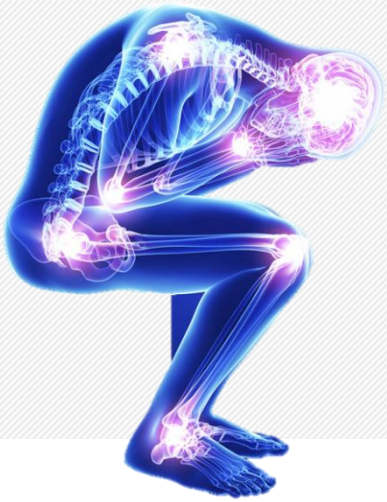

Optimization of Non-opioids Analgesics: From the Theory to the Practice

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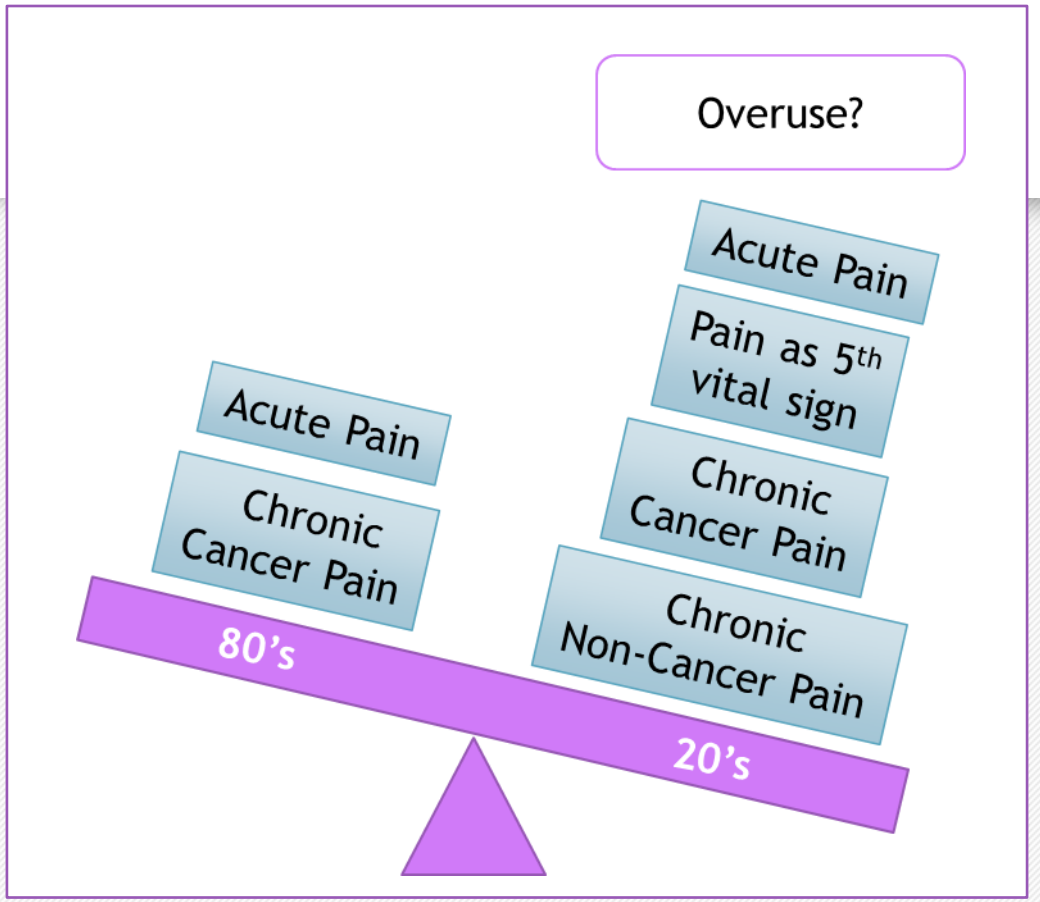
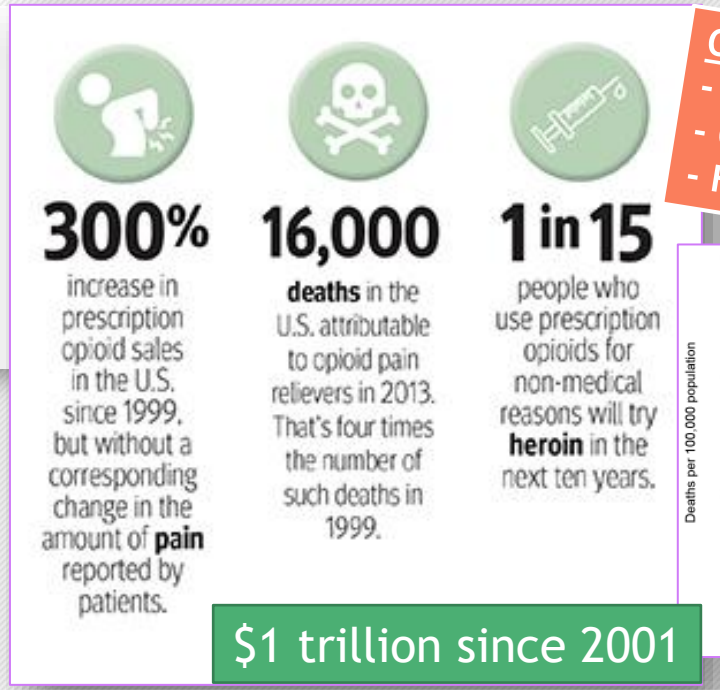
Disclosure

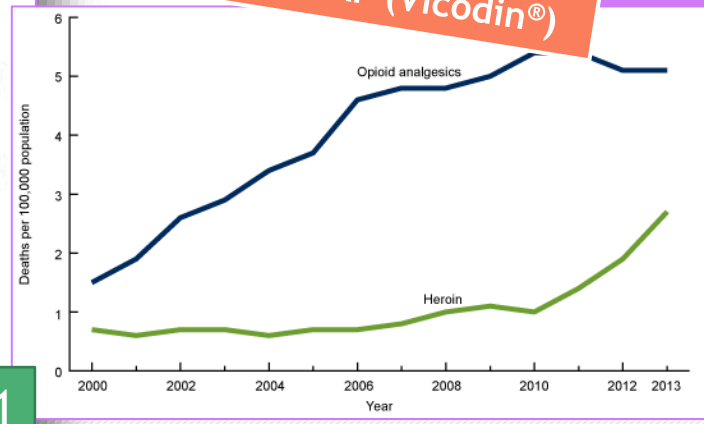
I have no actual or potential conflict of interest in relation to this presentation.

Opioids Crisis



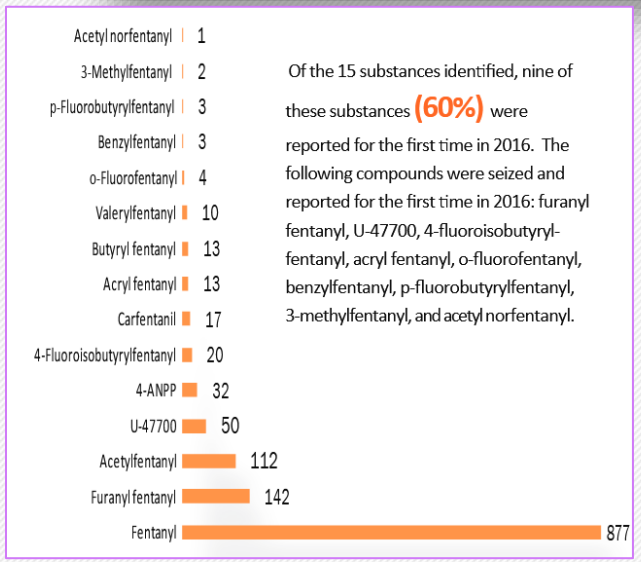


Opioids most commonly abused:
- Oxycodone/APAP (Percocet®)
- Oxycodone (Oxycontin®)
- Hydrocodone/APAP (Vicodin®)



$1 trillion since 2001

CDC/NCHS National Vital Statistics System NCHS Data Brief, No. 190, March 2015



Of the 15 substances identified, nine of these substances (60%) were reported for the first time in 2016. The following compounds were seized and reported for the first time in 2016: furanyl fentanyl, U-47700, 4-fluoroisobutyryl-fentanyl, acryl fentanyl, o-fluorofentanyl, benzylfentanyl, p-fluorobutyrylfentanyl, 3-methylfentanyl, and acetyl norfentanyl.

2016: DEA Special Testing and Research Laboratory's Emerging Trends Program Report
https://ndews.umd.edu/sites/ndews.umd.edu/files/emerging-threat-report-2016-annual.pdf

https://www.youtube.com/watch?v=h0fZ5zoVIP0

https://www.primerahora.com/noticias/puerto-rico/notas/crisis-de-los-opioides-se-siente-con-fuerza-en-la-isla/

https://www.cdc.gov/drugoverdose/epidemic/
https://www.cnbc.com/2018/02/12/economic-cost-of-the-opioid-crisis-1-trillion-and-growing-faster.html
https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

Approved in September 18, 2018

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

- One strategy among multiple national and state efforts
- Training be made available to health care providers who are involved in the management of patients with pain, and not only to prescribers (for example nurses and pharmacists).
- Education cover broader information about appropriate pain management, including:
  - ALTERNATIVES TO OPIOIDS for the treatment of pain

Early management of patients with acute pain **IS PARAMOUNT** in minimizing the risk of chronic pain development

FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. September 2018.

Objectives

- Describe the pathophysiologic mechanisms of pain including:
  - Contrast nociceptive, inflammatory, neuropathic and functional pain
  - Distinguish between acute and chronic pain
- Describe the role of non-opioids analgesics in the pain management.
- Distinguish when opioids should be avoided.
- Establish appropriate treatments goals.
- Recommend a non-opioid analgesic with appropriate patient monitoring.

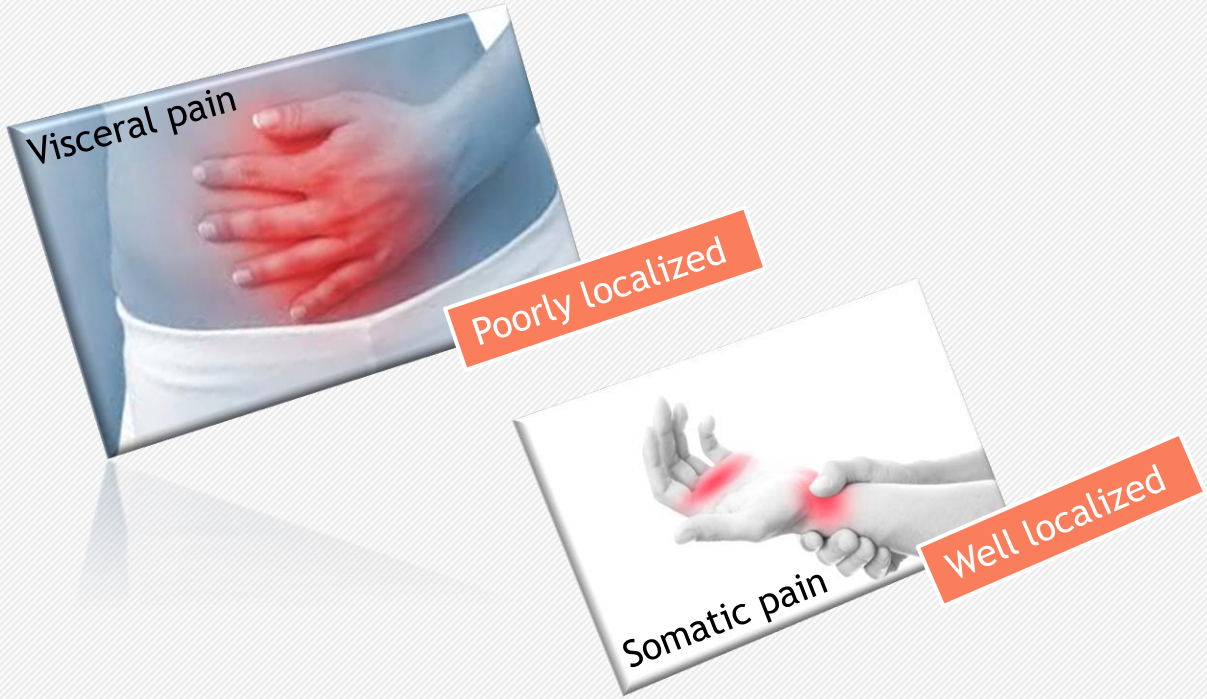
Objectives

- Recommend non-opioids medications for:
  - Acute pain
  - Arthritis, osteoarthritis, chronic low back pain, myofascial pain
  - Peripheral neuropathy
- Select a pharmacotherapeutic care plan for a patient in the setting of
  - Renal or hepatic dysfunction
  - Pregnancy or lactation
  - Clotting problems
  - Allergies
  - Risk of cardiac complications
  - Elderly
  - Risk of GI complications
- Recommend regimen adjustment to meet therapeutic goals in a patient with a complaint of pain.

