PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

Opioid Pharmacology

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Titles and Affiliations

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Disclosures

Learning Objectives

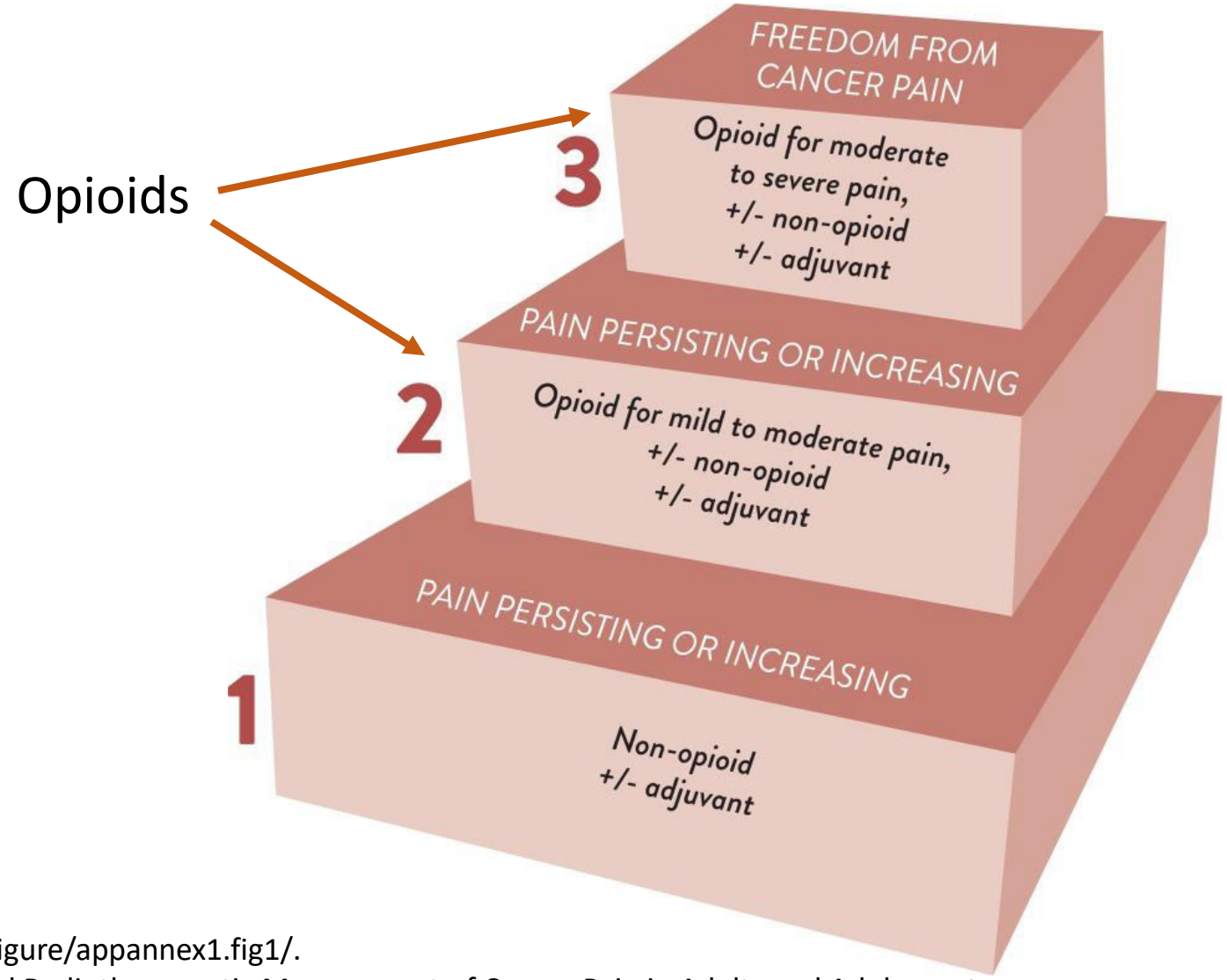
- Describe therapeutic roles for opioids in pain management.
- Select a safe and effective opioid and formulation based on patient- and agent-related variables.
- Identify a monitoring plan for an opioid regimen.
- Describe actual and potential opioid-induced adverse effects.
- List 4 opioid-related counseling points for an opioid regimen.

Opioid Nomenclature

- **Opiate**
  - Refers to compounds structurally related to products found in opium
  - A word derived from *opos*, the Greek word for “juice”
  - Opiates include the natural plant alkaloids such as morphine, codeine, thebaine and many semisynthetic derivatives
- **Opioid**
  - Any agent that has the functional and pharmacological properties of an opiate
  - Endogenous opioids – natural occurring ligands for opioid receptors found in animals
- **Narcotic**
  - Originally referred to any drug that induced narcosis or sleep
  - Has become associated with opioids and is often used in a legal context to refer to substances with abuse or addictive potential

Yaksh, Wallace. Chapter 20: Opioids, Analgesia, and Pain Management. In: *Goodman & Gilman’s The Pharmacologic Basis of Therapeutics*. McGraw-Hill Education / Medical; 13th edition (December 5, 2017)

Where do opioids fit in?



www.ncbi.nlm.nih.gov/books/NBK537489/figure/appannex1.fig1/.
WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents.

