes

HD 21 Concern for oversedation

PCA same dose from both PCA and PRN pushes

55 mg IV total total

PCA STOPPED, changed to nurse driven **standing dilaudid 3mg every 3 hours**

HD 22 Moderate myoclonus, confusion, fever *

Approx 24mg IV dilaudid total from standing dilaudid and only 1 dose of prn given

25 mg IV total

Standing dilaudid STOPPED, fentanyl patch STOPPED. PRNS only continued

Started on aggressive IV hydration, abx for UTI

HD 23; mental status improved back to baseline

approx 8 IV mg used (~33% preceeding of needs)

Dilaudid total from prns only

Remainder of hospital course

HD 24- HD 40

Pt with fluctuating pain needs thereafter:

- had fluctuating prn IV dilaudid requirements with daily dosing varying
- **venting G tube placed on HD 34 and pain needs improved**
- Fentanyl gradually in**creased with decreased prn IV dilaudid needs**
- Decision made to **transition patient to hospice**
- eventually **discharged with 200mcg/hr fentanyl with 4mg every 6 hours prn Dilaudid PO solution**

OPIOID INDUCED NEUROTOXICITY

Opioid Induced Neurotoxicity (OIN)

In a recent study, OIN was detected in 15% of patients receiving opioids as part of inpatient palliative care

Neuropsychiatric toxicity of opioid metabolites

- Confusion, somnolence, severe sedation
- Hallucinations
- Delirium
- Varying degrees of Myoclonus
- Seizures
- Allodynia; pain in response to non painful stimuli or Hyperalgesia

Lim KH, Nguyen NN, Qian Y, Williams JL, Lui DD, Bruera E, Yennurajalingam S. Frequency, Outcomes, and Associated Factors for Opioid-Induced Neurotoxicity in Patients with Advanced Cancer Receiving Opioids in Inpatient Palliative Care. J Palliat Med. 2018 Dec;21(12):1698-1704. doi: 10.1089/jpm.2018.0169. Epub 2018 Sep 27. PMID: 30260731; PMCID: PMC6308282.

Example of Opioid Induced Myoclonus

Rachão A, Pereira P, Grunho M. A Unique Case of Opioid-Induced Myoclonus. *JAMA Neurol.* 2024;81(11):1225. doi:10.1001/jamaneurol.2024.2780

Predisposing Factors for OIN

Opioid usage

-High opioid doses

- Prolonged opioid use

-Recent rapid dose escalation

Renal Failure

-decreased renal function

-First-pass metabolism can be substantially decreased in older adults

- enhanced pharmacodynamic sensitivity (ie, more pronounced effects compared with those that younger people experience while taking equivalent doses)

Advanced Age(>65)

Factors leading to dehydration

-nausea, vomiting, anorexia
-bowel obstruction
-infection
-hypotension
-electrolyte imbalance

Brain

Underlying brain disease or cognitive failure

Medications

-Other psychoactive medications

-Drug-drug; Cytochrome P450 (CYP) enzymes are among the principal pathways of drug metabolism for opioids

Infection

Prior episode of OIN

What were our patient's risk factors?

Opioid usage

-High opioid doses

- Prolonged opioid use

-Recent rapid dose escalation

Renal Failure

Brain

Underlying brain disease or cognitive failure

Advanced Age(>65)

-decreased renal function

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Prior episode of OIN

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Infection

Opioid Classes

Opioid Class	Drugs
Phenanthrenes	morphine; codeine; hydrocodone; oxycodone; oxymorphone; hydromorphone; levorphanol.
Phenylpiperadines	fentanyl; meperidine; sufentanil; remifentanyl
Diphenylheptanes	methadone; propoxyphene

