

Complex Patient Management in Serious Illness

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Contact Hours - Nursing 1.0 Contact Hour



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Successful Completion Criteria

- Register for the activity
- Complete and submit the sign in sheet
- View the entire presentation
- Complete and submit the participant evaluation
- Certificate will be emailed upon completion of the criteria



My mission....is for you to gain deeper understanding of...

- ▶ Given the assessment information for a pain complaint of a patient with serious illness, determine the likely pathogenesis of the complaint.
- ▶ Given a patient with pain of mixed pain pathology, or complex neuropathic pain, recommend a management strategy.
- ▶ Given a patient with opioid-induced hyperalgesia, recommend an appropriate management strategy.

Symptom Analysis

PORSTU
A Multidimensional
Pain Assessment

Unidimensional vs. Multidimensional Pain Assessment

Unidimensional pain assessment - severity
Multidimensional pain assessment
Brief Pain Inventory

- ▶ Location
- ▶ Severity (worst, least, average, now)
- ▶ Previous treatment
- ▶ How much relief
- ▶ Interference with ADLs
General activity, mood, walking ability, normal work, relations with others, sleep, enjoyment of life

The image shows a portion of the Brief Pain Inventory (BPI) form. It includes questions about the location of pain (head, neck, chest, back, arms, legs), the severity of pain (worst, least, average, now), and how much relief is obtained. It also includes a section for interference with activities of daily living (ADLs) such as general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. The form uses a 0-10 scale for most items.

Unidimensional vs. Multidimensional Pain Assessment

Multidimensional pain assessment
McGill-Melzack Pain Questionnaire

- Where is your pain ?
- What does it feel like ?
- How does it change with time ?
- How strong is it ?

The image shows the McGill-Melzack Pain Questionnaire (MPQ). It features a body diagram with arrows pointing to different areas of the body. The questionnaire includes a list of 20 pain descriptors (e.g., aching, burning, stabbing, throbbing) and a section for 'How strong is your pain?' with a scale from 0 to 10. There are also sections for 'How does your pain change with time?' and 'How strong is your pain?'.

Symptom Analysis Multidimensional Pain Assessment

- P (palliative / precipitating / previous therapy)
- Q (quality)
- R (region / radiating)
- S (severity)
- T (temporal)
- U (YOU - associated symptoms)



Palliative / Precipitating

What helps relieve pain ?

- Non-drug interventions: heat, cold, position change, walking, standing, lying

What brings it on ?

- Position changes, weight bearing, personal care, light touch, activities, bowel movement, change in weather



Previous Therapy

What methods have you used to manage the pain ?
(past and present)

- Medications
 - Herbal OTC
 - Prescription
- Natural products
- Coping strategies, e.g., prayer, distraction



Quality

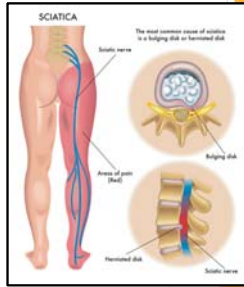
What does the pain feel like ?

- ▶ **Somatic Nociceptive Pain:** aching, deep, dull, throbbing, sharp, well localized
 - ▶ **Visceral Nociceptive Pain:** diffuse, gnawing, cramping, squeezing, pressure, distant sites
 - ▶ **Neuropathic Pain:** burning, numb, radiating, shooting, stabbing, tingling
- IMPORTANT: Use the patient's own words!
- ▶ Dull, sharp, sore, frightful, radiating, aching, flashing, penetrating, heavy, throbbing, shooting, tight, cutting, hot, stinging, spreading, piercing, searing, wrenching, etc.



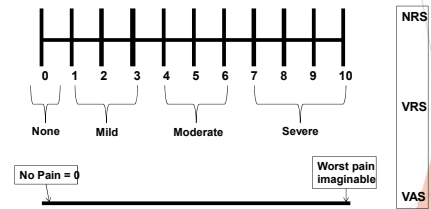
Region / Radiating

- Where does it hurt ?
- ▶ Can the patient point to an area?
 - ▶ Is it localized or referred?
 - ▶ Superficial or deep?
- Does it spread or radiate to other areas or stay in one place ?



Severity Rating

Best, worst, average, now
At rest, with movement



Breivik H, Borchgrevink PC, Allen SM et al. Assessment of pain. Br J Anaesth. 2008; 101(1):17-24.

Assessment of Neuropathic Pain

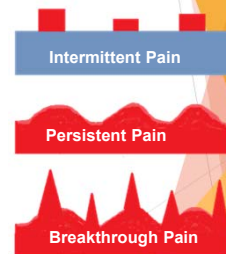
- Neuropathic Pain questionnaire - Short Form
- Rate the following aspects of your pain (0 - 10 scale; yes / no)
- ▶ Tingling pain
 - ▶ Numbness of pain
 - ▶ Increased pain due to touch



Backonja M, Krause SJ. Neuropathic pain questionnaire – short form. Clin J Pain. 2003; 19(5):315-6.