Pain Definition

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage"

IASP

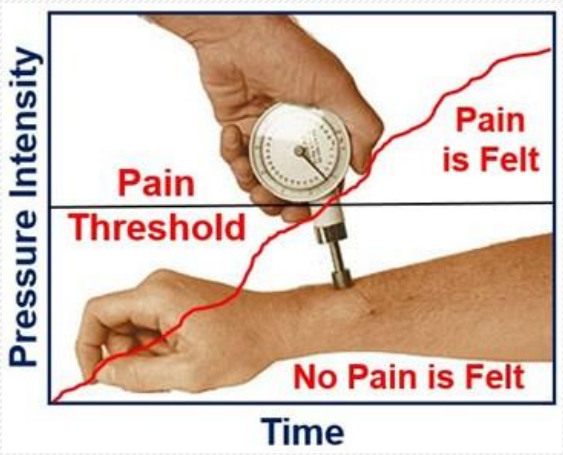


Pathophysiology

The 4 primary types of pain

- The presence of different pain types frequently coexists
- They can result in chronic pain

1. Nociceptive:
   - Somatic or visceral:
     - Somatic: Skin, muscles, skeleton, joints or connective tissues
       - Ex. Burns, tendonitis, arthritis, muscle pain
     - Visceral
   - High pain threshold



https://au.toluna.com/polls/8187612/Pain-Tolerance-Do-You-Have-A-Pain-Tolerance-How-Much

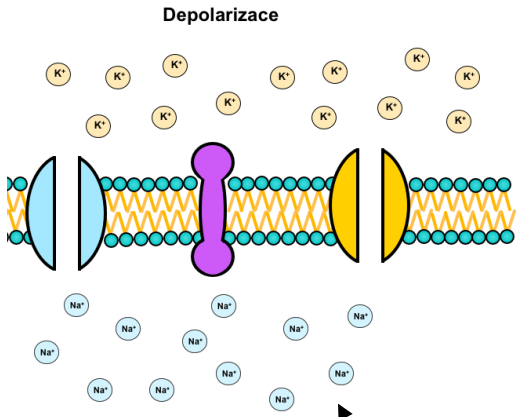
2. Inflammatory:
   - Tissue damage
   - Low pain threshold

3. Neuropathic:
   - Damage of the nervous system
   - Low pain threshold

4. Functional (Centralized Pain Augmentation):
   - Abnormal central processing of normal input
     - No noxious stimulus, no inflammation, no neuronal damage
   - Low pain threshold

Woolf CJ. Ann Intern Med. 2004 Mar 16;140(6):441-51.

1. Nociceptive Pain



1- Signal Transduction
(Somatic or visceral)
Conversion of a noxious stimulus into electrical activity. Somatic example.

2- Conduction
(action potential)

3- Ascending Transmission/modulation
Neuronal signal are transmitted up via spinal cord/nervous system can alter pain sensitivity

4- Perception
Thalamus which then routes the signals to different regions of the brain involved with sensation, motor responses, emotions, behavior, stress and autonomic nervous system activity

5- Descending Transmission/modulation

Facilitation	Inhibition
Glutamate, Substance P, serotonin, Dynorphin	Enkephalins, endorphins, serotonin, GABA, Norepinephrine

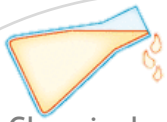
Na+/Ca 2+ influx

Aß and Aα fibers (large myelinated)

MDEG, DRASIC, TREK1 receptors

Na+/Ca 2+ influx

Aδ fiber (thinly myelinated)



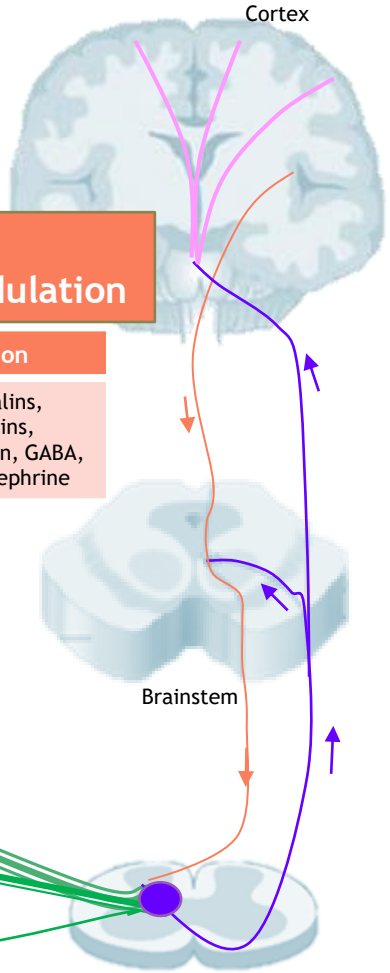
TRPV1, ASIC, DRASIC receptors

C fiber (unmyelinated)

TRPV1, TRPV2, TRPV3, TREK1 receptors

TRPM8 receptors

Na+/Ca 2+ influx

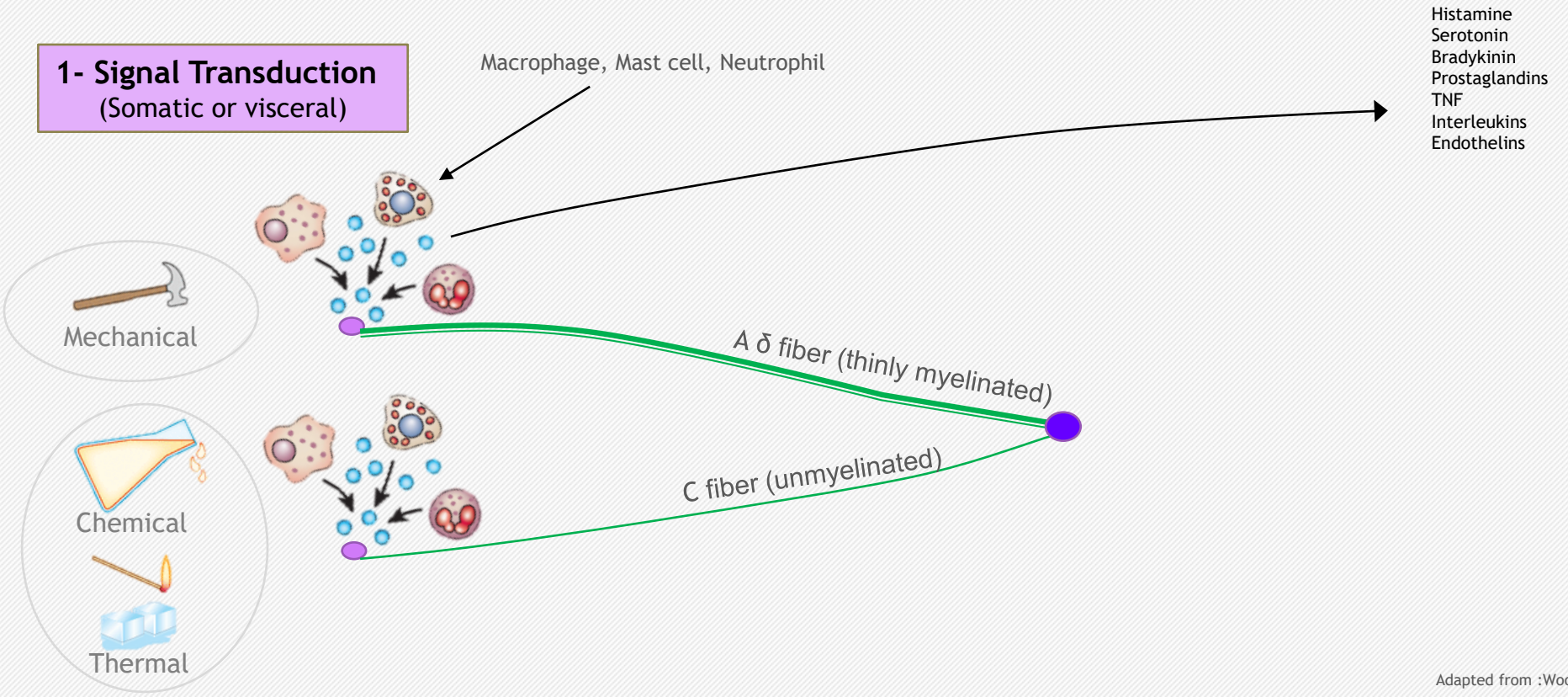


Emotions

Adapted from Woolf CJ. Ann Intern Med. 2004 Mar 16;140(6):441-51.

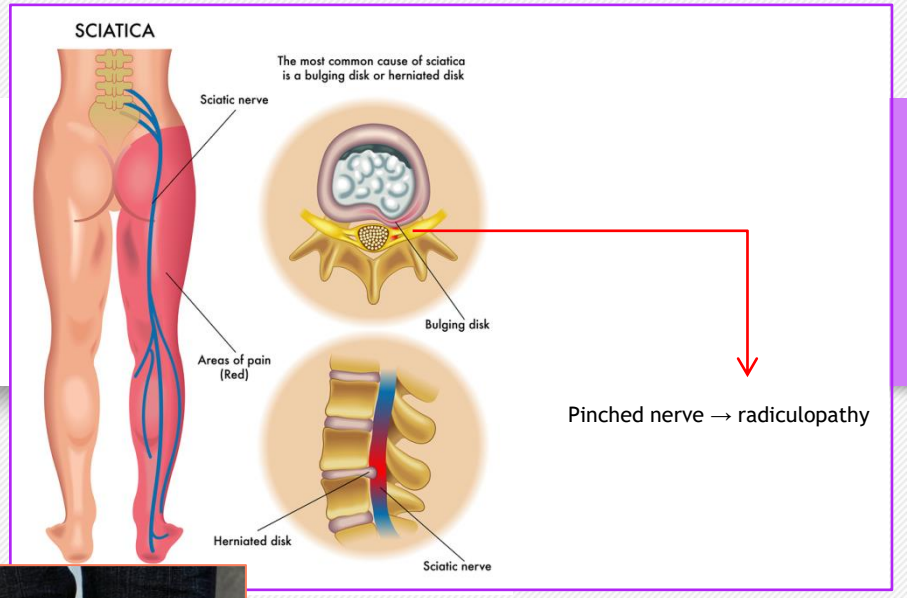
2. Inflammatory Pain

- At the same time that the transduction process is beginning, cells release inflammatory substances at the site of the “injury” that increase sensitivity to pain.



Adapted from :Woolf CJ. Ann Intern Med. 2004 Mar 16;140(6):441-51.

3. Neuropathic Pain



https://www.spineoptions.com/lumbarradiculopatysciata/

- May result from lesions to the
  - Peripheral nervous system
    - Diabetic or AIDS polyneuropathy, post-herpetic neuralgia, lumbar radiculopathy
  - Central nervous system
    - Spinal cord injury, multiple sclerosis, Central Post Stroke Pain, post-amputation pain

Phantom limb pain (PLP)

https://painresource.com/nervous-system/phantom-limb-pain-pain-lingers/

https://www.pinterest.co.uk/pin/410038741064622973/?nic_v2=1a3gj9yTe

Complex Regional Pain Syndrome (CPRS)

- Damage or malfunction of the peripheral and CNS
- Usually after an injury
- Duration: > six months
- Site: arm, leg, hand, or foot

Woolf CJ.Ann Intern Med. 2004 Mar 16;140(6):441-51.
Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res. 2013; 6:121-36.

4. Functional Pain (Central Pain Augmentation)

- Excessive amounts of pain-causing substances and not enough slowing it down.
  - Pain messages to places that don't even have an injury.

- Examples:
  - Visceral
    - Irritable bowel syndrome (begins with nociceptive stimuli)
    - Interstitial Cystitis/Bladder Pain Syndrome
    - Chronic Pelvic Pain (central)
    - Functional abdominal pain syndrome (FAPS) –
      - Considered a somatoform pain disorder(emotional and psychosocial conflicts play a major role in the onset, severity, exacerbation)
      - CBT is key with focus on self-efficacy (emotional and behavioral responding to anxiety-provoking situations)
  - Somatic
    - Fibromyalgia
    - Low back pain (persisting for at least 12 months, unexplained by MRI/radiographic changes)
    - Temporomandibular disorder

No opioids!!!!!
Increase sensitization!!!

Cognitive Behavioral Therapy (CBT) is important for these pts
(psychotherapy)

Migraine ?????

Woolf CJ.Ann Intern Med. 2004 Mar 16;140(6):441-51.

Acute vs Chronic Pain

Subacute
(3-6 months)

Characteristics	Acute	Chronic
Duration	**Short duration (< 3 -6 months), resolves with tissue healing**	≥ 3 - 6 months
Consequences	Endocrine: Altered ACTH, cortisol, catecholamines, insulin (weight loss, ↑RR, cardiovascular effects) Cardiovascular: ↑ HR, ↑BP, hypercoagulation Musculoskeletal: Muscle tension GI: delayed gastric emptying (constipation, anorexia) Immune: Impaired immune function	Physical functioning: ↓mobility, sleep disturbances, fatigue, anorexia, ↓ gray matter Affect: Depression, anxiety, anger, irritability, suicidal Social: ↓ relationships, ↓ sexual activity, loss of work, substance abuse, ↑ health care utilization
Goals	Resolution of underlying cause, usually self-limited	Underlying cause and pain disorder; outcome is often pain control, not cure

How acute pain become chronic?

Sensitization is an important self preservation mechanism

1. **Peripheral sensitization**
   - Prolonged inflammatory and neuropathic pain states leads an increased sensitivity to an afferent nerve stimuli of the peripheral nerve

2. **Central sensitization**
   - Continuous nociception stimulation contributes to:
     1. Changes in gene and protein expression in dorsal root ganglion and dorsal horn neurons (e.g. ↑ Na and TRPV1 receptors in spinal cord and nerves)
     2. Activation of NMDA receptors in the spinal cord
     3. Overstimulate glial cells (microglia) resulting in up-regulation of AMPA and NMDA receptors, activation of tetrodotoxin-resistant sodium channels, and down-regulation of GABA receptors.

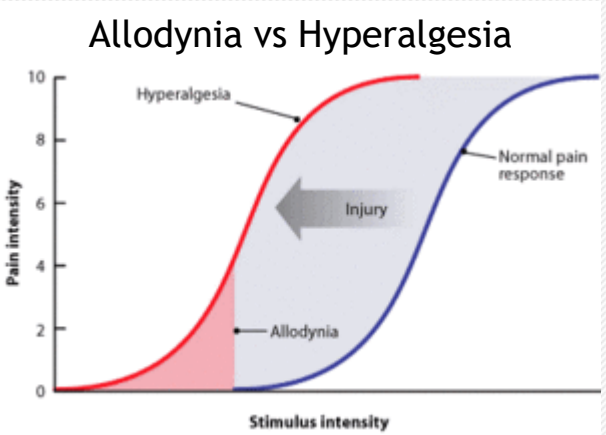
NMDA: N-methyl-D-aspartate

Wen YR, Tan PH, Cheng JK, et al. Microglia: a promising target for treating neuropathic and postoperative pain, and morphine tolerance. J Formos Med Assoc. 2011 Aug;110(8):487-94.

How acute pain become chronic?

