



End-of-Life Pain Management: How to do it right

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Objectives

- Discuss the rational use of opioid medications, including dosing and dose titration, routes of administration, and the use of long-acting vs. short acting preparations.
- Determine a dosing strategy of methadone and morphine in opioid naïve patients.
- Discuss the conversion of one opioid regimen to another with the use of opioid conversion tables.



Like most veterinary students, Doreen breezes through chapter 9.

What is pain?

“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”

- International Association for the Study of Pain

pain (n.)

- late 13c., "punishment," especially for a crime; also "condition one feels when hurt, opposite of pleasure,"
- from Old French peine "difficulty, woe, suffering, punishment, Hell's torments" (11c.),
- from Latin poena "punishment, penalty, retribution, indemnification" (in Late Latin also "torment, hardship, suffering"),
- from Greek poine "retribution, penalty, quit-money for spilled blood,"
- from PIE *kwei- "to pay, atone, compensate" (see penal). The earliest sense in English survives in phrase on pain of death.

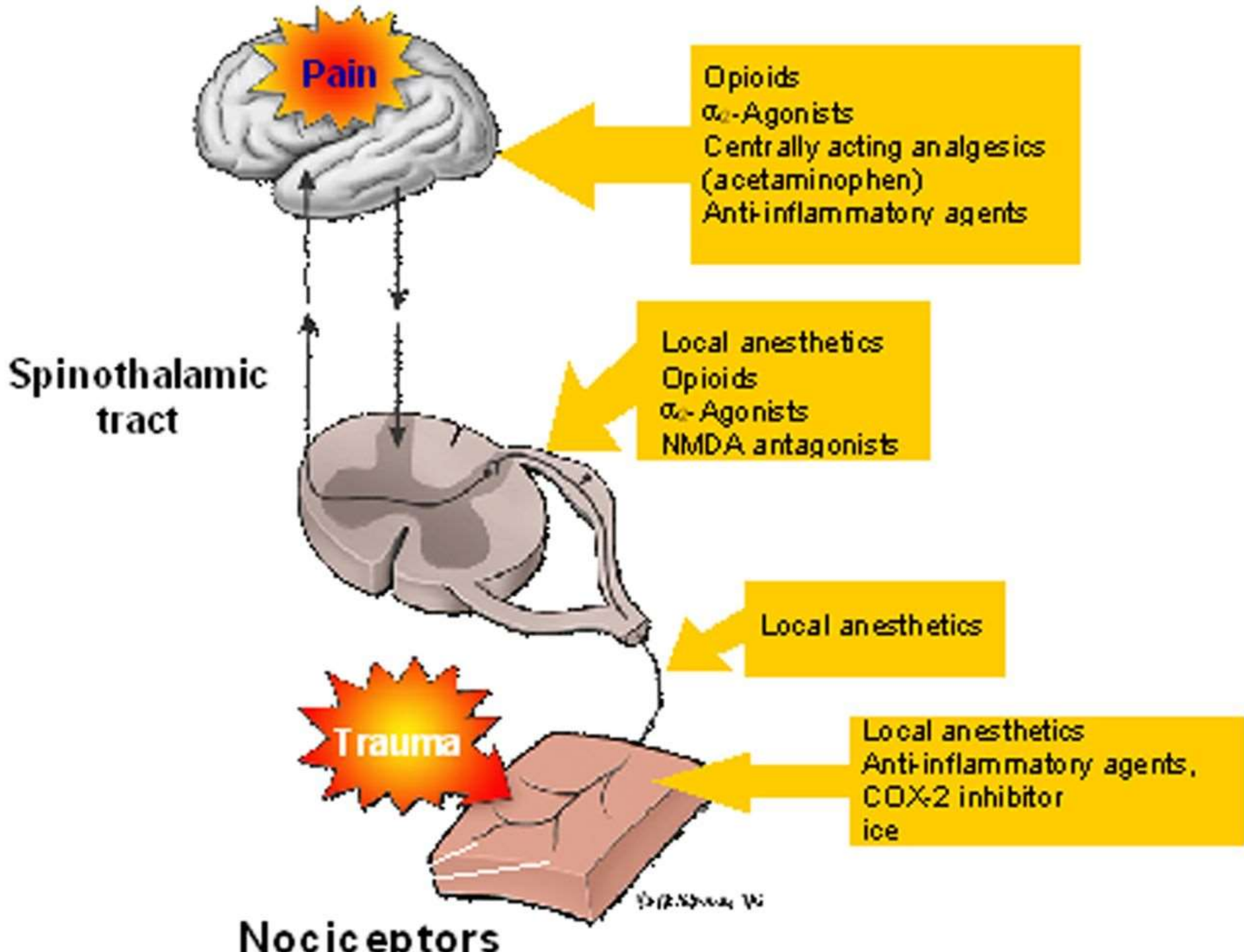
- Online Etymology Dictionary

Total Pain – Dame Cicely Saunders

“Total pain is the suffering that encompasses all of a person’s physical, psychological, social, spiritual, and practical struggles.”

Treatment of Pain

- So the treatment of the total pain and suffering that a patient is experiencing will include not only medications but other modalities as well such as emotional and spiritual support and counseling.
- I will focus today on treatment with medications.
- I will focus mostly on opioids, along with some other adjuvant medications.