Temporal

- Onset
- Duration
- Variation (course / daily)
- Frequency
- Patterns (constant or intermittent ?)
- Acute, current, or chronic ?



YOU - Associated Symptoms

How does the pain affect

- Mood / emotional state
- Work
- ADLs, e.g., chores, hobbies
- Personal relationships
- Sleep
- Appetite



Symptom Analysis Multidimensional Pain Assessment

- P (palliative)
 - P (precipitating)
 - P (previous therapy)
 - Q (quality)
 - R (region / radiating)
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 - U (YOU - assoc'd Sx)
- 1. R (region / radiation)
 - 2. T (temporal)
 - 3. Q (quality)
 - 4. P (palliative)
 - 5. P (precipitating)
 - 6. S (severity)
 - 7. U (YOU - assoc.'d Sx)
 - 8. P (previous therapy)

Self - Assessment

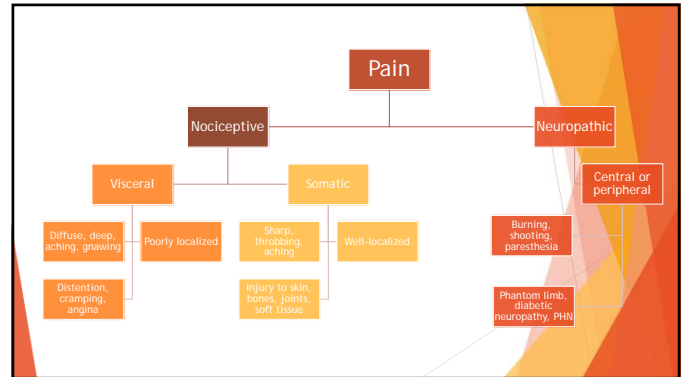
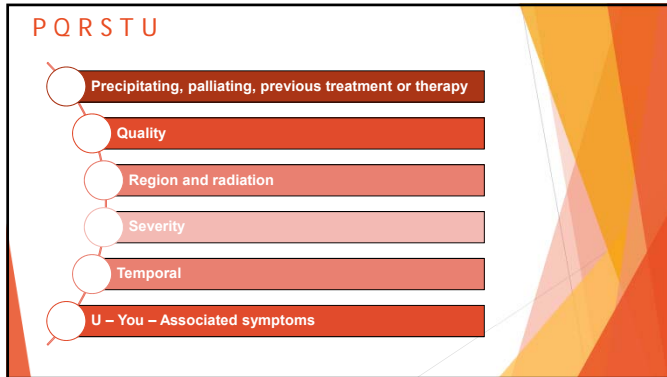
Match each description with the correct element of symptom analysis

- | | |
|---|-------------------------|
| 1. " It feels achy and colicky " | A. Precipitating events |
| 2. " The pain keeps me from working a full day, and I always wake up in pain " | B. Quality |
| 3. " I'm ok if I lie perfectly still, but rolling over makes the pain skyrocket " | C. Severity |
| 4. " The pain comes and goes, occurs about 4 times a day " | D. Temporal |
| 5. " I'd say it's a 5 on a 0 - 10 scale on average " | E. Impact on ADLs |

Self - Assessment

Match each description with the correct element of symptom analysis:

- | | |
|--|-------------------------|
| 1. " It feels achy and colicky " B | A. Precipitating events |
| 2. " The pain keeps me from working a full day, and I always wake up in pain " E | B. Quality |
| 3. " I'm ok if I lie perfectly still, but rolling over makes the pain skyrocket " A | C. Severity |
| 4. " The pain comes and goes, occurs about 4 times a day " D | D. Temporal |
| 5. " I'd say it's a 5 on a 0 - 10 scale on average " C | E. Impact on ADLs |

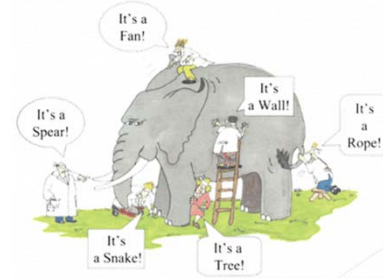


Scenario 1

- ▶ Ms. Johnson is a 48 year old woman with end-stage breast cancer, admitted to hospice
- ▶ She was admitted on MS Contin 30 mg po q12h with MSIR 15 mg po q4h prn additional pain
- ▶ Her pain persisted and the morphine regimen was eventually increased to
 - ▶ MS Contin 75 mg po q12h
 - ▶ MSIR 30 mg po q2h (using 3 - 4 times per day)
- ▶ She continues to rate her average pain as 7 / 10
- ▶ Why does this plan not work ?? What's the dealio ?