Opioid Mechanism of Action

- Opioid receptors are located on presynaptic terminals of the nociceptive C and A delta fibers
  - When activated voltage-dependent calcium channels are inhibited
    - Activation of potassium conductance and inhibition of calcium conductance
    - Results in decreases intracellular cAMP levels
    - Blocks release of pain neurotransmitters (glutamate, substance P, calcitonin gene-related peptide)
    - Results in analgesia
  - Inhibit release of GABA
  - May antagonize NMDA receptors (methadone)
  - Activate descending inhibitory pathway

James, Williams. *Br J Pain*. 2020;14(2):115-121.
Sharma et al. Opioid pharmacology: a review. *Int J Sci Res Sci Tech*. 2015;1(5):1-11.

Opioid Receptors

Receptor	Location	Effects
Mu (MOP)	Brainstem Medial thalamus	• Supraspinal analgesia • Respiratory depression, urinary retention • Euphoria, sedation, pruritus, anorexia • Decreased gastrointestinal motility, vomiting • Physical dependence
Kappa (KOP)	Limbic and other diencephalic areas, brain stem, spinal cord	• Spinal analgesia • Sedation, dysphoria, miosis, euphoria, dysphoria • Dyspnea, respiratory depression • Dependence, psychomimetic effects
Delta (DOP)	Brain	• Effects not well studied; analgesia • Possibly psychomimetic and dysphoria effects
Sigma	Not considered opioid receptors any longer	• Psychomimetic effects • Dysphoria • Stress-induced depression

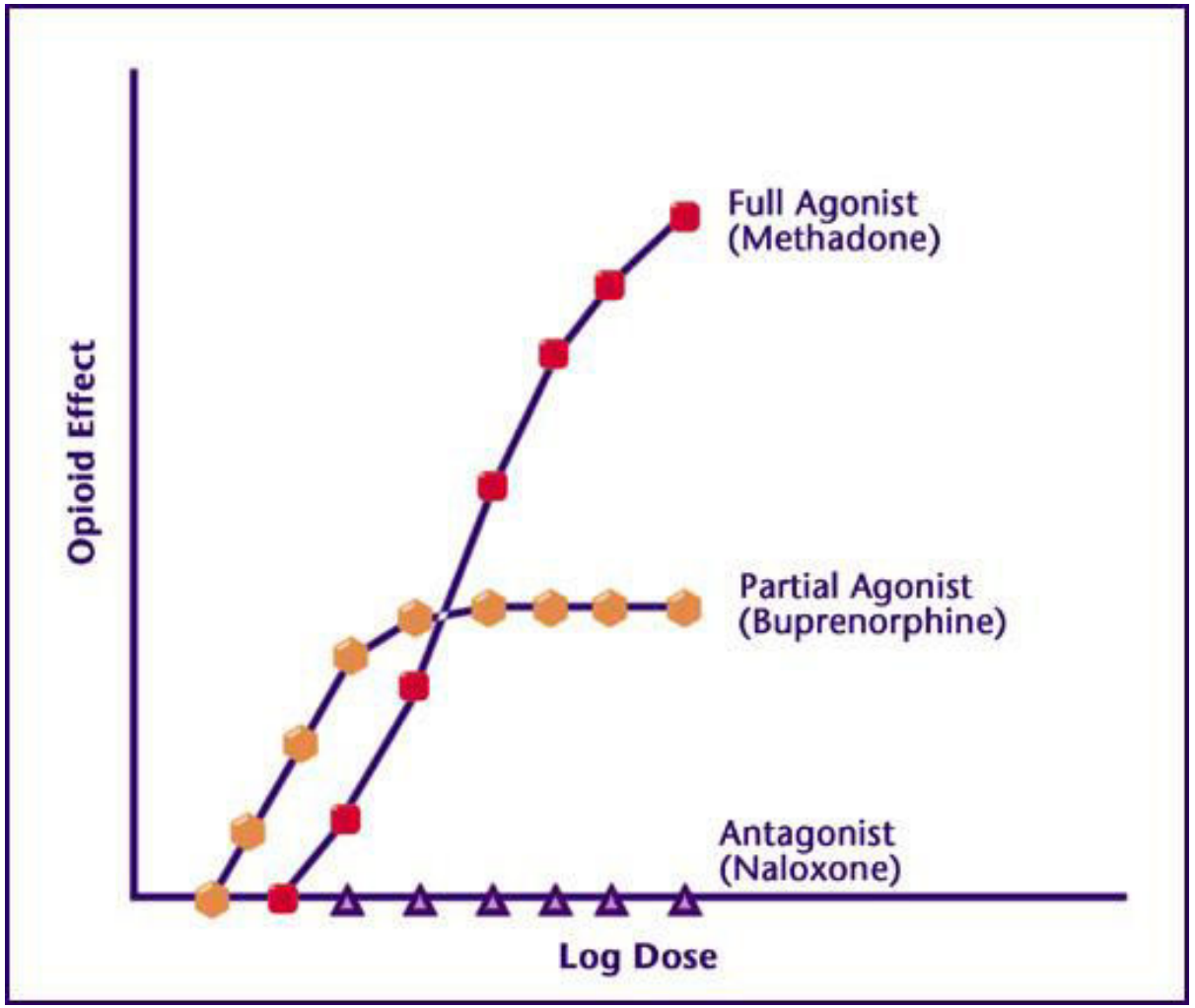
James, Williams. *Br J Pain*. 2020;14(2):115-121.
Sharma et al. Opioid pharmacology: a review. *Int J Sci Res Sci Tech*. 2015;1(5):1-11.