Pain

Opioids
 α_2 -Agonists
Centrally acting analgesics (acetaminophen)
Anti-inflammatory agents

Spinothalamic tract

Local anesthetics
Opioids
 α_2 -Agonists
NMDA antagonists

Local anesthetics

Trauma

Local anesthetics
Anti-inflammatory agents, COX-2 inhibitor
ice

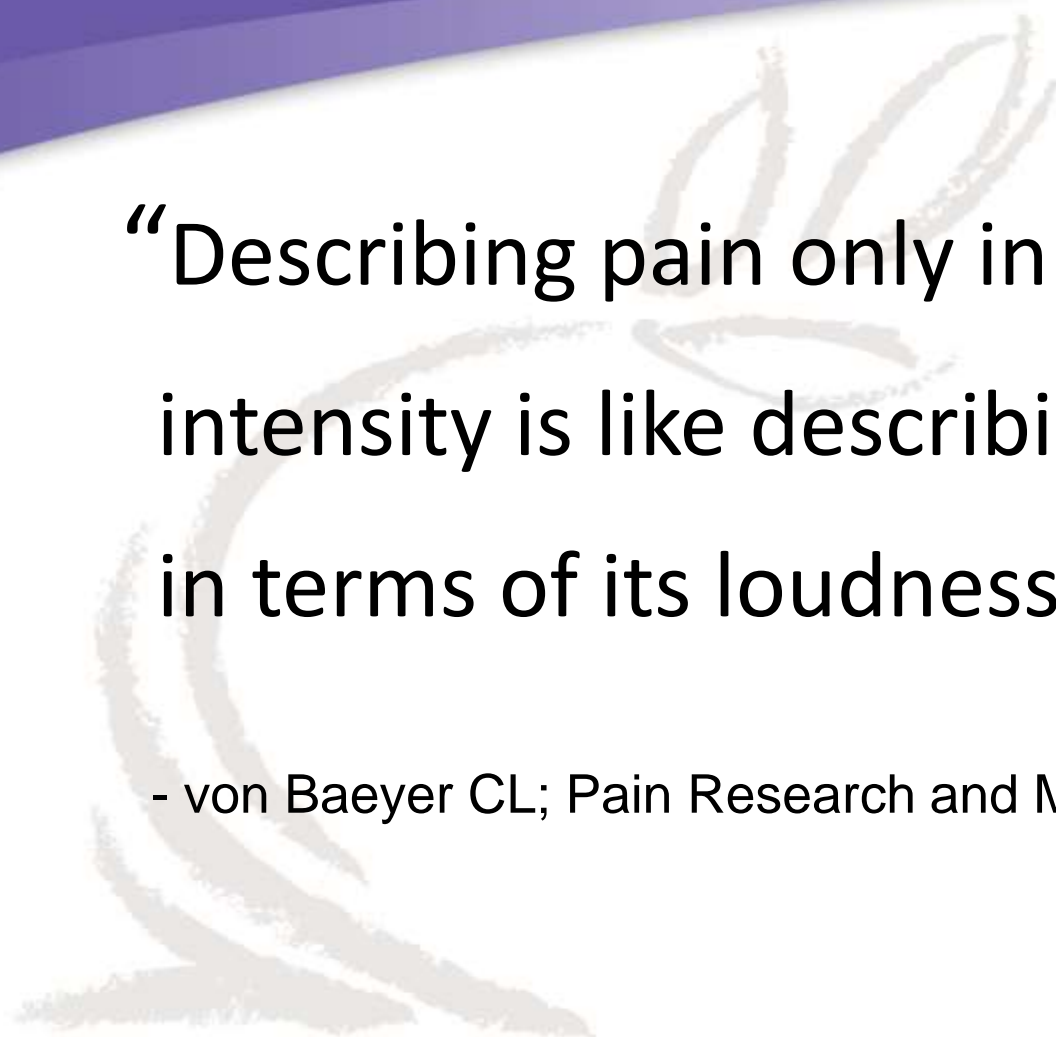
Nociceptors

Case #1 - AB

- AB is a 72 y/o previously healthy woman who presented to the hospital with abdominal pain and was found to have metastatic pancreas CA, stage IV. She declines any further disease directed therapies and is admitting to hospice at home.
- She is complaining of continued pain. She was discharged from the hospital on hydrocodone/acetaminophen 5/325 QID prn.

Pain Assessment

- Description: severity, quality, location, temporal features, frequency, aggravating & alleviating factors
- Previous history
- Context: social, cultural, emotional, spiritual factors
- Meaning
- Interventions: what has been tried?



“Describing pain only in terms of its intensity is like describing music only in terms of its loudness.”

- von Baeyer CL; Pain Research and Management 11(3) 2006; p.157-16

Case #1 - continued

- AB complains of a dull, achy sensation in her upper abdomen, radiating to the back. She rates it at 4/10 most of the time, at times it increases to 8/10.
- It is worse about 30 minutes after eating, and gets much worse at night when she tries to go to sleep.
- She is also having some left shoulder pain, achy with movement, chronic due to old rotator cuff tear.

Case #1 - continued

- She is not sleeping well because of the pain. She awakens at night and is unable to get comfortable enough to get back to sleep.
- She is worried about what she will do as her disease progresses. She is widowed and lives alone, her children have successful careers and live out of town.
- Her husband died of cancer after 4 years of treatment, while on a ventilator in ICU for 7 days.