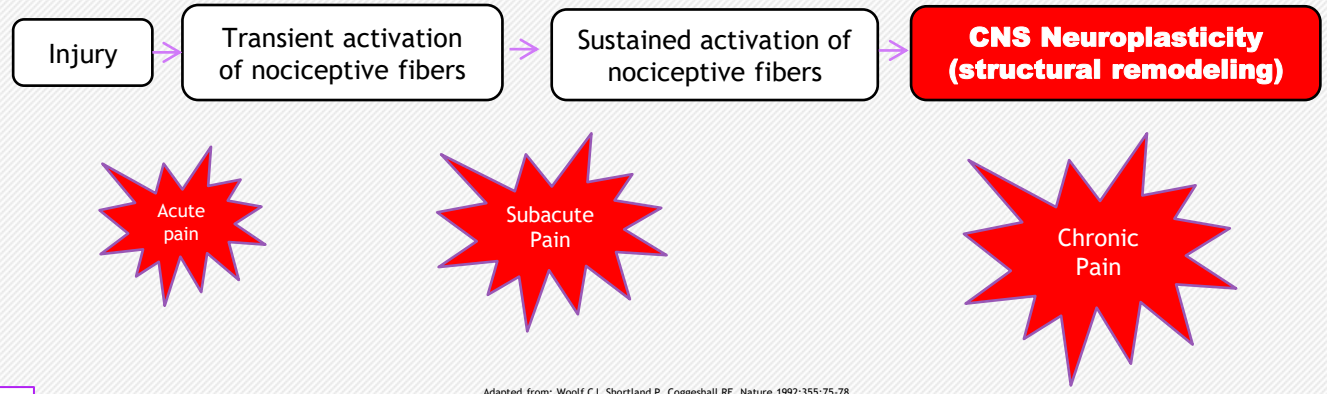
Peripheral and Central sensitization

- Contributes to allodynia and hyperalgesia
- Contributes to chronic and functional pain
- May be temporary or permanent, depending on neuronal changes



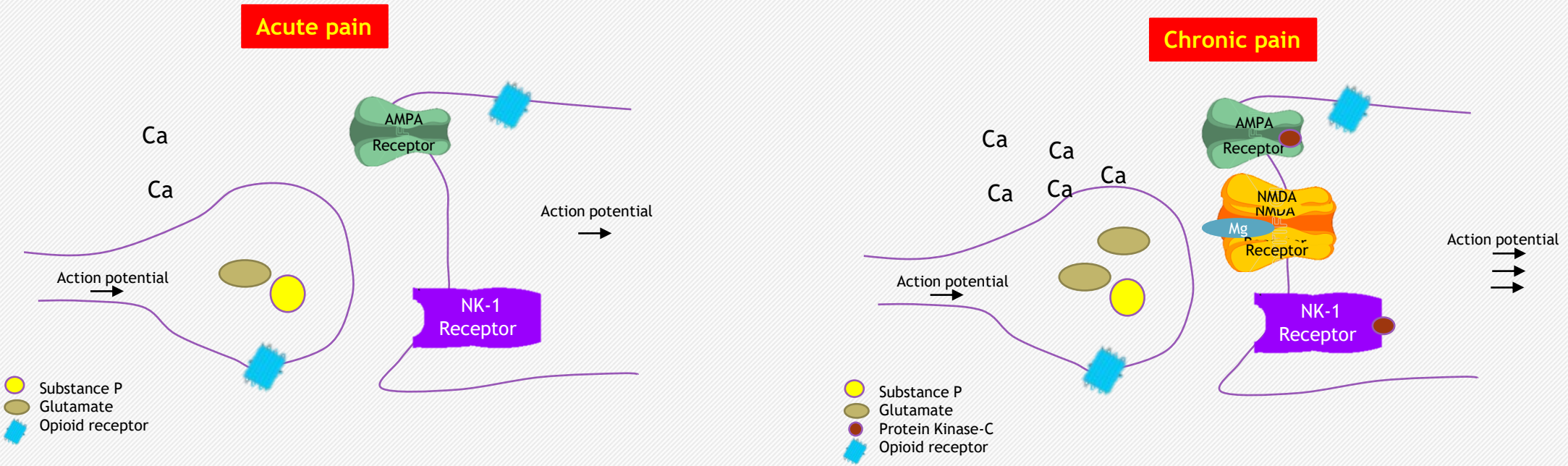
https://www.physio-pedia.com/Pain_Behaviours

- Hyperalgesia: Increase response to a painful stimulus
- Allodynia: Response to a non-painful stimulus (e.g. touching the sunburned skin)



Adapted from: Woolf CJ, Shortland P, Coggeshall RE. Nature.1992;355:75-78.

How acute pain become chronic?
NMDA receptor



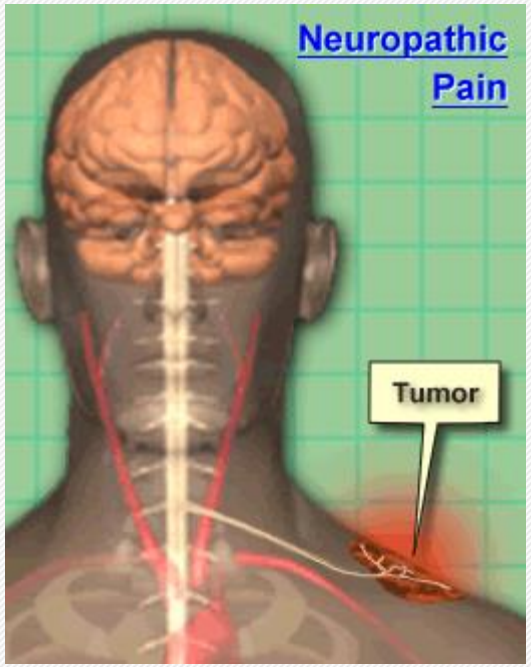
NMDA: N-methyl-D-aspartate
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Adapted from: Golan D. Tashjian AH Jr, Armstrong EJ et al. Principles of pharmacology: the pathophysiologic basis of drug therapy. 3rd ed. Baltimore: Lippincott Williams & Wilkins: 2012.

Cancer Pain Etiology

- tumor cells produce chemical signals that contribute directly to the pain (e.g. osteosarcomas)
- mechanical compression
- invasion of a nerve
- distention of an organ
- ischemia
- inflammatory reaction to tissue necrosis
- neurotoxic side effect of chemotherapy

Chemotherapy

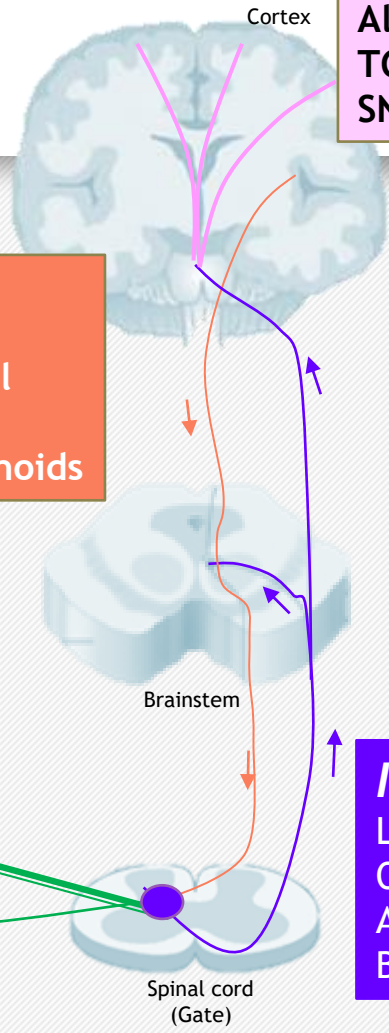


wdv.com

Pain Perception
- Physical Factors (Injury) and perception → Medications
- Emotional Factors (Anxiety/Depression) → Being in a 'good' mood
- Behavioral Factors (Concentrating on the pain) → Concentrating on things other than pain (CBT)

Medications MOA

Ketamine
Alpha2 agonists
TCAs
SNRIs



TCAs
SNRIs
Tramadol
Opioids
Cannabinoids

Carbamazepine
Oxcarbazepine
Topiramate
Lamotrigene
Lidocaine
TCAs

Ca++
Gabapentin
Oxcarbezepine
Lamotrigene

NMDA
Ketamine
Methadone
Lidocaine

Intrathecal/Epidural
Local anesthetics/corticosteroids
Opioids
$Alpha_2$ agonists
Baclofen

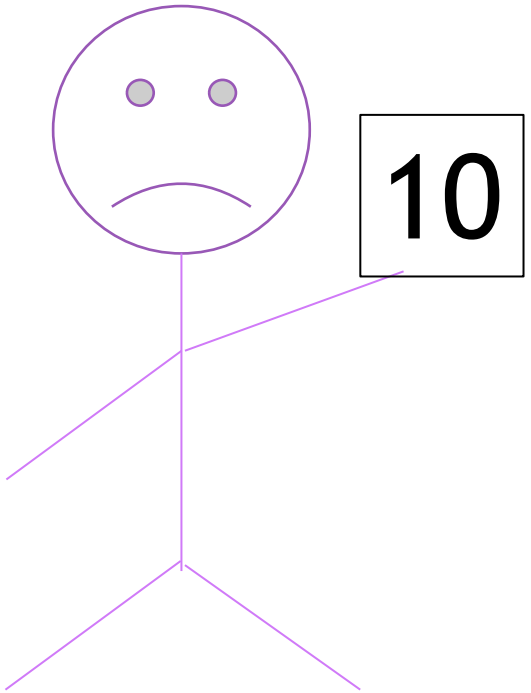
Local anesthetics
Anti-inflammatory drugs (corticosteroids, NSAID's)
Capsaicin
Counterirritants

TENS

Adapted from: Beydoun A, Backonja MM. J Pain Symptom Manage. 2003; 25(5 Suppl):S18-S30.
Moayedi M, Davis KD. Theories of pain: from specificity to gate control. J Neurophysiol. 2013;109(1):5-12.

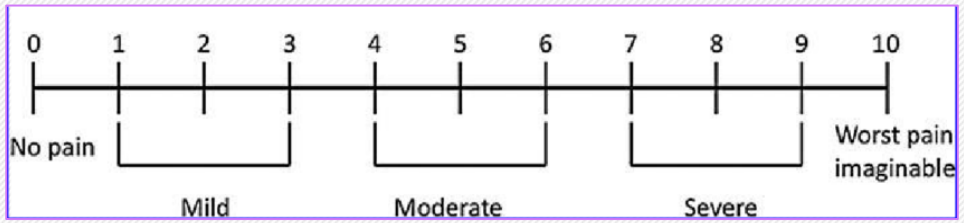
Assessment

Believe the patient in his/her report of pain



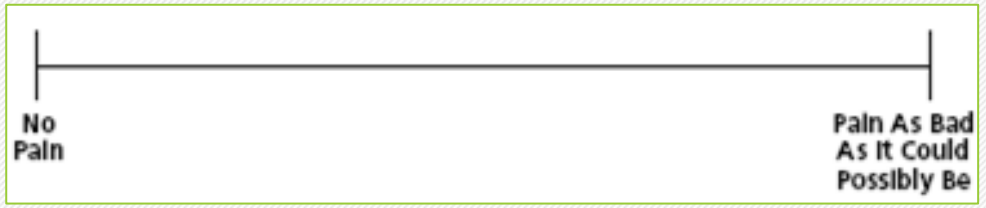
Scales
Unidimensional: Relates to pain severity alone

- Subjective measure



Numerical Rating Scale (NRS)

Verbal Rating Scale (VRS)



Visual Analog Scale (VAS)

Wong-Baker FACES

Scales
Unidimensional: Relates to pain severity alone

- Objective measure

Mankoski pain scale

	0	No pain. Feeling perfectly normal.
Minor Able to adapt to pain	1 Very Mild	Very light barely noticable pain, occasional twinges, no medication needed.
	2 Discomforting	Minor pain, like pinching the fold of skin, occasional strong twinges, no medication needed.
	3 Tolerable	Very noticeable pain, annoying enough to be distracting, over the counter (OTC) pain reliever needed.
Moderate Interferes with many activites	4 Distressing	Strong, deep pain, like an average toothache, can be ignored if one is very focused on a task. OTC pain reliever may be effective
	5 Very Distressing	Strong, deep, piercing pain, can't be ignored for more than 30 minutes. OTC pain reliever may reduce pain for 3-4 hours.
	6 Intense	Strong, deep, piercing pain, cannot be ignored however one may be able to work or attend social events. Narcotic pain relievers (Codeine, Vicodin) may be effective every 3-4 hours.
Severe Patient is disabled and unable to function independently.	7 Very Intense	It is difficult to concentrate or sleep. You can still function with effort. Stronger narcotic pain relievers are only partially effective. Strongest pain relievers relieve pain (Oxycontin, Morphine)
	8 Utterly Horrible	Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain. Stronger pain relievers are minimally effective. Strongest pain relievers reduce pain for 3-4 hours.
	9 Excruciating Unbearable	Unable to speak. Crying out or moaning uncontrollably - near delirium. Strongest pain relievers only partially effective.
	10 Unimaginable Untinkable	Unconscious. Pain makes you pass out. Srongest pain relievers only partially effective.