SOMETHING
AIN'T RIGHT

What's the differential diagnosis ?



Himmelfarb J et al. Kidney International 2003; 63: 1524
<https://emcrit.org/pulmcrit/the-tale-of-six-blind-physicians-and-the-elephant/>

It could be...

- Opioid poorly-responsive pain
- Type of pain; temporal pattern of pain (breakthrough)
- Opioid-induced tolerance / Disease progression
- Opioid-induced hyperalgesia
- Poorly managed opioid therapy
- Non-physical pain

Pain Management is NOT One-Sizes-Fits-All !

- ▶ The WHO method for cancer pain relief
 - ▶ Validated in thousands of patients
 - ▶ 1970's and 1980's - move away from invasive procedures to treat pain, to analgesics 80 %
- ▶ Up (to 90 %) of pain could be controlled with WHO ladder approach (non-opioids, opioids)
- ▶ What about the rest ?
 - ▶ Opioid-non-responsive pain or opioid-resistant pain

Titrating Opioids

- ▶ The end point when titrating an opioid dose against pain is not simply **pain relief** or **lack of pain relief**
- ▶ **Adverse effects** may limit dose titration



Opioid responsiveness is a continuum influenced by a number of patient-, drug- and pain-related variables

“ Opioid - poorly - responsive pain is pain that is inadequately relieved by opioid analgesics given in a dose that causes intolerable side-effects despite routine measures to control them ”

Hanks GW, Forbes K. Acta Anaesthesiol Scand 1997;41:154-158.

Opioid Responsiveness

- ▶ Most pain will respond at least partially to opioid therapy
- ▶ Patients with advanced illness (particularly cancer) more often than not have more than one type of pain (with varying degrees of responsiveness to opioid therapy)



Opioid responsiveness is defined as the degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the occurrence of acceptable analgesia

Types of Pain

Neuropathic pain

- ▶ Reported to be unresponsive to opioids at usually effective doses
- ▶ Morphine may change affective but not sensory dimension of neuropathic pain
- ▶ Neuropathic pain has negative predictive prognostication with cancer pain therapy
- ▶ Neuropathic pain reduces the likelihood of a favorable outcome
- ▶ Not a class effect; try opioid rotation

What's a "usually effective dose?"

Coanalgesic?

Breakthrough Pain

- ▶ "Transitory increase in pain over baseline pain in patients receiving regularly administered analgesics"
 - ▶ Affects 64 - 90 % cancer patients with pain
- ▶ Particularly problematic is achieving freedom from pain with movement with metastatic bone disease.
- ▶ Spontaneous, incident (volitional or non-volitional), end-of-dose deterioration
- ▶ Co-analgesic? (steroid or NSAID)

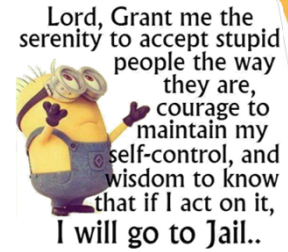
Other Types of Pain

- ▶ Skin ulceration
- ▶ Rectal tenesmus
- ▶ Muscle pain
- ▶ Development or worsening of a non-cancer pain syndrome such as painful diabetic neuropathy
- ▶ New non-cancer pain syndrome such as a dental abscess



Tolerance

- ▶ The repeated administration of opioids can lead to the development of tolerance
 - ▶ Good (to adverse effects)
 - ▶ Bad (to analgesic effects)



Tolerance to Opioids



Traditional Non-Opioids

- ▶ **Acetaminophen**
 - ▶ Analgesic, anti-pyretic
 - ▶ Oral, rectal, parenteral
- ▶ **Nonsteroidal anti-inflammatory drugs**
 - ▶ Analgesic, anti-pyretic, anti-inflammatory, antiplatelet
 - ▶ Aspirin, COX-nonspecific, COX-2 selective
 - ▶ Oral, rectal, parenteral, topical

Propionic Acids
<ul style="list-style-type: none"> • Ibuprofen • Flurbiprofen • Ketoprofen • Naproxen • Oxaprozin
Acetic Acids
<ul style="list-style-type: none"> • Diclofenac • Etodolac • Indomethacin • Ketorolac • Salsalac • Tolmetin
Enolic Acids
<ul style="list-style-type: none"> • Meloxicam • Piroxicam
Nonacetylated Salicylates
<ul style="list-style-type: none"> • Choline Magnesium Trisalicylate
Others
<ul style="list-style-type: none"> • Celecoxib • Meclofenamate • Nabumetone

