Managing Chronic Pain:
A Multi-Modal Approach Involving Pharmacotherapy

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Disclaimer/Disclosure

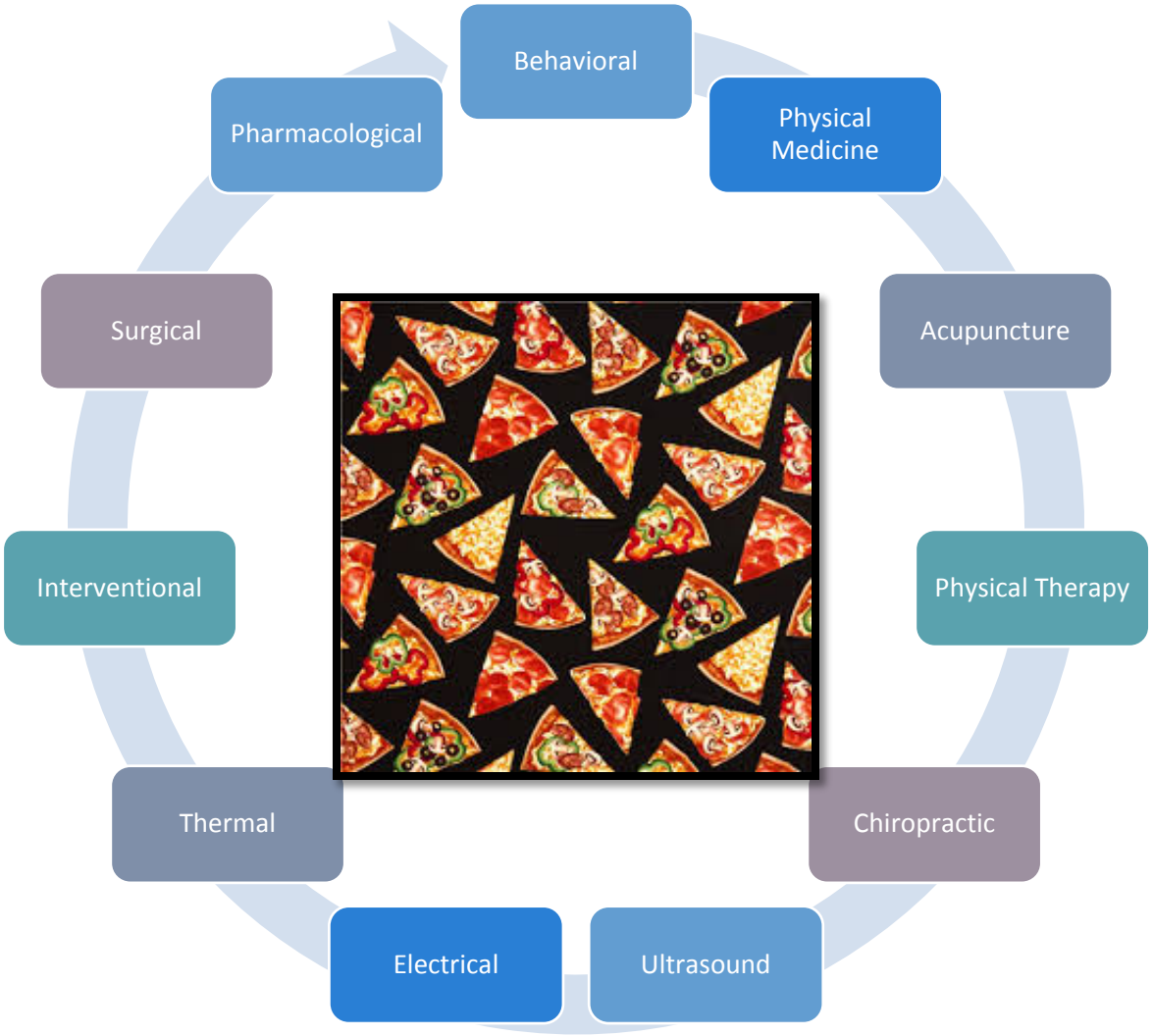
- I have *no* financial disclosures or conflicts of interests to make for this ACPE Educational Program

Objectives/Expectations

At the completion of this activity, the participant will be able to:

- Review the pharmacology of commonly used medications to manage chronic pain
- Understand the applications of naloxone in opioid overdose

The Multi-Modal Approach to Pain



Pharmacological therapy is only ONE slice of the pie

Ellen, 19 year old female

- Reason for visit
  - Bilateral knee pain
  - Swelling
- What are some options?

Ellen

- Social history
  - Athletic during high school
  - 1st year community college
  - Lives with her family
- PMH
  - Chronic Kidney Disease
- What are treatment options?