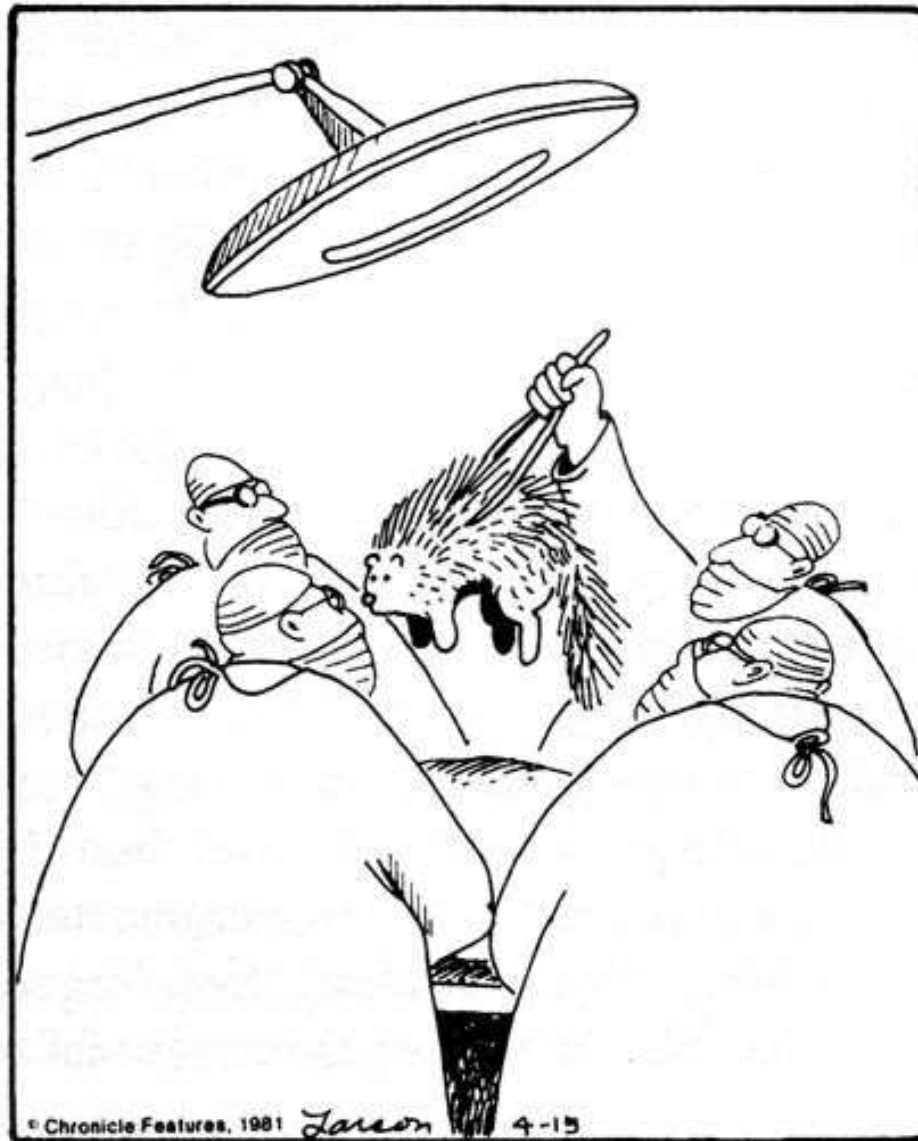
Case #1 - continued

- She does not want to try any stronger medications. Her husband died shortly after morphine was started for his comfort. She is worried about being “hooked on drugs,” and is also worried about the side effects that might keep her from being able to live alone and care for herself.

So where do we start?

THE FAR SIDE

By GARY LARSON



"Well, I guess that explains the abdominal pains."

Total Pain

- She obviously has some other issues that are contributing to her total suffering and those need to be addressed as well.
- This requires the involvement of the whole team, including the social worker and chaplain, to help the patient with her psychosocial, spiritual/existential, and practical needs.

Physical pain

- What is the cause of her pain?
- What can we do to treat it?
- How do we start the opioid?
- How do we monitor the effectiveness of the opioid?
- How do we monitor the side effects of our medications?

Types of Physical Pain

- Nociceptive
 - Somatic – sharp, localized, gnawing, aching, throbbing
 - Visceral – dull, poorly localized, cramping, pressure, squeezing, nauseous
- Neuropathic
 - Burning, tingling, electric, numb, stabbing, itching

Types of Physical Pain

- Why does the type of pain matter?
- Because that will determine which medication may work the best for this patient at this time.
- Our goal is to give the right medication at the right dose at the right time using the right delivery method.