Opioid Classification – Actions

Classification	Examples	Action
Opioid agonists	Morphine Fentanyl Hydromorphone Methadone Oxycodone, etc.	• Stimulate opioid receptors • Differences in activity and efficacy appear to be related to the relative stimulation of the various opioid receptors, and genetic differences in opioid receptor sensitivity
Opioid partial agonists	Buprenorphine	• Has a high affinity, but low efficacy at the mu receptor where it yields a partial effect
Opioid antagonists	Naloxone Naltrexone	• Competitive antagonists at the mu, kappa and delta receptors

James, Williams. *Br J Pain*. 2020;14(2):115-121.
Sharma et al. Opioid pharmacology: a review. *Int J Sci Res Sci Tech*. 2015;1(5):1-11.

Conceptual Representation of Opioid Effect vs Log Dose



www.naabt.org/education/technical_explanation_buprenorphine.cfm.

Agent-Related Variables: Opioid Class

Chemical class	Examples
Phenanthrenes	• Morphine • Codeine • Hydromorphone • Oxycodone • Hydrocodone • Oxymorphone • Buprenorphine Cross-allergenicity
Phenylpiperidines	• Fentanyl, alfentanil, sufentanil • Meperidine
Diphenyl heptanes	• Methadone

Patient Related Variable:
true opioid allergy
If allergic to a phenanthrene, can use a phenylpiperidine or diphenylheptane

www.sciencedirect.com/topics/medicine-and-dentistry/phenanthrene-derivative.

Opioid Pharmacokinetics

Onset & duration depends on opioid & formulation

Formulation/Route of Administration	Onset (minutes)	Peak (minutes)	Duration (hours)
Immediate release oral tablet*	30	60	3-4
Intravenous**	5	15	3-4

*morphine, hydromorphone, hydrocodone, oxycodone
**morphine, hydromorphone

Compelling Indication (for formulation): Severity of Pain

www.hhs.texas.gov/sites/default/files/documents/doing-business-with-hhs/provider-portal/QMP/PainMedicationTable.pdf.
www.sciencedirect.com/topics/medicine-and-dentistry/hydromorphone.
Alexander. Perioperative uses of intravenous opioids: Specific agents. UpToDate.

Opioid Pharmacokinetics

Methadone

- Long and variable half-life
- Available as a high concentration oral solution
- PRV – patient with persistent pain; cannot swallow

Transdermal fentanyl

- Poor absorption in cachexia
- PRV – patient with persistent pain; normal body habitus

Lugo. *J Pain Palliat Care Pharmacother*. 2005;19(4):13-24.
Kuip. *Br J Clin Pharmacol*. 2017;83(2):294-313.

Opioid Pharmacokinetics

All opioids metabolized by liver

- This is not a discriminating variable
- Caution with liver impairment
- For all opioids – start low and go slow
- Decrease dose, same dosing interval

Opioid Pharmacokinetics

- Some opioids and/or their metabolites are renally excreted
- How do we handle patients with renal impairment?
- Morphine- and hydromorphone-3-glucuronide can cause neurotoxicity
  - Hyperalgesia, myoclonus, seizures, death

Favorable	Unfavorable
Buprenorphine	Codeine
Fentanyl	Dihydrocodeine
Hydromorphone	Hydrocodone
Methadone	Morphine
Nalbuphine	Oxycodone
Tapentadol	Tramadol

Dean. *J Pain Symp Manag*. 2004;28(5):497-504.

Opioids

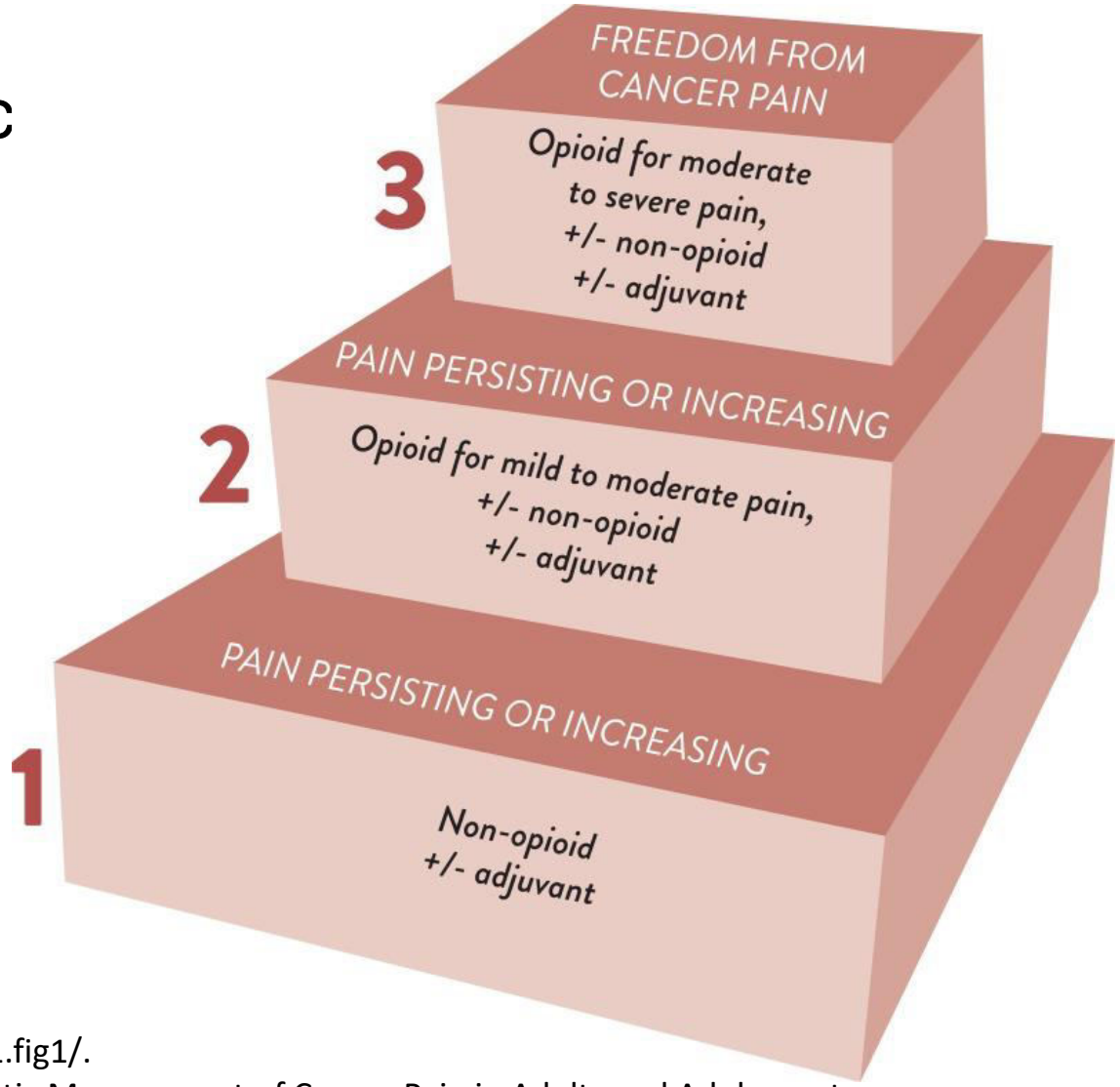
- Indications:
  - Treatment of severe pain that does not respond to nonopioids alone
  - Cough, diarrhea, dyspnea, opioid dependence
- Role in therapy:
  - Acute (trauma, postoperative pain)
  - Breakthrough pain
  - Cancer pain
  - Chronic noncancer pain (when all else has failed)
  - Effective in visceral and somatic pain; and (to a lesser extent) neuropathic pain
  - Frequently given with nonopioid therapy (opioid-sparing)
  - Management of opioid addiction (methadone, buprenorphine)

