Pain Management CME

JUNE 15, 2020

Session 1: Bringing pain management to a different Hight of safety

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Improving pain care in an era challenged by the opioid crisis

Pain is a national public health problem with profound physical, emotional, & societal costs

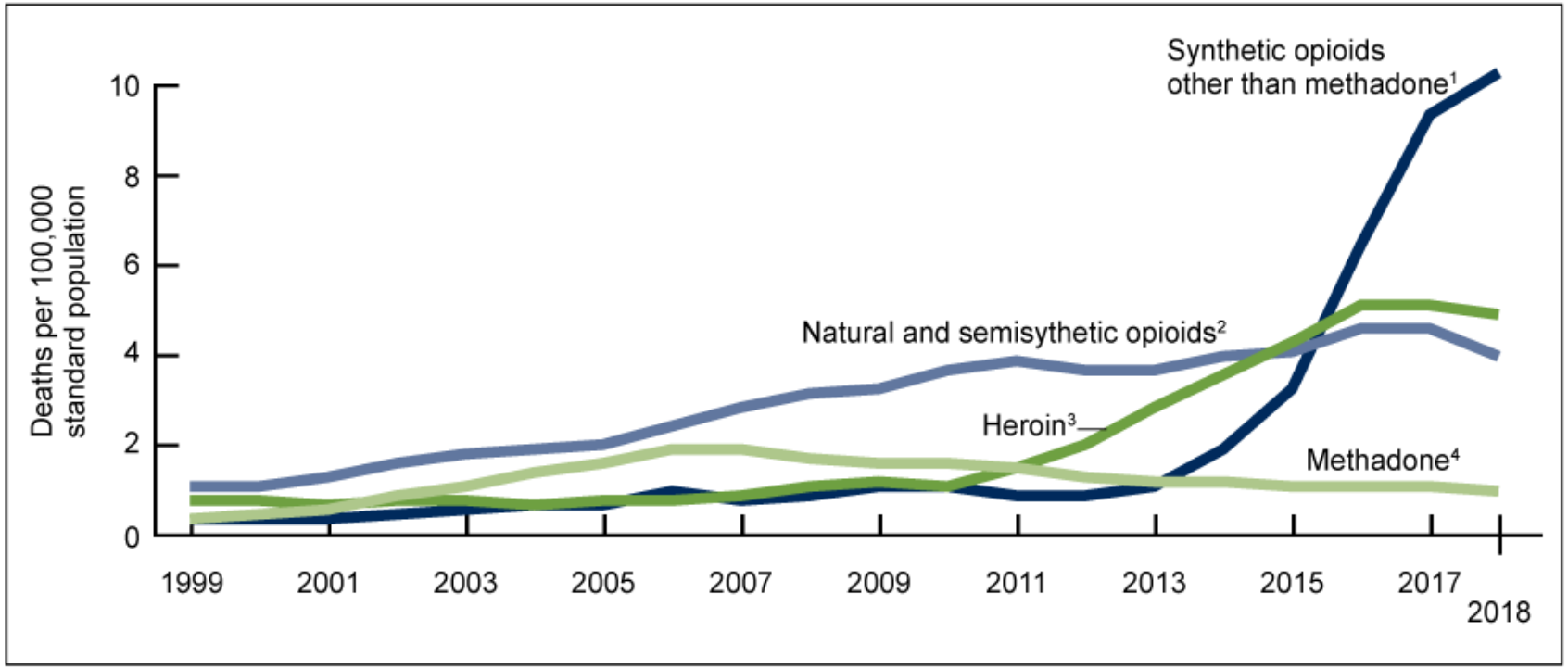
Chronic pain affects 50 M U.S. adults

19.6 M experience high-impact chronic pain that interferes with DLA[1]

The cost of pain in the US is estimated at $560-$635 billion annually

1-Dahlhamer J, et al. *MMWR*. 2018;67(36):1001-1006.

Age-adjusted drug overdose death rates involving opioids, by type of opioid: United States, 1999–2018

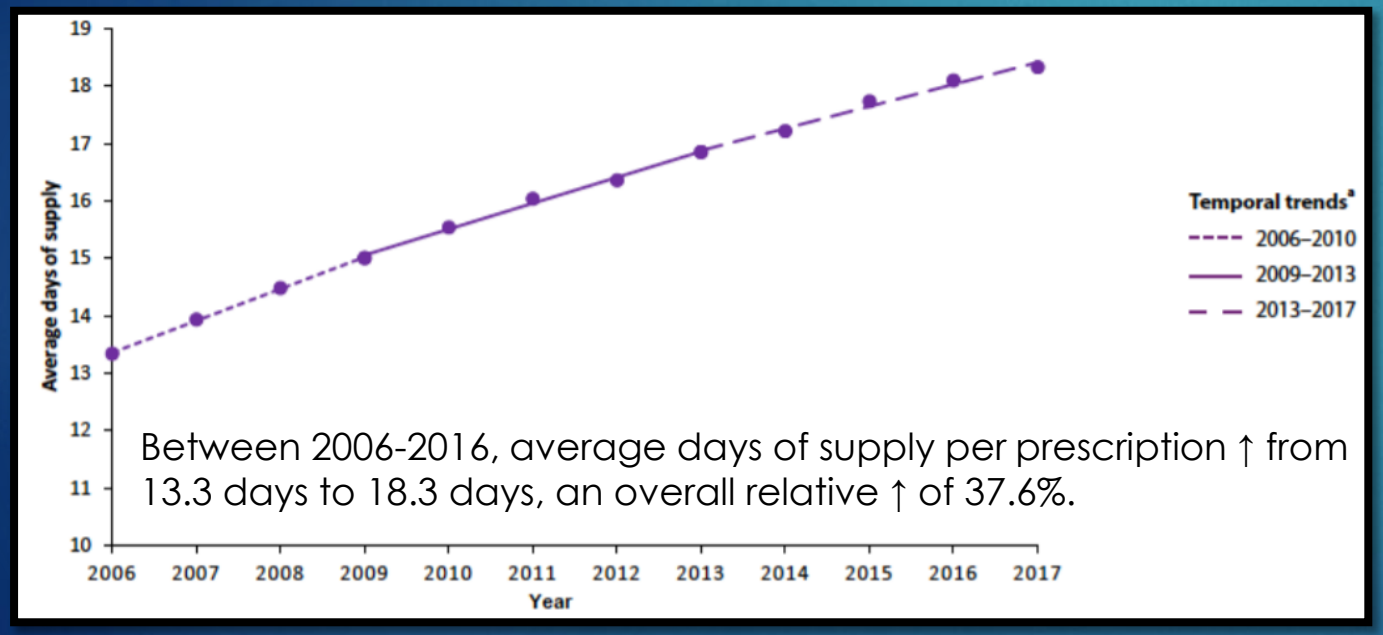


[1]Significant increasing trend from 1999 through 2006 and 2013 through 2018, with different rates of change over time, $p < 0.05$.
[2]Significant increasing trend from 1999 through 2018, with different rates of change over time, $p < 0.05$.
[3]Significant increasing trend from 2005 through 2015, with different rates of change over time, $p < 0.05$.
[4]Significant increasing trend from 1999 through 2006, then significant decreasing trend from 2006 through 2018, with different rates of change over time, $p < 0.05$.
NOTES: Deaths are classified using the *International Classification of Diseases, 10th Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (e.g., a death involving both methadone and a natural or semisynthetic opioid) are counted in both categories. Deaths may involve multiple drugs. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 through 2013 and 81%–92% from 2014 through 2018. Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3.
SOURCE: NCHS, National Vital Statistics System, Mortality.

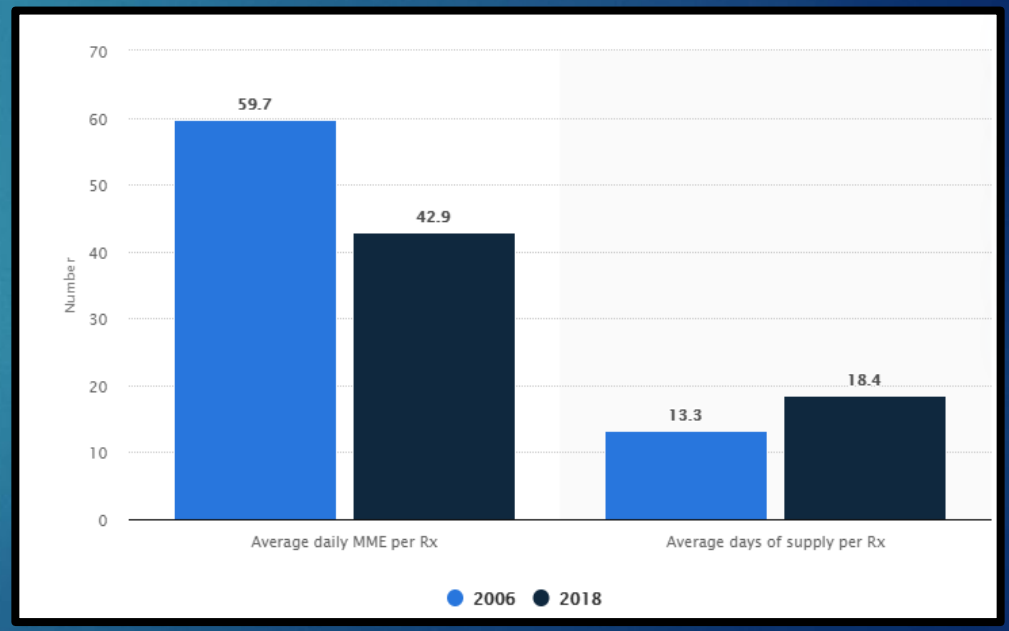
1. CDC. MMWR. 2011;60(43):1487-1492.
2. Banta-Green CJ, et al. Drug and alcohol dependence. 2009;104(1-2):34-42.
3. Boscarino JA, et al. Journal of addictive diseases. 2011;30(3):185-194.
4. Fleming MF, et al. J Pain. 2007;8(7):573-582.

- **Rising rates of overdose death were parallel to the dramatic increases in the number of OUD**
  - 1 in 4 pts on long-term opioid Rx have OUD (8-10)
  - In 2016,11.5 M Americans reported misusing prescription opioids in the previous year.

Average days of supply per opioid prescription in the U.S., 2006-2017



Dosage & supply key figures for prescribed opioids in the U.S. in 2006 & 2018



Mikulic M., et al. Rx opioids dosage and supply numbers U.S. 2006 vs 2018. retrieved from https://www.statista.com/aboutus/our-research-commitment

The surge in opioid prescribing affects patients of all ages, including the elderly

Nearly 1 in 3 Medicare beneficiaries received a prescription for oxycodone ER, hydrocodone-APAP, oxycodone-APAP, or fentanyl in 2016.[1]

Medicare spending under Part D for opioid pain meds exceeded $4 billion in 2015.[1]

APAP=acetaminophen

1. HHSOIG. High Part D Spending on Opioids and Substantial Growth in Compounded Drugs Raise Concerns. 2016; https:// oig.hhs.gov/oei/reports/oei-02-16-00290.pdf.