Andrea Mankoski Pain Scale (1995).
www.chronicallyawesome.org

Scales
Multidimensional Interview

P
Q
R
S
T
U

- P (precipitating / palliating)
  - What precipitates it?
    - Position changes (which one?), weight-lifting, personal care, light touch, activities (which one?), bowel movement, change in weather, exercise
  - What makes the pain better?
    - Medications (prescribed, OTC, herbal or natural products)
    - Non-drug interventions: heat, cold, position changes (which one?), walking, bed rest, chiropractic
    - Other strategies: prayer, quiet room, meditation
- Q (quality)
  - In your own words, describe what the pain feels like.
    - Nociceptive pain:
      - Somatic: Aching, deep, dull, throbbing, sharp, well localized
      - Visceral: Diffuse, gnawing, cramping, squeezing, pressure
    - Neuropathic Pain: Burning, numb, radiating, shooting, stabbing, tingling, needles

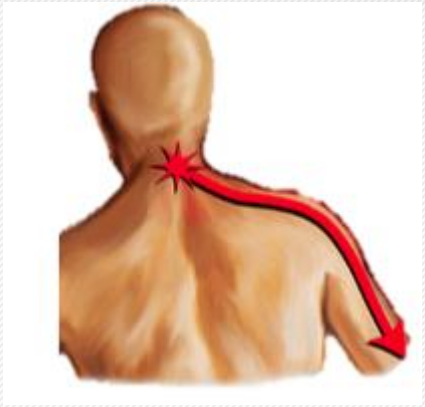
SOMÁTICO:
- Adolorido, constante, palpitante, bien localizado (toca el área con el dedo)

VICERAL:
- Persistente, acalambrante, opresivo, difuso (toca el área con la palma de la mano)

NEUROPÁTICO:
- Quemazón,adormecimiento, se irradia, disparante, puñalada, hormigueo, como agujas

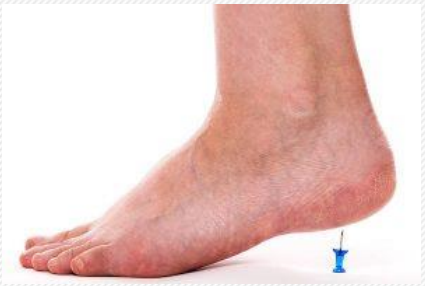
R. A. Powell, J. Downing, H. Ddungu, and F. Mwangi-Powell, "Pain History and Pain Assessment," in Guide to Pain Management in a Low Resource Setting, N. Patel, A. Kopf et al., Eds., IASP, 2010.
Buppractice. Pain history: a systemic approach using PQRSTU acronym. www.buppractice.com/node/5519.

Scales
Multidimensional Interview: Neuropathic Pain



Radiating

http://combohealthphysiotherapy.com.au/elbow%20pain.html.

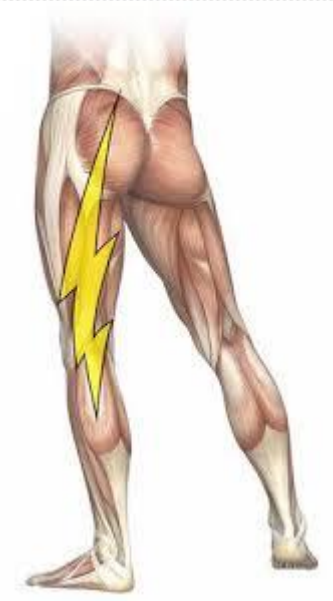


Needles

https://yourpodiatrycanberra.com.au/best-foods-foot-health/peripheral-neuropathy-foot-pin/.

Tingling

https://www.thehealthsite.com/diseases-conditions/pins-and-needles-causes-and-remedies-b815-322990/



Shooting

https://www.painscience.com/articles/sciatica.php

Stabbing

https://bpac.org.nz

Burning

https://www.webmd.com/pain-management/ss/slideshow-neuropathy

Numbness

https://stemcellpowernow.com/paresthesia/

Scales
Multidimensional Interview

P
Q
R
S
T
U

- R (region / radiation)
  - Where is the pain located?
  - The patient point to the site with one finger or hand?
  - Is it localized or referred?
  - Superficial or deep?
  - Does the place radiate? Where to?

- S (severity)
  - Pain right now?
  - Worst pain in the last week?
  - Best in the last week?
  - Pain on average in the last week?
  - What level is acceptable for you?
  - How does it change before and after medication?

- T (time)
  - Frequency
    - Constant or intermittent?
  - Intermittent:
    - Frequency of pain attacks?
    - How long are the pain free periods?
    - Onset
    - Duration
  - Variation (course / daily)

- U (YOU - How has this pain affected you?)
  - Patients' mood
  - Work/activities
  - Relationships
  - ADLs (hobbies)
  - Sleep
  - Appetite

R. A. Powell, J. Downing, H. Ddungu, and F. Mwangi-Powell, "Pain History and Pain Assessment," in Guide to Pain Management in a Low Resource Setting, N. Patel, A. Kopf et al., Eds., IASP, 2010.
Buppractice. Pain history: a systemic approach using PQRSTU acronym. www.buppractice.com/node/5519.

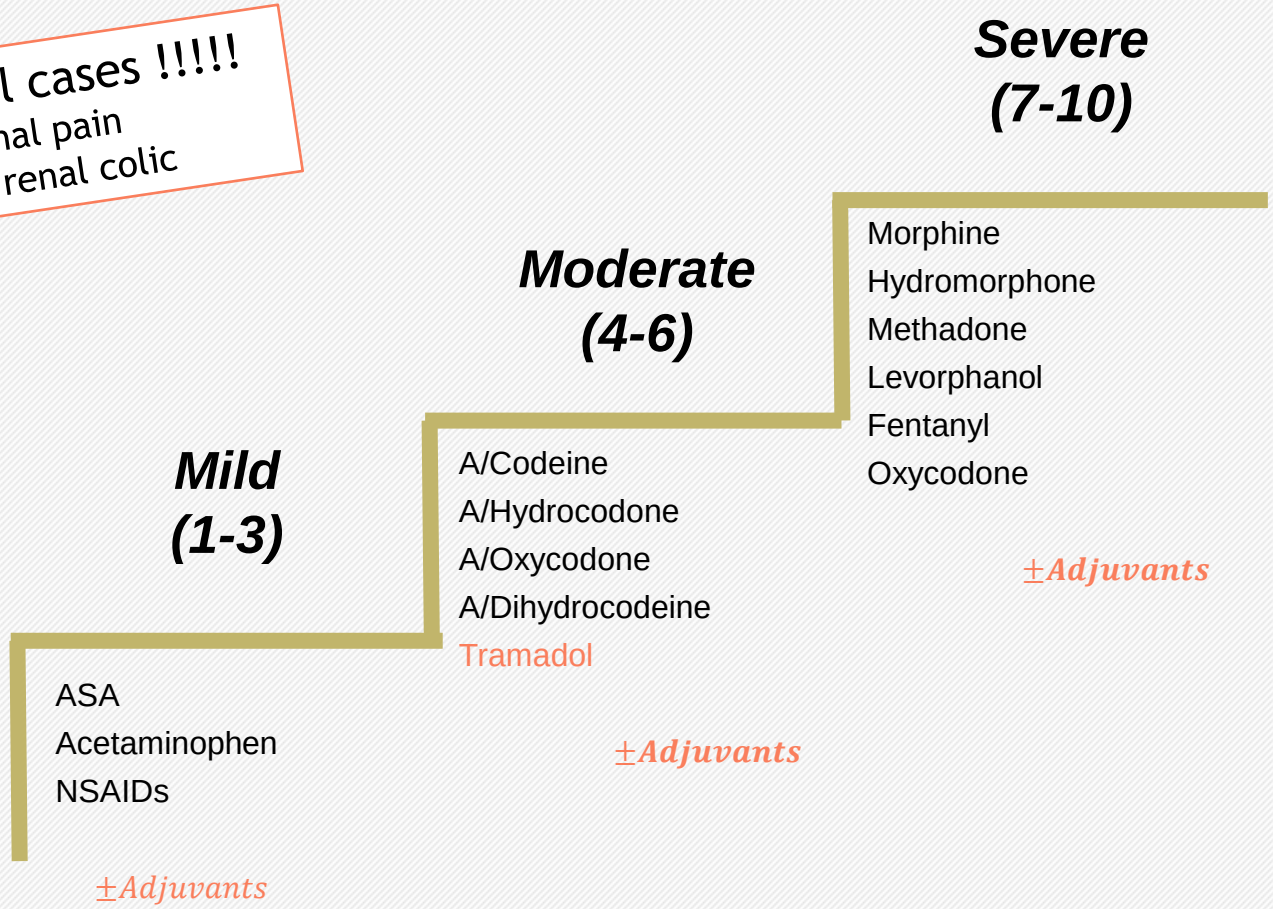
Other Scales

- Pediatrics (babies and children)
  - Assesses Crying, Oxygen requirement, Increased vital signs, facial Expression, Sleep (CRIES)
  - Neonatal/Infants Pain Scale (NIPS)
  - Face, Legs, Activity, Crying, Consolability (FLACC)
  - Children's Hospital of Eastern Ontario Scale (CHEOPS)

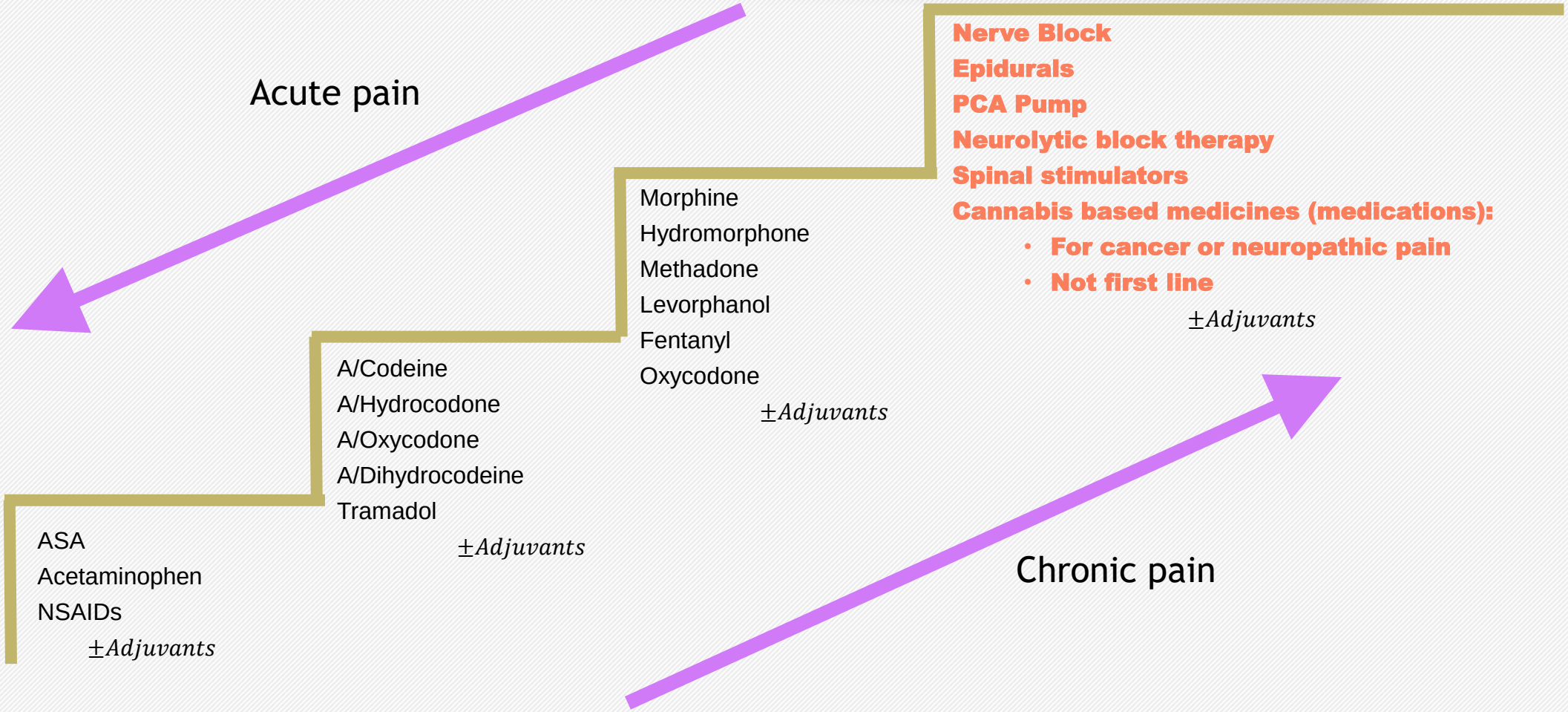
- Geriatrics / Cognitively Impaired
  - Pain Assessment for Seniors with Limited Ability to Communicate (2004)
  - Abbey pain scale (2004)
  - Pain Assessment in Advanced Dementia (PAINAD) (2003)
  - Pain Assessment for the Demented Elderly (2003)
  - Checklist of Nonverbal Pain Indicators (2000)
  - Assessment of Discomfort in Dementia Protocol (1999)
  - Doloplus-2 scale (1997)

WHO 3-Step Ladder Pain Scale

Does not apply to all cases !!!!!
- Not opioids for functional pain
- NSAID's for biliary and renal colic



New Adaptation of the Analgesic Ladder

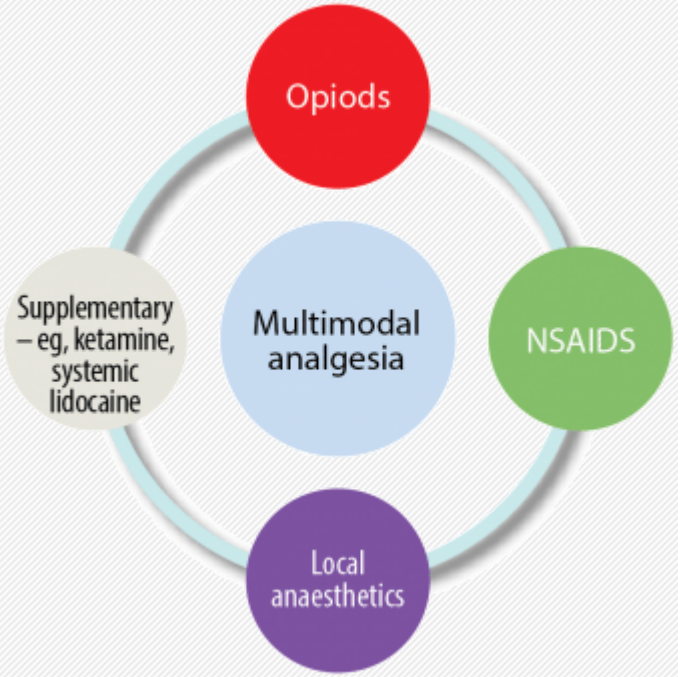


Adapted from: Can Fam Physician. 2010 Jun; 56(6): 514-517.