Acetaminophen (Tylenol)

Most commonly administered OTC analgesic

Known as paracetamol in Europe

Useful in mild pain, headaches, fever

- NO anti-inflammatory properties

Commonly combined with opioids to reduce the opioid dose (difficult to titrate)

Acetaminophen Combination Prescription Products

Product Name	Components	APAP strength
Tylenol w/ Codeine®	APAP Codeine	300mg
Lortab®	APAP Hydrocodone	500mg
Norco®	APAP Hydrocodone	325mg
Vicodin®	APAP Hydrocodone	500, 750mg (ES)
Percocet®	APAP Oxycodone	325, 500, 650mg
Ultracet®	APAP Tramadol	325mg
Fioricet®	APAP Butalbital Caffeine	325mg

FDA Update: March 26, 2014: Note: *Manufacturers discontinued combination products with APAP >325mg*

Josh, 27 year old male

- Reason for visit:
  - Bilateral knee pain
  - Swelling
- What are some options?

Josh

- Social history
  - Lives with two friends, eats out frequently
  - Employed, sits at a desk during the day
- PMH
  - Alcohol misuse
  - Pre-diabetes
- What are treatment options?

Non Steroidal Anti-Inflammatory Drugs

Primarily used for mild to moderate pain

- Anti-inflammatory at higher doses

Ketorolac often used for severe pain (it works)

- 5 day maximum (bleeding risks)

Tissue injury, strains, sprains, headaches, arthritis, gout

Synergistic with opioids

Common side effects:

- Bleeding (interfering with platelet aggregation)
- GI upset
- Nephrotoxic (reversible, vasoconstriction)
- CVD (interferes with ASA, potentiate heart failure, raises BP)?

NSAIDs and Cardiovascular Risk

FDA Warnings for NSAIDs

- Risk of CV events can occur as early as first weeks use and may increase over time
- Risk appears greater at higher doses
- Individual CV risk profiles should be evaluated prior to prescribing
- Administration of NSAIDs may interfere with aspirin's cardio-protective effect
- NSAIDs should be avoided in heart failure patients
- Lowest effect dose should be used for the shortest duration
- Use with caution in HTN patients

https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

Mike, 48 year old

- Reason for visit
  - Pain scores 5-7
  - Pain most days
- What are treatment options?

Mike, 48 year old

- Social history
  - Unknown
- PMH
  - Cirrhosis
  - GI bleeds
  - Misuse of substances
- What are treatment options?

Tramadol and Tapentadol

Not acetaminophen

- Can be an option in cirrhosis/alcoholic patients

Not an NSAID

- Can be an option in GI bleeds/ARF
- Note: Avoid in severe renal impairment

Not a true opioid

- Binds to the mu-receptor + inhibits serotonin/NE
- Similar side effects as opioids (but less)

Dosing

- Tramadol (Ultram) 25mg PO Q4-6H (max 300mg…Schedule IV in NY)
- Tapentadol (Nucynta) 50mg PO Q4-6H (max 600mg)…Schedule II in NY)

Note: Risk of interaction with serotoninergic drugs (serotonin syndrome)