Pharmacy Today
December 2018

Adjuvant Analgesics

- ▶ **Antidepressants**
- ▶ **Anticonvulsants**
 - ▶ Gabapentin, pregabalin
 - ▶ Oxcarbazepine, carbamazepine
 - ▶ Topiramate, zonisamide, (*levetiracetam, lamotrigine*)
- ▶ **Corticosteroids** - dexamethasone, prednisone
- ▶ **Bisphosphonates** - pamidronate, zoledronic acid
- ▶ **Skeletal muscle relaxants** - baclofen, dantrolene, tizanidine (spasticity); cyclobenzaprine, methocarbamol, carisoprodol, chlorzoxazone, metaxalone, orphenadrine (spasms)

SSRI	SARI	TCA	Atypical
• Escitalopram • Paroxetine	• Duloxetine • Milnacipran • Venlafaxine	• Amitriptyline • Clomipramine • Desipramine • Imipramine • Nortriptyline	• Bupropion

Friday, December 2018

Things to ponder...

- ▶ **NMDA receptor antagonists**
 - ▶ Ketamine, methadone, (*memantine, amantadine, dextromethorphan*)
- ▶ **Lidocaine** - Topical Lidoderm, parenteral lidocaine
- ▶ **Topical analgesics**
 - ▶ Diclofenac gel/drops, lidocaine, capsaicin
- ▶ **Compounded**
 - ▶ Local effect (e.g., wound care, mucositis)
 - ▶ Morphine, ketamine
 - ▶ Systemic effect - not so much

Neuropathic Pain
Ketamine, gabapentin, clonidine, lidocaine
Nociceptive Pain
Ketoprofen, baclofen, cyclobenzaprine, lidocaine
Mixed Pain
Ketamine, gabapentin, diclofenac, baclofen, cyclobenzaprine, lidocaine

Annals Int Med. 10-7326/M18-2736

Are you pulling my good leg now?

- ▶ Botulinum toxin
- ▶ Cannabinoids
- ▶ Opioid antagonist (naltrexone)



Scenario 2 - What's the Sitch ?

- ▶ Mrs. Madderhorn is an 82-year-old woman with multiple comorbidities:
 - ▶ Uterine cancer, post-stroke pain, diabetes, heart disease, osteoarthritis (knees, hips, spine) and Alzheimer's dementia
- ▶ Usual BP is 105 / 70 mmHg, HR 68 bpm, RR 16 bpm
- ▶ 5' 0", 86 pounds
- ▶ Appetite is poor; she appears to be malnourished
- ▶ Admitted to hospice with diagnosis of uterine cancer
- ▶ Receiving MS Contin 15 mg PO q12h with oral morphine solution for breakthrough (not using on admission), but as her dementia worsened she started to forget to take her medication

Scenario 2 - What's the Sitch ?

- ▶ Patient was switched to transdermal fentanyl (TDF) 12 mcg/hr with oral morphine solution for breakthrough pain, 5 mg q2h PRN
- ▶ The hospice nurse, Stephanie, observes that Mrs. Madderhorn is exhibiting signs of pain, even though the patient isn't verbal
- Stephanie uses the Checklist of Nonverbal Pain Indicators and decides the patient is in moderate pain
- On day 3, TDF is increased to 25 mcg/hr, and on day 5 to 50 mcg/hr

Scenario 2 - What's the Sitch ?

- ▶ Stephanie reports to the team that the patient doesn't seem to be getting the relief from the TDF patch that you would expect
- ▶ Based on the patient using TDF 50 mcg/hr and continued pain, the physician switched the patient to MS Contin 60 mg po q12h with oral morphine 15 mg q2h PRN pain
- ▶ Stephanie was instructed to remove the TDF and start MS Contin 12 hours later
- ▶ Within 24 - 36 hours, Mrs. Madderhorn is completely zonked and very hard to wake up. The newly hired paid caregiver says she can't awaken the patient to administer the MS Contin. Uh oh!

Scenario 2 - What's Wrong with this Picture ?

- A. The patient was never an appropriate candidate for transdermal fentanyl (TDF)
- B. The patient was wasted and cachectic, making her a poor candidate for TDF
- C. TDF was titrated too quickly
- D. The conversion OFF TDF was incorrectly calculated
- E. All of the above

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- C. TDF was titrated too quickly
- D. The conversion OFF TDF was incorrectly calculated
- E. **All of the above (duh)**
- ▶ She was not receiving ≥ 60 mg oral morphine per day for at least a week
- ▶ Patient cachectic and unlikely to get full benefit from TDF
- ▶ Titrated way too quickly - day 3 and day 5
- ▶ Physician gave her full credit for TDF AND increased the dose of morphine - too aggressive !
- ▶ Transitioned too quickly to MS Contin (should have waited 24 hours)

Scenario 2 - Play it Again Sam!