Opioids for Pain Management

- Are all painful conditions amenable to opioid treatment?
  - Consider benefits and burdens of therapy
- If an opioid is appropriate, should it be monotherapy? Which opioid? When should an adjuvant be used?
- If an opioid is appropriate, should a tamper-resistant formulation be used?
- If the patient doesn't respond to the first opioid, or has an adverse outcome, should we switch to a different opioid?
- Are there special considerations when switching to methadone?

Management of Cancer Pain

- Pharmacologic and nonpharmacologic interventions
- Patient, family, caregiver education
- Ongoing evaluation and modification of the treatment plan
- WHO 3-step ladder



www.ncbi.nlm.nih.gov/books/NBK537489/figure/appannex1.fig1/.
WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents.

WHO Step II-III Opioids

- For patients with mild to moderate pain, or pain is not adequately controlled by acetaminophen or an NSAID given regularly:
  - Addition of a step II opioid recommended (codeine, tramadol)
  - Consider use of a lower-dose step III opioid (morphine, oxycodone)
- The data show no importance differences between morphine, oxycodone and hydromorphone given by the oral route of administration
- Any can be used as the first choice step III opioid for moderate to severe cancer pain

Caraceni et al. *Lancet Oncol*. 2012:13:e58-e68.

Opioid Effectiveness in Cancer Pain

- Opioids are considered the gold standard for treatment of moderate to severe cancer pain
- Literature search 1996-2010
  - Observational studies for chronic cancer pain treated with opioids
  - 18 studies reviewed; 7 met inclusion criteria
- Result was a 1C/strong recommendation with benefits clearly outweighing risks and burdens

Colson et al. *Pain Physician*. 2011;14:E85-102

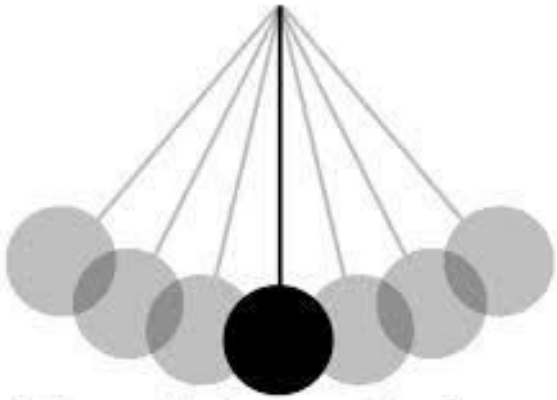
Oral Morphine for Cancer Pain

- Effectiveness of oral morphine in treating moderate to severe cancer pain.
- 62 studies with 4241 participants
- > 9/10 had pain that went from moderate or severe before taking morphine to pain that was ≤ mild pain
- > 6/10 were very satisfied with morphine treatment; results very good or excellent
- 1 in 20 DC'ed therapy due to side effects (N, V, C)

Wiffen, Wee, Moore. Oral morphine for cancer pain. *Cochrane Database Syst Rev.* 2013;7. Art. No.: CD003868. DOI: 10.1002/14651858.CD003868.pub3.

Opioids in Chronic Noncancer Pain?