Multimodal Analgesia

IMPORTANT

- Use or 2 or more analgesic with different MOA
- Benefits
  - Synergistic analgesia
  - Lower doses of each agent = fewer adverse effects
    - ↓ opioids doses



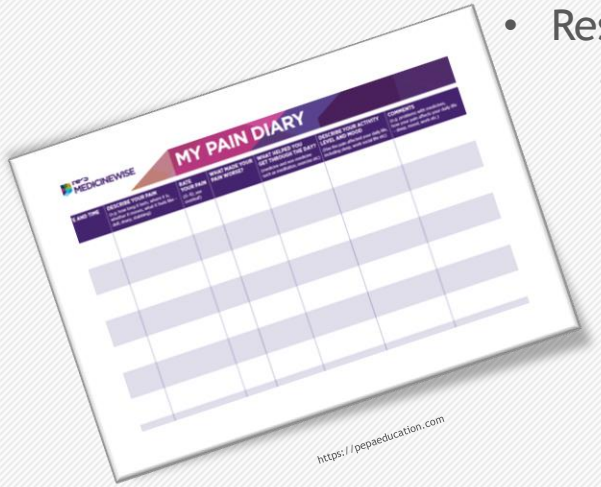
Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011; 377(9784):2215-25.

Goals

Treatment Goals

ACUTE PAIN

- Relieve or eliminate the pain
  - Severe: may be ↓ 50 % or more
- Minimize pharmacologic side effects
- Prevent chronic pain



CHRONIC PAIN

- Reduction of pain to acceptable level
  - ↓ 30%, ↓30 - 50%, 3 points reduction on a numeric pain scale
- Minimize pharmacologic side effects
- Improve functional status
  - Restore physical, emotional and social function
    - Subjective description: sleeping better, performing ADL better
    - Objective description: longer sleep, able to walk further, able to work, work longer, correct secondary consequences of pain as postural deficits

Physical, Emotional and Social Function: Examples

- What would you like to do that you can't do now because of your pain?
  - "I want to be able to play with my grandchildren"
  - "I want to go back to work"
  - "I want to go to the bathroom alone"
  - "I want to dress myself"

https://www.saga.co.uk/magazine/relationships/family/grandparenting/indoor-activities-to-do-with-kids

Pharmacological Treatment

Cognitive Behavioral Therapy

Hypnotherapy

Thermal

Interventional

Massage

Physical Therapy

Surgical

Physical Medicine and Rehabilitation

Ultrasound

Acupuncture

Laser

Electrical

Chiropractic

Medications for Nociceptive or Inflammatory Pain

Mild to moderate

Adjuvant (moderate, severe)

Acetaminophen (APAP)

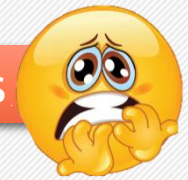
- Mild-moderate pain
- Moderate-severe pain with opioids
- Comparable efficacy to oral
- Fever reduction in adults and children
- Contraindicated: Severe hepatic impairment

- Indications:
  - Lower a fever
  - Mild to moderate: non-inflammatory, nociceptive pain
  - Adjuvant for moderate /severe, example postoperative pain
- MOA: Acts in the CNS (Inhibits COX enzymes, interactions with nitric oxide, block substance P)
- Role in therapy
  - Acute and chronic pain. Examples:
    - Self-limiting painful conditions (tension headache, mild to moderate musculoskeletal pain, dental pain)
    - First line for nociceptive Chronic Low Back Pain* (acute or chronic) (May be ineffective for long-term use**)
    - Second line osteoarthritis [short term or on regular basis(monitoring for hepatotoxicity)]
      - Others for osteoarthritis: NSAID's 1st line, topical NSAIDs (not for hip), intra-articular corticosteroid injections (for knee and hip, not hands), duloxetine (Cymbalta®), **tramadol prn**
    - Opioid-sparing effect

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care & Research 2020;72:149-162.
Machado GC, Maher CG, Ferreira PH et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2014; 350:h1225.
Brown JP, Boulay LJ. Ther Adv Musculoskelet Dis. 2013; 5(6):291-304.
Myers J, Wielage RC, Han B et al. BMC Musculoskeletal Disord. 2014; 15:76.
*Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147(7):478-91.
** Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225.

Acetaminophen (APAP)

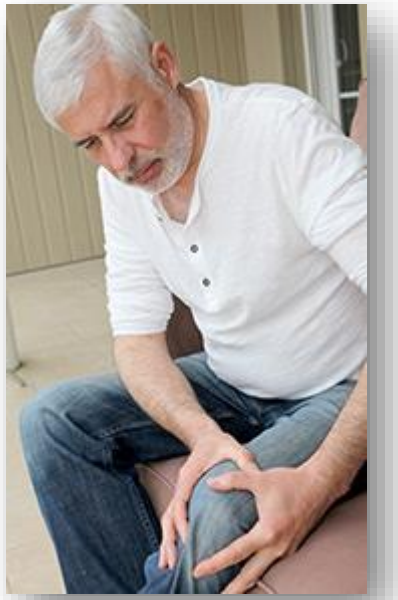
- Adverse effects
  - Very well-tolerated
  - Renal adjustment (IV, ClCr < 30 ml/min): No dosage adjustment likely to be necessary*. Some suggest:
    - 10-50 mL/min: increase interval q6h
    - < 10 mL/min: increase interval q8h
  - Hepatotoxicity seen with acute and chronic use
    - Doses over 4 g/day: Glutathione conjugation becomes insufficient to meet metabolic demand causing an increase in NAPQI → hepatic cell necrosis.
    - Non-prescription max dose: 3 - 3.9 g/day, health care professionals recommended: Max 4 g/day
    - Avoid use or Max dose ≤ 2 g/day
      - Active alcohol use (≥ 3 alcoholic drinks per day…….. )
      - Hepatic impairment/cirrhosis (short term)
      - Elderly (May be 2-3 g day)

2 or more factors 

*Berg KJ, Djøseland O, Gjellan A, et al. Acute effects of paracetamol on prostaglandin synthesis and renal function in normal man and in patients with renal failure. Clin Nephrol. 1990;34(6):255-262.
*Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet. 1982;7(2):93-107.
*Martin U, Temple RM, Winney RJ, Prescott LF. The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. Eur J Clin Pharmacol. 1991;41(1):43-46
*Prescott LF, Speirs GC, Critchley JA, Temple RM, Winney RJ. Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. Eur J Clin Pharmacol. 1989;36(3):291-297.

A 70 y/o man has hx of osteoarthritis and rated his pain 5/10. He takes acetaminophen 1000 mg every 4 hours with adequate control pain (2/10).

The patient has a history of alcoholic cirrhosis and currently drinks 5 beers per day or more.


https://www.uwhealth.org

Acetaminophen would be safe for this patient if:

A. If he reduces the dose to < 3 g/day
B. If he agrees to stop drinking alcohol
C. If he agrees to take it prn
D. Acetaminophen is not safe for this patient

NSAID's

- Role in therapy:
  - Principally acute pain or acute exacerbation of chronic pain
    - PRN !!!
    - Shortest duration of time!!!!!!!!!!
    - Remember: Lowest effective dose !!!
  - Especially helpful in certain types of somatic pain:

<table>
<tr><td colspan="2">Muscle and joint pain
• Rheumatoid arthritis 1st line (starting therapy with DMARDs or acute exacerbation)
• Diclofenac blocks Ach-induced muscle contraction</td><td>Inflammatory pain (e.g. gout- rare opioids, last choice)</td></tr>
<tr><td colspan="2"></td><td>First line for nociceptive chronic low back pain (acute or chronic)</td></tr>
<tr><td>Bone pain</td><td>Dental pain</td><td>Osteoarthritis (first line)</td></tr>
</table>

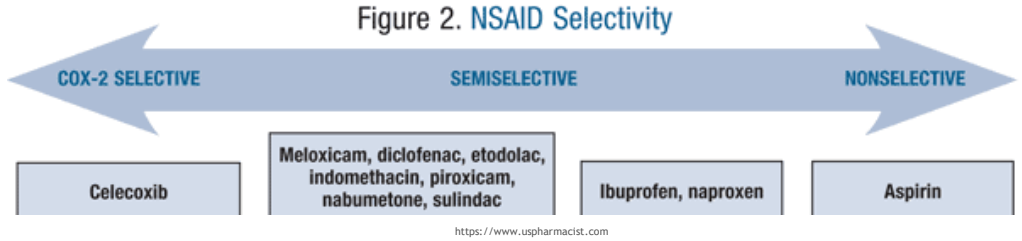
  - Visceral: Dysmenorrhea, better than opioids for biliary and renal colic 

  - Post-operative pain ("unless contraindicated, pts should receive NSAID's or acetaminophen ATC) Anesthesiology 2012; 116:248-73
  - Opioid-sparing effect
  - Lower a fever

It is appropriate combine APAP + NSAID or COXIBs

Kolasinski SL, Neogi T, Hochberg MC, et al. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee Arthritis Care Res. 2020;72(2):149-162.
Hyllested M, Jones S, Pedersen JL, et al. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth. 2002 Feb;88(2):199-214
Ong CK, Seymour RA, Lirk P, et al. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010 Apr 1;110(4):1170-9.
Sivaganesan A, et al The effect of NSAIDs on spinal fusion: A cross-disciplinary review of biochemical, animal, and human studies, European Spine Journal, 2017;26(11):2719-28.
*Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147(7):478-91.

NSAID's



Categories						
COX-2 Selective	Acetylated Salicylates	Non-acetylated Salicylates (weak inhibitors of COX-1)	Acetic Acid	Propionic Acids	Fenamates	Oxicam
• Celecoxib ↑♥ ↓ GI Safer aspirin "allergy" Safer with warfarin	• Aspirin (ASA)	• Salsalate • Diflunisal • Choline trisalicylate Safer aspirin "allergy" Safer with warfarin	• Etodolac • Diclofenac • Indomethacin • Ketorolac • Nabumetone • Sulindac • Tolmetin	• Ibuprofen • Fenoprofen • Flurbiprofen • Ketoprofen • Naproxen • Oxaprozin	• Meclofenamate • Mefenamic acid	• Piroxicam • Meloxicam

Adverse effects	Interactions	Interaction with ASA
• Nausea/Vomiting • Diarrhea/Constipation • Decreased appetite • Rash	• HTN: ACE-I, Antihypertensives • Renal: Diuretics, Cyclosporine, Lithium, bisphosphonates • GI: Corticosteroids, Bisphosphonates (oral) • Hematologic: Anticoagulants (avoid) • Methotrexate toxicity	• All NSAIDS may potentially antagonize cardioprotection effects of ASA • Relative risk of GI bleeding increases more than 10 times

NSAID's
Cardiovascular and Gastrointestinal Precautions

- CHF or recent MI: Avoid NSAIDs
- HTN: Use with caution

	Low CV Risk	High CV Risk (require low dose of ASA)
Low GI risk (no risk factors)	NSAID (Lowest dose of least ulcerogenic agent: diclofenac, namubetone, ibuprofen)	Naproxen + PPI or misoprostol
Moderate GI risk (1-2 risk factors)	NSAID + PPI or misoprostol	Naproxen + PPI or misoprostol
High GI risk: - Hx of complicated ulcer (ie, bleeding, perforation) - ≥ 3 risk factor	COX-2 Inhibitor + PPI or misoprostol	Avoid NSAIDs *or* COX-2 inhibitors

- GI risk factors:
  - Age > 65 y
  - High dose NSAIDs
  - Hx of uncomplicated ulcer
  - Concurrent use of aspirin, corticosteroids or anticoagulants

- Greater GI toxicity: Sulindac, indomethacin, piroxicam, and ketorolac (Toradol®)

Fendrick AM. COX-2 inhibitor use after Vioxx: careful balance or end of the rope? Am J Manag Care. 2004;10:740-741.

A 75 y/o woman was recently diagnosed with rheumatoid arthritis.

- The physician wants to start a NSAID to treat this inflammatory pain for 1-2 months and DMARDs treatment.
- She has a PVD and takes aspirin 81 mg PO daily.

https://www.oklahomapaintreatmentcenters.com

Which of the following is the best option for her?

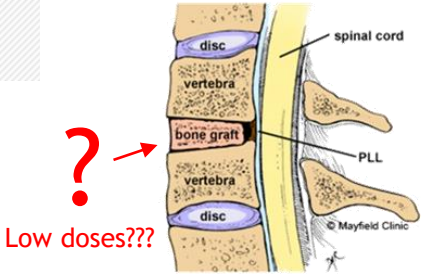
A. Celecoxib 200 mg po qd

B. Celecoxib 200 mg po qd plus omeprazole 20 mg po qd

C. Naproxen 500 mg po q12h

D. Naproxen 500 mg po q12h plus omeprazole 20 mg po qd

NSAID's
Other Precautions



Bone graft during spinal surgery

https://www.stgeorgesurgical.com

Anastomotic leak after colorectal surgery

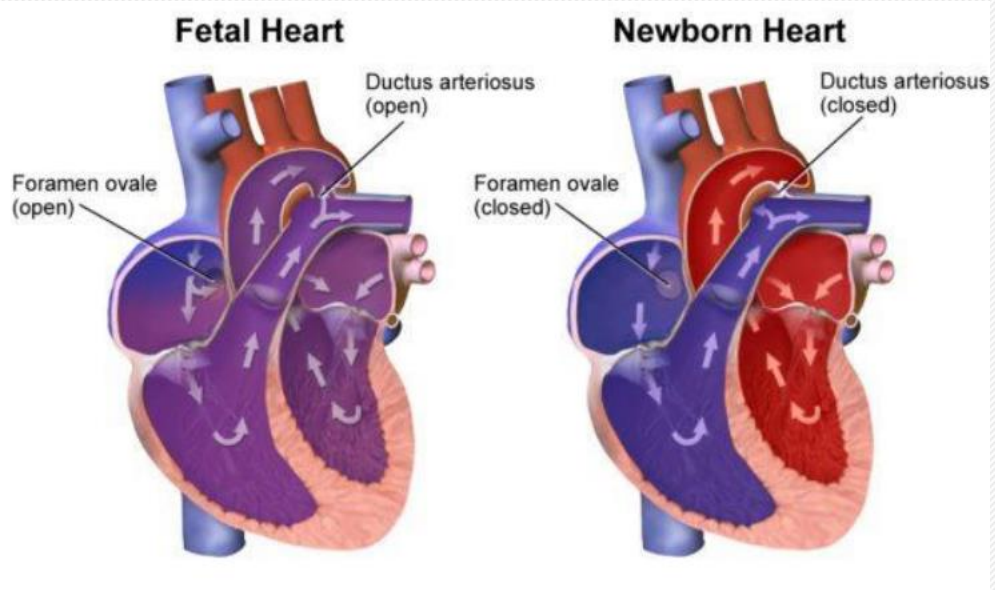
https://www.journalofsurgicalresearch.com