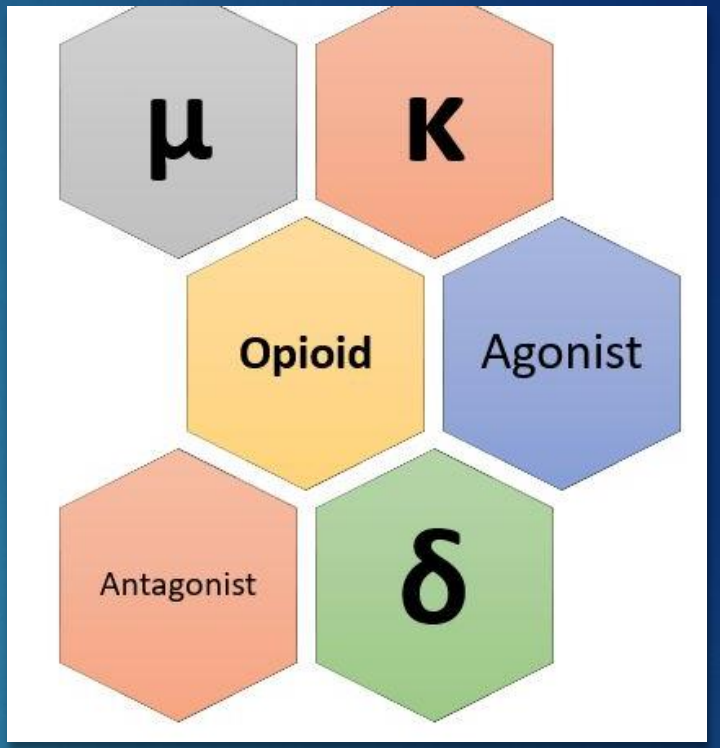
The challenge of pain management

Opioid: any psychoactive chemical resembling morphine, and binding to opioid receptors in the brain

Opiate: "natural" opioids derived from the opium poppy (e.g., opium, morphine, heroin)

Semi-synthetic opioids: analgesics containing both natural & manufactured compounds (e.g., oxycodone, hydrocodone, hydromorphone, oxymorphone)

Synthetic opioids: fully-human-made compounds (e.g., methadone, tramadol, and fentanyl)



Characteristics of different types of pain

Nociceptor pain[1,2,3]

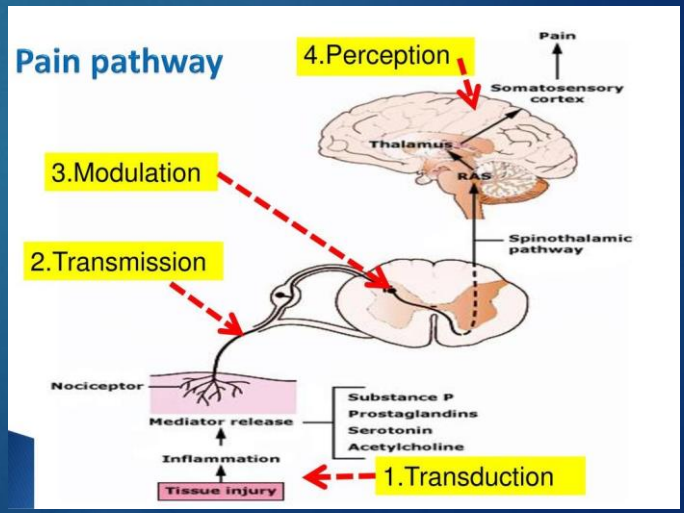
- Somatic (delta-fibers): superficial (skin)
- Visceral (C-fibers): deep (MS)

Neuropathic pain[1,2,4,5]

- Peripheral nerves
- Nerve roots
- CNS

Psychogenic pain

- Psychodynamic (conflicts, emotional trauma, …)
- Behavioral (rewarding pain behavior, illness benefit, …)



1-Carr DB, Goudas LC. Lancet. 1999;353(9169):2051-2058.
2-Alexander J, Black A. Current opinion in neurology and neurosurgery. 1992;5(2):228-234.
3-Chu LF, et al. The Clinical journal of pain. 2008;24(6):479-496.
4-Arner S, Meyerson BA. Pain. 1988;33(1):11-23.
5-Covington EC. Cleveland Clinic journal of medicine. 1998;65 Suppl 1:SI21-29

Pain is a distressing experience which is multi-dimensional, multi-level process which may start with a specific tissue injury but can lead to a biopsychosocial cascade of events that can include:

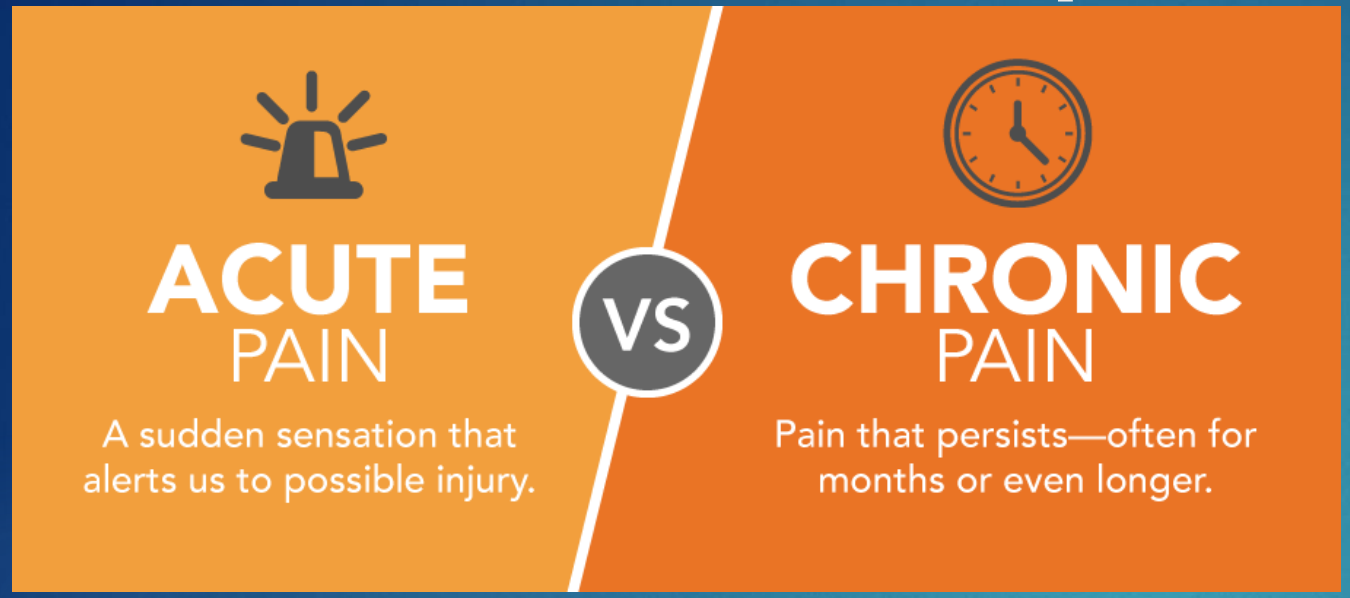
Nature of pain

- 1-physical deconditioning
- 2-psychological & emotional burdens
- 3-Social impact
- 4-dysfunctional behavior patterns

That affect not just the sufferer, but their entire social milieu[1,2]

1. HHS. Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. 2019; https://www.hhs.gov/ash/advisory-committees/pain/reports/ index.html. Accessed June 10 2019.
2. Williams AC, Craig KD. Pain. 2016;157(11):2420-2423.

Acute vs. chronic pain



Type of pain	Acute	Chronic
Characteristics	One of the most common presenting complaints in ambulatory care[1,2]	Intensity of pain is influenced by Ψ distress, heightened illness concern, ineffective coping strategies, personality, culture, & beliefs[1,3]
Duration	<4 weeks	>3 months or past the time of normal tissue healing
Cause	Known injury	Medical dz, injury, inflammation, or unknown
Outcome	Usually self-limited	Often pain control & not cure

1-Carr DB, Goudas LC. Lancet. 1999;353(9169):2051-2058. 2-Mularski RA, et al. Journal of general internal medicine. 2006;21(6):607-612.
3-Dowell D, et al. MMWR Recomm Rep. 2016;65(1):1-49.

Initial assessing pain:

-Clinician-patient relationship
-Overview of the assessment process

Engagement, Rx expectations, coordinated approach to mgt

Patient history is the most reliable indicator of pain

Information to be elicited during the initial assessment of pain includes:

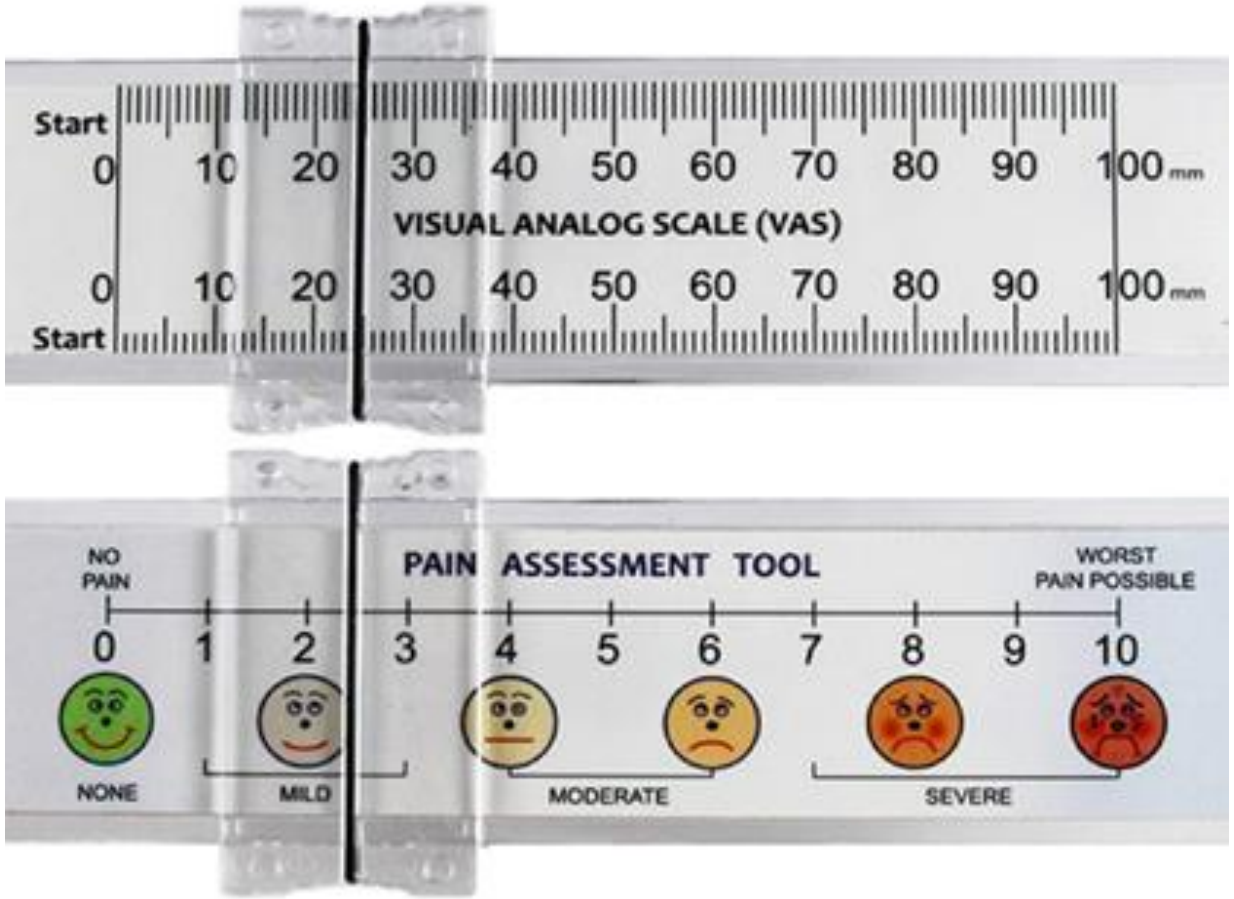
- **Characteristics of the pain** (DEALIQ)
- **Present & past pain mgt strategies & their outcomes**
- **Past & present medical problems**
- **Relevant family history** (EtOH, PWID, OUD, Ψ illnesses)
- **Current & past psychosocial issues or factors**
- **Pregnancy/contraceptive status**
- **Impact of the pain on the pt's daily life & functioning**

Gordon DB, et al. Archives of internal medicine. 2005;165(14):1574-1580.