- Until latter part of the 1990s, long-term opioid therapy for CNCP was prohibited in most US states.
- Data on long-term safety emerged; advocacy groups lobbied to lift the relative prohibition on opioid use in CNCP
- Data on efficacy for opioid use in CNCP lacking
- Increasing mortality from accidental poisoning, concomitant with dramatically increasing average daily morphine equivalent doses developed quickly



Pendulum Swing

Franklin; American Academy of Neurology. *Neurology*. 2014;83(14):1277-1284.

AHRQ and CDC

- **The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain**
  - "Evidence on long-term opioid therapy for chronic pain is very limited but suggests an increased risk of serious harms that appears to be dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies."
- **CDC**
  - ***"The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use."***

www.ahrq.gov/research/findings/evidence-based-reports/opoidstp.html.
CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016; www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm.

Opioid Responsiveness

- Pseudo-resistant
  - Dose too low, patient not absorbing opioid, genetic variation
- Semi-opioid resistant pain
  - Bone metastases, some neuropathic pain, activity-related (some musculoskeletal pain)
  - Skin ulceration, bladder and rectal tenesmus
- Opioid-resistant pain
  - Some neuropathic pain, muscle spasm
  - Chronic visceral or central pain syndromes
    - Abdominal or pelvic pain; pancreatic pain
    - Fibromyalgia
    - Headaches
    - Chronic low back pain

Sacks et al. Fast Facts and Concepts #215: Opioid poorly-responsive cancer pain. Palliative Care Network of Wisconsin. 2015. www.mypcnow.org/fast-fact/opioid-poorly-responsive-cancer-pain/.
Berland, Rodgers. *Am Fam Physician*. 2012;86(3):252-258.

American Academy of Neurology

- **Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology**
- Opioids are not recommended for treating:
  - Tension-type headaches
  - Fibromyalgia
  - Chronic low back pain

Franklin; American Academy of Neurology. *Neurology*. 2014;83(14):1277-1284.

Self-Assessment!

- For which patient populations have opioids been shown to be consistently, conclusively effective?

  A. Cancer pain
  B. Noncancer pain
  C. Both A and B
  D. Neither A nor B

Self-Assessment!

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C. Both A and B
D. Neither A nor B

Which Opioid?

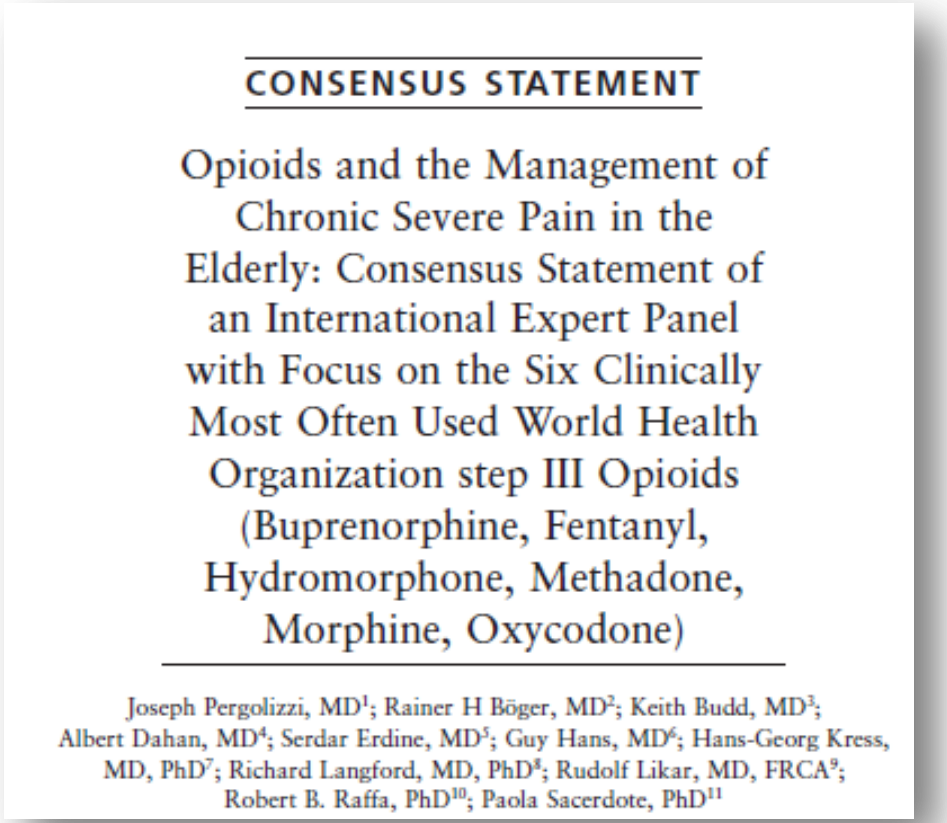
- Eenie-Meenie Miney Mo'phine:
  Why morphine isn't ALWAYS the answer to pain

www.greekmyths-greekmythology.com/morpheus-the-god-of-dreams/.

First Line Opioids

- Morphine
- Oxycodone
- Hydromorphone
- Methadone
- Buprenorphine
- Fentanyl

So what?
Pick any opioid?



CONSENSUS STATEMENT

Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization step III Opioids (Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone)

Joseph Pergolizzi, MD[1]; Rainer H Böger, MD[2]; Keith Budd, MD[3]; Albert Dahan, MD[4]; Serdar Erdine, MD[5]; Guy Hans, MD[6]; Hans-Georg Kress, MD, PhD[7]; Richard Langford, MD, PhD[8]; Rudolf Likar, MD, FRCA[9]; Robert B. Raffa, PhD[10]; Paola Sacerdote, PhD[11]

Pergolizzi, Böger, Budd, et al. *Pain Pract*. 2008;8(4):287-313.