- ▶ If the family had a paid caregiver all along, the caregiver could have given the MS Contin and the breakthrough morphine, avoiding the need to consider TDF
- ▶ Patient was NOT a candidate for TDF (not receiving 60 mg oral morphine per day for at least a week)
- ▶ TDF increased too quickly - can increase on Day 3, then every 6 days thereafter
- ▶ Converting OFF TDF 50 mcg/hr ~ 100 mg oral morphine, then MD increased to 120 mg oral morphine - too high
 - ▶ Should have gone back to MS Contin 15 mg po q12h (or even used short-acting morphine around the clock until the dust settled)
 - ▶ Safer to wait 24 hours before starting scheduled morphine; can start PRN dose as soon as the TDF was removed

Scenario 3 - What's the Sitch ?

- ▶ Mrs. Gladson is a 78 year old woman diagnosed with end-stage hepatic cancer. She was admitted to hospice on MS Contin 15 mg po q12h with oral morphine solution 5 mg every 3 hours as needed for additional pain
- ▶ Hospice RN reports patient is having a pain crisis; she is taking her MS Contin as directed and several doses of oral morphine solution with no relief at all
- ▶ Patient rates pain as greater than a 10 on a 0-10 scale, family is insistent she be admitted to the hospice inpatient unit...

Scenario 3 - What's the Sitch ?

- ▶ She is transported to the inpatient unit, arriving at 6 pm. The attending on call is Dr. Doogie Howser (he's so excited - this is his first position post-fellowship!)
- ▶ Dr. Howser calculates that the patient was receiving approximately 40 mg oral morphine in the past 24 hours, which he figures in about 16 mg IV morphine per day (0.6 mg/h)
- ▶ He orders a 2.5 mg IV morphine loading dose, and a continuous infusion at 1.2 mg/hr, with an order to titrate to comfort per nursing judgment...

Scenario 3 - What's the Sitch ?

- ▶ The family stays with the patient and keeps the nurse informed as to the patient's response to the morphine infusion
- ▶ The family is concerned that she's still complaining of pain that she rates as 9/10 at 8 pm, so the nurse increases the infusion to 3 mg/hour and the clinician bolus to 5 mg
- ▶ At 10 pm the family reports the patient is still grimacing and crying out, so the nurse repeats the 5 mg IV morphine loading dose and increases the continuous infusion to 5 mg/hr...

Scenario 3 - What's the Sitch ?

- ▶ The patient seems to settle down, and the family leaves around midnight.
- ▶ When the nurse checks on Mrs. Gladson at 3 am, she is nonresponsive, even to sternal rub
- ▶ Her respiratory rate is 6 breaths/minute with periods of apnea. She has pinpoint pupils, and the nurse calls Dr. Howser in a panic!

Scenario 3 - What's Wrong with this picture?

- A. The family must have increased Mrs. Gladson's infusion before they left
- B. The nurse was trigger happy with the hourly clinician bolus
- C. Dr. Howser incorrectly calculated the starting dose of morphine (bolus and infusion)
- D. The infusion rate was titrated incorrectly (too quickly)

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 - B. The nurse was trigger happy with the hourly clinician bolus
 - C. Dr. Howser incorrectly calculated the starting dose of morphine (bolus and infusion)
 - D. **The infusion rate was titrated incorrectly (too quickly)**
- ▶ The family didn't do anything. The nurse gave the hourly bolus as ordered. Dr. Howser's math was fine. That leaves us with the order was inappropriate - "titrate to comfort?"
 - ▶ The infusion started at 6 pm, increased at 8 pm and again at 10 pm
 - ▶ The patient is elderly and has a terminal illness, so her half-life of morphine is probably closer to 5 hours. To get to 87.5 % or 93.75 % of the way to steady-state it would take 15 - 20 hours, NOT 4 hours
 - ▶ The infusion was titrated way too aggressively, too quickly

Scenario 3 - What's wrong with this picture ?

We need to recognize the two issues at play here:

1. We need to FULLY appreciate the clinical impact of the current continuous opioid infusion dose when it achieves a steady-state serum level (both therapeutic gain and potential toxicity) BEFORE we increase the dose (and make the situation worse, and that always seems to happen at 3 am when no one is really paying close attention); and
 2. We don't want the patient to suffer with pain while we wait for the magical moment of steady-state to make sure we haven't overdosed the patient
- ▶ Doogie, Doogie, DOOGIE... this is why we never let 14 year-olds be doctors - EVER !



Scenario 3 - Play it Again Sam !