Types of Physical Pain

- Nociceptive
 - Somatic – sharp, localized, gnawing, aching, throbbing – **Opioids, NSAIDs**
 - Visceral – dull, poorly localized, cramping, pressure, squeezing, nauseous – **Opioids, NSAIDs, gabapentin**
- Neuropathic
 - Burning, tingling, electric, numb, stabbing, itching
 - **gabapentin, duloxetine**

Opioid Initiation Dosing

(Opioid naïve patients)

- Morphine sulfate (oral)
 - 2.5-5mg every 4 hours prn
- Hydromorphone (oral)
 - 1-2mg every 3-4 hours prn
- Oxycodone (oral)
 - 2.5-5 mg every 4 hours prn
- Methadone (oral)
 - 2.5-5 mg every 8-12 hours prn

Opioid Initiation Acute Pain Crisis

- Cleveland Clinic protocol: To be given in a supervised inpatient setting, by physician or licensed independent practitioner:
 - Morphine 1mg IV every minute for 10 minutes, followed by 5 minute break, repeat for up to 30 mg total
 - May use fentanyl 20mcg IV or hydromorphone 0.2mg IV

Opioid Initiation Acute Pain Crisis

- Subcutaneous
 - Morphine 2mg every 5 minutes, fentanyl 40mcg or hydromorphone 0.4mg, same protocol
- Oral
 - Morphine 5mg every 30 minutes, or hydromorphone 1mg or oxycodone 5mg

Opioid Initiation - Acute Pain Crisis

Chaplaincy Hospice Care

- Look for causes of acute pain episode
 - Delirium
 - Fall or other injury
 - Constipation
 - Psychological, social or spiritual pain
- If not on routine opioids
 - Start with 5-10 mg of oral or rectal morphine. Repeat dose in 20 - 30 minutes as needed, if no control of pain after 3 doses then double dose. Continue to double dose every 3 doses.
 - If morphine intolerance in past, can use 5-10 mg of oxycodone or 2 mg of hydromorphone
- If on routine opioids
 - Use usual rescue dose or double dose, repeat in 20 minutes as needed, doubling dose every 3 doses.
- If no effect of oral dosing, consider rectal or IV/SQ dosing.

Opioid Initiation Acute Pain Crisis

- Administer above regimens “until pain is controlled”
 - That would be a 2-4 point drop in pain rating, not complete pain relief.
 - If medication is given until complete pain relief then the patient will be over-medicated when the drugs reach their peak levels.

Opioid Side Effects

- Common
 - Constipation, dry mouth, nausea, vomiting, sedation, sweating
- Less common
 - Respiratory depression, bad dreams, hallucinations, dysphoria, delirium, myoclonus, seizures, pruritus, urticaria, urinary retention, amenorrhea, sexual dysfunction

Case #1 - continued

- So what kind of pain is she having?
 - Deep abdominal pain, likely due to pancreas tumor, visceral type of pain. This likely would respond to opioids
 - The right shoulder pain would be somatic type of pain. This likely would respond to NSAIDs and opioids.

Case #1 - continued

- So we start AB on morphine IR, 5 mg every 2-3 hours as needed, after discussion of the risks and benefits, and discussed her concerns of addiction.
- We start ibuprofen 400mg tid.
- We also start Senna, 2 tabs daily.
- After a few days, she is taking 5 mg about every 4 hours, averaging 30 mg daily.
- She asks about taking something less frequently.

Monitor your treatment

- Therapeutic effectiveness
 - Pain rating, sleeping, eating, mood
 - Weight, prn use of breakthrough meds
- Potential toxicity
 - Constipation, abdominal pain, nausea and vomiting, sedation, confusion, itching

Case #1 - continued

- So we switch her to Morphine ER 15mg every 12 hours. We tell her to use 5 mg of morphine IR for breakthrough pain every 2-3 hours as needed. She does well for a couple weeks, not needing any morphine IR.
- Three weeks later she begins to use the morphine IR on a regular basis, complaining of pain more frequently. She is taking an extra 20 mg of morphine IR daily on average.

Breakthrough Pain

- Incidental
 - Secondary to an identifiable stimulus
- End-of-dose failure
 - Pain at the end of the dosing interval of a long-acting opioid
- Spontaneous
 - Occurs with no known stimulus

Case #1 - continued

- AB complains of pain that is worsening about 5 o'clock every evening, and pain that is waking her up in the morning. She is taking her Morphine ER at 7am and 7pm.
- She is also noticing increased pain associated with eating, especially when she eats larger meals. It comes on about 30 minutes after eating.

Case #1 - continued

- So she is having both end-of-dose and incidental pain.
- So to treat the end-of-dose pain, we can either increase the dose or the frequency of the long acting preparation.
- In this case we decide to increase the Morphine ER to 15mg every 8 hours.

Case #1 - continued

- For incidental pain, we have several things that we can do, depending on the cause. In this case it is caused by eating larger meals.
 - We could have her take some morphine IR prophylactically when she is planning on eating a larger meal.
 - We could educate her about frequent smaller meals. Maybe she could keep a food diary and see if she can figure out other patterns that she can avoid.

Breakthrough Pain

- Dose of rescue opioid
 - One dose of rescue medication should be about 10-15% of the total daily dose.
 - So in the case of our example, she was taking 15 mg of Morphine ER twice daily, TDD equals 30mg.
 - Breakthrough dose would then be 3-5 mg.
 - After we increased her TDD to 45mg, then the breakthrough dose is 5-7.5mg.
- Make sure to rate pain before and after the rescue dose.