The Opioid Parade – Morphine

- Trade name – MS Contin, Kadian, Infumorph, Oramorph
- MOA – agonist at the mu and kappa (weak) opioid receptors
- Metabolism – glucuronidation
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other
  - 55% is metabolized to morphine-3-glucuronide causes neurotoxicity in severe renal impairment (hyperalgesia, myoclonus, seizures, death)
  - Causes most histamine release of all opioids (itching, hypotension)
  - Morphine is the active metabolite of codeine via 2D6 CYP enzyme.

go.drugbank.com/drugs/DB00295.

The Opioid Parade – Hydromorphone

- Trade name – Dilaudid
- MOA – agonist at the mu and kappa (weak) opioid receptors
- Metabolism – glucuronidation
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other – hydromorphone-3-glucuronide causes neurotoxicity in severe renal impairment (hyperalgesia, myoclonus, seizures, death)

go.drugbank.com/drugs/DB00327.

The Opioid Parade – Oxycodone

- Trade name – OxyContin, Roxicodone, Xtampza ER; Percocet, Endocet
- MOA – agonist at the mu receptor
- Metabolism – CYP 3A4 and 2D6
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other
  - Often given in combination with acetaminophen

go.drugbank.com/drugs/DB00497.

The Opioid Parade – Fentanyl

- Trade name – Duragesic (TD); Fentora, Lazanda, Subsys, Actiq
- MOA – agonist at the mu receptor
- Metabolism – CYP 3A4
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other
  - TD and TM require patient to be “opioid tolerant”
    - Receiving 60 mg a day or oral morphine or equivalent for at least a week
  - Fentanyl is highly lipophilic, therefore faster onset, shorter duration for immediate release formulations
  - Reduce dose for continuous infusion and TDF in severe renal impairment
  - Caution with TDF with cachexia
  - Better choice for patients with renal impairment

go.drugbank.com/drugs/DB00813. online-lexi-com.ezproxymcp.flo.org/lco/action/doc/retrieve/docid/patch_f/6903.
online-lexi-com.ezproxymcp.flo.org/lco/action/doc/retrieve/docid/patch_f/6903.

The Opioid Parade – Methadone

- Trade name – Dolophine
- MOA – agonist at the mu receptor; NMDA receptor antagonist (probably at higher doses); inhibits reuptake of serotonin
- Metabolism – CYP 2B6, 3A4, 2D6, 2C19, 2C9
- Drug interactions
  - Caution with CNS depressants (benzodiazepines, alcohol)
  - Caution with other medications that prolong QTc
  - Caution with enzyme inhibitors (there are MANY; ask about 3 A's – anti-infectives, antidepressants, amiodarone)
  - Note combination with enzyme inducers

online-lexi-com.ezproxymcp.flo.org/lco/action/doc/retrieve/docid/patch_f/7262.

The Opioid Parade – Methadone

- Other
  - Methadone is lipophilic, long and variable elimination half-life (average 24 hours); 4-14 days to steady state
  - Prolongs QTc
  - Opioid-naïve patients – 2-5 (or even 7.5 mg po qd)
  - Opioid-tolerant patients ($\geq$ 60 mg OME per day)
    - 10:1 (morphine:methadone) if < 200 mg OME and 65 yo
    - 20:1 (morphine:methadone) if $\geq$ 200 mg OME and/or $\geq$ 65 yo
    - Do not exceed 30-40 mg as a TDD starting dose
  - Do not adjust dose before 5 days if possible

Add citation

The Opioid Parade – Hydrocodone

- Trade name – Hysingla ER, Zohydro ER; Vicodin, Lortab, Norco (with acetaminophen)
- MOA – agonist at the mu and kappa receptors
- Metabolism – CYP 3A4, 2D6
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other
  - IR not available as a single entity product
    - With acetaminophen (Vicodin, Lortab, Norco)
    - With ibuprofen (Vicoprofen)
    - With cough agents in cough syrups

Add citation

The Opioid Parade – Buprenorphine

- Trade name – Butrans, Buprenex, Belbuca, Probuphine (Implant Kit)
- MOA – partial agonist at mu opioid receptor and antagonist at the kappa opioid receptor
- Metabolism – CYP 3A4
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol)
- Other
  - Higher affinity for mu opioid receptor than full opioid agonists – may diminish analgesic effect of full mu opioid receptor agonists
  - Used for opioid replacement therapy for recovering substance abusers, often in combination with naloxone (Suboxone, Zubsolve, Bunavail)
  - TDB may be used in opioid-naïve patient
  - May prolong QTc

Add citation

The Opioid Parade – Tramadol

- Trade name – Ultram, Ultram ER, ConZip
- MOA – weak mu opioid agonist; inhibits reuptake of serotonin and norepinephrine
- Metabolism – CYP 3A4, 2D6, 2B6
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol, bupropion, TCAs, SSRIs, SNRIs)
- Other
  - Increases seizure risk; may increase risk of hypoglycemia
  - Increases risk of serotonin syndrome
  - Often in combination with acetaminophen (Ultracet)

Add citation

The Opioid Parade – Tapentadol

- Trade name – Nucynta, Nucynta ER
- MOA – agonist at mu opioid receptor; inhibits reuptake of norepinephrine
- Metabolism – CYP 2D6, 2C9
- Drug interactions – caution with CNS depressants (benzodiazepines, alcohol, SSRIs, SNRIs)
- Other
  - Increases risk of serotonin syndrome
  - Unknown if it increases seizure risk (seizure history was an exclusion in clinical trials)