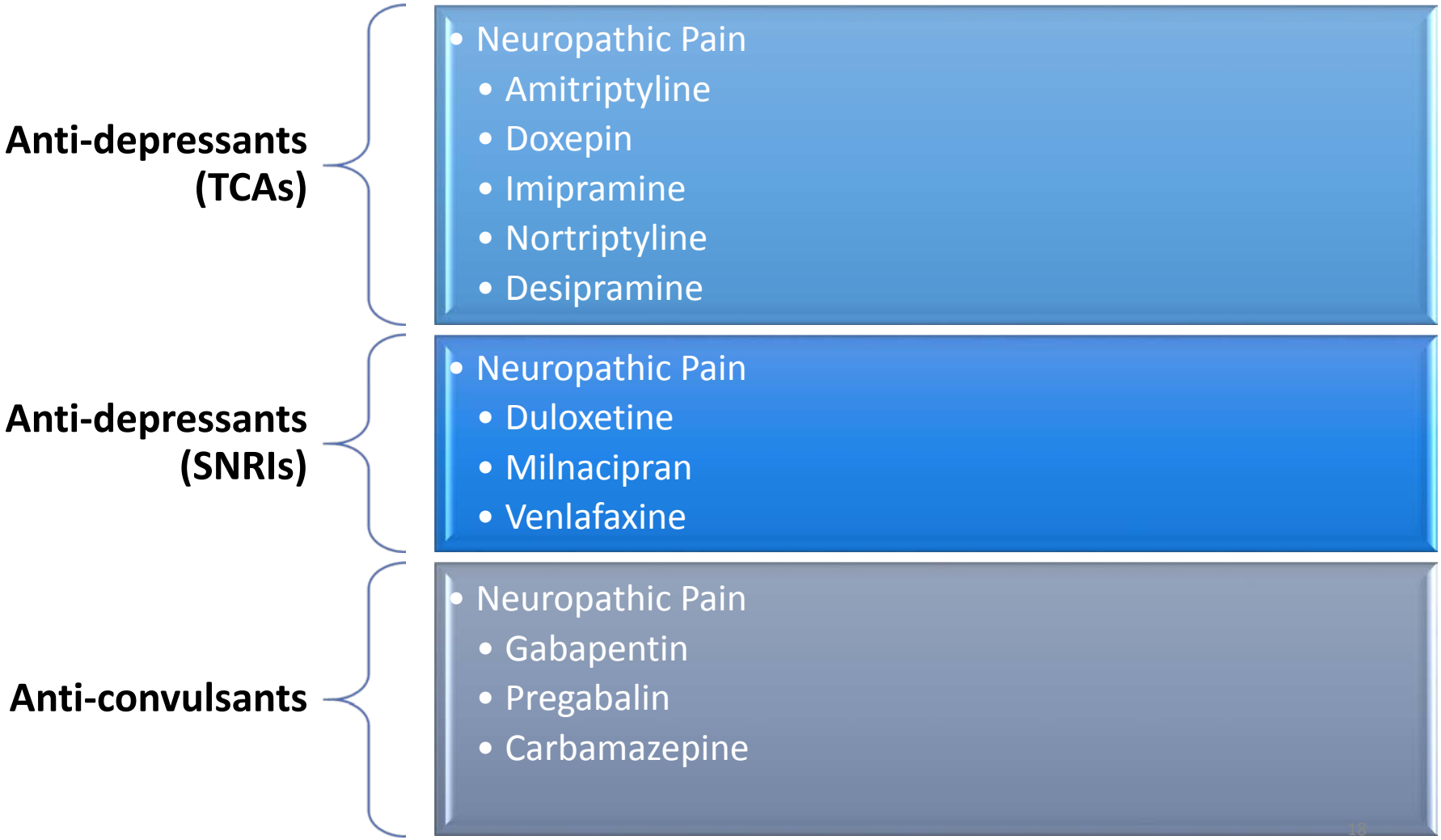
Jessica, 61 year old female

- Reason for visit
  - Medication review
  - Elevated A1c
- What is the main concern for this patient?

Jessica

- Social history
  - Lives with family
  - Unemployed but wants to be employed
- PMH
  - Diabetes for 17 years
  - Feet are sore
  - Wants to put a needle in toe to help relieve the pain
  - No touching the feet!

Neuropathic Pain



Anti-depressants for Pain

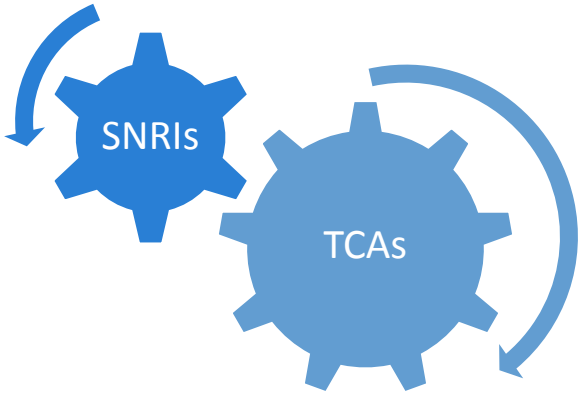
Considered 1st or 2nd line for neuropathic pain

Analgesic effect appears sooner vs. anti-depressant effects

Doses are lower for pain vs. depression

All TCAs are used off-label for pain (no FDA indication)

Some SNRIs (duloxetine & milnacipran) have FDA indications



Structurally similar agents

TCAs

Drug	Starting Doses for Pain	Frequency	Maximum Dose	Side effects
Amitriptyline (Elavil)	25-50mg	daily	150mg/day	• Anticholinergic • Orthostatic hypotension • QT prolongation • Sedation
Desipramine (Norpramin)	25mg	daily	150mg/day	
Imipramine (Tofranil)	50mg	daily	150mg/day	
Nortriptyline (Pamelor)	10-20mg	daily	160mg/day	

Should all be taken at bedtime for sedation reasons

SNRI's

Drug	Starting Doses for Pain	Frequency	Maximum Dose	Side effects
Duloxetine (Cymbalta)	60mg	daily	120mg/day	• Headache • Drowsiness • Weight loss
Milnacipran (Savella) ***Approved only for Fibromyalgia***	50mg	Twice daily	200mg/day	• Headache • Hot flashes • Nausea
Venlafaxine (Effexor) ***Used "off label"***	37.5 – 75mg	daily	225mg/day	• Headache • Drowsiness • Sweating • Weakness • Hypertension

Anti-convulsants for Pain

Considered 1st or 2nd line for neuropathic pain

Binds to calcium channels to inhibit neurotransmitter release

Used for diabetic neuropathy, post-herpetic neuralgia, fibromyalgia

Pregabalin may work faster than gabapentin

Pregabalin is a Schedule V medication (euphoria)

Carbamazepine approved for Trigeminal Neuralgia (5th cranial nerve)

Anti-convulsants for Pain

Drug	Starting Doses for Pain	Frequency	Maximum Dose	Side effects
Gapabentin (Neurontin)	300mg	daily	3600mg/day	• Dizziness • Sedation
Pregabalin (Lyrica)	75mg	Twice daily	600mg/day	• Peripheral edema • Dizziness • Drowsiness
Carbamazepine (Topamax)	100mg	Twice daily	1200mg/day	• 232323

Don’t forget your Topical Options..

