

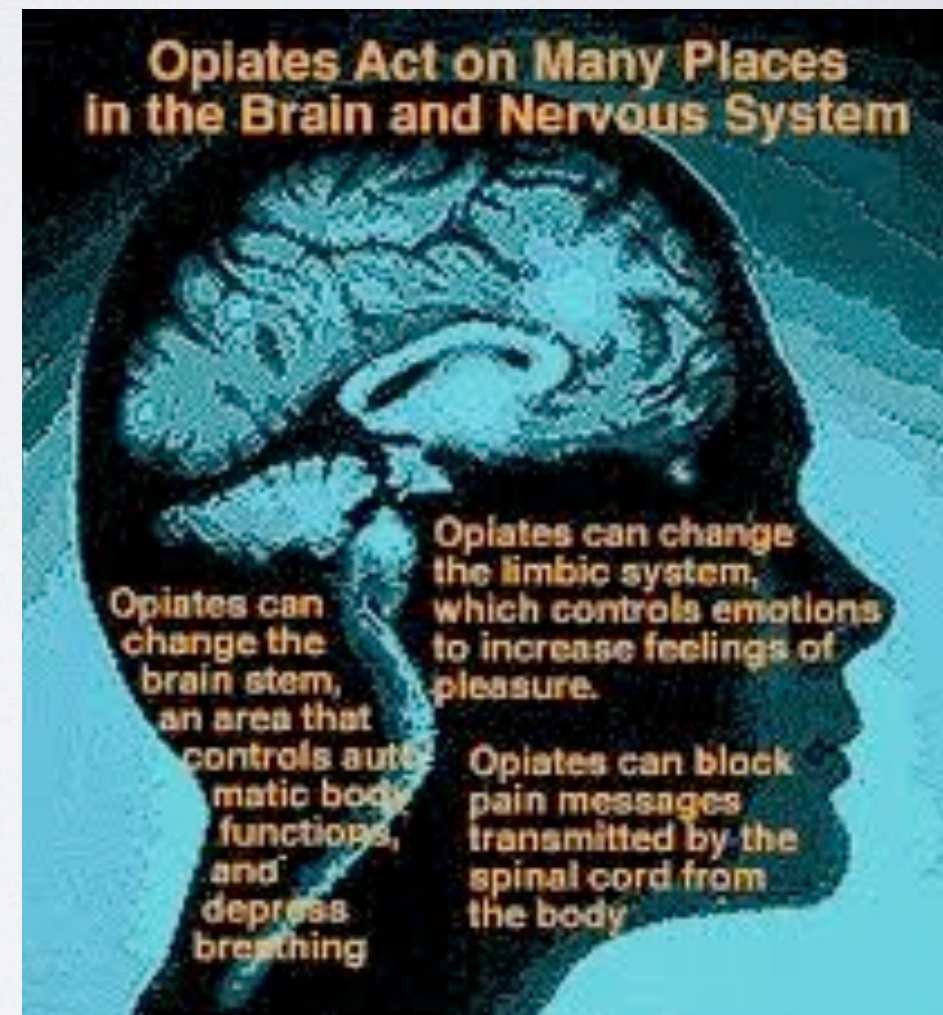


OPIOID NEUROTOXICITY - BACK TO BASICS

Dr. Suzy Pinnick (PGY-3): Palliative Medicine Fellow

OBJECTIVES

- Some Cases
- Definitions: Including what is opioid neurotoxicity
- A bit of biochemistry
- What patients are at risk of neurotoxicity
- Treatment of Opioid Neurotoxicity



OPIOID INDUCED NEUROTOXICITY (DEFINITION)

- Opioid Induced Neurotoxicity (OIN): Is a group of adverse central nervous symptoms that are due opioids.
- Mechanism unclear - however symptoms of OIN thought to be due to the metabolites of various opioids

CASE 1 (OKON & GEORGE, 2008)

JOURNAL OF PAIN AND SYMPTOM MANAGEMENT

- 76 y/o caucasian female with “locally advanced metastatic leiomyosarcoma of the uterus”
- Case was referred to the palliative care unit from an outside facility. Pt had intractable cancer pain and history of iatrogenic opioid excess.
- Before heading to palliative care: Pt on tramadol 50mg q6hrs prn. This was stopped by the facility and started on PCA morphine 1mg/hr. demand doses of 2mg q10min prn.
- Day 4 unit d/c PCA and placed pt on fentanyl patch of 100 ug/hr. That same day developed fever of 101 F and became hypotensive. Bld cultures done which grew Methicillin susceptible Staphy. Aureus (MSSA)
- Bacteremia thought to be from the neurotic pelvic tumour mass or pneumonia.