- ▶ Dr. Howser correctly calculated the patient's home use of oral morphine (40 mg a day) and converted this to an IV infusion (0.6 mg/h)
- ▶ Given patient's severe pain he correctly doubled it to 1.2 mg/hr as a continuous infusion
- ▶ He correctly ordered a clinician bolus - 10 - 20 % of the total opioid taken in the previous 24 hours [10 % 16 mg IV morphine equivalent = 1.6 mg; 20 % = 3.2 mg] for the RN to give as often as hourly

Scenario 3 - Play it Again Sam !

He should NOT have ordered "titrate to comfort per nursing judgment" - he should have given better guidance

- ▶ Administer 2.5 mg IV morphine now, then begin continuous morphine infusion at 1.2 mg/hour
- ▶ Reassess pain every 30 minutes x 3 and repeat morphine 2.5 mg IV bolus dose if pain decreased but not adequately controlled, or increase to 5 mg if pain unchanged or increased
- ▶ If pain is not adequately controlled after 3 IV bolus doses, contact prescriber
- ▶ Do not increase continuous infusion before 8 am (morning rounds)"

Scenario 4 - What's the sitch ?

- ▶ Ms. Ives is a 32 year old woman with end-stage cervical cancer, referred to hospice
- ▶ On admission she is receiving IV morphine 30 mg/hr, with a 10-mg bolus every 15 minutes as needed (using at least once, often twice, per hour)
- ▶ Her 24-hour use of IV morphine is 1,080 mg, which is about equivalent to 2,700 mg oral morphine per day.
- ▶ *Wow, that's a lotta morphine !*

Scenario 4 - What's the Sitch ?

- ▶ The attending physician, Dr. Rosenthal says, "This dose of morphine is ridiculous! She can swallow and she has a fair prognosis - let's switch her to methadone"
- ▶ Dr. Rosenthal asks you to do the conversion calculation
- ▶ Oh my - where to start - so many methods recommended in the literature!

Scenario 4 - What's the Sitch ?

- ▶ You decide to use Ayonrinde methadone which calls for a 20 : 1 (oral morphine : oral methadone) conversion for a total daily oral morphine dose over 1001 mg/day. This calculates to 135 mg oral methadone per day.
- ▶ The patient declines to be admitted as an inpatient (she's a single mother with three small children at home), so you decide to do this as a rapid switch at home.
- ▶ You stop the morphine infusion, start methadone 45 mg by mouth every 8 hours, and you decide to use morphine 60 mg by mouth every 2 hours as needed for breakthrough pain

Scenario 4 - What's the Sitch ?

- ▶ For the first couple of days things are a little rough; the patient uses the morphine breakthrough pain dose frequently
- ▶ They by Day 2 - 3, things are starting to look up. The patient has achieved a reasonable level of pain control, and she's actually happy to not be dragging the IV pump around with her
- ▶ Day 4 she complains of being really sleepy, and Day 5 she can't get OOB. What's the scoop ?

Scenario 4 - What's wrong with this picture ?

1. Ayonrinde was all washed up
2. Research has shown there should be a MAXIMUM starting dose of methadone
3. You shouldn't have included the breakthrough morphine doses in your calculation
4. The conversion should have been done over three days instead of a rapid switch

Scenario 4 - What's wrong with this picture ?

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Ayonrinde was NOT all washed up, but Dr. Eduardo Bruera argues WHY there is a sort of proposed maximum starting dose for methadone, regardless of how much opioid you are switching FROM:

- Slight binding differences at the opioid receptor
- Methadone has multiple mechanisms of action
- High dose of current opioid may be proalgesic (causing pain - hyperalgesia)

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- Slight binding differences at the opioid receptor
 - Methadone has multiple mechanisms of action
 - High dose of current opioid may be proalgesic (causing pain - hyperalgesia)
- ▶ Chatham and colleagues reported a series of 10 patients receiving very high-dose morphine
 - ▶ The vast majority were converted to, and stabilized on methadone 10 mg PO q8h
 - ▶ APS guidelines on methadone use suggest starting no higher than 30 - 40 mg oral methadone per day

Converting to Methadone

- ▶ Opioid-naïve patients
 - ▶ 2 - 7.5 mg oral methadone per day
- ▶ Opioid-tolerant patients
 - ▶ Do not increase before 5 - 7 days
 - ▶ < 30 mg TDD methadone - increase by up to 5 mg per DAY
 - ▶ ≥ 30 mg TDD methadone - increase by up to 10 mg per DAY

Total daily dose oral morphine equivalent	Conversion ratio to oral methadone
0 - 60 mg	Follow opioid-naïve dosing
61 - 199 mg OME and < 65 years old	10 mg OME : 1 mg oral methadone
≥ 200 mg OME and/or > 65 years old	20 mg OME : 1 mg oral methadone

Is it a bird? Is it a plane?
Is it tolerance? Is it hyperalgesia?