NSAIDs	• Diclofenac 1.5% topical (Voltaren Gel)
Local Anesthetics	• 5% Lidocaine patch or gel • Good for localized neuropathic pain
Counterirritants	• Capsaicin 0.025% cream (Zostix) • Methylsalicylate 15% cream (BenGay) • Menthol 2.5% cream (Icy Hot) • Camphor 11% (Tiger Balm)

Sandy, 53 year old female

- Reason for visit:
  - Follow up with Primary Care Provider after emergency/urgent care visit

Sandy

- Social history
  - Lives alone
  - Has adult children
- PMH
  - Pain, breathing difficulty, hypertension
  - Lisinopril 5mg
  - Amitriptyline 100mg every night
  - Xanax 1mg as needed
  - Opioid naïve

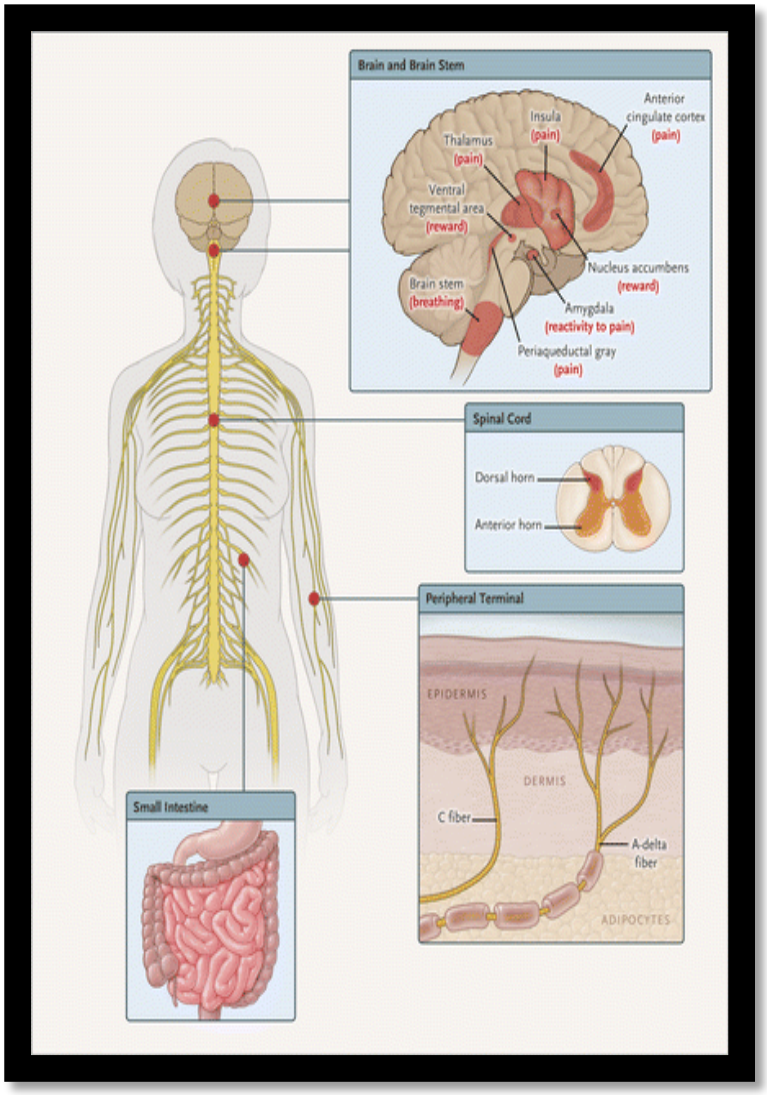
Patient has a rx for Norco 7.5/325mg 1-2 tabs every 4 hours for pain. #90

Opioid Receptors

- Three opioid receptors:
  - mu (μ)
  - delta (δ)
  - kappa (κ)
- Mechanism of Action:
- All opioids produce effects through binding mu-receptors
  - Full agonists
  - Partial agonists
  - Mixed (partial agonists/antagonists)
  - Antagonists

mu receptors found throughout the body (CNS + PNS + Stomach)

Note: we have endogenous opioids called "endorphins"



http://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2016/nejm_2016.374.issue-13/