Tools to document & assess pain

Unidimensional:

Multidimensional (comprehensive approach using QOL & DLA to assess pain & response to pain):



Acute pain assessment using unidimensional tools: Visual Analog Survey Scale & Wong-Baker Faces Pain Scale

1-Olsen MF, et al. J Clin Epidemiol. 2018;101:87-106 e102.
2-Krebs EE, et al. Journal of general internal medicine. 2007;22(10):1453-1458.

Brief Pain Inventory (Short Form)

Study ID# _____ Hospital # _____
Do not write above this line.

Date: _____

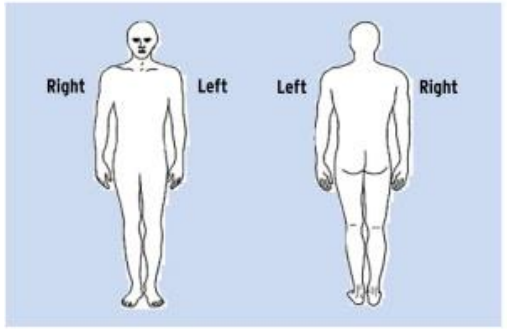
Time: _____

Name: _____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. yes 2. no

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tell how much pain you have **RIGHT NOW**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

8) In the past 24 hours, how much **RELIEF** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9) Circle the one number that describes how, during the past 24 hours, **PAIN HAS INTERFERED** with your:

A. General Activity:

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

D. Normal work (Includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

E. Relation with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

G. Enjoyment of life

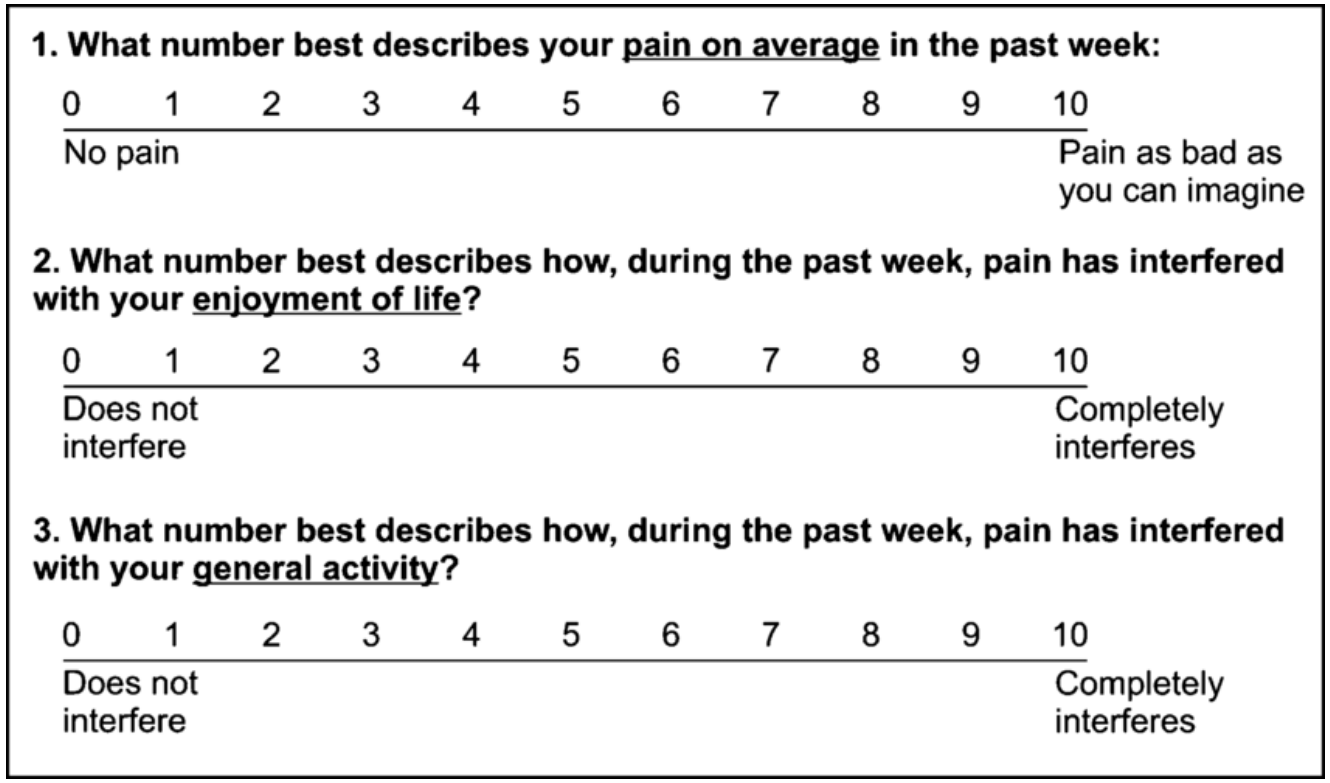
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

Multidimensional Brief Pain Inventory (BPI)

→Clinical trials
→Pts with chronic pain
→BPI captures the impact of pain on function & QOL

Keller S, et al. The Clinical journal of pain. 2004;20(5):309-318.

Multidimensional PEG score



1. What number best describes your pain on average in the past week:

0 1 2 3 4 5 6 7 8 9 10

No pain — Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

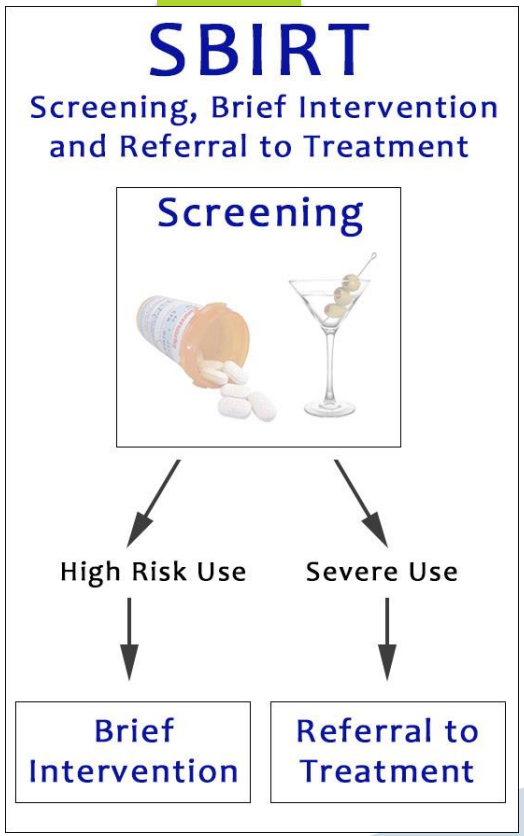
PEG score= average the 3 questions (30% improvement is clinically meaningful)

Pain Enjoyment General Activity PEG scale: Validated 3 item tool to assess **P**ain intensity, interference with **E**njoyment of life and interference with **G**eneral activity (Krebs, 2009)

Krebs EE, et al. Journal of general internal medicine. 2009;24(6):733-738.

It is crucial to identify patients at risk of OUD and overdose as well as improve overall patient care by gauging treatment decisions

Tool	Use	Who Administers?	Length
Current Opioid Misuse Measure (COMM)	Monitor for misuse by patients currently on long-term opioid therapy	Patient self-report	17 items
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Screen for risk of opioid addiction	Clinician	7 items
Opioid Risk Tool (ORT)	Screen for risk of opioid addiction	Clinician or patient self-report	5 yes/no questions
Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP, and SOAPP-R)	Screen for risk of opioid addiction	Patient self-report	24 items

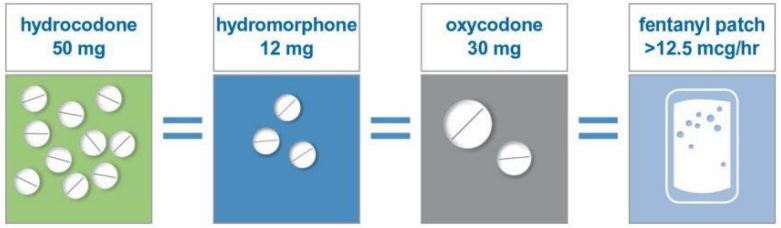


Other tools for substance abuse screening:
DAST, ASSIST, TAPS, CAGE-AID

Tools for patient risk assessment:
Screening & monitoring for opioid use disorder (OUD) risk factors:
Hx, Ψ, UDS, EtOH

1-Chou R, et al. J Pain. 2009;10(2):113-130.
2-Babor TF, et al. Subst Abus. 2007;28(3):7-30.
3-CDC. MMWR. 2016;65(1):16.
4-Fleming MF, et al. J Pain. 2007;8(7):573-582.

"5 A's" approach



1. **A**sk about opioid use
2. **A**dvise pts to use MAT for OUD +/- psychotherapy or CBT
3. **A**ssess the pts' willingness to enter Tx & dg OUD using **DSM-5** criteria
4. **A**ssist pts by linking them to care
5. **A**rrange F/U appointments & use **PDMPs** (KASPER)[1]
   - Check the PDMP before starting anyone on opioid therapy
   - Review the PDMP periodically throughout opioid therapy (at least Q 3 months)
   - Look for prescriptions for other controlled substances, like BZDs, that can ↑ risk of overdose death
   - Review the **total morphine milligram equivalent dose (MMED)**

OPIOID (doses in mg/day except where noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

What is KASPER?

KASPER is Kentucky's Prescription Monitoring Program (PMP). KASPER tracks Schedule II – V controlled substance prescriptions dispensed within the state as reported by pharmacies and other dispensers.

KASPER is a real-time Web accessed database that provides a tool to help address one of the largest threats to patient safety in the Commonwealth of Kentucky; the misuse, abuse and diversion of controlled pharmaceutical substances.