CASE 1: CONTINUED

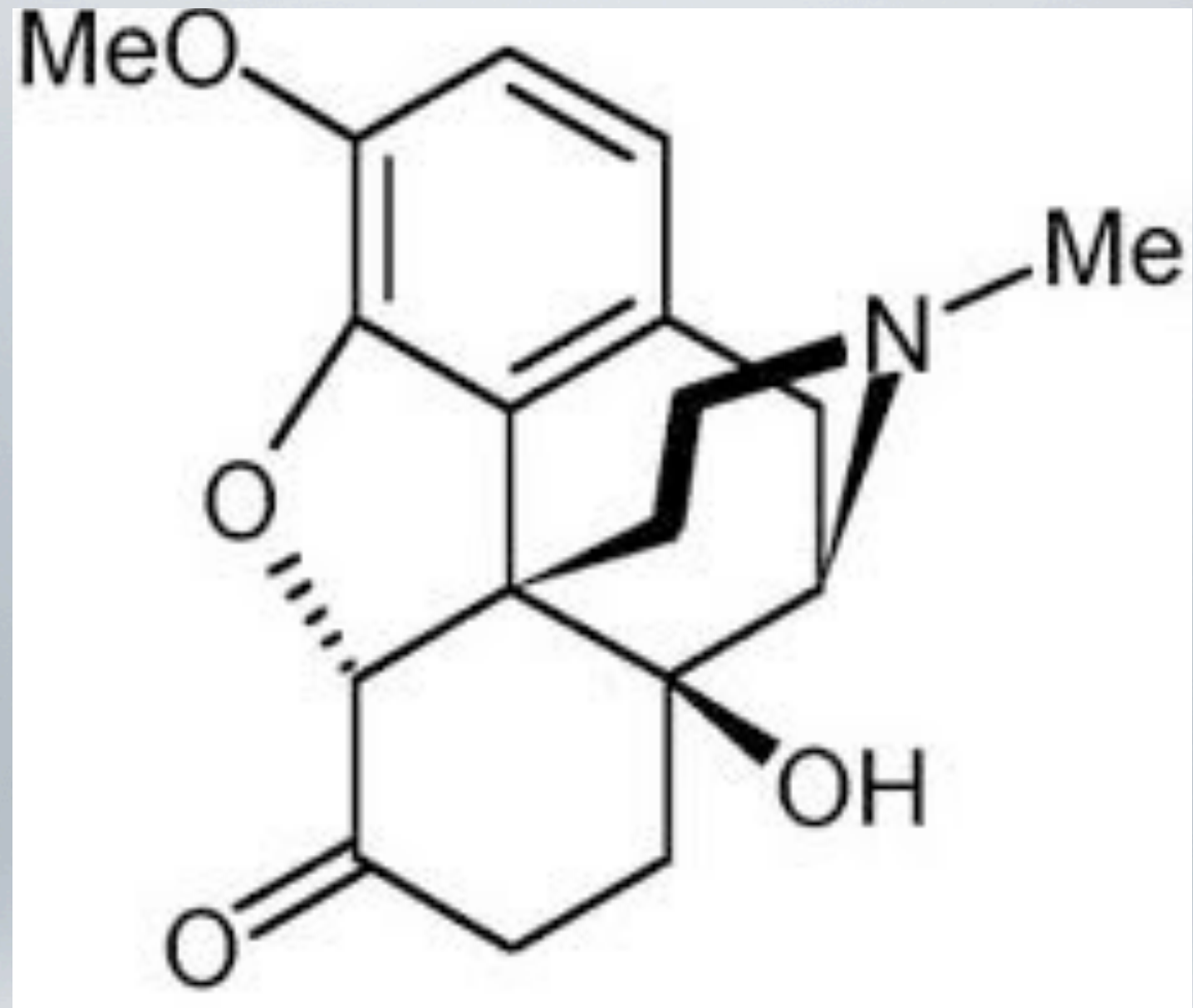
- Pain inadequately controlled so transdermal patch was increased to 200 ug on day 5. Gabapentin was at 300 mg TID. Pt became somnolent and bradypnea (RR8) Naloxone given. Patch decreased to 100 ug/hr.
- Pt now having severe pain. Transferred on 11th day to a hospital. No hallucinations, resp. depression, or sedation seen. Pt stated pain 8/10. Patch removed PCA 25 mcg/hr basal rate with 25 ug q15 mins. Acetaminophen 650 mg QID added. Pain remained unchanged over 24 hrs. CT scan done showing tumour involving majority of iliac bone pushing on sacral plexus and left sciatic nerve.
- Palliative care consulted on 2nd day of hospitalization. Patient on exam showed guarding behaviour and pushed physicians hand away, was hallucinating, agitated. Haldol 2mg given IV and Ketorolac 30mg.
- Pain severe, 2 consecutive 100 ug fentanyl boluses given. Pt did get comfortable so started on 60

CASE 1

- Good for 90 mins then started showing myoclonus and animated conversations with self. Fentanyl infusion stopped. Alertness improved and she reported no pain. PCA restarted at 33% reduction. She was somnolent next day reduced by another 25%. No improvement in cognition and so stopped.
- Started on PCA of 25 ug q 15 mins prn. 6th day switched to tramadol 50 mg qid staggered with hydrocodone/acetaminophen 5-500 mg qid. Scheduled olanzapine and gabapentin. Good pain control. Discharged and died 10 months later.