Breakthrough Pain

- For morphine, hydromorphone, oxycodone, the onset of analgesia is 30-40 minutes, duration of analgesia is about 4 hours.
- For methadone, the onset of analgesia is 10-15 minutes and duration of analgesia is 4-8 hours.
- For submucosal fentanyl, the onset of analgesia is 5-10 minutes and duration of analgesia is 1-2 hours. (about \$30/dose)

Opioid Escalation

- Short acting, IR formulations can be safely dose escalated every 2 hours.
- Long acting, ER or SR formulations can be safely dose escalated every 24 hours (not fentanyl TD or methadone.)
- For moderate to severe pain, can increase the TDD by 50-100%
- For mild to moderate pain, can increase the TDD by 25-50%

Opioid Escalation

- For increasing pain, ideally the patient is using increasing doses of breakthrough medication. Use the TDD to increase the long acting preparation.
- For a sudden, severe increase in pain, search for a cause such as fall, pathologic fracture, delirium, infection, constipation, urinary retention, DVT, poor absorption of medication, etc.....

Opioid Rotation

- At times, we may need to change from one opioid to another
 - Current opioid not effective
 - make sure that you have pushed the doses higher and are limited by side effects
 - Side effects are bothersome
 - A different delivery system is needed
 - Patient unable to swallow

Opioid Rotation

- We need to understand how to calculate 2 different numbers:
 - TDD (total daily dose)
 - This is the total amount of the medication actually taken by the patient on a daily basis. May need to use an average number as the breakthrough may vary from day to day.
 - MEDD (morphine equivalent daily dose)
 - This is the TDD put into equivalent morphine doses

Case #1 - continued

- AB is now taking the morphine sulfate LA at 15 mg q8h and is using 5mg of morphine IR for breakthrough dosing about 4 times daily. She is having trouble swallowing the LA preparation and the IR preparation makes her nauseated. She would like to try something different. You decide to try fentanyl TD for long acting with hydromorphone for breakthrough.

Case #1 - continued

- So her TDD is:
 $(15\text{mg} \times 3\text{doses}) + (5\text{mg} \times 4\text{doses}) = 45\text{mg} + 20\text{mg} = 65\text{ mg daily.}$
- Since this is morphine, her MEDD = 65mg daily

Opioid Equianalgesic Dose

- Different doses of two medications that produce the same pain relief
- Dose that produces the same analgesia as a standard dose of morphine (10mg IV or 30 mg po)
- There are different versions of these tables
- The analgesia of different drugs are affected by multiple factors including absorption, excretion, liver function, kidney function, other medications, age, fat stores,

Opioid Equianalgesic Dose Table

<u>Opioid</u>	<u>Oral Dose</u>	<u>Parenteral Dose</u>
Morphine	30mg	10mg
Oxycodone	20mg	-----
Hydromorphone	7.5 mg	1.5 mg
Hydrocodone	30mg	-----
Fentanyl	-----	0.1mg (100 mcg)
Codeine	200mg	100mg
Tramadol	120mg	-----

Opioid Equianalgesic Dose Table

- For fentanyl TD, the package insert says the 25mcg/hr patch is equal to 45 – 135 mg of morphine daily.
- A much easier conversion is 2mg morphine/day = 1 mcg/hr fentanyl TD

Case #1 - continued

- So her MEDD is 65 mg
- That would equal fentanyl TD 32.5 mcg/hr.
- The fentanyl TD comes in 12mcg/hr, 25mcg/hr, 50mcg/hr, 75mcg/hr, 100mcg/hr
- When doing conversions, err on the side of less medication especially with the long acting medications, so will start a 25mcg/hr patch.
- For breakthrough dosing, we were using 5 mg morphine, which equals 1.25mg hydromorphone, so will use hydromorphone 2mg, 0.5-1 tab q4 prn

Case #1 - continued

- So we decide to convert AB from morphine to Fentanyl TD and hydromorphone – how exactly do we do this?
- It takes about 12-18 hours to reach steady state levels of the TD patch, so apply the patch at the time of the last dose of morphine LA.
- Explain to the patient that she may need to take more doses of breakthrough medication during the transition period.

Case #2

- CD is a 50 y/o male with non-small cell carcinoma of the lung who is currently on fentanyl TD at 300 mcg/hr, Oxycontin 60mg q8h and is prescribed hydromorphone 16mg orally q2h prn and is taking 5 doses daily on average.
- He is no longer able to swallow and we want to start him on continuous IV opioids, we decide to use morphine.

Case #2 - continued

- So to calculate his MEDD:
 - Fentanyl TD at 300mcg/hr = 600mg/day of morphine
 - Oxycodone at 60mg q8h = 180 mg/day of oxycodone = 270mg of morphine
 - Hydromorphone 16mg x 5doses = 80 mg/day of hydromorphone = 320mg of morphine
- $600 + 270 + 320 = 1190$ mg of oral morphine daily

Case #2 - continued

- So, 1190mg of oral morphine = 397mg parenteral morphine daily
- To get the hourly rate, $397\text{mg}/24\text{hr} = 16.52\text{mg/hr}$
- If we decide to decrease the dose by 25% as we make the change, it comes out to 12.4mg, so starting the morphine at 12 mg/hr, and using a breakthrough dose of 6mg q20min makes sense.

Case #2 - continued

- Another option for the patient, if pain is well controlled and patient is imminent, would be to switch to fentanyl patches with morphine oral solution for breakthrough.
- So MEDD = 1190 = almost 600mcg/hr of fentanyl. (I would probably start with 500mcg/hr.)
- Breakthrough dose of morphine would be 120-180 mg of morphine IR (10-15%).