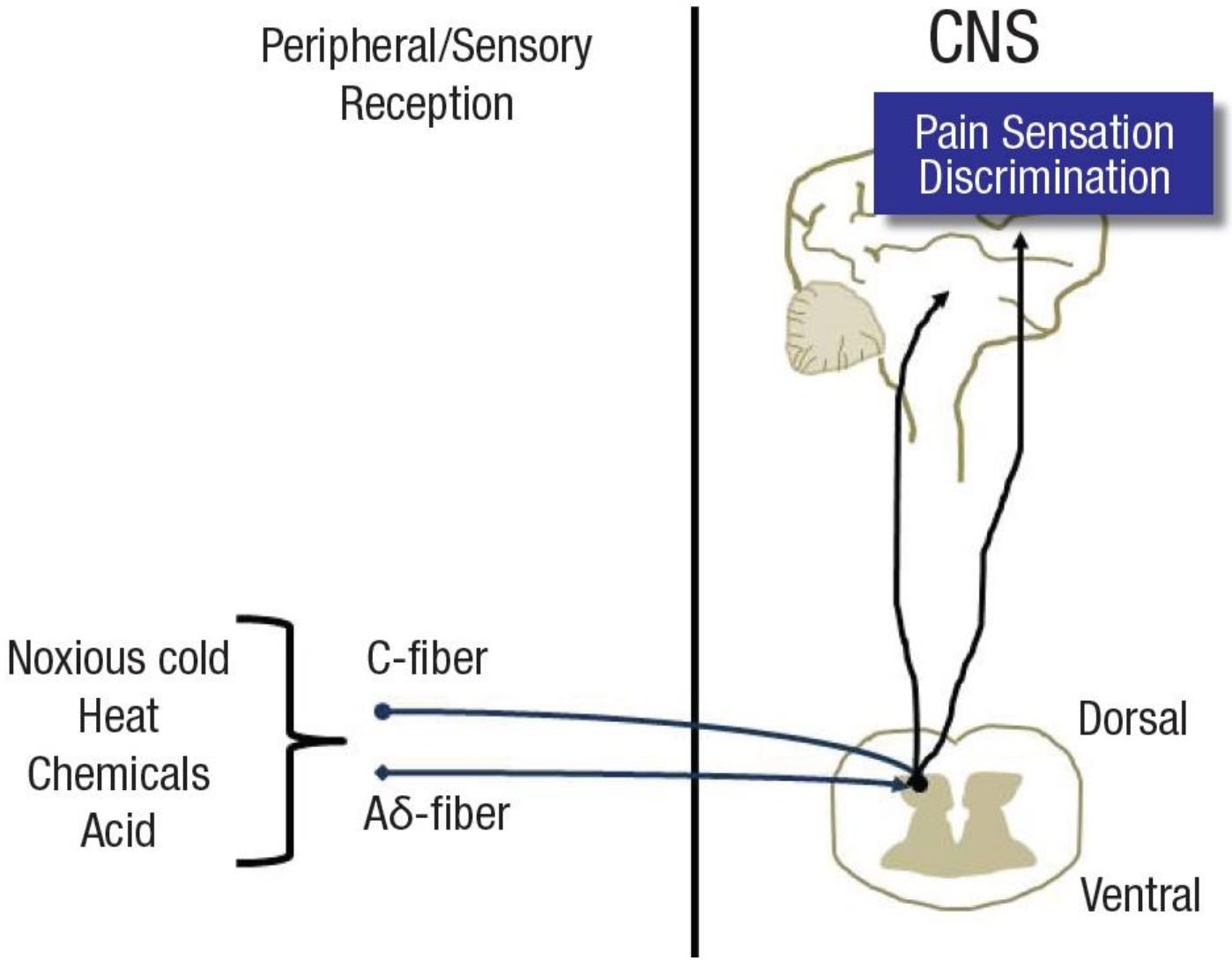
Cabinet for Health and Family Services

Kentucky UNBRIDLED SPIRIT

Diagnostic & Statistical Manual of Mental Disorders 5 (DSM-5)
Prescription drug monitoring programs (PDMPs)

1-Federation of State Medical Boards. Prescription Drug Monitoring Programs State-by-state overview. 2019; http://www.fsmb.org/siteassets/advocacy/key-issues/prescription-drug-monitoring-programs-by-state.pdf. Accessed April 24 2019.

Pathways of pain reception



Pain management options

1-Interventions:

- Injections into specific joints with steroid & viscosupplements
- Epidural steroid injections
- Radiofrequency ablation
- Pulsed radiofrequency
- Neuromodulation treatments
- Nerve block

2-Non-opioid drugs:

- Acetaminophen
- NSAIDs (oral or topical)
- Antidepressants
- Anticonvulsants
- Topical lidocaine or capsaicin
- Cannabinoid-based therapies
- Ketamine
  Acetaminophen

3-Opioids

- mu, kappa, & delta opioid receptors
- Agonists: stimulate at least one of the receptors & provide continued analgesia with increasing doses
- Partial Agonists: high affinity at mu-receptors, have a ceiling for analgesic effect, & are less likely to cause respiratory depression

Pain management options

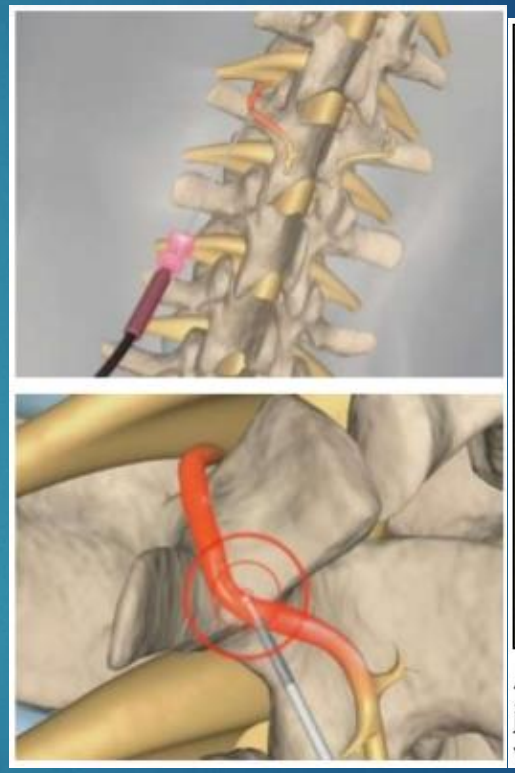
1-Interventions:

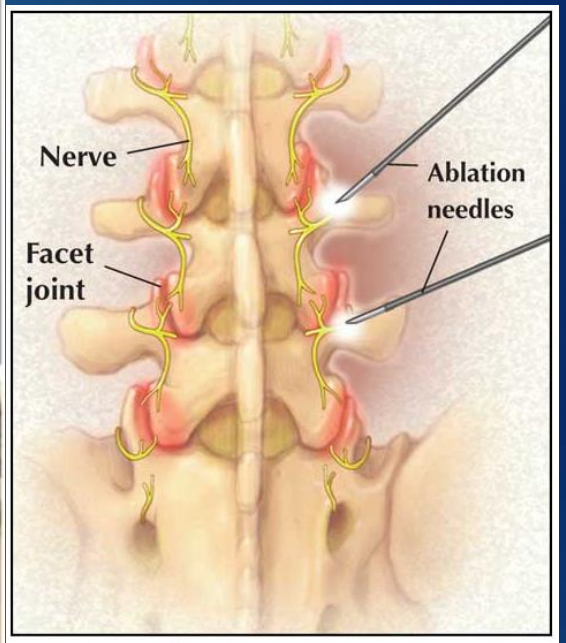
- Injections into specific joints with steroid & viscosupplements
- Epidural steroid injections
- Radiofrequency ablation
- Pulsed radiofrequency
- Neuromodulation treatments
- Nerve block

1-Chou R, et al. Annals of internal medicine. 2017;166(7):493-505. 2-Bicket MC, et al. Spine J. 2015;15(2):348-362. 3-Gupta A, et al. Pain physician. 2017;20(3):155-171. 4-Deer TR, et al. Neuromodulation. 2014;17(6):515-550; discussion 550.

Advanced treatment for pain

- Radiofrequency is a minimally invasive procedure
- A small radiofrequency current will travel through eh electrode into the surrounding tissues, causing the tissue to heat and eliminate the pain pathways
- Results usually last 6-9 months
- Outcomes:
  - Pain relief
  - Improvement in quality of life
  - Increased range of motion
  - ↓ need to take pain medications when compared to more conservative treatment options

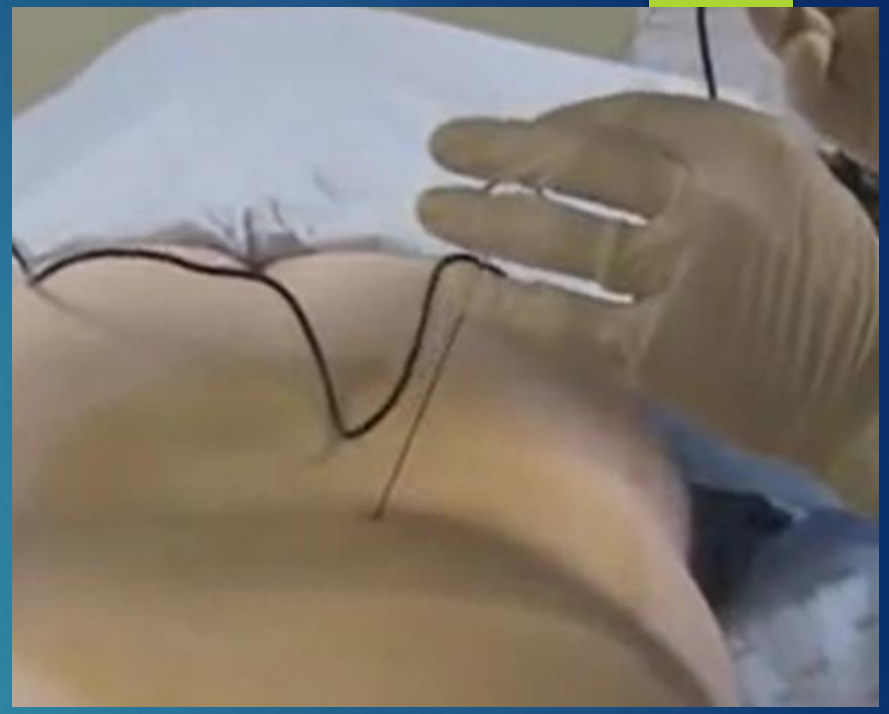


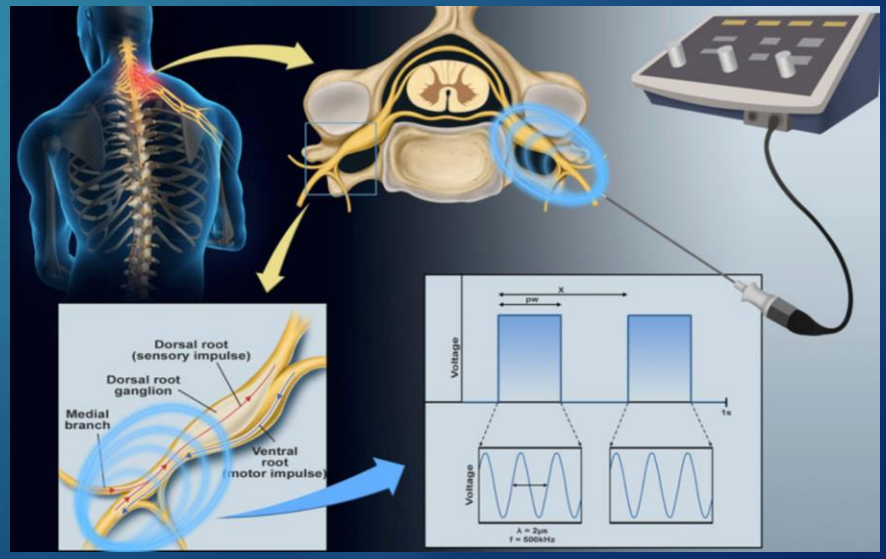


Applying radiofrequency energy to the facet joint nerve involves placing an insulated wire near the nerve tissue.