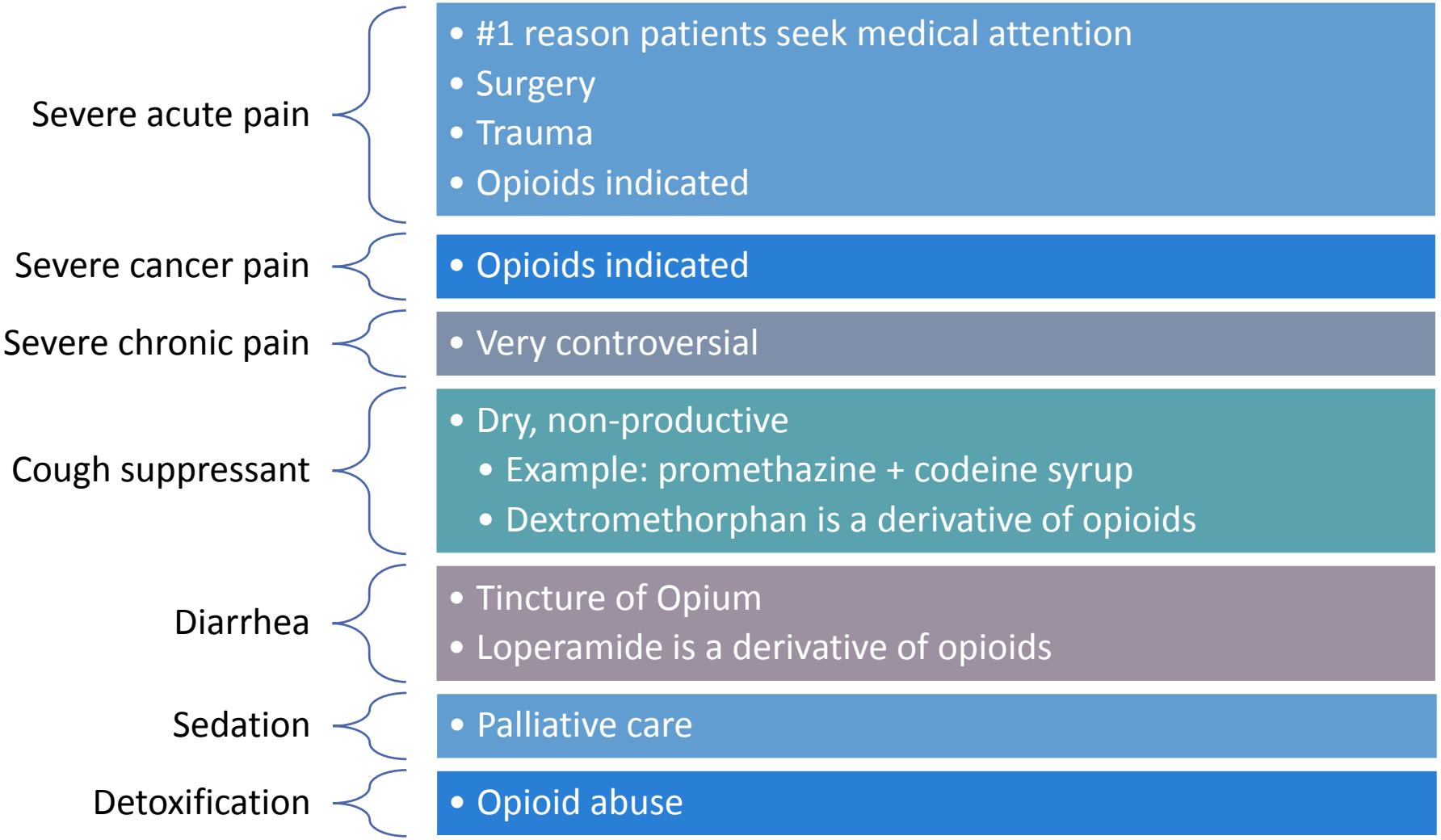
Opioid	mu (μ)	delta (δ)	kappa (κ)
Morphine Hydromorphone Oxymorphone Methadone Fentanyl	+++ (full)		
Codeine Hydrocodone Oxycodone	± (partial)		
Buprenorphine	± (mixed)	-- (mixed)	-- (mixed)
Naloxone Naltrexone Methylnaltrexone	--- (antagonist)	- (antagonist)	- (antagonist)

Binding: mu receptors

Desired: analgesia

Other Effects: bradycardia, sedation , euphoria, respiratory depression, dependence , miosis

Medical Uses of Opioids



Common Opioids

Codeine	• Used mainly for mild pain or cough (off-label) • Antitussive effects directly suppresses cough reflex in the medulla • Converted to active morphine via CYP2D6
Hydrocodone	• Used in moderate pain with APAP • Converted to hydromorphone by CYPD6
Morphine	• Used for moderate to severe pain • Standard to compare all opioids
Oxycodone	• Used in moderate-severe pain • IR also available with ibuprofen or aspirin
Hydromorphone	• Very potent opioid (severe pain)
Fentanyl	• Most potent opioid (doses are in mcg and NOT mg) • Mainly used in cancer pain or palliative care (sedation)

All C-II medications

Starting Opioids…Not so fast!