- **Hepatic:**
  - AVOID NSAIDs in patients with cirrhosis:
    - Increased risk of variceal bleed and portal hypertension
    - Precipitation of renal impairment
- **Renal:**
  - Avoid NSAIDs in patients with CrCl < 30 ml/min (retention of sodium and water, edema, hyperkalemia). Exception: ibuprofen
  - Hemodialysis
    - Increased risk for GI bleeding
    - Avoid if patient also has HT or CHF
    - If needed, low dose ibuprofen (200-400 mg)
- **Clotting:**
  - Avoid NSAIDs in patients with platelet defects or thrombocytopenia
  - Option: Cox-2 inhibitors
- **Respiratory:**
  - Use NSAIDs and aspirin with caution in patients with asthma, especially with nasal polyps or recurrent sinusitis
    - Prevalence of *aspirin-exacerbated respiratory distress*: 0.07% in general population, up to 21% in adults with asthma
- **Pregnancy:**
  - Risks Avoid NSAIDs during 1st trimester
    - DO NOT use starting at 30 weeks (Ductus arteriosus)

May use with caution: During chemotherapy (antipyretic action), bone surgeries and colorectal surgeries

NSAID's
Other Precautions

- Pregnancy (3rd trimester)



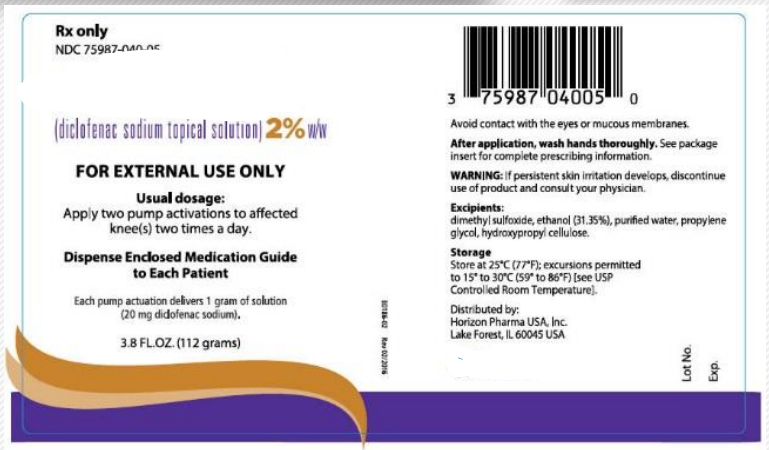
- Ductus arteriosus:
  - Blood vessel that connects the aorta and the pulmonary artery
  - Protects lungs against circulatory overload
  - Usually closes 2-3 days after birth

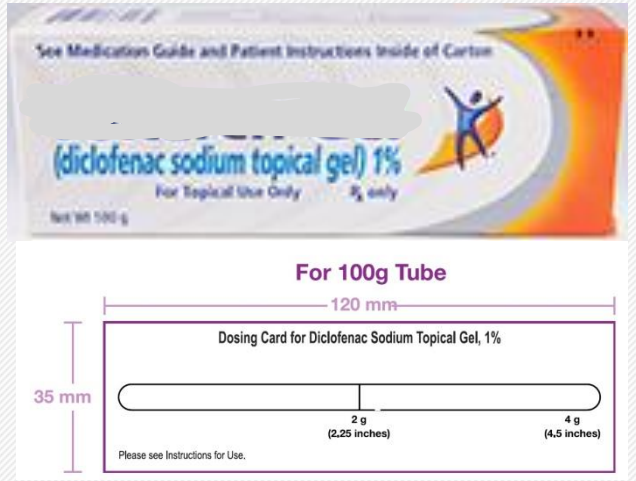
- NSAID's increased risk of premature closure of the ductus arteriosus

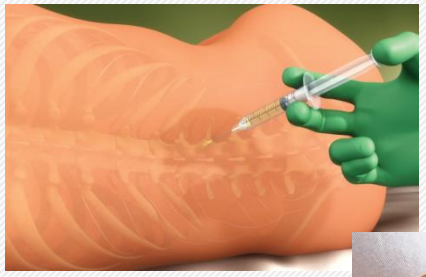
NSAID's Special Considerations

- Ketorolac IM/IV/Oral (Toradol®), Nasal (Sprix®)
  - Comparable to 10 mg Morphine with longer duration.
  - Use should be limited to 5 days
- Ibuprofen IV (Caldolor®)

- Topical NSAID's
  - Persons age ≥ 75 should use topical rather than oral NSAIDs (American College of Rheumatology 2012)
  - Less systemic side effects
  - Less pain-relieving effect







Medications for Neuropathic Pain, Local/Regional Anesthesia and Other Topical Treatments

Neuropathic Pain Ladder

Step I

Antidepressants

Anticonvulsants

Lidocaine patch (post-herpetic neuralgia)

Step II

Combination of antidepressant and Anticonvulsive

Topical treatment

Tramadol

Step III

Add Cannabinoids

Nerve Compression

Corticosteroids

Special indications

Ketamine

Clonidine

Inpatient

Neuropathic Pain: Guidelines/Recommendations Summary

	EFNS				NICE		CPS		NeuPSIG
	Diabetic neuropathy	**Post-herpetic neuralgia**	**Trigeminal neuralgia**	**Central neuropathic pain**	**All neuropathic pain**	**Trigeminal neuralgia**	**All neuropathic pain**	**Trigeminal neuralgia**	**All neuropathic pain**
1st line	Duloxetine Gabapentin Pregabalin TCA Venlafaxine	Gabapentin Pregabalin TCA Lidocaine patch	Carbamazepine Oxcarbazepine	Gabapentin Pregabalin TCA	Amitriptyline Duloxetine Gabapentin Pregabalin Capsaicin cream *(localized pain, cannot tolarate oral tx)*	Carbamazepine	Gabapentin Pregabalin Duloxetine Venlafaxine TCA	Carbamazepine	Gabapentin Pregabalin Duloxetine Venlafaxine TCA
2nd line	Tramadol	Strong opioids Capsaicin cream		Tramadol Strong opioids	One of the remaining first line tx		Tramadol Strong opioids Lidocaine cream Lidocaine patches		Capsaicin patches Lidocaine patches Tramadol
3rd line	Strong opioids			Strong opioids	One of the remaining first line tx		Cannabinoids (nabilone, nabiximols, and dried cannabis)		Botulinum toxin Strong opioids
4th line				Lamotrigene *(Central Post Stroke Pain)* Cannabinoids (THC, oromucosal sprays) *(Multiple Sclerosis)*			Methadone Lacosamine Lamotrigene Botulinum toxin Lidocaine cream Lidocaine parches		

European Pain Federation (EFIC): Cannabis based medicines (medications) can be considered as third line therapy for chronic neuropathic pain

European Federation of Neurological Societies (EFNS)
National Institute for Health and Care Excellence (NICE)
Canadian Pain Society (CPS)
Special Interest Group on Neuropathic Pain (NeuPSIG)

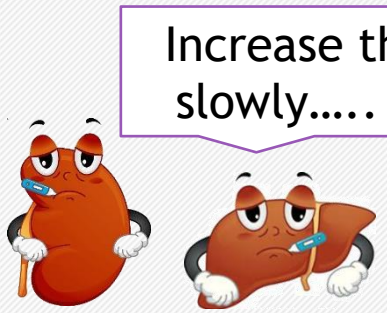
Adapted from Cruccu G, Truini A. A review of Neuropathic Pain: From Guidelines to Clinical Practice. Pain Ther. 2017; 6(Suppl 1):35-42.
Attal N, Cruccu G, Baron R, et al. European Federation of Neurological Societies. Eur J Neurol. 2010; 17(9):1113-e88.
National Institute for Health and Care Excellence (NICE). Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings. 2013.
Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain: review of the Canadian Pain Society consensus statement. Can Fam Phys. 2017;63:844---52.
Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis.mLancet Neurol. 2015;14(2):162-73.
European Pain Federation (EFIC) position paper on appropriate use of cannabis based medicines and medical cannabis for chronic pain management. Eur J Pain. 2018;22:1547-1564.

Tricyclic Antidepressants (TCA's)

Antidepressants (instead anticonvulsants) are preferred for:
Fibromyalgia
IBS
Functional Abdominal Pain Syndrome

Increased risk of depression relapse during pregnancy with antidepressants discontinuation!!!

- MOA:
  - Block the reuptake of norepinephrine and serotonin (centrally and descending pathways), sodium and calcium channels
- Tertiary amines:
  - Amitriptyline (Elavil®), doxepin (Sinequan®), Clomipramine (Anafranil®), Imipramine (Tofranil®)
- Secondary amines:
  - Desipramine (Norpramin®), nortriptyline (Pamelor®), protriptyline (Vivactil®), amoxapine (Asendin®)



- Neuropathic pain (not FDA approved)
- Effectivity studies:
  - Fibromyalgia, Central Post Stroke Pain, radicular pain for chronic low back pain
- Tension HA prophylaxis
- Inexpensive
- Once daily administration
- Therapeutic response: 3-10 days

Tricyclic Antidepressants (TCA's)
Side Effects

- Anticholinergic effects (Tertiary amines ↑↑↑↑↑) TOLERANCE OCURRS
  - Sedation (may given at bedtime!!!!!)
  - Dry mouth
  - Postural hypotension
  - Glaucoma exacerbation
  - Constipation (also with opioids)
  - Urinary retention (also with opioids)

- Cardiac conduction disturbances:
  - Baseline ECG (older pts or preexisting cardiac disease)
- Monitoring BP and HR
- Interaction with tramadol: Monitoring serotonin syndrome
- Fatal in overdose (not for suicidal pts)

RR is a 56 y/o male who presents with burning pain in his feet (7/10).

- PMH: Diabetes x 20 years, hypertension (155/85 mm Hg), BPH
- Laboratory Values:

  Hgb A1c 10%

  Scr 2.2

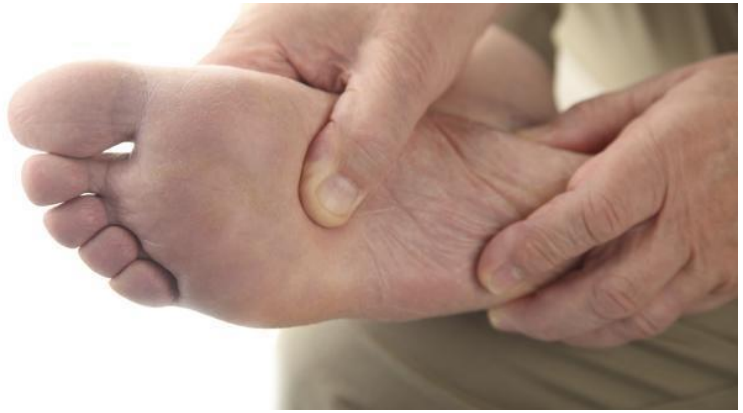
Which of the following factors could be more worrying to recommend a TCA for RR?

A. Renal insufficiency

B. Hypertension

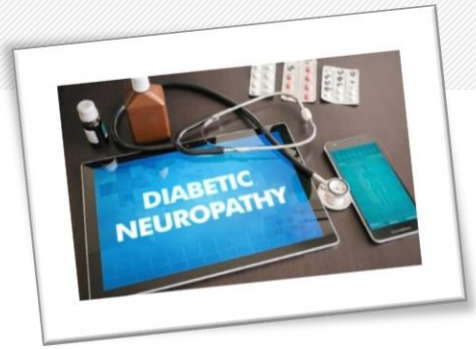
C. Age

D. Diabetes



https://www.thehealthsite.com

Antidepressants: SNRI's



Antidepressants (instead anticonvulsants) are preferred for:
Fibromyalgia
IBS
Functional Abdominal Pain Syndrome

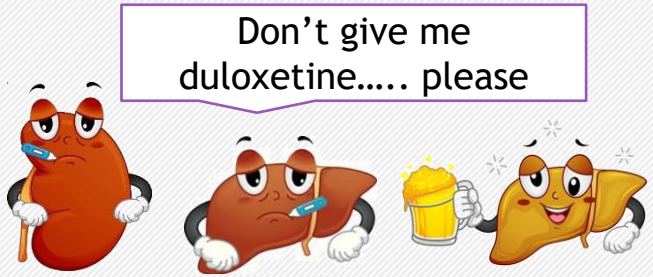
Increased risk of depression relapse during pregnancy with antidepressants discontinuation!!!

- MOA: Serotonin and norepinephrine reuptake inhibitors
- Headache, drowsiness, may ↑ BP, interaction with tramadol (monitoring serotonin syndrome), NSAID's may increase bleeding risk

1. **Duloxetine** (Cymbalta®)
   - **FDA APPROVED** for:
     - Diabetic Peripheral Neuropathy (DPN)
     - Fibromyalgia
     - **Chronic Musculoskeletal Pain!!!**
       - e.g. Chronic Low Back pain with muscle pain (second line)
     - Major Depressive Disorder
     - Generalized Anxiety Disorder (GAD)
   - Higher potency than venlafaxine (Effexor®)
   - Dose: 60 mg daily, titrate slowly to avoid nausea.
   - Not recommended for CrCl < 30 ml/min, hepatic impairment or in pts drinking alcohol
     - Hepatic impairment = (Child-Pugh)

2. **Venlafaxine (Effexor®) - Off label**

3. **Milnacipram** (Savella®)
   - Fibromyalgia
   - ADR's: Nausea, headache, insomnia, constipation



Waldfogel J, Nesbit SA, Dy SM et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. Neurology. 2017; 88(20):1958-67.