Pulsed Radiofrequency Treatment (PRF)

- Small current in brief bursts via an electrode sheathed in a hollow needle (Teflon)
  - Silent phases in between current bursts, where heat can dissipate, and the area cools down
  - Temperature stays <40°C: the temperature threshold for causing damage
- PRF alters the way nerves function (not destructive like continuous radiofrequency ablation)
- Reset the nerve to alter transmission of pain signals: neuromodulation



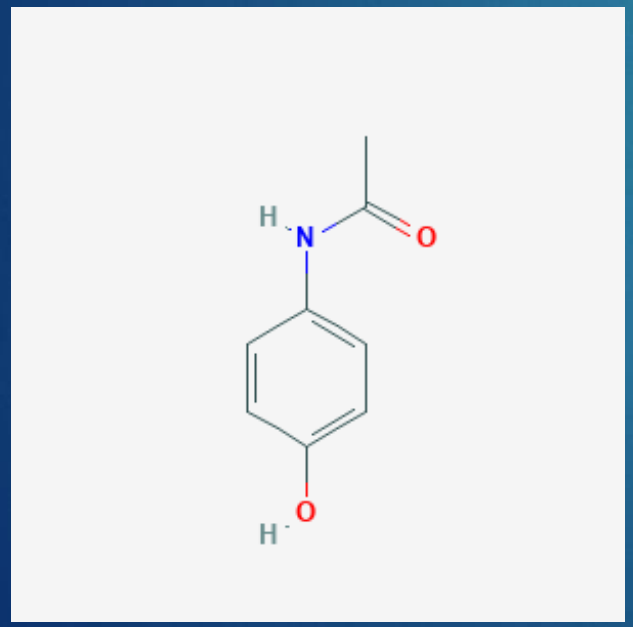


Pain management options

2-Non-opioid drugs:

- Acetaminophen
- NSAIDs (oral or topical)
- Antidepressants
- Anticonvulsants
- Topical lidocaine or capsaicin
- Cannabinoid-based therapies
- Ketamine Acetaminophen

1-APAP Acetaminophen (C8H9NO2)



Available in # doses OTC: 325 mg, 500 mg, & 650 mg tablets

Lower doses are recommended to ↓ risk of SEs

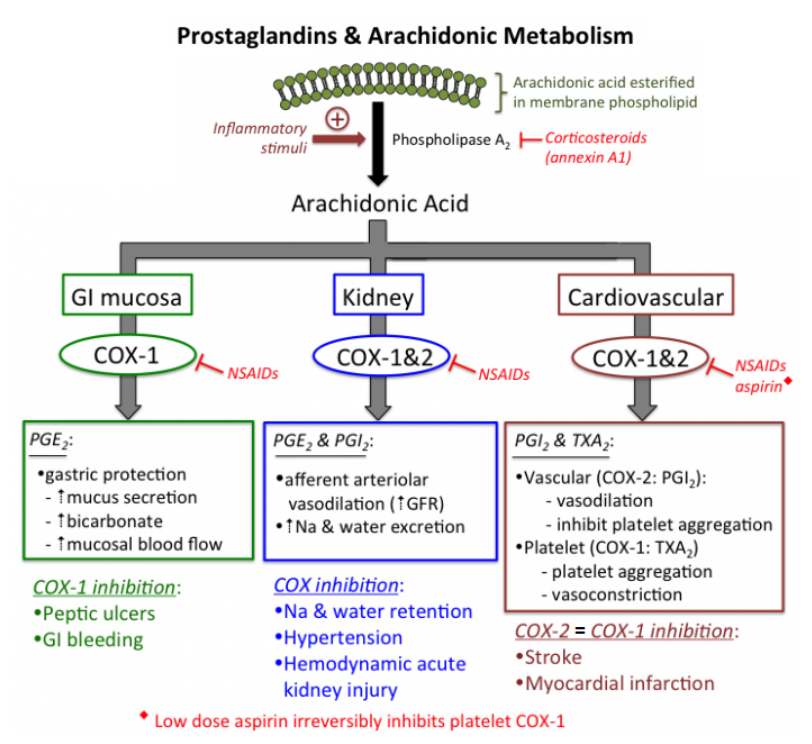
Max dose: 1 g in a single dose; 4 g/d for healthy adults; 3 g/d for elderly pts; use in divided doses Q4-6 h[1]

The most severe potential SE is liver toxicity

- **Most common cause of acute liver failure (46% of all cases)[2]**
- **Stay within recommended doses to help prevent SEs**
- **One APAP-containing product at a time**
- **Read labels of all meds to determine if the product contains APAP**

1-Food and Drug Administration. Questions and Answers about Oral Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit. 2016; https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239871.htm.
2-Lee WM. J Hepatol. 2017;20(17):32148-32147.

2-NSAIDs (COX-1&2 & COX-2 inhibitors)



cycloxygenase (COX)

GI toxicity (GI bleeding, upper GI symptoms, ulcers)

- For high-risk pts (elderly; antiplatelets & anticoagulation) adding PPI may help ↓ the risk[1,2]

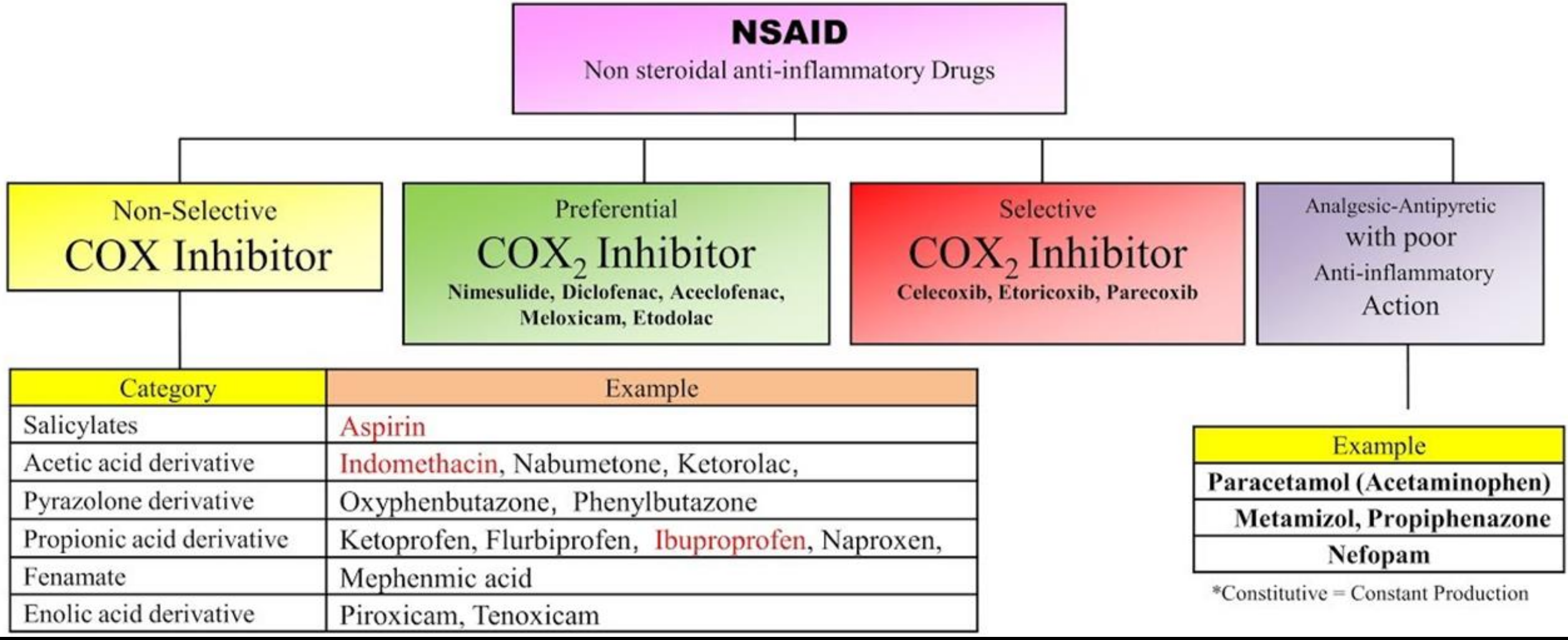
↑ risk of renal & cardiac complications

- The risks of CV events with COX-2 inhibitors (celecoxib)= to those of other NSAIDs

SEs with NSAIDs are typically lower with topical formulations (diclofenac topical)

- The effects on coagulation & renal fct are unknown, but likely not clinically significant given limited systemic absorption[3]

1-Hawkey CJ, et al. Clinical drug investigation. 2009;29(10):677-687.
2-Desai JC, et al. Digestive diseases and sciences. 2008;53(8):2059-2065.
3-Makris UE, et al. JAMA. 2014;312(8):825-836.



Category	Example
Salicylates	Aspirin
Acetic acid derivative	Indomethacin, Nabumetone, Ketorolac,
Pyrazolone derivative	Oxyphenbutazone, Phenylbutazone
Propionic acid derivative	Ketoprofen, Flurbiprofen, Ibuproprofen, Naproxen,
Fenamate	Mephenmic acid
Enolic acid derivative	Piroxicam, Tenoxicam

Example
Paracetamol (Acetaminophen)
Metamizol, Propiphenazone
Nefopam

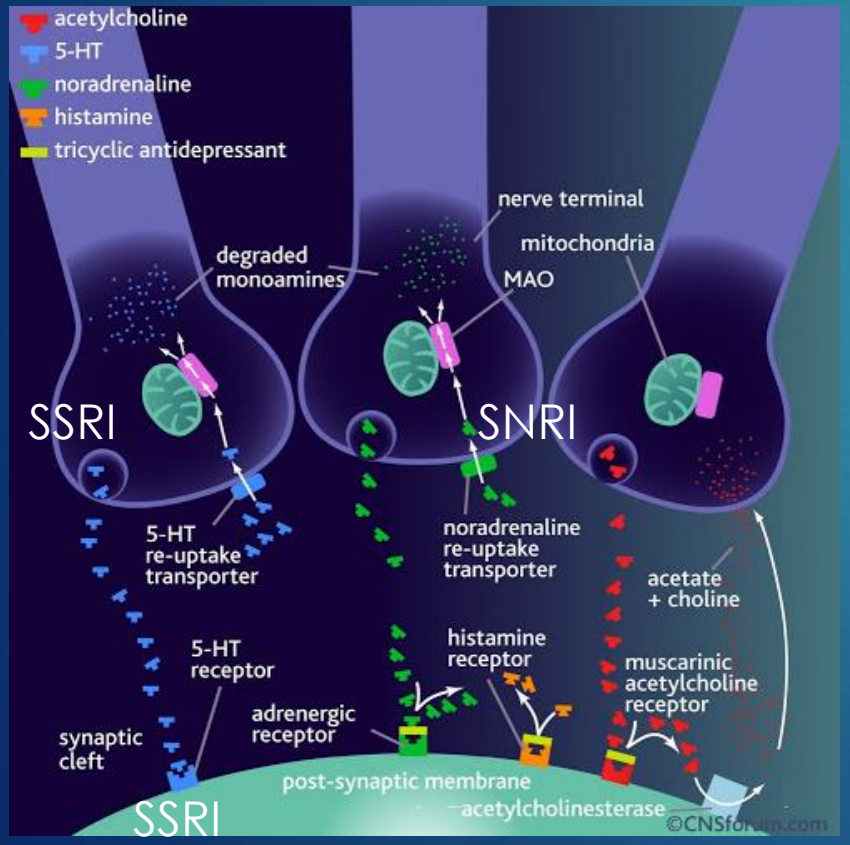
*Constitutive = Constant Production

-NSAIDs are agents used to get relief from pain, inflammation and fever
-COX-1 and COX-2 form prostaglandin (PG) which initiates perception of pain and inflammation
-Blocking the synthesis of PG ↓ pain and inflammation