Define Treatment Success:

- Weigh expected benefits vs. risks ***carefully*** before initiating opioids
- Relieves pain while body heals and improves function

Opioids do not eliminate the pain:

- Decreases the unpleasantness of pain (perception)
- Patients will report that although pain is still present, it bothers them less

Short acting

- Can be used for severe acute pain
- Start with the lowest dose
- Start with easiest route (PO/IV/PR/PCA)

Long acting

- Not recommended upon initiation; avoid in opioid-naïve patients
- Not used PRN
- Reserved for cancer pain or palliative care
- Controversial for chronic pain

Side Effects of Opioid Use

Short-Term

- Constipation
- Itching
- Nausea & Vomiting
- Respiratory Depression
- Sedation
- QT Prolongation

Long-Term

- Hyperalgesia
- Fractures and falls
- Opioid Use Disorder

Controversy of Opioids for Chronic Pain

Opioids have not produced desired outcome

- Can worsen pain (hyperalgesia) and function

Long-term opioid use has NOT been validated in trials

- Most studies only go up to 6 weeks

Escalated doses in chronic pain

- Doses 50-100MED increases mortality 9 fold

Extensive evidence shows possible harms of opioids

- Abuse, dependence, overdose, side effects, hyperalgesia

Opioids controlling pain is no longer the ultimate goal

- Substantial risk vs. uncertain benefits

Signs of Opioid Overdose

http://www.fraserhealth.ca/health-info/health-topics/harm-reduction/overdose-prevention-and-response/recognizing-an-overdose/

What is Naloxone?

First approved as Narcan in 1971

- 80% was used for heroin overdoses

Reverses opioid effects

- Effective for 30-90mins

Can cause sudden withdrawal (unpleasant)

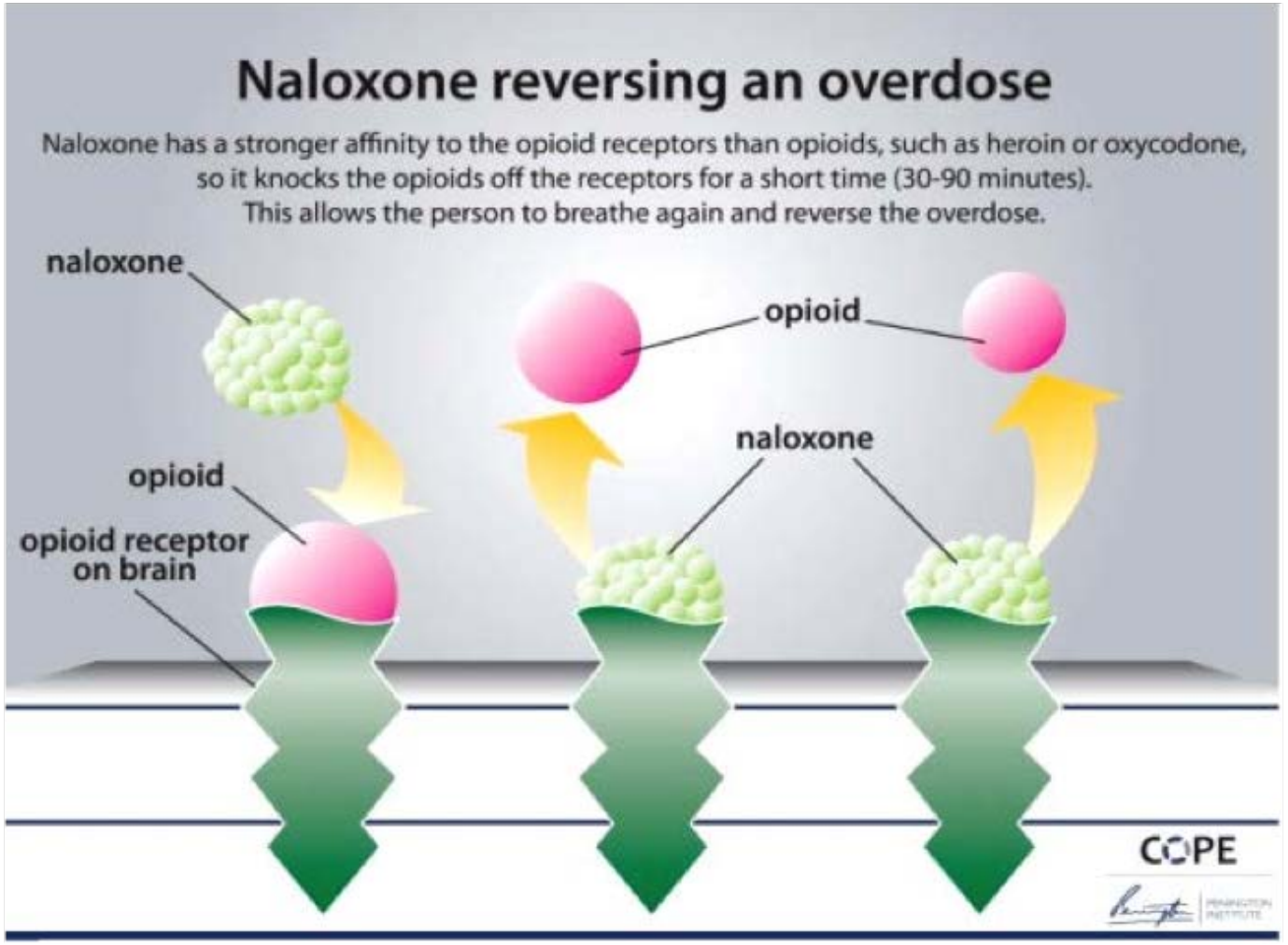
- Agitation, hypertension, violent behavior, fever, sweating