DEFINITIONS

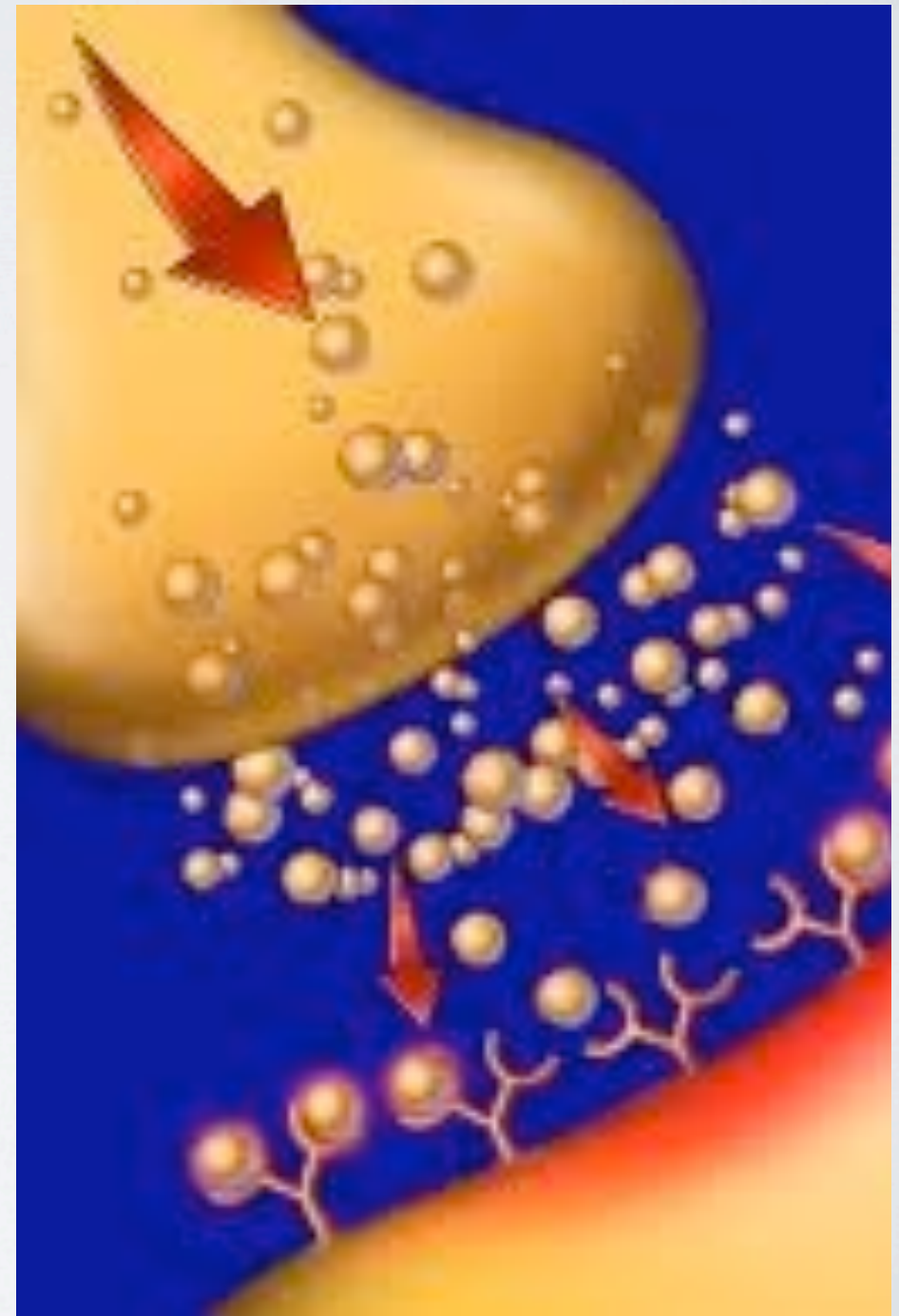
- Hyperalgesia: An excessive sensitivity to pain (usually that is already present).
- Allodynia: The condition of in which an ordinarily painless (non-noxious) sensation is experienced as being painful (noxious).
- Myoclonus: Twitching or clonic spasm of a muscle or group of muscles.
 - can be seen in any muscle groups/ limbs
 - can be mild and sporadic vs severe and continuous