Codeine and Hydrocodone

- Codeine is metabolized to morphine via the cytochrome P2D6
 - Not effective in persons lacking P2D6 (27% of caucasians)
 - Not effective with P2D6 inhibitors
 - Haloperidol, paroxetine, fluoxetine
- Hydrocodone metabolized to hydromorphone by CY P2D6
- Little to no analgesia with these two drugs in poor metabolizers of CY P2D6

Morphine and Hydromorphone Metabolism

- Morphine is metabolized to M3G and M6G
 - M6G “good” - analgesia
 - M3G “bad” – neuroexcitatory effects
- Both metabolites accumulate in renal dysfunction and dose needs to be adjusted
- Hydromorphone major metabolite is H3G
 - Neuroexcitatory effects such as myoclonus, seizures, allodynia
 - Accumulates in renal failure

Fentanyl -Transdermal

- Forms a depot under the skin
- Takes about 18 hours to form depot
- Not useful for acute pain episodes
- Change patch every 48-72 hours
- Maybe less constipation
- Metabolized by liver and metabolites have little or no activity
- Useful in renal failure and less likely to get neuroexcitatory effects

Fentanyl -Transdermal

- Not for use in uncontrolled pain – always use short acting medications and not long acting medications in uncontrolled pain
- Should not be used in patients weighing less than 50 kg and use cautiously in frail and elderly
- It will work in thin and cachectic persons
- Absorption affected by temperature and blood perfusion

Methadone

- Synthetic mu receptor agonist
- NMDA antagonist
- Inhibits reuptake of NE and serotonin
- Useful in:
 - Neuropathic pain
 - Opioid tolerance – less dose escalation needed when treating cancer pain

Methadone

- Oral bioavailability is 80%
- Rapidly taken up by tissues from where it is slowly released
- Metabolized in liver to inactive metabolites and excreted in feces
- No adjustment needed for renal failure
- Variable half life 15-60 hours
- Accumulation leads to prolonged sedation
- Can cause QT interval prolongation

Methadone

- Interactions with CYP3A4 drugs
 - Inhibitors of CYP3A4 will increase methadone levels
 - Ciprofloxacin, erythromycin, clarithromycin, fluconazole, ketoconazole, paroxetine, fluoxetine, cimetidine, amiodarone
 - Inducers of CYP3A4 will decrease methadone levels
 - Carbamazepine, phenytoin, primidone, phenobarbital, rifampin

Analgesic Pharmacokinetic Comparison Table

Drug Name	Onset of Effect	Peak Effect	Duration of Effect	Half-life
	Minutes	Hours	Hours	Hours
Buprenorphine	10-30	0.5-1	6-8	2-3
Buprenorphine Transdermal	Slow	17	168	26
Codeine	15-30	0.5-1	4-6	3
Fentanyl Transdermal	Slow	18-24	48-72	variable
Fentanyl Intravenous	Immediate	< 1 minute	1-2	1-4
Fentanyl Transmucosal	5-15	0.3-0.5	5-15	2-4
Hydrocodone	10-20	0.5-1	4-8	3.3-4.5
Hydromorphone	15-30	0.5-1	4-5	2-3
Meperidine	10-45	0.5-1	2-4	3-4
Methadone	30-60	0.5-1	4-8	15-120
Morphine	15-30	0.5-1	3-7	2-4
Oxycodone	15-30	0.5-1	2-5	3-4
Oxymorphone	5-10	0.5-1	3-6	2-4
Tapentadol	--	1-1.5	4-6	4-5
Tramadol	15-30	1-2	4-6	5-6

Adjuvant Medications for Analgesia

- Use for:
 - Pain poorly responsive to opioids (such as neuropathic pain)
 - To improve responsiveness of opioids so that a lower dose can be used to decrease side effects

Adjuvant Medications for Analgesia

- General/non-specific pain
 - Corticosteroids
 - Cannabis
- Neuropathic pain
 - Gabapentin
 - Antidepressants
 - Ketamine
 - Topiramate
- Bone pain
 - bisphosphonates

Corticosteroids

- Decrease inflammation and edema that are there due to tumor mass effects
- Decrease spontaneous nerve depolarization
- Dexamethasone has less mineralocorticoid effects but is often given more than once daily

Corticosteroids – side effects

- Immediate
 - Psychiatric
 - Hyperglycemia
 - GI bleeding
 - Immunosuppression
- Long term
 - Proximal myopathy
 - Osteoporosis
 - Avascular necrosis
 - Cushing's syndrome
 - Adrenal suppression

Cannabis

- Inhaled cannabis has quick onset of action and is easier to titrate. Oral ingestion has later onset of action (peak levels at 6 hours) and half-life is 20 – 30 hours.
- Has been shown to be efficacious for cancer pain, nausea and vomiting due to chemotherapy, spasticity and insomnia in multiple sclerosis and in HIV patients for AIDS wasting syndrome and sensory neuropathy.

Gabapentin

- Start low and titrate up to 900 – 3600 mg daily.
- Side effects are usually mild but include sedation, confusion, ataxia, dizziness.
- Pregabalin (Lyrica) has quicker onset of action, quicker to titrate, may be more effective, but is much more costly.