Safe and effective

- Not addictive

Pure opioid antagonist at the opioid receptors

- Inserting glue into a door lock
- Does not prevent deaths caused by other drugs
  - Benzodiazepines
  - Alcohol
  - Cocaine



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Naloxone

IV or IM or Intranasally

Evzio – Auto Injector

Naloxone Prices

Naloxone Product	Manufacturer	Previous price per year	Current Price (2016)
Injectable • 0.4mg/ml vial	Mylan	$23.72 (2014)	$23.72
Nasal spray • Single use • 2 pack	Adapt	$150 (2015)	$150
Auto-Injector (Evzio) • 2 pack pre-filled	Kaleo	$690 (2014)	$4500

Gupta R, Shah N, Ross J. The rising price of naloxone. Dec. 2016. NEJM 375;23. 2213-15

Sample prescription

Naloxone Prescription

Patient name: _____ DOB: _____

Origin Code: "5" – Pharmacy Created

- ☐ **EVZIO:** 2-Pack Auto-Injector 2mg/0.4mL or 2mg/0.4ml Solution for Injection
  SIG: Inject into outer thigh as directed by voice-prompt system. Place black slide firmly on outer thigh, depress, and hold for 5 seconds. Repeat with second device in 2-3 minutes if no or minimal response.
- ☐ **Naloxone:** HCl 0.4mg/mL vial (dispensed in 1 mL vial) and 1-3 mL syringe with 21-23 gauge 1-1.5 inch IM needle (dispense 2 vials and 2 syringes)
  SIG: Inject 1 mL intramuscularly into deltoid or thigh. Repeat after 2-3 minutes with no or minimal response.
- ☐ **Naloxone 2mg/2ml** pre-filled syringe
  SIG: Inject 2ml intramuscularly into deltoid or thigh. Repeat after 2-3 minutes with no or minimal response (dispense 2 pre-filled syringes with 2 refills).
- ☐ **Narcan:** 4mg/0.1mL Nasal Spray
  SIG: Spray 0.1ml into one nostril. Repeat with second device into other nostril after 2-3 minutes if no or minimal response.

Physician:

Leslie Belkov, MD

Naloxone kits

- Co-prescribe with long-term or high dose opioid use

What happens if you administer Naloxone to a person NOT using opioids?

A. Withdrawal
B. Sedation
C. Pain Relief
D. Nothing

Only Addicts Overdose?

Tolerance	• Decrease in pharmacologic response • Increase dose to achieve similar effects
Dependence	• High or chronic doses are abruptly d/c'd • Withdrawal symptom
Addiction	• Change in behavioral patterns • Despite the potential side effects and harm

Fred, 38 year old

- Reason for visit:
  - Refill on control substance medications

Fred

- Social history
  - Lives with partner and kids
  - Sits for work
- PMH
  - Tobacco smoker (wants to quit)
  - ADD, anxiety, chronic pain
  - MED = 480
  - Stimulant, BZD, sleeping pill
  - Naloxone kit at home

Discontinuing Opioids

Ideal

- Success of therapy + Quick cessation
- Patient returns to normal daily function

Less ideal

- Failure of therapy (use alternatives)
- Intolerable side effects (opioid rotation)
- Discuss withdrawal symptoms and agree on exit strategy (scheduled taper)

Not ideal at all

- Opioid hyperalgesia
- Development of opioid use disorder

Worse case

- Overdose
- Death

Clinical Pharmacist Tapering

- Slow and steady
  - 10% decrease per week
  - Reassess each week
- Patient centered
  - Address concerns and questions
- Alternative treatments
  - Non-opioid, NO BZDs
  - PT, RT, OT, Acupuncture
- Interdisciplinary team