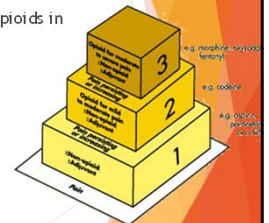


Opioid Therapy

Cornerstone of therapy for the treatment of moderate to severe pain (cancer, non-cancer)

Increased availability and comfort level in using opioids in recent years

- Greater attention to pain management
- Better education
- Used earlier in disease process
- Used in higher doses



Adverse Effects of Opioids

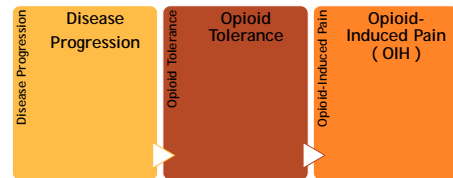
- ▶ Nausea, vomiting
- ▶ Constipation
- ▶ Pruritus
- ▶ Sleepy



What's Going On?

A common clinical observation:

- Opioid-requiring patients need a dosage increase to maintain adequate analgesia. Why?



CNS Adverse Effects of Opioids

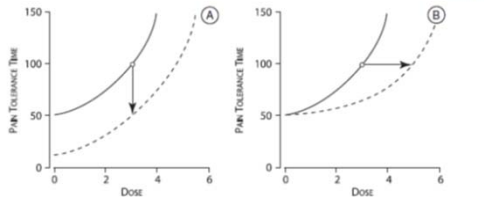
Adverse effects of opioids on CNS
(neurotoxicity - damage to nerve cells)

- Reduced level of consciousness
 - ▶ Sedation, drowsiness, sleep disturbance
- Adverse effects on thinking process and ability to react
 - ▶ Cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams, nightmares
- Direct toxic effect on neurons
 - ▶ Myoclonus, seizures, hyperalgesia and tolerance

OIH and Opioid Tolerance



OIH vs. Tolerance



Progression of Disease

Is it tolerance, or disease progression ?

- Difficult to differentiate
- Do we even need to differentiate ?

Patients given chronic opioids for pain and remain clinically stable for a substantial period of time on the same dose will experience increased pain intensity with disease progression

- Increase TDD 25 - 50 % for moderate pain
- Increase TDD 50 - 100 % for severe pain

Scenario 5

- ▶ Ms. R. is a 43 year old woman with end-stage cervical cancer. She is admitted to hospice on MS Contin 60 mg po q12h with morphine solution 20 mg PO q2h prn
- ▶ She complains of continued abdominal pain, which she rates as an 8 - 9 / 10 when the morphine solution wears off
- ▶ When she uses 4 doses of the Roxanol per day, her pain is fairly well controlled
- ▶ Her prescriber increases the MS Contin to 100 mg PO q12h with morphine solution 30 mg PO q2h prn pain with good results

Scenario 5

Several months later, Ms. R. has experienced significant disease progression

She was admitted to the hospital for pain out of control, and was sent back home after a week IV morphine 20 mg/hr with a 5 mg bolus every 15 minutes (uses about once an hour)

She is experiencing mild myoclonus, and the hospice medical director prescribed lorazepam 2 mg PO q6h scheduled

Two days after admission the patient went on vacation for a week to the ocean

Scenario 5

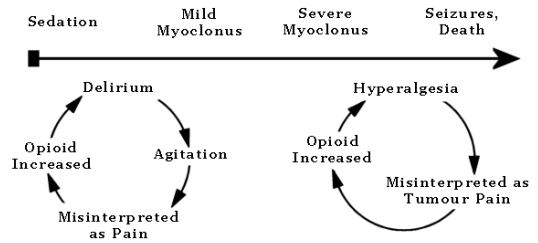
When the patient returned from vacation, she was admitted directly back to the hospital. It was discovered that she spent most of her ocean side vacation in the local hospital complaining of increased pain and myoclonus

On returning home, she is now on IV morphine 40 mg/hr plus a 20 mg bolus, which she uses once or twice an hour, plus a continuous infusion of midazolam at 10 mg/hr

She continues to experiences significant myoclonus

Now what ??

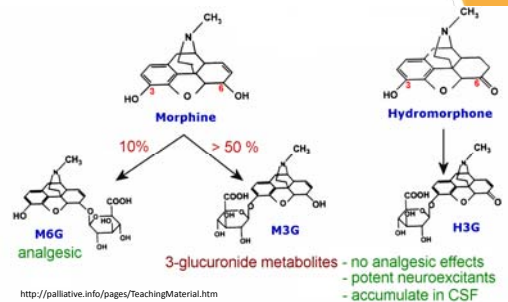
Vicious Cycle of Opioid-Induced Neurotoxicity