Add citation

The Opioid Parade – Prefer to Avoid

- Codeine
  - Very nauseating
  - Pro-drug – must be metabolized to morphine by CYP 2D6 (genetic variability)
  - Very dangerous in pediatrics
- Meperidine
  - Metabolized to normeperidine, a neurotoxin. May cause myoclonus, seizures, coma, death
  - Used to present post-op and amphotericin-induced twitching/rigors

Add citation

Other Opioid Effects

- Opioid bowel dysfunction
- Somnolence and mental clouding
- Nausea and vomiting
- Myoclonus
- Neuroendocrine effects
- Sleep-disordered breathing
- Respiratory depression
- Pruritus
- Allergic reaction
- Urinary retention
- Opioid-induced hyperalgesia

Opioid Adverse Effects (Cochrane Database)

- Absolute event rate for any adverse event with opioids in trials vs placebo was 78%
- Absolute event rate of 7.5% for any serious adverse event (chronic non-CA pain)
- Risk ratio greater for
  - Any adverse event with opioids vs placebo (RR 1.42)
  - Compared to nonopioid active pharmacological comparator (RR 1.21)
  - A serious adverse event with opioids vs placebo (RR 2.75)
  - Increased RR for specific adverse events (constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, vomiting)

Els, Jackson, Kunyk, Lappi, Sonnenberg, Hagtvedt, Sharma, Kolahdooz, Straube.
Cochrane Database Syst Rev. 2017;10. Art. No.: CD012509.

Opioid Adverse Effects

- Constipation
  - Up to 90% of patients receiving opioids
  - AVOIDABLE!
  - MOA
    - Inhibition of propulsive peristalsis through the small bowel and colon
    - Colonic transit time is lengthened
    - Exacerbates fluid and electrolyte absorption, leading to harder, dryer stools
    - Occurs within 5-25 minutes of opioid use
  - Patient complain of
    - Development or worsening of straining
    - Sensation of incomplete evacuation
    - Reduced frequency
    - Harder stool consistency

Happy is the patient in the PM, who has a bowel movement in the AM!

addcitation

Opioid Adverse Effects

- Bowel regimens
  - Surfactants – docusate sodium/calcium
  - Stimulant laxatives – bisacodyl, senna, senna/docusate
  - Osmotic agents – polyethylene glycol, lactulose, sorbitol, glycerin, magnesium sulfate/citrate
  - PAMORAs – methylnaltrexone, naloxogol, naldemidine
  - Enemas – docusate, sodium phosphate, bisacodyl, mineral oil, enemeez (docusate/PEG/glycerin/benzocaine)
  - Other – lubiprostone, linaclotide
- Fecal Impaction/Incontinence

Add citation

Opioid Adverse Effects

- Nausea and vomiting
  - Prevalence ~ 25%
  - Due to activation of the chemoreceptor trigger zone and vomiting center
  - Tolerance usually develops in 3-5 days
  - Treatment
    - Dopamine antagonist (haloperidol, prochlorperazine, olanzapine)
    - Ondansetron less effective
- Sedation
  - Incidence 20-60%
  - Common in opioid-naïve patients and with dosage escalation
  - Rule out pain-induced sleep deprivation, other causes
  - Management – opioid dose reduction/rotation, psychostimulant (methylphenidate)

Add citation

Opioid Induced Sedation

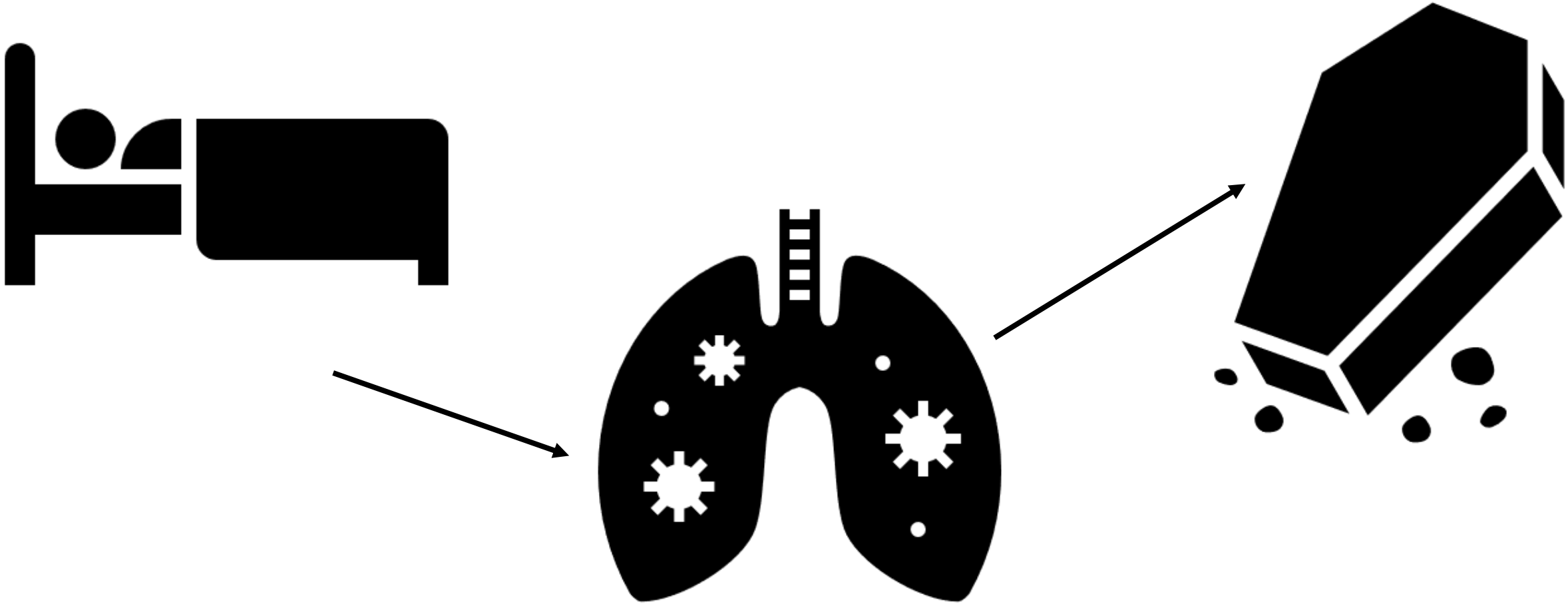
- Sedation most common upon dose initiation and escalation.
- Most patients develop tolerance within days to weeks.
- Symptoms may persist in patients with contributing factors such as early dementia, or concurrent drugs (benzodiazepines)
- Severity ranges from slight inattention or fatigue to disorientation and extreme confusion and delirium.