Anticonvulsants
Calcium Channel A2-δ Ligands

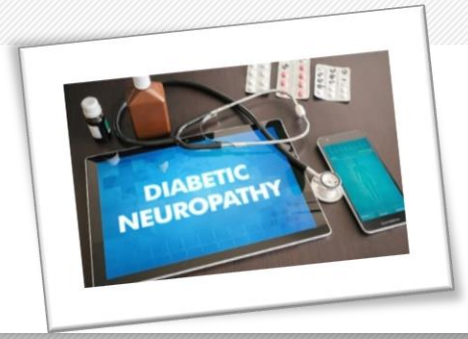
- **Gabapentin** (Neurontin®, Hotizant®, Gralise®)
  - Indications:
    - Peripheral neuropathy (off label)
    - Post herpetic neuralgia (PHN)
    - Other: Fibromyalgia, Central Post Stroke Pain
  - Postoperative: Consider using for major surgeries (reduce opioid use, reduce chronic pain)
    - 600-1200 mg pre-op, 600 mg X1, or multiple doses post-op
  - Dose range: 300 mg -3,600 mg day. Gabapentin dosing
    - Day 1: 300 mg
    - Day 2: 300 mg twice daily
    - Day 3: 300 mg three times daily.
    - Titrate further as needed for pain relief

- Bioavailability: Inversely proportional to dose due to saturable absorption:
  - 900 mg/d: 60%
  - **1,200 mg/d: 47%**
  - 3,600 mg/d: 33%
- Needs renal adjustment
- Do not need hepatic adjustment
- Side effects: Sedation, blurred vision, weight gain, peripheral edema, cognitive changes
- Few interactions

Gabapentinoids in chronic low back pain*

Ho K, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain. 2006: 126(1-3):91-101.
**Shanthanna H, Gilron I, Rajarathinam M et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017; 14(8):e1002369.*

Anticonvulsants
Calcium Channel A2-δ Ligands



- **Pregabalin** (Lyrica®)
  - Indications:
    - Diabetic neuropathy
    - PHN
    - Fibromyalgia
    - Neuropathic pain associated with spinal cord injury
  - Other: Central post stroke pain
  - Ineffective for Radicular Low Back Pain*
  - Postoperative: Consider using for major surgeries + opioid-tolerant patients
    - 150-300mg pre-op, 150-300mg X1, or multiple doses post-op

- Bioavailability: 90%, linear pharmacokinetics (different to gabapentin)
- Needs renal adjustment
- Do not need hepatic adjustment
- Adverse effects: Same as gabapentin
- Euphoria (1-12%): C-V
- Provides analgesia more quickly than gabapentin

Gabapentinoids in chronic low back pain* 

Gianesello L, Pavoni V, Barboni E et al. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. J Neurosurg Anesthesiol. 2012; 24:121-6.
*Shanthanna H, Gilron I, Rajarathinam M et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017; 14(8):e1002369.

Anticonvulsants

- **Carbamazepine** (Tegretol®)
  - Structurally related to TCA's.
  - Trigeminal Neuralgia (FDA approval)
  - Serious ADR's: Leukopenia, aplastic anemia, thrombocytopenia, anemia, hyponatremia.
  - Other side effects: Rash (2-8 weeks), sedation, dizziness, upset GI.
  - Monitoring: Baseline electrolytes, CBC and LFT's, repeat every three months
  - Potential for interactions: Potent CYP3A4 inducer

- **Oxcarbazepine** (Trileptal®)
  - Off label use
  - Hyponatremia more common
  - Blood dyscrasias and rash less common

- Lamotrigine (Lamictal®) (2nd line for central post-stroke pain)
- Others used for neuropathic pain (unlabeled use):
  - Topiramate, valproic acid, phenytoin, tiagabine, levetiracetam, zonisamide

Due to BPH symptoms and hypertension, you recommend pregabalin.

The insurance company indicates that you should start gabapentin as there is a “step therapy” policy with this drug.

Which of the following is an important factor to consider with gabapentin?

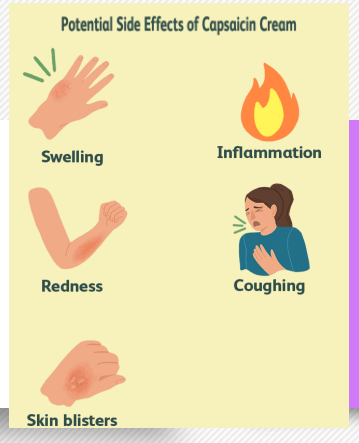
A. Euphoria

B. Anticholinergic effects

C. Is too expensive

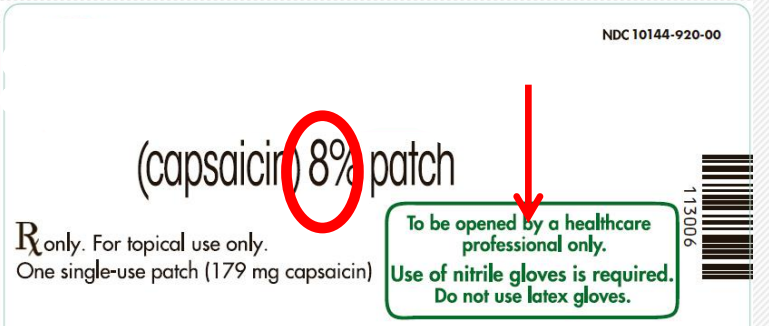
D. Needs renal adjustment

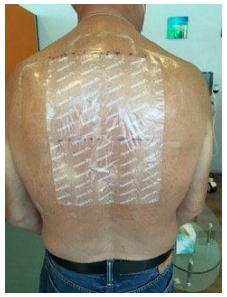
Capsaicin



https://www.verywellhealth.com

- Enzyme isolated from hot chili peppers
- For muscular, joint or neuropathic pain
- Depletes substance P from sensory C fibers, producing analgesia after repeated application.
- Must be applied four to five times daily for a few weeks before relief is obtained.
- Side effects: Burning and stinging after application
- Not well tolerated
  - May be mixed with lidocaine ointment for better tolerance
- Patient education: Thoroughly wash hands after application




https://www.breakthrupain.com

Must be applied only by health professional
Leave for 1 hour and then remove
Onset: 1 week
Treatment may be repeated every 3 months
Duration: up to 5 months

Baranidharan G, Das S, Bhaskar A. A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain. Ther Adv Neurol Disord. 2013;6:287-297.

Counterirritants

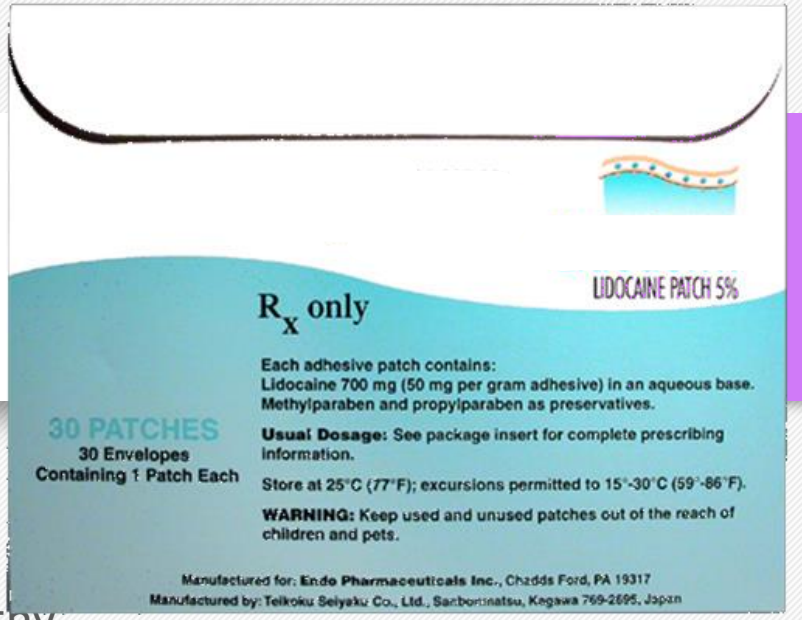
- Cause irritation/inflammation of the skin, lessening discomfort in another location

- Muscular and joints

- Types of counterirritants:
  - Camphor- toxic if ingested
  - Menthol- cool initially, then feeling of warmth
  - Methyl salicylate (produce redness and warmth)
  - Trolamine salicylate 10% (not producing redness)

It's a trap!!!!

Local Anesthesia



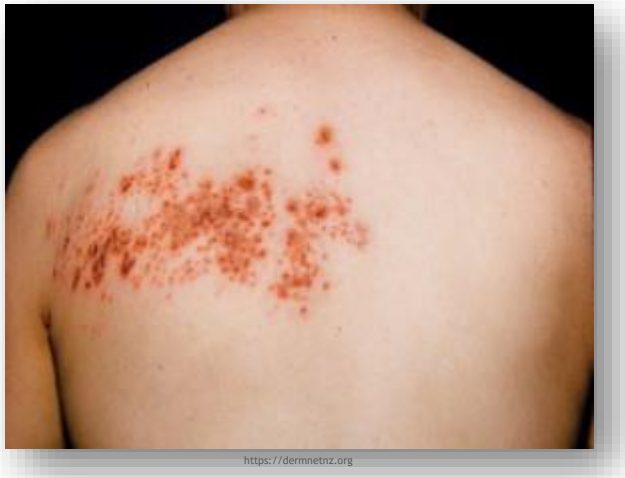
- **Lidocaine** 5% patches (Lidoderm®)
  - PHN (FDA approved)
  - Efficacy demonstrated in other disease states with peripheral neuropathy (ex. CLBP), allodynia
  - Useful for well-localized pain
  - Up to 3 patches applied once daily for 12 hours over painful site
    - May leave on for 24 hrs*
  - Onset: ~ 4 hours
  - Patches may be cut
  - Side effects: Sensitivity reactions at application site
  - Do not apply to burned, broken or inflamed skin; may result in increased absorption and possible toxicity
  - Do not provide complete sensory block
  - Caution with severe hepatic disease
- Lidocaine gel 5%: Less expensive, every 4 hours

http://healthcare.info/lidoderm-patch-cost-side-effects-and-high-pain-uses/

*Gammaitoni AR, Alvarez NA, Galer BS. Pharmacokinetics and Safety of Continuously Applied Lidocaine Patches 5%. Am J Health Syst Pharm. 2002;59(22).

Question 4

A 55 y/o man who was diagnosed with herpes zoster along the T-2 – T-5 dermatomes. His lesions have healed but continues with pain. He does NOT want to be sedated.



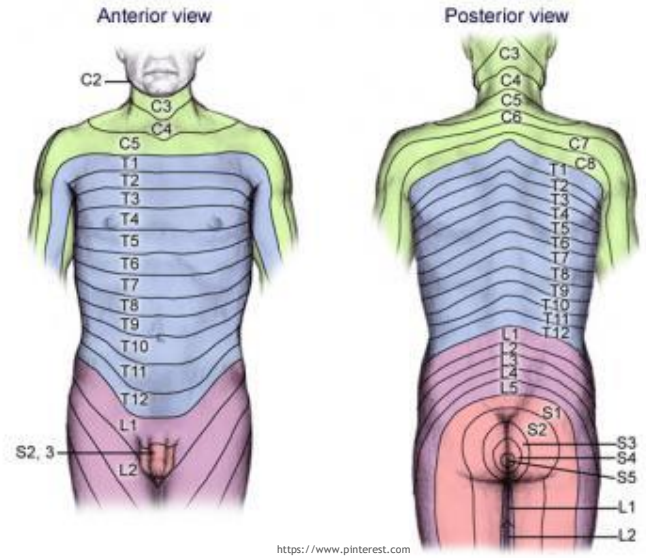
What do you recommend?

A. Desipramine

B. Venlafaxine

C. Gabapentin

D. Lidocaine 5% patches



Dermatomes

Question 5

Severe neuropathic pain

A 78 y/o male who presents to ER with severe (9/10) burning and shooting pain in his face.

https://paindoctor.com

Medical history:

- Recently diagnosed and treated for **herpes zoster** in the cranial nerve.
- His lesions have healed but continues with pain.

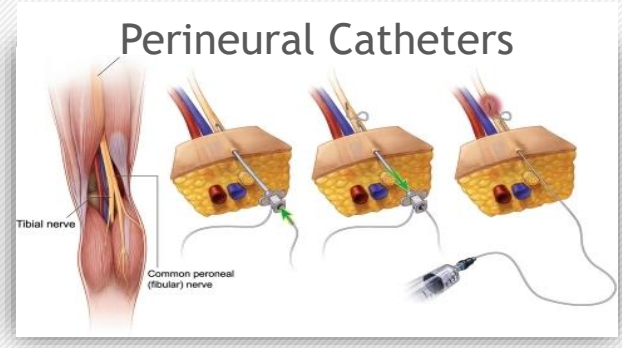
What pharmacotherapy is most important for his PHN pain?

A. Morphine
B. Capsaicin patch 8%
C. Nortriptyline
D. Pregabalin

Local Anesthesia

https://www.completepaincare.com/patient-education/services-provided/peripheral-nerve-blocks/

- Medications
  - Lidocaine, mepivacaine (Duration: 2-3 h)
  - Long acting: Bupivacaine, ropivacaine (Duration: 6-8 hours)
- Peripheral nerve block:
  - Commonly used for upper and lower extremity surgery
  - Single shot: May add 6-10 h of analgesia: epinephrine, clonidine, dexamethasone to enhance duration.
  - Perineural catheter (continuous) x 2-3 days
  - Compared to opioids:
    - Improved pain relief up to 48 hours
    - Reduced opioid-related adverse drug effects
    - Better patient satisfaction, sleep, reduced length of stay



https://openi.nlm.nih.gov/detailedresult.php?img=PMC2937147_12630_2010_9364_Fig1_HTML&req=4

Video:

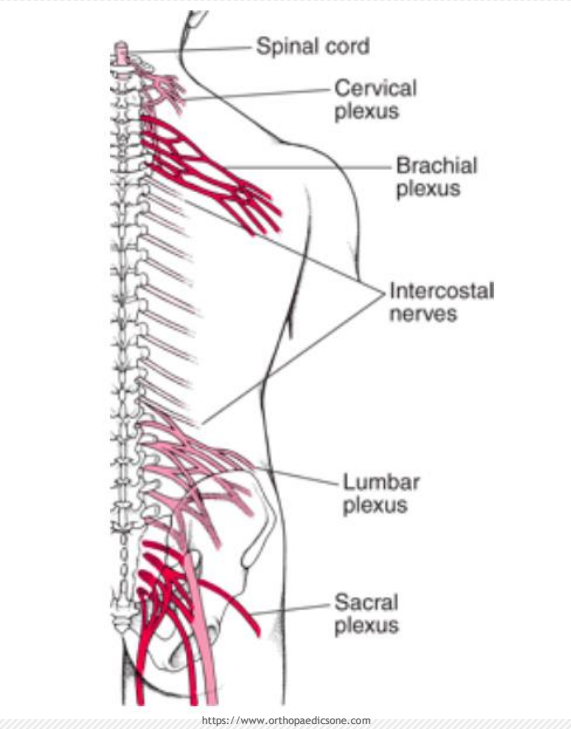
https://www.youtube.com/watch?v=hqtLPYsDTKA

https://doctorlib.info/anatomy/hadzic-peripheral-nerve-blocks-anatomy-ultrasound/6.html

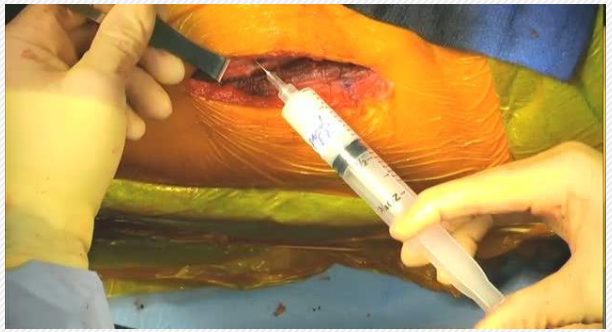
Richman JM, Liu SS, Courpas G et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006; 102(1):248-57.