Ketamine

- FDA approved as a parenterally administered general anesthetic.
- The parenteral solution can be given orally or parenterally in smaller doses for pain control.
- Works as NMDA antagonist, a weak opioid receptor agonist, blocks reuptake of serotonin and norepinephrine as well as other effects.
- No large controlled trials to support its use but many case reports and small uncontrolled studies.

Treatment of Neuropathic Pain

- Pharmacologic treatment
 - Opioids
 - Steroids
 - Anticonvulsants (gabapentin, topiramate)
 - TCAs
 - NMDA antagonists (ketamine, methadone)
 - Anesthetics
- Radiation therapy
- Interventional therapies
 - Nerve blocks
 - Intrathecal pain pumps

Case #1 - continued

- AB has continued to decline over time, though her pain has been well controlled with the fentanyl TD (now at 50 mcg/hr) and hydromorphone 4mg for breakthrough. One of her daughters has taken FMLA from work and moved in with her mother to care for her. Over the past 2-3 days she has become more confused and her pain has been increasing. She has been receiving more breakthrough medications. She is now having hallucinations and delusions.

Case #1 - continued

- Over the past 24 hours, her daughter has not been able to get the pain lower than 9/10. AB often rates her pain at 25/10. She is brought into Hospice House for GIP care to get her pain under control.

Case #1 - continued

- History

- Pain medications fentanyl 50mcg/hr TD and she has had 60 mg of hydromorphone orally the past 24 hours.
- Last BM 4 days ago.
- No fever.
- Frequent, small amounts of urination.
- She has also taken several doses of lorazepam, total of 10 mg, in the past 24 hours.

Case #1 - continued

- Physical
 - Confused, appears uncomfortable, and screams with touching any part of her body
 - Lungs clear, cor reg but tachy 2/6 SEM
 - Abdo distended but soft and quiet bowel sounds
 - Rectal exam shows no stool in vault
 - Frequent myoclonic jerking noted in arms and legs
 - 2 beat clonus at ankle

Case #1 - continued

- Dx: Acute pain crisis
- Cause?
 - Delirium
 - Terminal delirium
 - Constipation
 - Infection
 - Urinary retention
 - Opioid induced neurotoxicity (OIN)
 - Other

Opioid Induced Neurotoxicity

- Severe sedation
- Cognitive failure
- Hallucinations/delirium
- Myoclonus, seizures
- Hyperalgesia, allodynia

Opioid Induced Neurotoxicity

- Risk factors
 - Pre-existing cognitive impairment/delirium
 - Opioid dosage
 - Duration of exposure
 - Dehydration
 - Renal function
 - Other psychoactive medications
 - Mixed agonists/antagonists

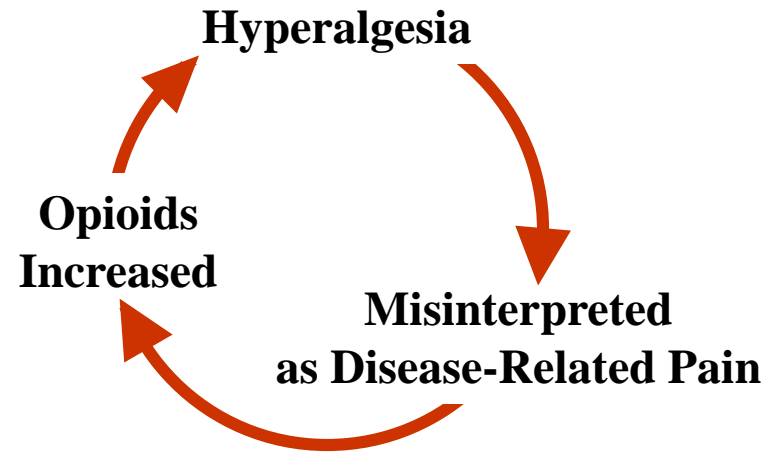
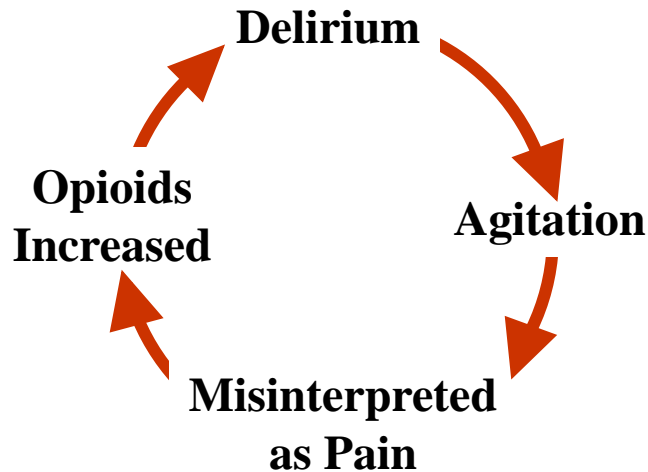
Spectrum of Opioid-Induced Neurotoxicity

Opioid
tolerance

Mild myoclonus
(eg. with sleeping)