Drugs with antiplatelet & anticoagulation activities	When to stop prior to surgery
Aspirin 325 mg	7 days
ASA 81mg	None
Apixaban (Eliquis)	3 days
Rivaroxaban (Xarelto)	3 days
Dabigatran (Pradaxa)	5 days
Clopidogrel (Plavix)	5-7 days
Ticagrelor (Brilinta)	5-7 days
Cilostazol (Pletal)	2-3 days
Dipyridamole (Persantine)	2-3 days
Dipyridamole SR+ ASA (Aggrenox)	7 days
Enoxaparin (Lovenox)	12 hours
Fondaparinux (Arixtra)	24 hours
Warfarin (Coumadin)	4-5 days (nl INR)
NSAIDs: Diclofenac (Voltaren), Indomethacin (Indocin), Ibuprofen (Motrin)	1 day
NSAIDS: Naproxen (Naprosyn, Aleve)	2-3 days
NSAIDs: Meloxicam (Mobic)	10 days

NSAIDs, anti-platelets & anti-coagulation & surgery

3-Antidepressants: mechanism of analgesia is unknown



Selective norepinephrine reuptake inhibitors (SNRIs) have mixed action on NE & 5-HT: duloxetine (Cymbalta), venlafaxine (Effexor), & milnacipran (Savella)

- SEs: N/V, H/A, dizziness, somnolence, nervousness, dry mouth, diaphoresis, anorgasmia
- Monitor BP (duloxetine & venlafaxine), HR (venlafaxine), & DDI (duloxetine)
- SNRIs can be very helpful in pts who have central sensitization.

Tricyclic antidepressants (TCAs) inhibit reuptake of NE & 5-HT: amitriptyline (Elavil), desipramine (Norpramin), & nortriptyline (Pamelor)

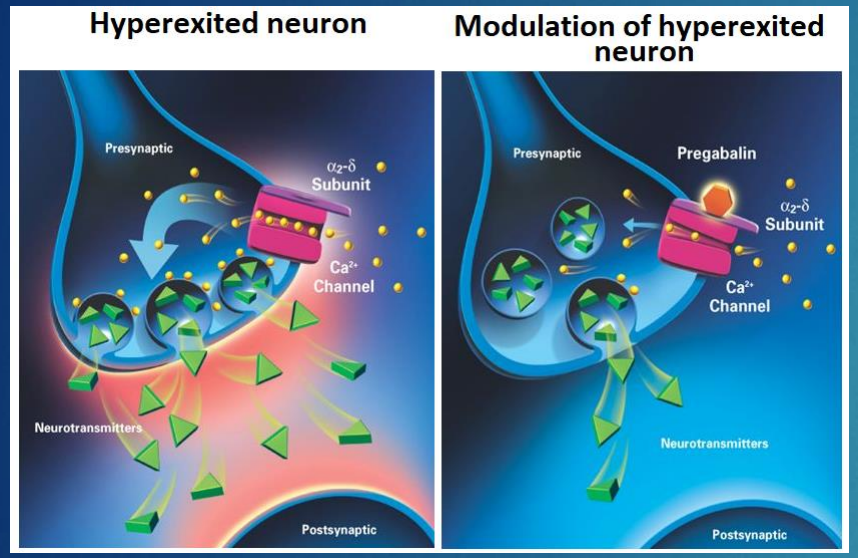
- SEs: anticholinergic effects (dry mouth, constipation, dizziness, urinary retention) & ↑QTc

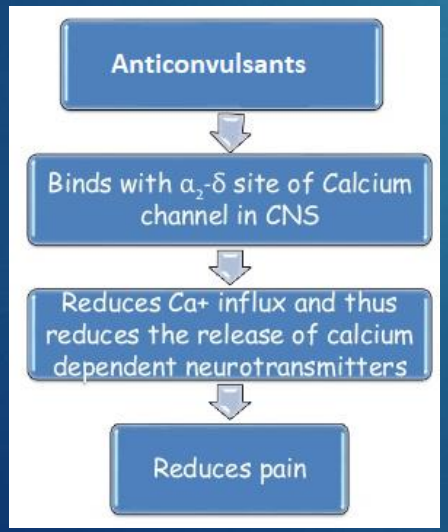
Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of 5-HT in the brain, making more 5-HT available in the synapse: citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxel), & escitalopram (Lexapro)

- Little evidence in treating chronic pain conditions[1]
- SEs: weight gain, sexual dysfct, & QTc prolongation (citalopram)

1-Chou R, et al. J Pain. 2009;10(2):113-130.

4-Anticonvulsants: Neuropathic pain





Gabapentin (Neurontin), pregabalin (Lyrica), oxcarbazepine (Trileplal), and carbamazepine (Tegretol)

SEs: sedation, dizziness, & peripheral edema

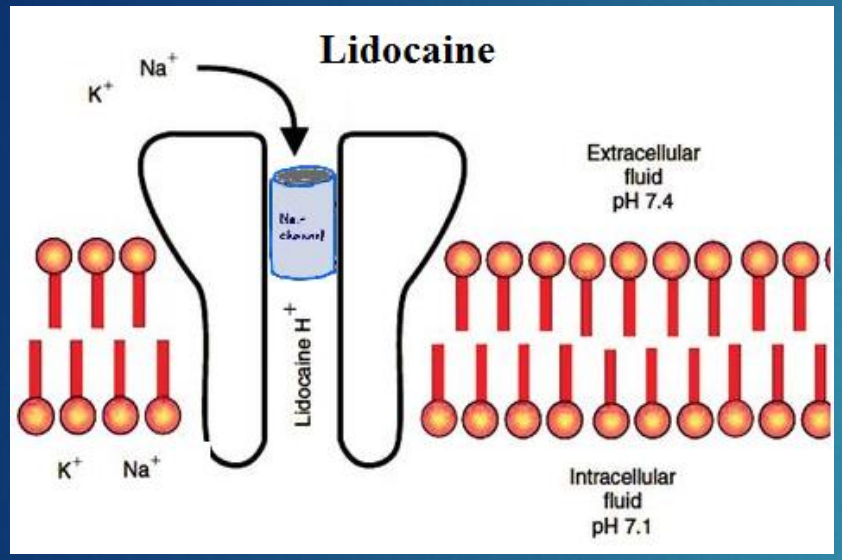
Pregabalin & gabapentin have abuse potential in the general population

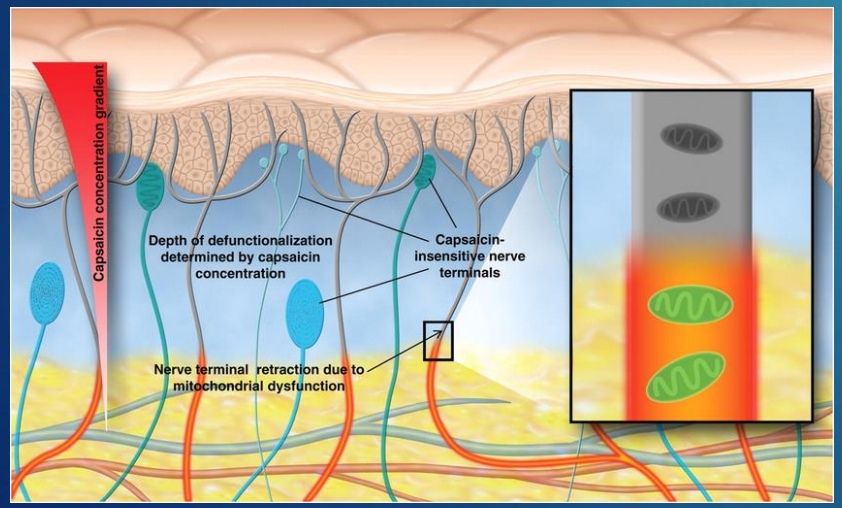
Classified as Schedule V by the DEA & need to be tracked by State PDMPs

Neuropathic pain with central sensitization

PDMPs= Prescription Drug Monitoring Programs

5-Topical lidocaine and capsaicin





Topical lidocaine inhibits the conduction of nociceptive nerve impulses

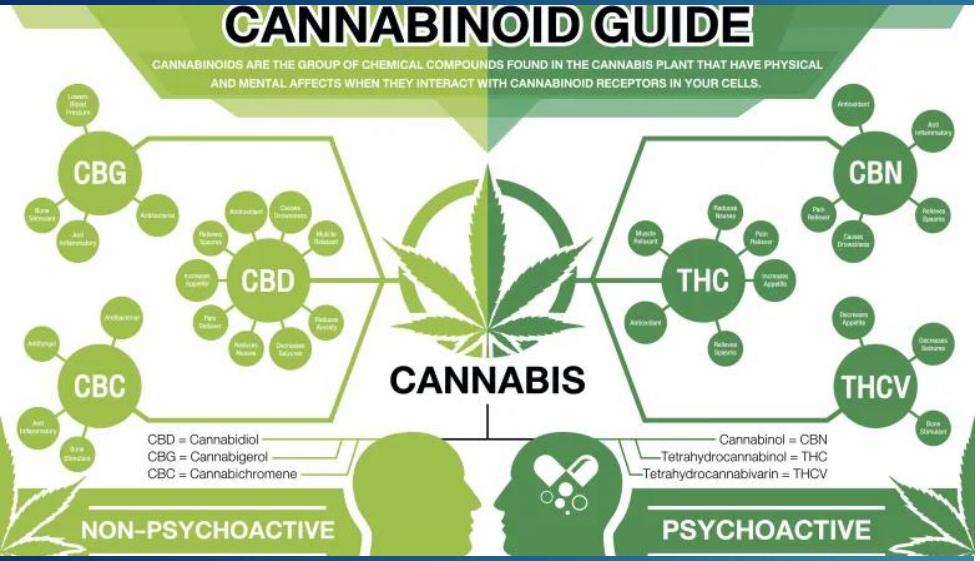
- Alters depolarization in the neurons by blocking the fast VG-Na channels in the cell mb→ No AP
- Irritation @ the application site
- Lidocaine 5% patches: available by prescription
- lidocaine 4% patches: available OTC

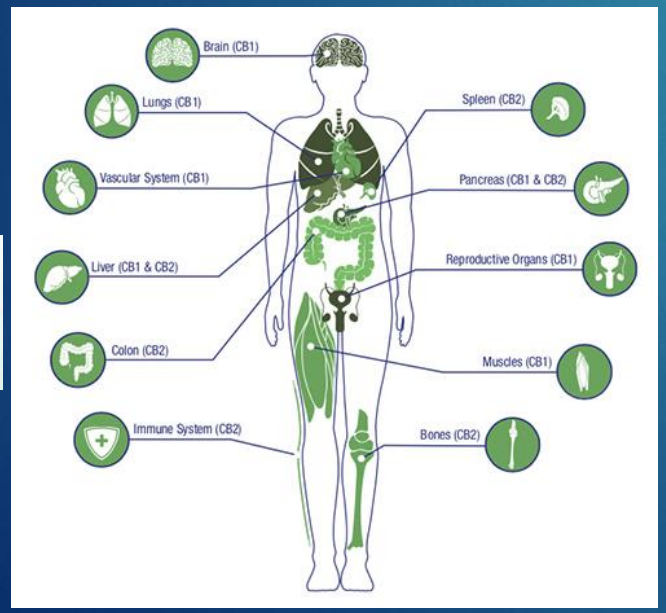
Capsaicin is an active component of chili peppers & has moderate analgesic properties at 8% concentrations for musculoskeletal & neuropathic pain[1]

- Mild-to-severe burning sensation @ the application site.