A LITTLE BIOCHEMISTRY

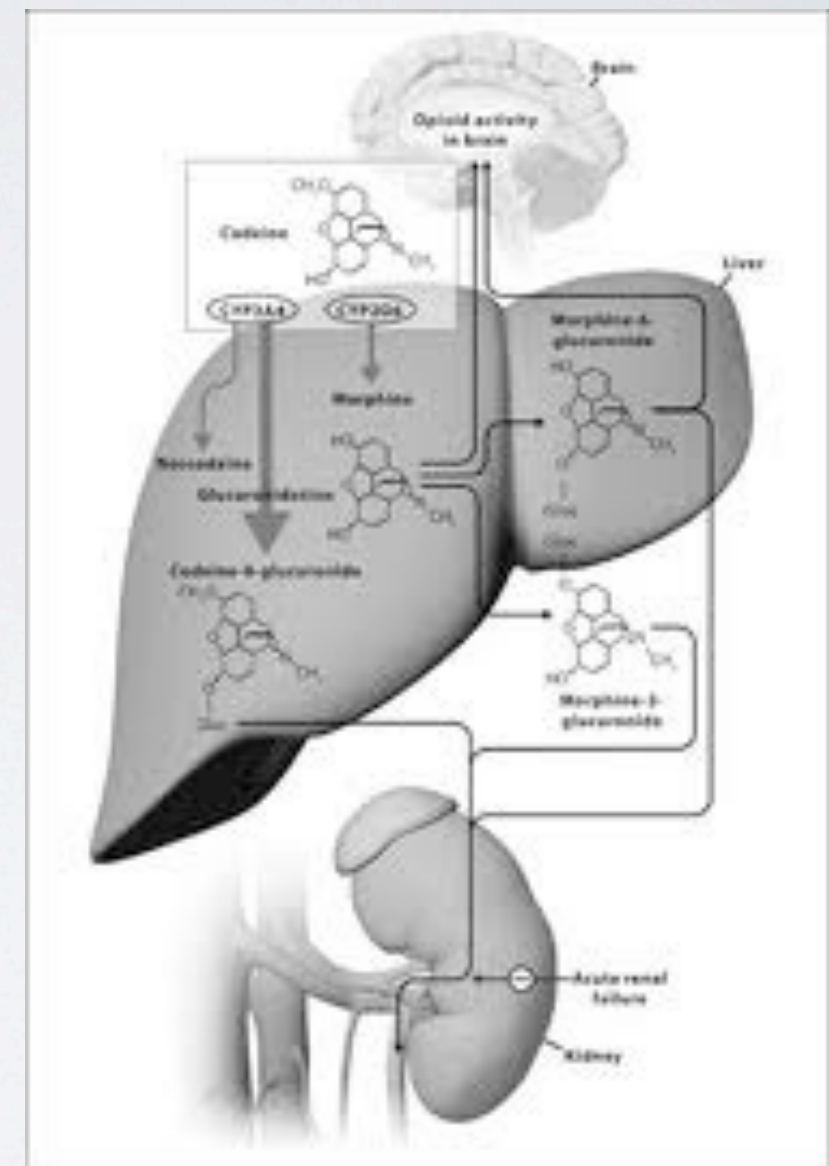
PHARMOKINETICS

- volume of distribution of opioids
- wide variability of protein binding for example methadone is 89% and 7.1% in hydrocodone
- metabolized by liver into the active metabolites



MORPHINE METABOLITES

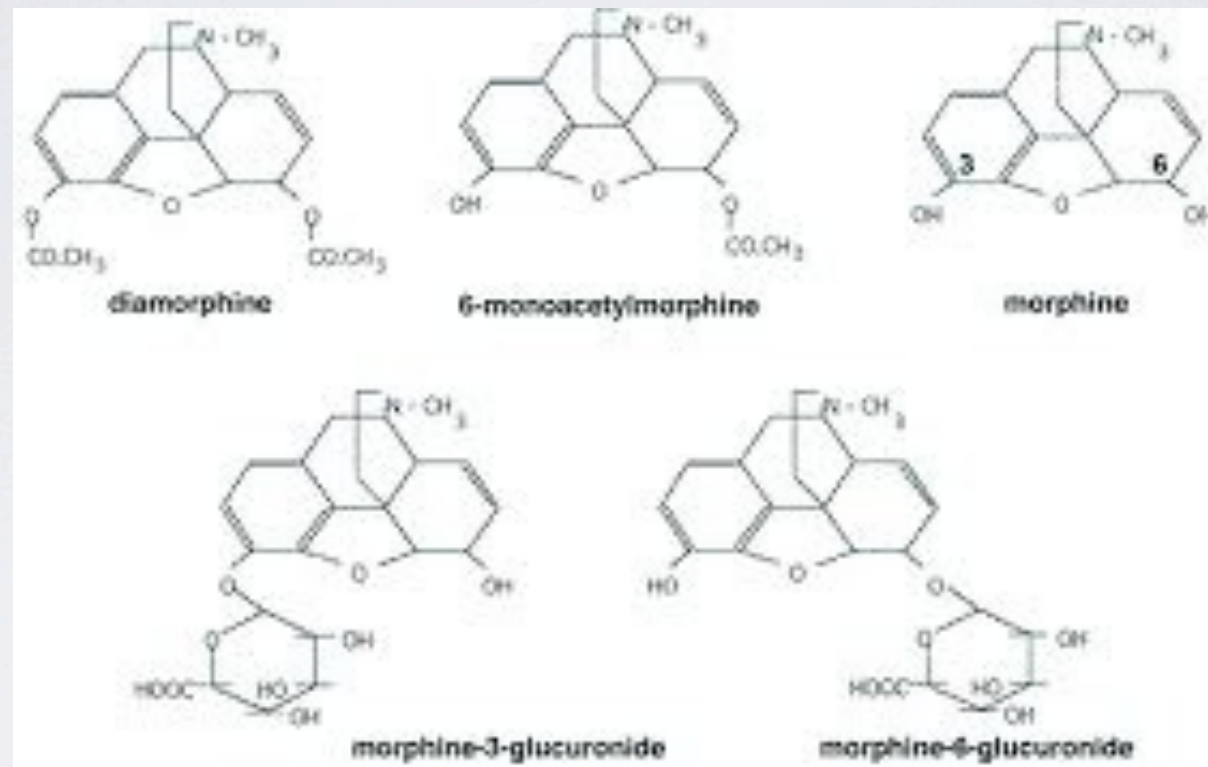
- Morphine is formed into glucuronides
- Enzyme uridine diphosphoglucuronic glucuronyl transfereases (UDPGT)
- This enzyme is found in kidney, liver, intestines.