Severe myoclonus

Seizures,
Death

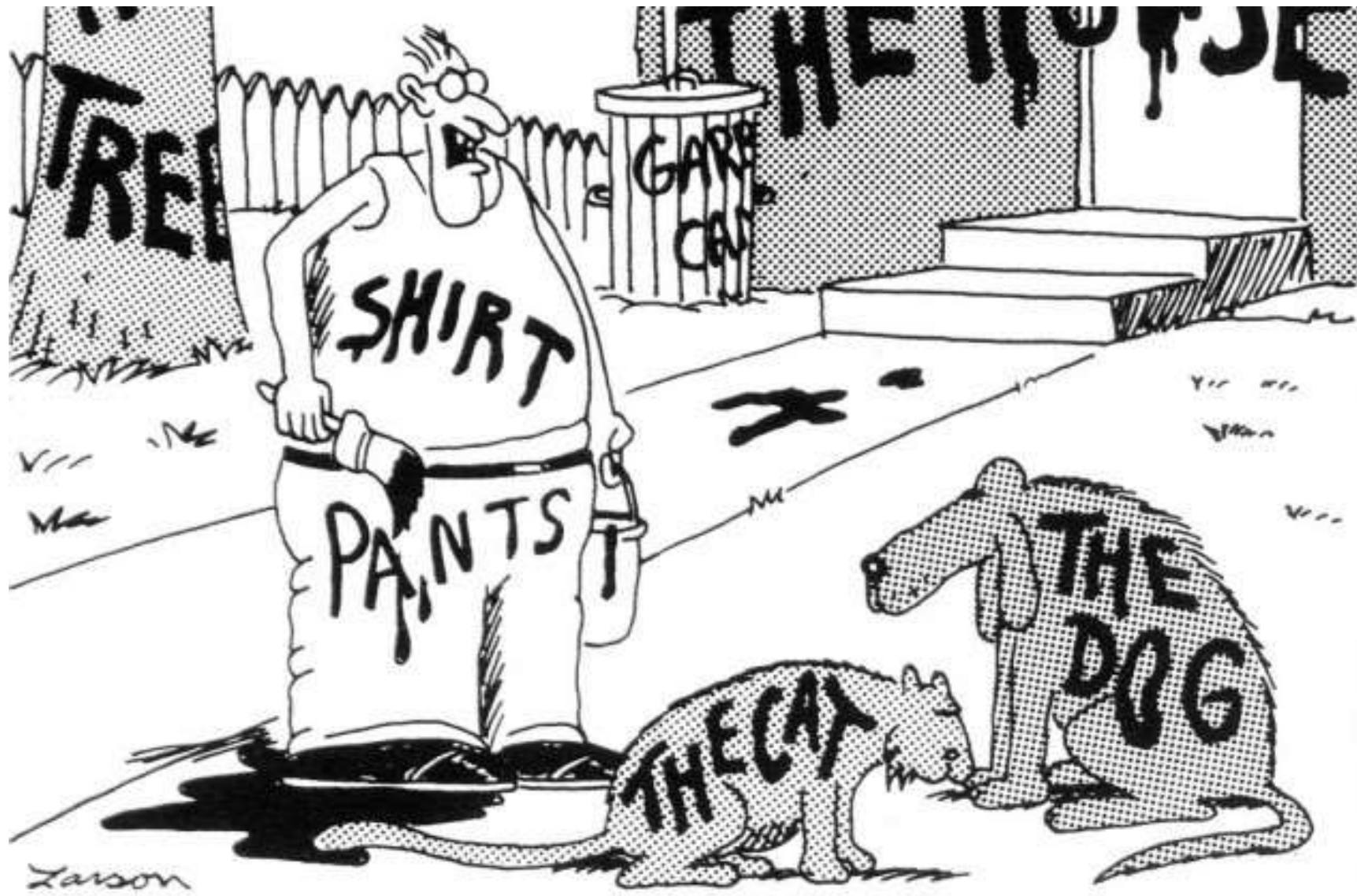


OIN: Treatment

- Switch opioid (rotation) or decrease dose. May want to use prn dosing initially.
- Hydration.
- Benzodiazepines for neuromuscular excitation.

Case #1 - continued

- AB was assessed and felt to have likely terminal delirium, with some OIN as well. A long discussion of treatment options as well as goals of care was held with the daughter and the decision was that comfort was more important at this point in time for AB than reversibility of the OIN or delirium. She was treated with haloperidol and lorazepam and her opioid regimen was changed to SQ fentanyl by CADD pump. She died peacefully 2 days later with her daughters by her side.



THE KISS PRINCIPLE

KEEP

IT

SIMPLE,

STUPID

Principles of Pain Treatment

- Use only one long acting preparation
 - An exception might be the use of methadone in a low dose along with another long acting medication.
- Use only one short acting preparation
 - Resist the urge to use a mild opioid like hydrocodone for mild pain and a strong opioid like morphine for worse pain.
- Empower the patient with liberal prn dosing.

Principles of Opioid Treatment

- Treat persistent basal pain with around the clock long acting preparations
- Treat episodic breakthrough pain with regular release opioids
- Titrate doses to optimal pain relief
- Use least invasive and best tolerated route of administration
- Anticipate and proactively treat side effects

ABC's of Pain and Symptom Assessment and Management

- **A**sk about pain and other symptoms
- **B**elieve the patient and family in their reports
- **C**hoose treatment options appropriate for the patient, family, and setting
- **D**eliver interventions in a timely, logical and coordinated fashion
- **E**mpower the patients and family. **E**nable them to control their course to the greatest extent possible



**"Mr. Osborne, may I be excused?
My brain is full."**