*

Opioid Metabolites

*Affected by CYP 450 inhibitors

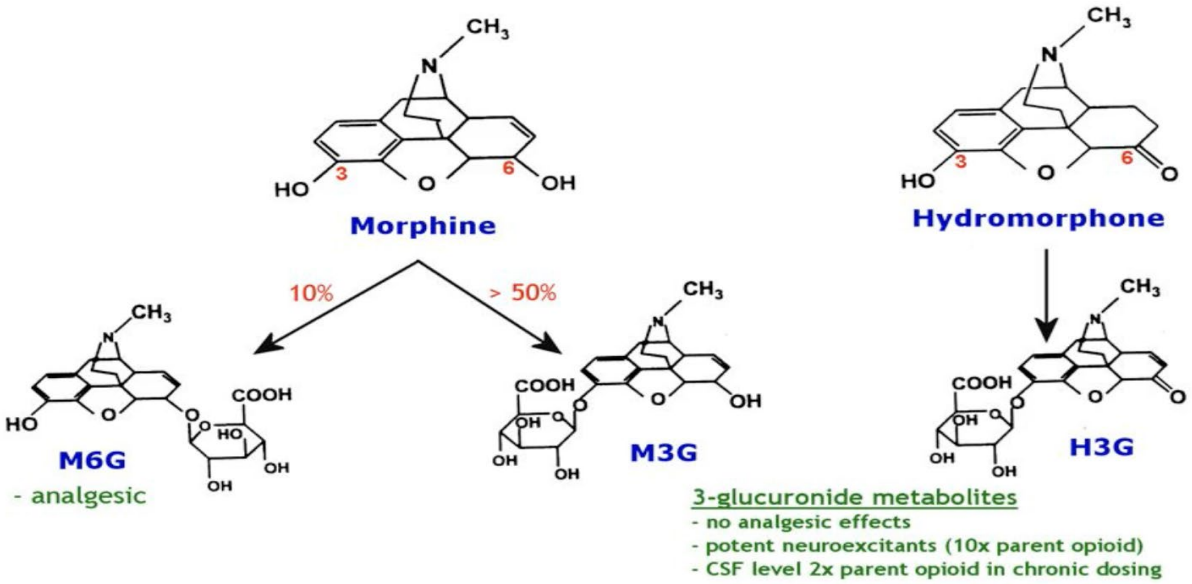
	Opioid	Key Enzyme	Major metabolites
	Morphine	UGT2B7	M3G and M6G *
	Hydromorphone	UGT1A3, 2B7	H3G * caution
	Oxycodone	CYP3A4, 2D6	Noroxycodone, oxymorphone * caution
	Oxymorphone	UGT2B7	6-OH-oxymorphone, oxymorphone-3-glucuronide
*	Fentanyl	CYP3A4	Norfentanyl
*	Codeine	CYP3A4, 2D6	Morphine, C6G * *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

*Avoid in Renal failure

*Avoid in liver failure

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

Yennu , S., MD, MS, FAAHPM. *"Opioid induced neurotoxicity"*. https://www.mdanderson.org/content/dam/mdanderson/documents/education-training/project-echo/Palliative_CEA_Opioid-Induced%20Neurotoxicity.pdf


Morphine
Hydromorphone
10%
> 50%
M6G
- analgesic
M3G
H3G
3-glucuronide metabolites
- no analgesic effects
- potent neuroexcitants (10x parent opioid)
- CSF level 2x parent opioid in chronic dosing

Pathophysiology of Opioid Induced Neurotoxicity

- ↑ **accumulation of parent opioid and its metabolites** with high opioid doses or decreased excretion
- Metabolites may cause toxicity via **non mu-receptor actions**
- Neuroexcitation by **phenanthrene metabolites** (e.g. morphine-3 and -6 glucuronide)
- **NMDA receptor** activation by opioids
- **Release of neurotransmitters** (spinal dynorphin, substance P, nociceptin)

Inter-individual Variability and side effects

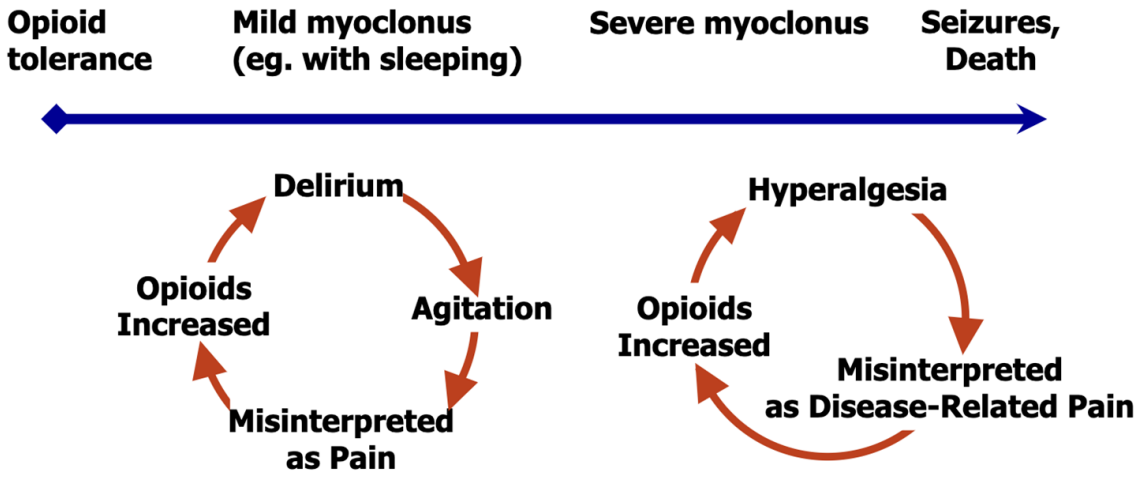
- **Several opioid receptor subtypes** -> Mu-receptor has many (~7) subtypes
- Subtle differences between opioids in **binding t**o these various subtypes
- **Genetic differences** between pts in receptor sensitivity
- **Trials of several opioids** are often needed before finding one that provides an acceptable balance of analgesia and tolerability for an individual patient.