MORPHINE METABOLITES

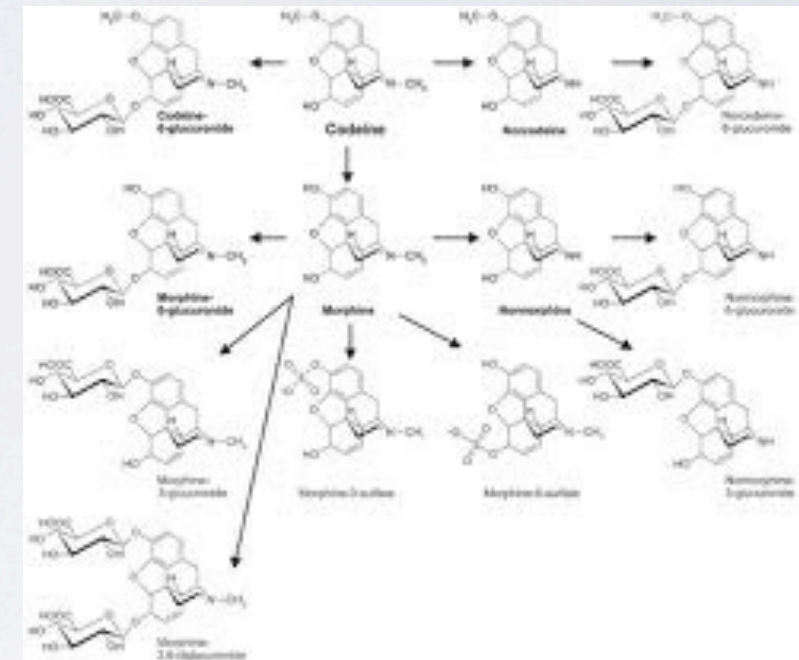
- Morphine is metabolized into morphine-6-glucuronide and morphine-3-glucuronide
- Morphine glucuronides are very water soluble and are excreted in urine.
- Morphine-3-glucuronide thought to have no analgesic activity however stimulates the CNS through non-opioid receptors. Thought to be linked to adverse side-effects of morphine.
- M6G is a more selective for mu receptors

MORPHINE METABOLITES



OTHER OPIOID METABOLITES

- Hydromorphone is converted to hydromorphone-3-glucuronide
- Fentanyl-is converted to norfentanyl (inactive metabolite)
- B2 adrenergic receptor ADRB2 gene has been associated with developing OIN such as allodynia



RECEPTORS AND EFFECTS

- Opioids bind to 3 major receptors which are mu, delta, and kappa
- Under each of these receptors there are sub-types of these receptors
- $\mu 1$: supraspinal analgesia, peripheral analgesia, sedation, euphoria
- $\mu 2$: respiratory depression, g.i. dysmotility, bradycardia

SYMPTOMS AND SIGNS OF OIN

- OIN can start within 3-5 days of starting an opioid
- sedation
- hallucinations (usually visual)
- confusion/cognitive impairment
- agitation
- myoclonus
- hyperalgesia/allodynia

SIGNS AND SYMPTOMS OF OIN

- can have a side-effect that can occur on it's own
- can have two symptoms occurring at the same time

CASE 2 ROMAYNE GALLAGHER: (CANADIAN FAMILY PHYSICIAN, 2007)

- George 82 y/o m. severe COPD: Patient became short of breath with eating, talking, very little movement.
- Used continuous oxygen via concentrator, and was on maximum doses of bronchodilators.
- Co-morbidities included congestive heart failure, renal impairment (35ml/min)
- He had no cognitive impairment and enjoyed visits with his daughter and grandchildren.