Patient Says - Provider Sees

What the patient says...	What the provider sees...
Increased sensitivity to pain stimulus (hyperalgesia)	Any dose of an opioid, but particularly with high-dose morphine or hydromorphone, and in renal impairment / failure
Worsening pain despite increasing doses of opioids	Pain elicited from ordinary nonpainful stimuli, e.g., stroking skin with cotton (allodynia)
Pain that becomes more diffuse, extending beyond the distribution of the pre-existing pain	Presence of other manifestations of opioid-induced hyperexcitability: myoclonus, delirium, seizures

Morphine and Hydromorphone
Active Metabolite Accumulation in Renal Failure



Management of OIH

- ▶ Hydration if clinically appropriate
- ▶ Reduce the opioid dose
 - ▶ Consider use of an opioid-sparing coanalgesic
 - ▶ Acetaminophen, NSAID
- ▶ Opioid rotation
 - ▶ Allows comparable analgesia at a lower equianalgesic dose
 - ▶ Fentanyl
 - ▶ Methadone
 - ▶ NMDA receptor antagonist
- ▶ Ketamine (NMDA receptor antagonist)

Ketamine Mechanism of Action

- ▶ N-methyl-D-aspartate (NMDA) receptor antagonist
- ▶ Interact with other sodium and calcium channels
- ▶ Weak opioid receptor agonist
- ▶ Muscarinic receptor antagonist
- ▶ Blocks reuptake of serotonin and norepinephrine

Ketamine Routes of Administration

- ▶ Intravenous
- ▶ Intramuscular
- ▶ Intrathecal
- ▶ Epidural
- ▶ Subcutaneous
- ▶ Oral
- ▶ Transdermal
- ▶ Sublingual
- ▶ Intranasal
- ▶ Rectal



Ketamine Analgesic Dosage

Intravenous / subcutaneous bolus

- 2.5 – 5 mg as needed

Intravenous / subcutaneous infusion

- Starting dose: 0.2 mg/kg/hr or 100 – 200 mg/24 hrs
- Usual dose: 100 – 400 mg/24 hrs
- Maximum reported dose: 3.6 gm/24 hrs

Oral

- Starting dose: 10 mg every 6 – 8 hrs
- Maximum reported dose: 240 mg/day

J Pain Symptom Manage. 2011; 41:640-649.

Ketamine Pharmacokinetics

Onset of action: 5 minutes (SC), 30 minutes (PO)

Hepatic metabolism to active metabolite norketamine

- Extensive first pass metabolism after oral administration

Duration of action: 2 hours (IM) and 4 – 8 hrs (PO)

Renally excreted (< 10 % unchanged)

Ketamine. In: DRUGDEX® System [Internet database]. J Pain Symptom Manage. 2011; 41(3):640-649.

Ketamine Adverse Effects

- ▶ Fatigue
- ▶ Nausea
- ▶ “ Emergence phenomena ”
- ▶ Tachycardia
- ▶ Hypertension
- ▶ Dizziness
- ▶ Nystagmus



Scenario 5

- ▶ Begin ketamine 10 mg po q6h, mixed in orange juice
- ▶ Empirically reduce morphine infusion by 30% to 25 mg/hr; keep bolus in place
- ▶ Empirically reduce midazolam infusion by 50% to 5 mg/hr
- ▶ Increase ketamine by 10 mg per dose every 2-3 days (while titrating morphine and midazolam down)

Total Pain - Dame Cicely Saunders



Opening the Door...

- ▶ We know people diagnosed with a serious illness have a thousand thoughts running through their head

- ▶ Physical
- ▶ Emotional
- ▶ Spiritual
- ▶ Practical
- ▶ Financial
- ▶ Work vs. home
- ▶ Family



Questions...

**WHAT'S THE
ONE
THING
I CAN DO
RIGHT NOW?**

- ▶ What do you fear ?
- ▶ What do you hope for ?
- ▶ What's bothering you the most ?
- ▶ What helps you cope ?
- ▶ What do I need to know about you to provide the best care I can ?



When an Analgesic IS the Answer...

Caring for the informal caregivers (IFC)

Five themes that have been identified by IFC

- ▶ " I'm not a doctor, and I don't know if I helped her go faster or slower "

Themes included

- Difficulty with administration of pain medicine
- Concerns about side effects of medications
- Insecurity with pain assessment
- Frustration with communication among health care team members
- Memories of unrelieved pain

Oliver DP et al. J Pain Symptom Manage 2013; 46:846-858

Questions?

References

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- ▶ *J Pain Symptom Manage*. 2011; 41:640-649
- ▶ *J Pain Symptom Manage*. 2011; 41(3):640-649.
- ▶ Oliver DP et al. *J Pain Symptom Manage* 2013;46:846-858.
- ▶ McPherson ML. *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, 2nd ed. 2018. ASHP, Bethesda, MD.