Approach to Diagnosis of OIN

Consider if the any of the following are present receiving ANY opiod:

- At least 2 **opioid dose escalations**
- No improvement in pain or **worsened pain**
- **Volume depletion** or **renal insufficiency**
- Hyperesthesia, allodynia or **hyperalgesia**
- **Delirium** (somnolence, agitation, hallucinations)
- Multifocal **Myoclonus**
- Seizures
- Confirm diagnosis on **improvement with treatment by 36 h**

Spectrum of OIN

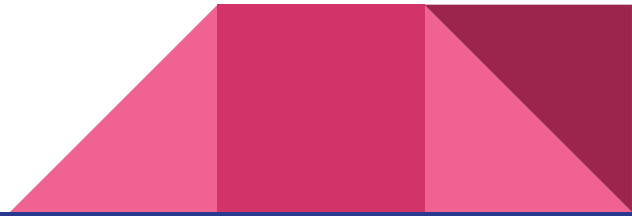


John Mulder, MD “Opioid Induced Neurotoxicity”
https://slideplayer.com/slide/6426794/

Management of Opioid Induced Neurotoxicity

Treatment

- **Elimination/ reduction of metabolites**
- **Symptomatic** management of OIN features
- **Management of Pain** in presence of OIN



Management of Opioid Induced Neurotoxicity

Rotate or Reduce the Opioid

- **Stop** current opioid, start another low risk opioid at 25%-50% MEDD or
- **Reduce** current opioid to 25%-50% MEDD

If able, consider

Methadone (NMDA-R antagonist) or Fentanyl

- No active metabolites
- Non-phenanthrene

Remove the metabolites

- Aggressive hydration
- Hemodialysis?; studies show most efficacy in meperidine induced

Prevention!Reverse any predisposing or potentiating factors

- Evaluate and **treat risk factors**
  - (i.e can they maintain hydration?, small bowel obstruction)
  - Underlying renal and liver function?
  - underlying brain disease, sepsis, or hypoxia
  - Is patient on sedating medication
- Initiate and **titrate opioids cautiously**
- Frequent **Re-assessment** for analgesic and adverse effects of opioids

Calm the CNS (depending on severity)

- Benzodiazepines; caution with respiratory depressant effects
- Stop other neurotoxic medications
- Consider haloperidol

Continue to treat pain (with different or reduced opioid and consider) opioid sparing adjuvants

- NSAIDS
- Steroids
- Ketamine
- Lidocaine
- Gabapentin
- nerve blocks

What NOT to Do

Reverse analgesic activity. NO NALOXONE. May precipitate pain crisis

Forget to treat the pain. Avoid withdrawal; taper if mild sx

When opioid switching for OIN, be wary of the **usual conversion ratios** as escalating opioid doses caused the problem in the first place, and hyperalgesia should be considered as a side effect of the drug and not as the **actual pain**

Treatment of Specific OIN Symptoms: **MYOCLONUS**

If mild:

- -Opioid reduction/ rotation if myoclonus more frequent, or if associated with other features of OIN

If severe/frequent:

- If despite reduction/ rotation; can use: **Baclofen, clonazepam**

Treatment of Specific OIN Symptoms:
SEVERE DELIRIUM

Neuroleptics:
Haloperidol most commonly used for agitation or mixed delirium

Atypical antipsychotics, such as olanzapine, risperidone, and quetiapine have been used for delirium

Chlorpromazine if above not options/refractory; frequently causes hypotension

Increased pain with increased use?
- Opioid Induced Hyperalgesia

-Morphine first isolated in 1804 from opium, use really started in 1850 after hypodermic syringe invented

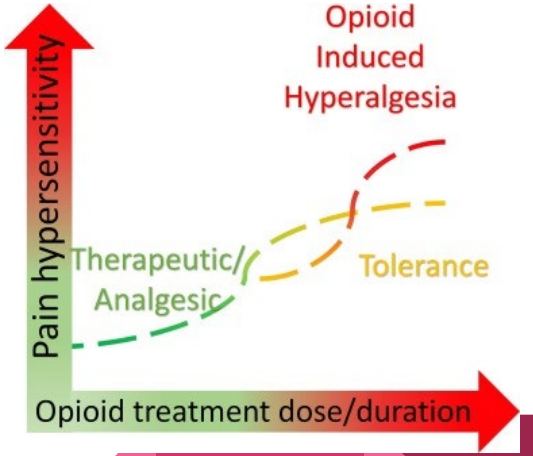
-Albutt in **1870.** Albutt described that,

"At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil."