1-Derry S, et al. The Cochrane database of systematic reviews. 2017;1:CD007393.

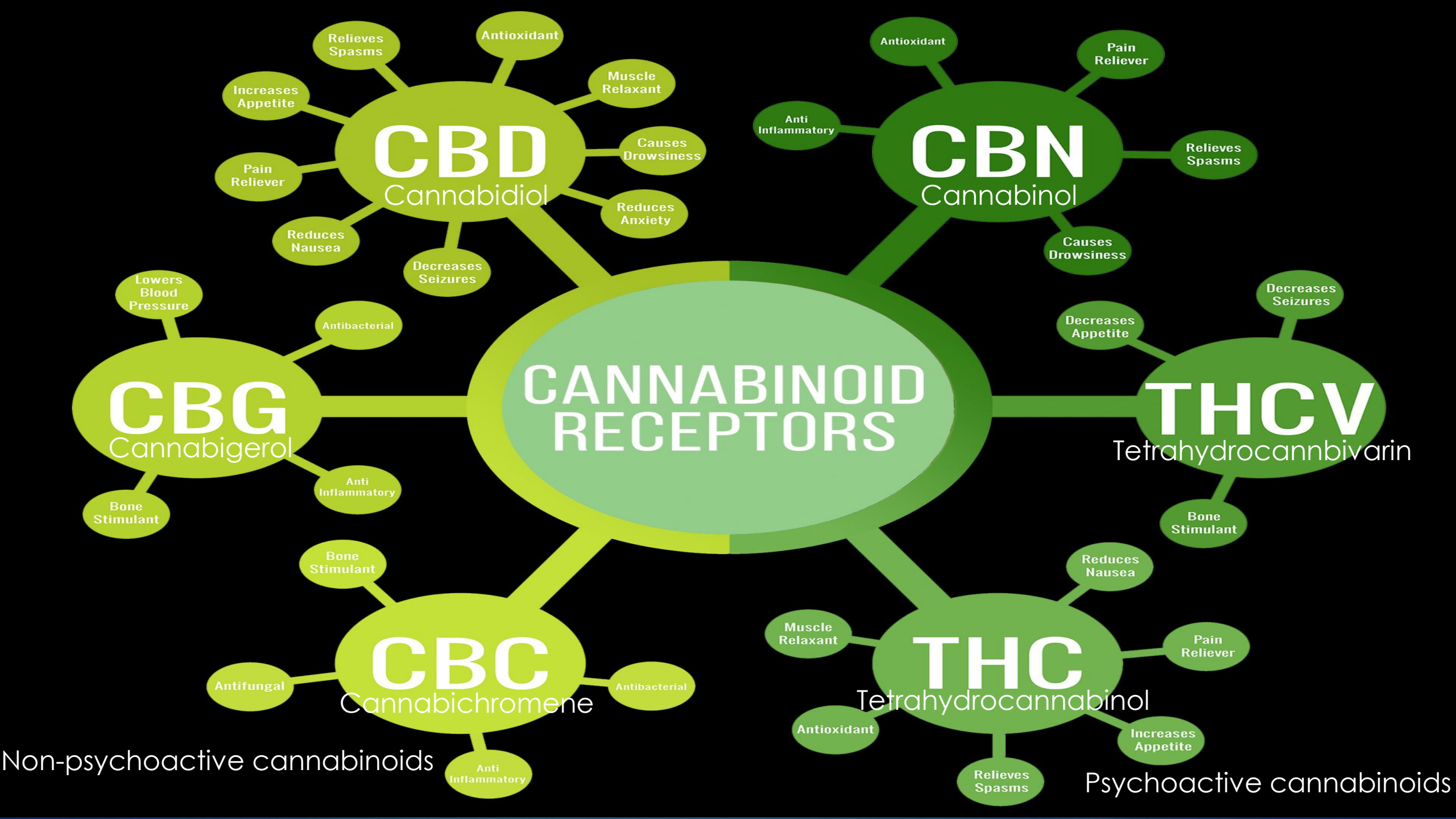
6-Cannabinoid preparations



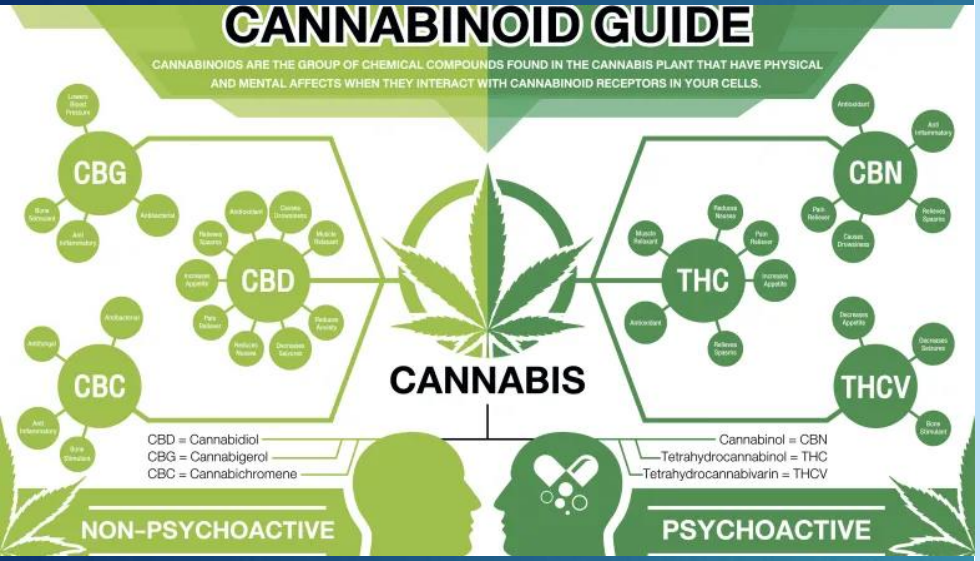


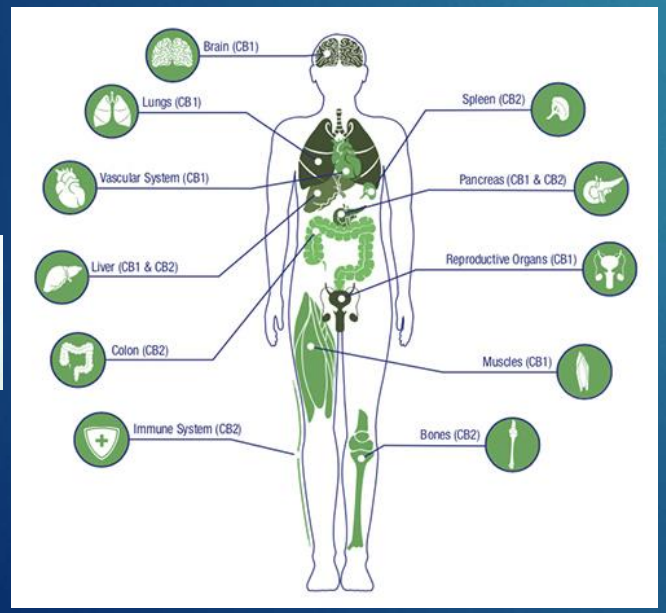
- Medical cannabis is legal in 33 States (April, 2019)[1]
  - The CB1 & CB2 receptors
- Moderate analgesic effect[2,3]
- Benefit for an acute pain is limited[4] or mixed[5]
  - Dose dependent benefit[5]
- Short terms SEs: ↓memory, motor coordination, & ↓ judgment and psychotic ∑s (THC)
- Long terms SEs: impaired brain development in young adults, habituation, & ↑risk of anxiety or depression
- Abrupt cessation of marijuana causes withdrawal ∑s: anxiety, irritability, craving, dysphoria, & insomnia.
- ↑risk of respiratory infections with inhaled products[6]
- Opioid-sparing effect: 25% ↓in opioid overdose mortality[7]

1-ProCon.org. 33 legal medical marijuana states and DC. https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Accessed April 19 2019. 2-Messier SP, et al. JAMA. 2013;310(12):1263-1273. 3-Stockings E, et al. Pain. 2018;159(10):1932- 1954. 4-Kraft B, et al. Anesthesiology. 2008;109(1):101-110. 5-Wallace M, et al. Anesthesiology. 2007;107(5):785-796. 6-Hill KP. JAMA. 2015;313(24):2474-2483. 7-Bachhuber MA, et al. JAMA Intern Med. 2014;174(10):1668-1673.


CANNABINOID RECEPTORS
CBD
Cannabidiol
Relieves Spasms
Antioxidant
Muscle Relaxant
Causes Drowsiness
Reduces Anxiety
Decreases Seizures
Reduces Nausea
Pain Reliever
Increases Appetite
CBN
Cannabinol
Antioxidant
Pain Reliever
Relieves Spasms
Causes Drowsiness
Anti Inflammatory
CBG
Cannabigerol
Lowers Blood Pressure
Antibacterial
Anti Inflammatory
Bone Stimulant
THCV
Tetrahydrocannbivarin
Decreases Seizures
Decreases Appetite
Bone Stimulant
CBC
Cannabichromene
Bone Stimulant
Antifungal
Antibacterial
Anti Inflammatory
THC
Tetrahydrocannabinol
Reduces Nausea
Muscle Relaxant
Pain Reliever
Antioxidant
Increases Appetite
Relieves Spasms
Non-psychoactive cannabinoids
Psychoactive cannabinoids

6-Cannabinoid preparations





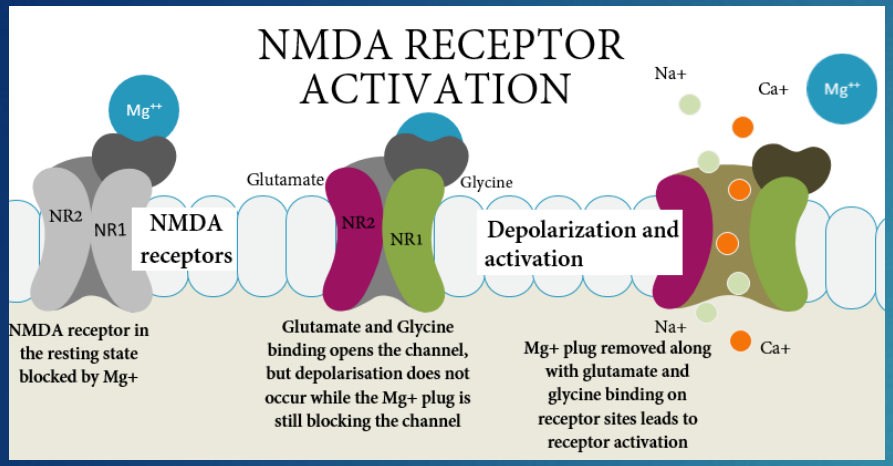
FDA-approved cannabinoids:

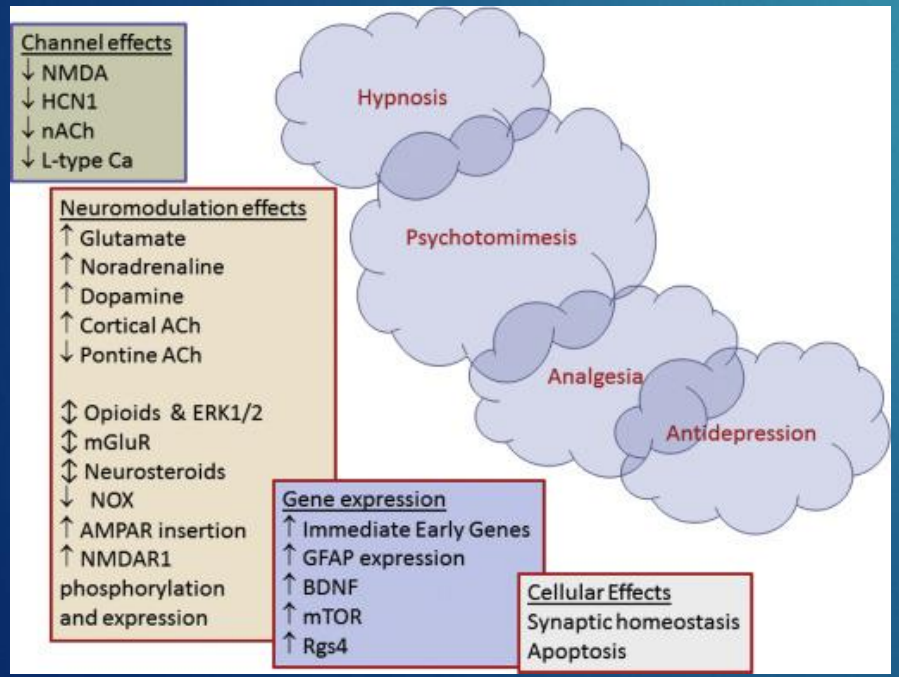
- **Dronabinol** indicated for 2nd-line Tx of chemoRx-induced nausea & vomiting, & anorexia-associated weight loss in HIV-pts
  - SEs: N/V, abdominal pain, & abnormal thinking
- **Nabilone** is indicated for chemoRx-induced N & V
  - SEs: dizziness, euphoria, ataxia & dry mouth[1-3]
- None of these are indicated for the treatment of pain
  - The analgesic properties of cannabis are only attributed to the **CBD** component, not the **THC** component

CBD=Cannabidiol
THC=Tetrahydrocannabinol

1-Hill KP. JAMA. 2015;313(24):2474-2483.
2-Narang S, et al. J Pain. 2008;9(3):254-264.
3-Walitt B, et al. The Cochrane database of systematic reviews. 2016;18(7).

7-Ketamine (IV or transdermal)





Ketamine anti-analgesic use is rapidly growing to combat the risks of chronic opioid use

- ❑ Acute pain conditions: sickle cell crises, renal colic, & trauma
- ❑ **Subanesthetic ketamine for acute pain**
  - Periop use in Sx with moderate-to-severe postop pain
  - Periop use in patients with opioid tolerance
  - Adjunct in opioid-tolerant pts with sickle cell crisis
  - Adjunct in pts with OSA
- ❑ **Dose:** Bolus IV: up to 0.35 mg/kg; Infusion: up to 1 mg/kg/hour
- ❑ **Contraindications:**
  - Poorly-controlled CVD
  - Pregnancy
  - Psychosis
  - Severe hepatic disease
  - Elevated ICP
  - Elevated IOP

CVD= cardiovascular disease; ICP= intracranial pressure; IOP= intraocular pressure; OSA= obstructive sleep apnea

Schwenk ES, et al. Regional anesthesia and pain medicine. 2018;43(5):456-466.

Pain management options

3-Opioids

- mu, kappa, & delta opioid receptors
- **Agonists:** stimulate ≥1 opioid receptor & provide continued analgesia with ↑doses
- **Partial Agonists:** high affinity at mu-receptors, have a ceiling for analgesic effect, & are less likely to cause respiratory depression

Opioids' Relative Effectiveness

Mechanism of action

- Receptors
- μ,δ, κ receptors.
- All 3 subtypes are involved in antinociceptive and analgesic mechanisms at both spinal and supraspinal levels.
- μ receptors-respiratory depressant+ GI
- δ receptors- development of tolerance
- κ receptors- involved in sedation + GI

Generally-accepted 2-point minimum clinically important difference for pain on a 10-point scale

Opioids

- ❑ **Reliable for acute moderate-to-severe pain**
- ❑ **Effectiveness cannot be extended to chronic pain**
- ❑ Neuronal & physiologic adaptations to long-term use:
  - ↓ analgesic effectiveness
  - Paradoxical hyperalgesia
- ❑ **Metanalysis** of 96 trials with **26,169 non-cancer pts**[1]
  - Opioids slightly ↓ pain & ↑ fct vs. placebo **but not** vs. non-opioids (F/U=1-6 mos)
  - SEs (Vomiting) 4X higher in the opioid arm
- ❑ **SPACE trial** randomized **240 pts** with moderate-to-severe chronic low back pain or knee or hip OAs to opioids vs. non-opioids (F/U for 1 year)[2]
  - Pain intensity was better in the non-opioid group (P<0.05)
  - Opioids are not recommended for OAs or back pain

1-Busse JW, et al. JAMA. 2018;320(23):2448-2460.
2-Krebs EE, et al. JAMA. 2018;319(9):872- 882.

Common opioids by schedule

Drug Scheduling Guide United States

Schedule I
Most potential for abuse and dependence
No medicinal qualities
Heroin, LSD, Marijuana Ecstasy, Peyote

Schedule II
High potential for abuse and dependence
Some medicinal qualities
Vicodin, Cocaine, Meth, OxyContin, Adderall

Schedule III
Moderate potential for abuse/dependence
Acceptable medicinal qualities
Doctor's prescription required
Tylenol with Codeine, Ketamine, Steroids, Testosterone

Schedule IV
Low potential for abuse and dependence
Acceptable medicinal qualities
Prescription required - fewer refill regulations
Xanax, Darvon, Valium, Ativan, Ambien, Tramadol

Schedule V
Lowest potential for abuse/dependence
Acceptable medicinal qualities
Prescription required - fewest refill regulations
Robitussin AC, Lomotil, Motofen, Lyrica

Source: United States Drug Enforcement Agency

Common opioids by schedule

Schedule I Controlled Substances

No medical use, a lack of accepted safety, and a high potential for abuse.

Heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine ("Ecstasy").

Schedule II/IIN Controlled Substances (2/2N)

High potential for abuse which may lead to severe psychological or physical dependence.

Examples of Schedule II narcotics: hydromorphone (Dilaudid®), methadone (Dolophine®), meperidine (Demerol®), oxycodone (OxyContin®, Percocet®), and fentanyl (Sublimaze®, Duragesic®). Other Schedule II narcotics: morphine, opium, codeine, and hydrocodone.

Examples of Schedule IIN stimulants: amphetamine (Dexedrine®, Adderall®), methamphetamine (Desoxyn®), and methylphenidate (Ritalin®).

Other Schedule II substances include: amobarbital, glutethimide, and pentobarbital.

Schedule III/IIIN Controlled Substances (3/3N)

Less potential for abuse less than substances in Schedules I or II, low or moderate physical dependence and high psychological dependence.

Examples of Schedule III narcotics: products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with Codeine®), and buprenorphine (Suboxone®).

Examples of Schedule IIIN non-narcotics: benzphetamine (Didrex®), phendimetrazine, ketamine, and anabolic steroids such as Depo®-Testosterone.

Schedule IV Controlled Substances

Low potential for abuse relative to substances in Schedule III.

Examples of Schedule IV substances: alprazolam (Xanax®), carisoprodol (Soma®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), lorazepam (Ativan®), midazolam (Versed®), temazepam (Restoril®), and triazolam (Halcion®).

Schedule V Controlled Substances

Low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.

Examples of Schedule V substances: cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan with Codeine®), and ezogabine.

Atypical Opioids (schedule IV)
-Tramadol
-Tapentadol
(NMS pain)

- mu receptor agonists & NERIs
- Similar opioids' SEs (GI & CNS)[1]
- Potential serotonin sd (5-HT toxicity): Adding to SSRIs, SNRIs, or TCAs[2]
- Not less potent or safer than other opioids
  - The 2016 NSDUH found that 1.7 M people (>12 yo) in the U.S. reported misusing tramadol products in the previous year[3]
  - A 2019 cohort study of 88,902 pts with OAs showed ↑ risks of death at 1 year compared to NSAIDs[4]
- Atypical withdrawal manifestations (numbness/tingling)[5]

HT= serotonin; SNRIs= Selective norepinephrine reuptake inhibitors; SSRIs= Selective serotonin reuptake inhibitors; TCAs= Tricyclic antidepressants;

1-Malonne H, et al. Clinical therapeutics. 2004;26(11):1774-1782.

2-Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57(8):1331-1346

3-Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health HHS Publication No SMA 18-5068, NSDUH Series H-53. 2018

4-Zeng C, et al. JAMA. 2019;321(10):969-982.

5-Drug Enforcement Administration. Tramadol information. Diversion Control Division, Drug & Chemical Evaluation Section. 2018.

Potential serotonin sd (5-HT toxicity): Adding to SSRIs, SNRIs, or TCAs

Serotonin sd

Mydriasis, diaphoresis, shivering, change in MS, delirium, autonomic activity (rigidity, hyperthermia >40C, tachycardia), NM abnormalities (hyperreflexia, clonus)

Admission (ICU), cardiac monitoring, BZD, cyproheptadine, esmolol/nitroprusside, cooling measures, sedation/paralysis, MV

	Serotonin Syndrome	Anticholinergic Toxicity	Malignant Hyperthermia
Inciting Agents	5-HT agonists	Anticholinergics • Atropine-like drugs • Anti-histamines • Parkinson's meds • Many others	• Halogenated/Inhaled Anesthetics
Onset	<24 hrs	<24 hrs	<24 hrs
Symptoms	• Hyperreflexia • Rigidity • Hyperthermia • Increased bowel sounds • Diaphoretic	• Normal reflexes • Normal muscle tone • Decreased bowel sounds • Dry skin	• Hyporeflexia • Rigidity • Hyperthermia • Flushing

Immediate-release vs. extended-release (ER)/long-acting (LR) opioids

	Immediate-release formulations	Extended-release/Long-acting formulations
Indications	Opioid-naïve Acute moderate-severe pain	Longer duration of action and smoother PKs are needed ≥60 MMED for ≥1 week
Formulations	Codeine	Buprenorphine transdermal patch
	Hydrocodone + APAP	Fentanyl transdermal patch
	Hydromorphone	Hydrocodone ER
	Levorphanol	Hydromorphone ER
	Meperidine	Methadone
	Morphine	Morphine ER
	Oxycodone	Morphine ER + naltrexone
	Oxymorphone	Oxycodone ER
	Tapentadol	Oxycodone ER + naloxone
	Tramadol	Oxymorphone ER
		Tapentadol ER
		Tramadol ER

True or False

- Immediate Release formulations
- Order as prn
- Are indicated for acute pain
- Provide the cornerstone for acute pain management

True

False

- Extended Release (ER)/LA formulations
- Most dosage units contain more opioid than a starting dose
- Take days to weeks to obtain steady state after 3-5 t1/2
- Must be swallowed whole (cannot be cut, chewed or crushed)
- Are indicated for tolerant patients only


Thank you