Opioid Withdrawal Symptom Management

- Opioid withdrawal symptoms should not be treated with opioids or benzodiazepines
- Keep the withdrawal symptoms in the mild category
- First step to management of withdrawal symptoms = SLOW THE TAPER

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

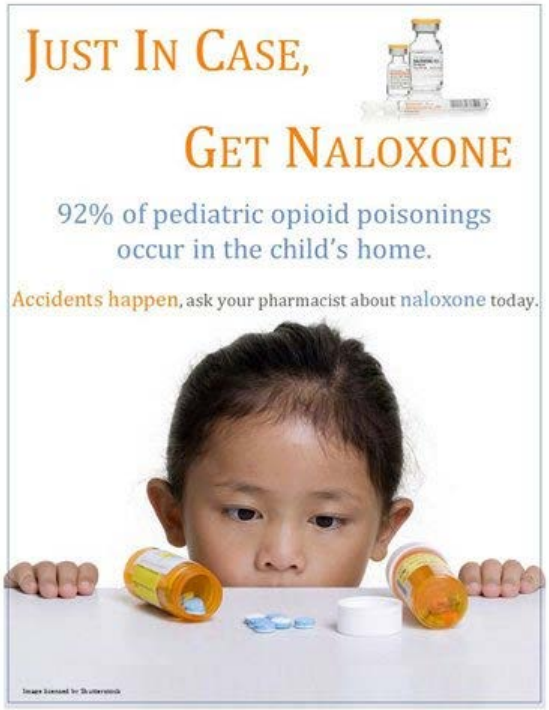
Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

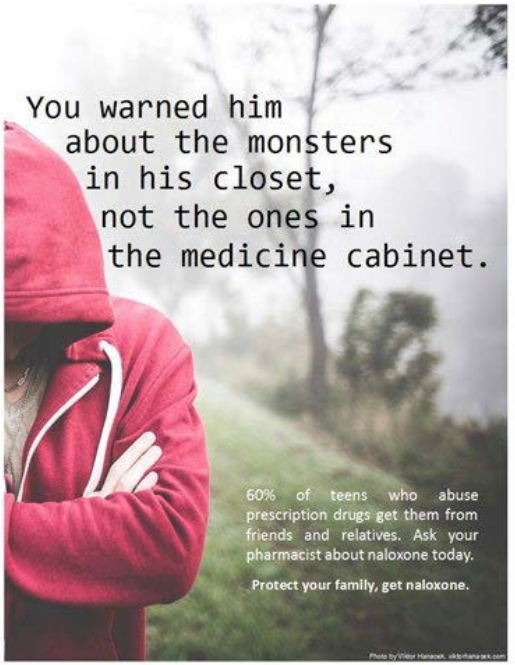
If needed, adjunctive therapy options:

- Clonidine 0.1mg PO two to three times daily as needed for hypertension, nausea, cramps, diaphoresis, tachycardia
- Trazodone 25-50 mg PO at bedtime as needed for insomnia
- Diphenhydramine 25-50 mg PO every four hours as needed for insomnia, restlessness
- Ibuprofen 200-400 mg PO every eight hours as needed for muscle aches
- Acetaminophen 500-1000 mg PO every six hours as needed for muscle aches; do not exceed 4000 mg / 24 hours
- Loperamide 2 mg PO after each loose stool; do not exceed 16 mg/day

Conclusions

- Assess pain, establish realistic goals, and form a plan before starting treatment
- Using a multi-modal approach is highly recommended
- Opioids are useful for severe acute and cancer pain
- Recognizing overdoses is important when prescribing opioids





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Pharmacological Options

Mild/Moderate Pain

- Non-opioid analgesic
  - APAP, Aspirin, NSAIDs, COX-2 Inhibitors
- Tramadol

Neuropathic pain

- Anti-depressants (TCAs or SNRIs)
- Anti-epileptics (gabapentin, pregabalin)

Adjuvant

- Muscle relaxants
- Topical analgesics

Severe pain

- Opioids

Table of Select Non-Opioid Analgesics

Drug	Average Dose	Frequency	Maximum Dose	Side effects
Acetaminophen	500-1000mg	Q4-6H	4 grams	Liver toxicity in overdose
Aspirin	500-1000mg	Q4-6H	4 grams	GI, bleeding, renal
Ibuprofen	200-400mg	Q4-6H	2400mg	GI, bleeding, renal
Naproxen	250-500mg	Q6-8H	1500mg	GI, bleeding, renal
Ketorolac	15-30mg	Q6H	150 mg first day then, 120mg thereafter. 5 day maximum	GI, bleeding, renal
Celecoxib	100-200mg	Q12H	400mg	GI (less), bleeding, renal Cardiac/Stroke risk?