Richmond Agitation Sedation Scale (RASS)

Target RASS	RASS Description
+ 4	Combative, violent, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent nonpurposeful movement, fights ventilator
+ 1	Anxious, apprehensive , but not aggressive
0	Alert and calm
- 1	awakens to voice (eye opening/contact) >10 sec
- 2	light sedation, briefly awakens to voice (eye opening/contact) <10 sec
- 3	moderate sedation, movement or eye opening. No eye contact
- 4	deep sedation, no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable, no response to voice or physical stimulation

Adapted from Sessker et al. *Am J Respir Crit Care Med*. 2002;166:1338-1344.

Respiratory Depression



Respiratory Depression

- If minimal/no response and resting respiratory rate < 8 bpm and pinpoint pupils, strongly consider opioid antagonist such as naloxone
- Naloxone
  - Semisynthetic derivative of thebaine, competitive antagonist at opioid receptors in the brain
  - In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression and hypotension within:
    - 1-2 minutes after IV administration
    - 2-5 minutes after IM or SC administration
  - Half-life is 30-80 minutes; protective effect may wear off in 45 minutes after IV administration of a low dose

Respiratory Depression

- If minimal/no response and resting respiratory rate < 8 bpm and pinpoint pupils, strongly consider opioid antagonist such as naloxone
- Naloxone
  - 0.4 and 1 m/ml solution available for IV, IM or SC administration
  - Dose 0.4-2 mg IV for adults
    - Can repeat every 2-3 minutes up to a total of 10 mg
    - In monitored settings: Push 0.04 mg/minute until patient rousable
  - Naloxone can be administered intransally using a mucosal atomizer device
    - Syringe attached to a spray tip that fragments the medication into a fine mist
    - Dose if 2 mg (1 mg per nostril) which can be repeated in 3-5 minutes

add

Opioid Adverse Effects

- Delirium and Confusion
  - Elderly at greatest risk
  - Minimize other delirium/confusion risk factors
  - Can occur with initiation and with dosage escalation
  - Treatment
    - Maximize nonpharmacologic interventions
    - Use lowest opioid dose possible
    - Consider mood stabilizer, if patient at risk for harming themselves or other, may consider antipsychotic agent

aaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaaa

Opioid Adverse Effects – Other

- Pruritus
  - Incidence 2-10%
  - Probability increases when opioids are given by neuraxial route
  - Considered an adverse effect, not an allergic reactions
    - Opioid rotation, nondrug therapy, antihistamines (not preferred)
- Bradycardia, hypotension
  - Incidence 3% (morphine closer to 10%)
  - Rule out other causes; consider opioid rotation
- Urinary retention
  - Less common
  - Minimize anticholinergic drugs and rule out other causes
  - Opioid rotation, reduce opioid dose, catheterization if needed

Chronic Opioid Use (Opioid-induced):

Immunologic effects
Hormonal changes
Hyperalgesia
Breathing disorders

add

Take it back! Not true!

- Taking an opioid or increasing the dose means the end is near, OR…
- If the end of life is near, morphine or other opioids can't be increased without causing death
- Addiction to opioids is very common and occurs easily
- Addiction to opioids when used for advanced illness never occurs
- Pain medications can and should only be prescribed to be given to the patient for "prn" use – when the pain occurs
- Pain is an unavoidable part of any illness
- The only way that pain can be treated is with injections
- The side effects of opioids can kill a patient
- Enduring pain builds strength and character
- Providers have to choose between treating the disease and treating the pain

Palliative Care and the Opioid Crisis

- Ten Pragmatic Steps Towards a More Rational Use of Opioids
  1. Admit the problem
  2. Understand the neurobiology of non-nociceptive systems
  3. Screening: identify patients at risk
  4. Tapering: do not forget to stop opioids whenever possible
  5. Monitor over time and consider further surveillance measures
  6. Consider alternative interventions and be aware of the psycho-social aspects of pain
  7. Be cautious with rapid onset formulations
  8. Establish structured interdisciplinary collaborations
  9. Start educating patients and staff about the safe use, storage, and disposal of opioids
  10. Continue fighting opioiphobia

Gaertner, Boehlke, Simone, Hui. *Ann Palliat Med*. 2019;8(4):490-497. doi:10.21037/apm.2019.08.01

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Opioid Pharmacology

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