It was questioned that, ***"Does morphia tend to encourage the very pain it pretends to relieve? "***

Opioid Induced Hyperalgesia

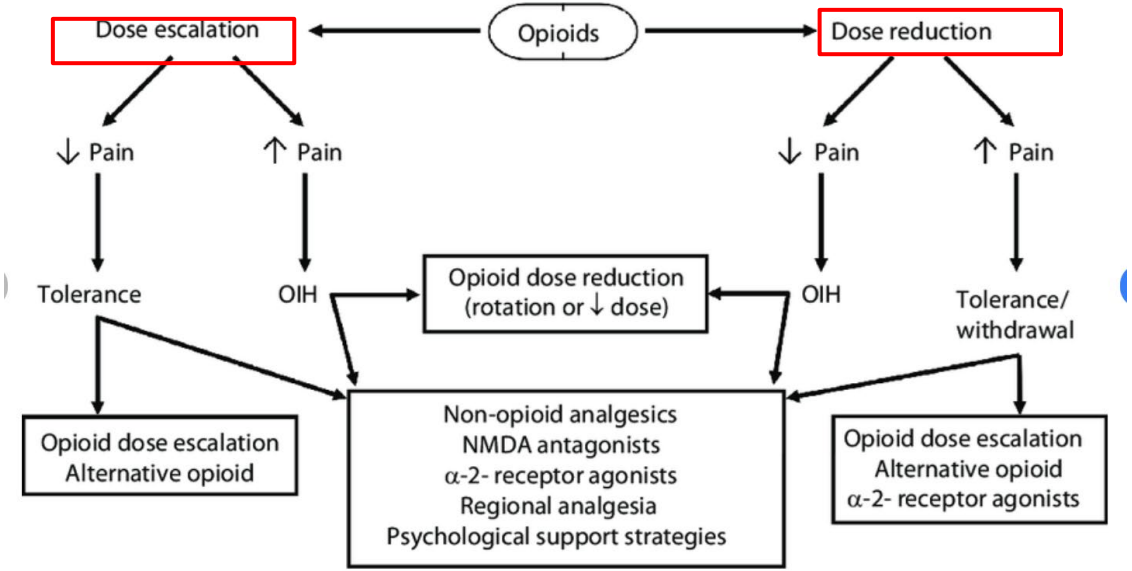
- Opioids **paradoxically increase pain**
- Experience **Allodynia:** Painful response to a stimulus that is normally not painful (such as light touch)
- **Hyperalgesia:** Severe pain response to a stimulus that normally produces only mild pain response.
  - **More severe than pre-existing pain**
  - More **diffuse**
  - extends to **other areas of distribution** from the preexisting pain.
  - **less defined** in quality “all over”
  - Gets **worse with increasing** the opioid dose



Mechanism of action

- similar to OIN with increased expression and sensitization of NMDA receptors

Opioid Tolerance vs Hyperalgesia



Giving less= more pain=tolerance

Giving less= less pain= OIH

Wilson, Sylvia & Hellman, Kevin & James, Dominika & Adler, Adam & Chandrakantan, Arvind. (2021). Mechanisms, Diagnosis, Prevention and Management of Perioperative Opioid-Induced Hyperalgesia. Pain Management. 11. 10.2217/pmt-2020-0105.

Why Are We Seeing More Opioid Induced Neurotoxicity?

There has been a dramatic increase in morphine consumption worldwide (**3x increase** in morphine from 1986)

There has also been an increase in **reports and awareness of neuroexcitatory side effects** (allodynia, hyperalgesia, myoclonus, seizures) of morphine and hydromorphone.

As we succeed in **educating** and encouraging health care providers to be aggressive in pain management, we can expect to see more opioid- induced neurotoxicity

SUMMARY

All opioids have potential of side-effects

- Screen regularly for side-effects, including OIN

Recognize the syndrome of Opioid Induced Neurotoxicity

- Myoclonus, Agitation Confusion
- Pain “everywhere” not relieved/ exacerbated by opioids- OIH

Recognize risk factors for OIN

- High opioid dose, rapid escalation of opioid
- Underlying renal, liver and brain impairments
- Dehydration , Sepsis

Treatment:

- Opioid rotation, treatment of contributing factors, hydration
- Opioid reduction if none of above possible.

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