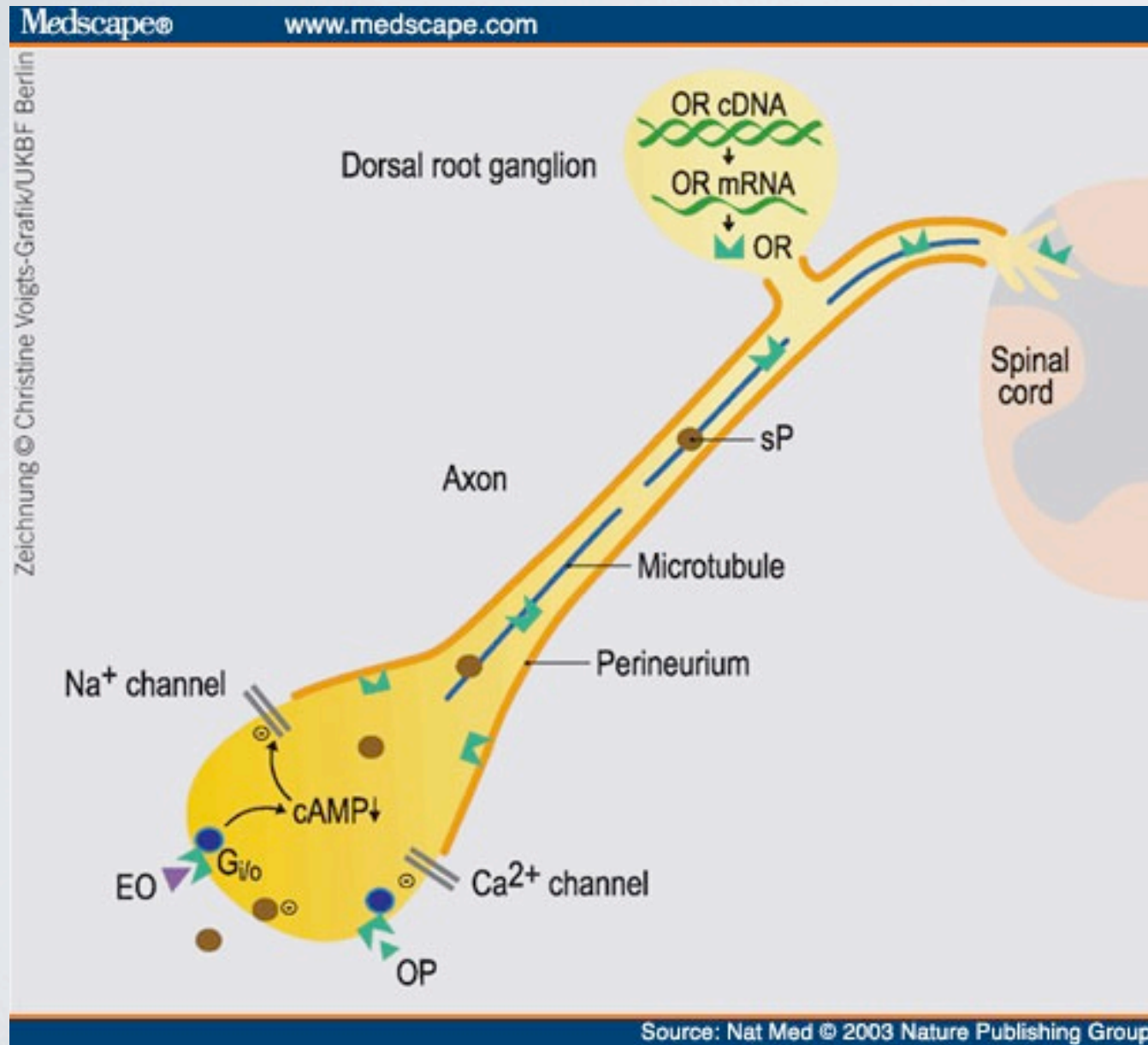
CASE 2 (CONTINUED)

- George was started on morphine 2.5mg q4hrs to help with dyspnea. This was effective and patient was increased to 7.5mg q4hrs.
- Over 3 wks dyspnea stabilized and he was placed on long-acting morphine 20mg q12hrs.
- 2wks later develops increased confusion, not eating, vomited.
- vitals: 38.1 c, 140/90, 92% on 3litres, 92bpm.
- c/o dysuria the day before.

CASE 2

- sent to ER, sepsis diagnosed and treated. Hospital stopped opioid as it was seen as cause of confusion. Pt placed on loxapine which helped a bit.
- Returned to his home, and the RNs notice he is very short of breath and confused. Physician called but due to opioids being stopped at the hospital they were not restarted.
- Pt had oxygen increased to 4 litres and ordered more loxapine.
- Shortness of Breath continued, lorazepam ordered q8hrs (increased somnolence, and confusion). Reduced anxiety and dyspnea.
- George died several days later

WHO IS AT RISK OF OIN



- Renal impairment
- long-term opioid therapy at high doses (relative term)
- Increased Age
- Dehydration
- Concurrent treatment with other drugs
- Rapidly escalating doses

HYDROMORPHONE NEUROTOXICITY

DR. D.THWAITES, DR. S. MCCANN, DR. P. BRODERICK

- in the journal of palliative medicine, 2004
- retrospective chart review on 48 palliative patient from a hospice. Patients received continuous parenteral hydromorphone (cph)for pain control.
- had three symptom parameters: seizures, agitation, myoclonus
- Goal was to “determine the incidence of agitation, myoclonus, and seizures in palliative hospice patients on cph”

THWAITES ET AL.

- looked at the relationship of these symptoms to duration of and/or maximal basal dose.
- 4 patients had seizures (no known brain mets): Note no seizures seen in pts on cph less than 15 days, and basal rate under 20mg/hr
- if kept below 20mg/hr 18% had agitation, 3% had myoclonus.
- Pts on min. 20mg/hr and at greater than 15 days agitation was 50%, and 60% myoclonus.

DIFFERENTIAL DIAGNOSIS

- hypoglycemia
- electrolyte imbalances
- hypothyroidism
- encephalopathy
- brain mets
- infections

TREATMENTS OF OIN

- determine other causes of delirium, seizures, etc.
- rehydration: especially when pt was on morphine or hydromorphone
- if neurotoxicity is “mild” can reduce the dose of opioid without rotating it
- rotate the opioid and reduce the dose 20-30%
- reduce opioid dose and add an adjuvant

TREATMENTS CONTINUED

- treat the toxicity symptomatically: For example delirium can use haldol.
- Switch the route of the opioid
- Naloxone not recommended for neurotoxicity

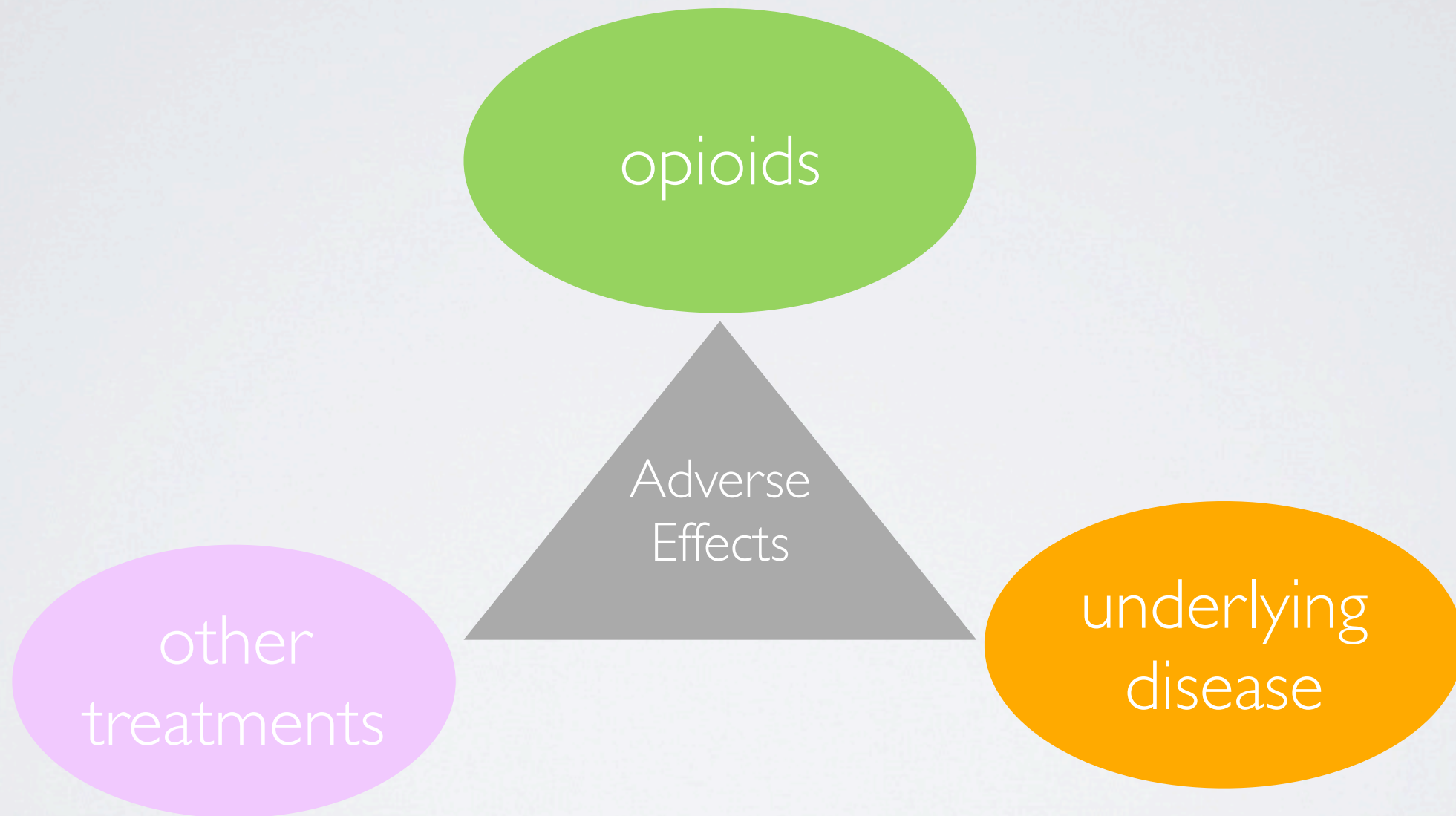
SOME ADJUVANT THERAPIES

- NSAIDS
- alpha 2 agonist: clonidine
- ketamine: NMDA
- TCAs
- Gabapentin/pregabalin
- carbamazepine
- benzodiazapines

OVER-DOSING VS NEUROTOXICITY

- Over-dosing: respiratory depression, pinpoint pupils, decreased mental status difficulty arousing, decreased bowel sounds.
- In over-dosing treatment with naloxone if severe respiratory depression or a dose reduction. Opioid neurotoxicity is managed via reducing dose/ switching opioid. As well OIN improves with hydration.
- mild overdosing (respiratory rate >8 /min) reduction in dose. Severe overdosing (respiratory rate <8 /min) treat with naloxone. 0.02-0.04 mg IV/ subcut.

WHICH IS IT?



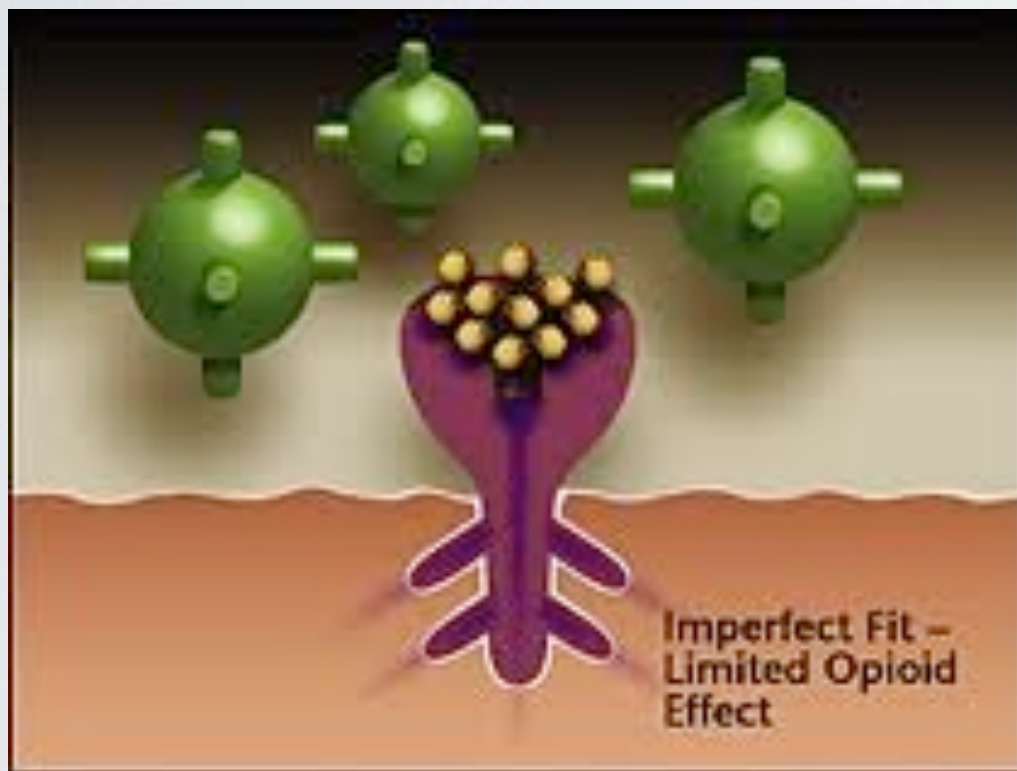
WHAT IT COMES DOWN

- do a history and physical exam. Might need to do a mmse, looking at any new changes.
- don't ignore subtle clues: "a little off"
- Look at what has happened over the past 2 days.
- After doing a focused history and physical: if appropriate to goals of care do investigations.

IMPORTANT THINGS TO REMEMBER

- just because you rotated from an opioid due to toxicity does not mean this opioid is permanently inappropriate for this patient.
- no specific dose triggers neurotoxicity
- more complex pain spectrum may lead to more adverse effects.
- renal impairment: may increase the interval, reduce dose, or use an opioid less prone to metabolite build-up.

GOAL OF CARE



SUMMARY

- OIN is a collection of symptoms associated with “toxic” levels of an opioid.
- Some of these symptoms include: confusion, myoclonus, hyperalgesia, allodynia, agitation, sedation.
- Factors that cause a person to be more vulnerable to OIN are: renal impairment, dehydration, age, rapid escalation of opioid, or drug interactions.
- One way to differentiate is when cancer pain escalates rapidly without catastrophic disease progression consider OIN
- Reducing dose of opioid, rotating the opioid, hydrating patient, using a benzo. to help with the myoclonus, or using haldol to settle the hallucinations.
- Doing a good focused history and physical performed serially will help for diagnosis.

QUESTIONS?

Opioid Induced Neurotoxicity