Abdelsattar JM, Boughey JC, Fahy AS et al. Comparative Study of Liposomal Bupivacaine Versus Paravertebral Block for Pain Control Following Mastectomy with Immediate Tissue Expander Reconstruction. Ann Surg Oncol. 2016; 23(2):465-70.

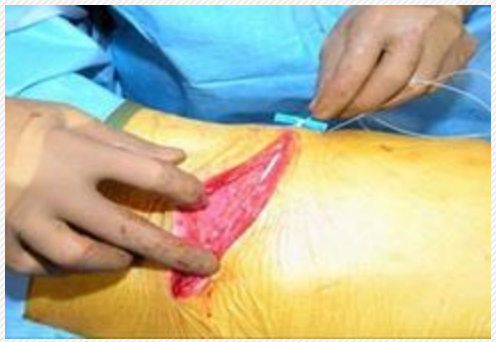
Local Anesthesia



- Local infiltration analgesia
  - Reduce postoperative pain
  - Incisional: At the time of surgery, into the tissues around the surgical field
    - Long-acting local anesthetic agent +/- adjuvants (e.g., epinephrine, ketorolac, +/- opioid)
  - Continuous: At the end of the surgical procedure, the surgeon directly places a catheter into the wound.



Incisional



Continuous

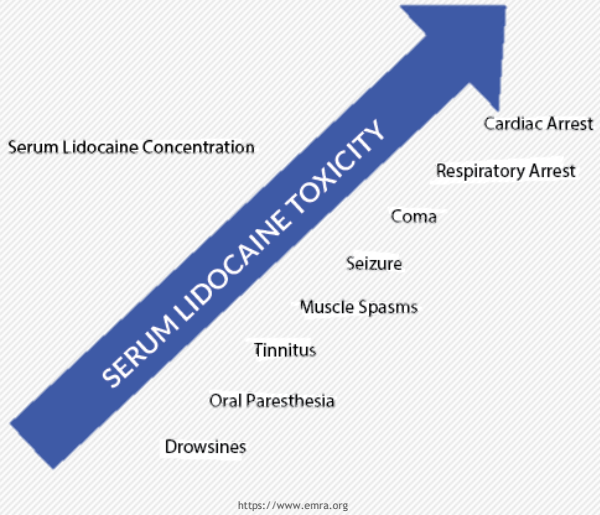
https://www.orthopaedicsone.com

- Intercostal or plexus nerves block
  - Reduce postoperative pain or severe intensity-chronic pain (every 3-6 months)
  - Anesthetic: hours
  - Steroids: Starts working in about 3-5 days and its effect can last for several days to a few months.
- Intra-articular injections
  - Reduce postoperative pain, osteoarthritis joint pain, joint dislocation pain

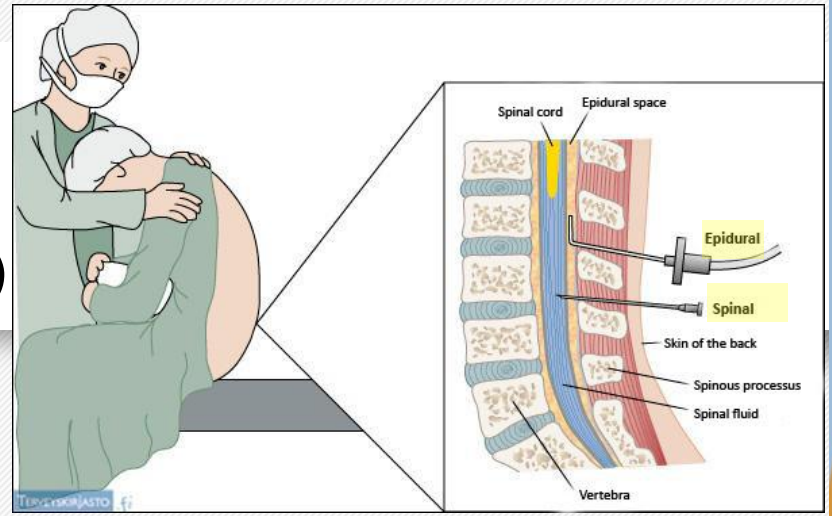
Local Anesthesia

- Adverse effects
  - Extremity:
    - Numbness, weakness
  - Arm or shoulder surgery:
    - Harder to take a deep breath, stuffy nose, drooping eyelid, unequal pupils
  - Severe:
    - Seizure, bradycardia, cardiac arrhythmia
  - Toxicity management: Different to cardiac arrest
    https://www.asra.com/content/documents/asra_last_checklist_2018.pdf
  - Procedure/catheter-related: Nerve injury, Hematoma

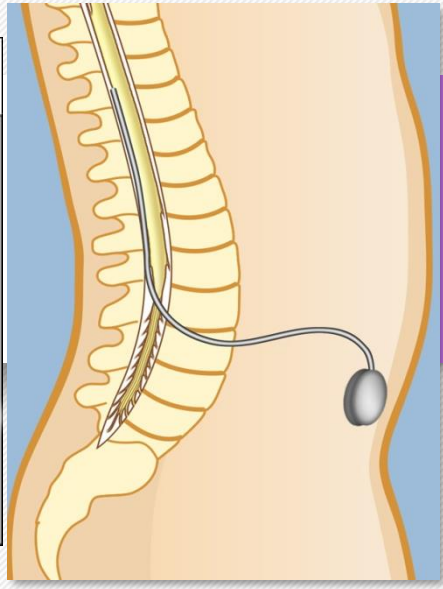
- Liposomal bupivacaine
  - Biphasic release
    https://www.youtube.com/watch?v=dyWb4KtYiaw
  - Has been compared to placebo
    - Study drug better than placebo only for 24 hours or less
  - Expensive, cost effective ???



Regional Anesthesia
Local Anesthetics
Neuraxial Block: Epidural vs Intrathecal (Spinal)



http://www.soat.fi/parturient.html


https://weillcornellbrainandspine.org

Epidural

- Greater dose
- Less complications:
  - Reduced risk of respiratory depression
  - Reduced risk of PDPH
  - Reduced risk of neuronal injury
- Injection: Local anesthetics ± steroids, opioids, clonidine
- Ex., Chronic low back pain, neck (anesthetics + steroids)
  - GOAL: Reduce pain enough to allow physical rehabilitation, or to prolong need for surgery
  - Duration: ~6 months

Other general risks:
- Local anesthetic-related: Hypotension
- Procedure/catheter-related: Intraspinal hematoma or Infection
- Intrathecal use: NOT preservative (considered for epidural), solution is preferred over suspension (suspension is more effective but ↑ risk of embolism)

Post-dural puncture headache (PDPH)

Intrathecal (Subarachnoid space)

- Smaller dose
- Injection: Opioids (morphine, fentanyl, hydromorphone), clonidine, bupivacaine (long acting anesthetic)
- Pumps: Morphine pump, baclofen pump (severe spasticity) or ziconotide pump
- Lower cost

Hayek S. Intratecal Dosing and Medication Selection. ASRA.
Wickboldt A, Guiguis M. Updates to the ASRA Guidelines for interventional Pain Procedures. ASRA 2019.

Regional Anesthesia
Local Anesthetics
Neuraxial Block: Epidural vs Intrathecal (Spinal)

High risk:
- Spinal cord stimulation (SCS) implant
- Dorsal root ganglion (DRG) stimulation implant
- Intrathecal catheter and pump implant

Intermediate risk:
- Interlaminar epidural steroid injections (ESI) cervical, thoracic, lumbar, sacral
- Transforaminal epidural steroid injections (ESI) cervical, thoracic, lumbar, sacral

Drug	High risk- discontinuation before procedure	Intermediate risk	When to restart
ASA or combinations with ASA	- Primary prophylaxis: 6 days - Secondary prophylaxis (6 days): Shared assessment (physician, primary physician, patient)	- Shared assessment (physician, primary physician, patient) - 4 days (if d/c)	24 h
NSAID'S	5 half-lives	NO	24 h
diclofenac	1 day		
ketorolac	1 day		
ibuprofen	1 day		
etodolac	2 days		
indomethacin	2 days		
naproxen	4 days		
meloxicam	4 days		
nabumetone	6 days		
oxaprozin	10 days		
piroxicam	10 days		
Phosphodiesterase inh			
cilostazol	2 days	NO	24 h
dipyrimadole	2 days	NO	
Anticoagulants	Coumadin: May consider bridge therapy for high risk pts of VTE- Shared assessment (physician, primary physician)-(LMWH, d/c 24 h before)		
coumadin	5 days (normal INR, < 1.2)	5 days (normal INR, < 1.2)	6 hours
IV heparin	6 hours	6 hours	- 2 hours - 24 hours (intervenciones con mayor sangrado)
SQ heparin (BID or TID)	24 hours	6 hours	- 2 hours (low risk procedures) - 6-8 hours (intermediate/high-risk procedures)

Adapted from: Narouze S, Benzon HT, Provenzano D, et al. Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition): Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med. 2018; 43(3):225-262.

Regional Anesthesia
Local Anesthetics
Neuraxial Block: Epidural vs Intrathecal (Spinal)

Drug	High risk- discontinuation before procedure	Intermediate risk	When to restart
LMWH	**Antiplatelets, NSAIDs, SSRIs or other anticoagulants should be used with EXTREME care in combination with LMWH**		
Enoxaparin prophylactic	12 hours	12 hours	- 4 hours (low risk procedures) - 12-24 hours (intermediate/high-risk procedures)
Enoxaparin therapeutic	24 hours	24 hours	- 4 hours (low risk procedures) - 12-24 hours (intermediate/high-risk procedures)
Dalteparin	24 hours	24 hours	- 4 hours (low risk procedures) - 12-24 hours (intermediate/high-risk procedures)
P2Y12 inh	**Coumadin: May consider bridge therapy for high risk pts of VTE- Shared assessment (physician, primary physician)-(LMWH, d/c 24 h before)**		
Clopidrogel	- 7 days - SCS (Spinal cord stimulation) :5 days for high risk of thromboembolic events	7 days	- 12 h (75 mg) - 24 h (higher doses for loading dose)
Prasugrel	7-10 days	7-10 days	24 h
Ticagrelor	5 days	5 days	24 h
Cangrelor (IV)	3 hrs	3 hrs	24 h
NOACs	**Coumadin: May consider bridge therapy for high risk pts of VTE- Shared assessment (physician, primary physician)-(LMWH, d/c 24 h before)**		
Dabigatran	4 days 5 days (impaired renal function)	4 days 5 days (impaired renal function)	- 24 h - Half the dose at 12 hours if the risk of VTE is high
Rivaroxaban	3 days	3 days	
Apixaban	3 days	3 days	
Edoxaban	3 days	3 days	
SSRI/SNRI			
	The following applies to: Elderly, advanced liver disease or concomitant ASA, NSAID's, antiplatelet, or anticoagulant **- Stable depression:** Tapering down 1-2 weeks before the procedure. Beware of paroxetine and venlafaxine, they can present symptoms during tapering down. Fluoxetine should be tapering down 5 weeks prior (long half life). - **Unstable depression or with suicidal risk** switched to bupropion, mirtazapine or TCAs	NO	- 24 hours
Herbal/dietary			
Garlic	Test of platelet function should be ordered when patients with several comorbidities take doses greater than 1000 mg/d or when there is concomitant intake with ASA, NSAIDs, or SSRIs.	NO	
Vit E	Dose > 400 IU, d/c 6 days		
Fish oil	6 days		
Pentosan polysulfate (Elmiron)	5 days	5 days	24 days

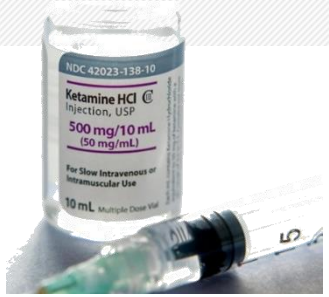
Pts with high risk of bleeding (old age, hx of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advance liver disease, advanced renal disease), undergoing low or intermediate risk procedures should be treated as intermediate or high risk, respectively.

IV Anesthestics

- Post-operative pain management
- Best results seen with laparoscopic and open abdominal surgery
- MOA
  - Reduces release of pro-inflammatory cytokines
  - NMDA receptor blockade
  - Plasma levels are too low to get strong sodium channel blockade
- Agents
  - Lidocaine
    - Loading dose 1.5-2 mcg/kg followed by 2-3 mcg/kg/hr infusion for up to 24 hours
    - Shorter duration of ileus, less n/v, improved analgesia, opioid sparing
  - Ketamine

Kranke P, Jokinen J, Pace NL et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev. 2015; (7):CD009642.

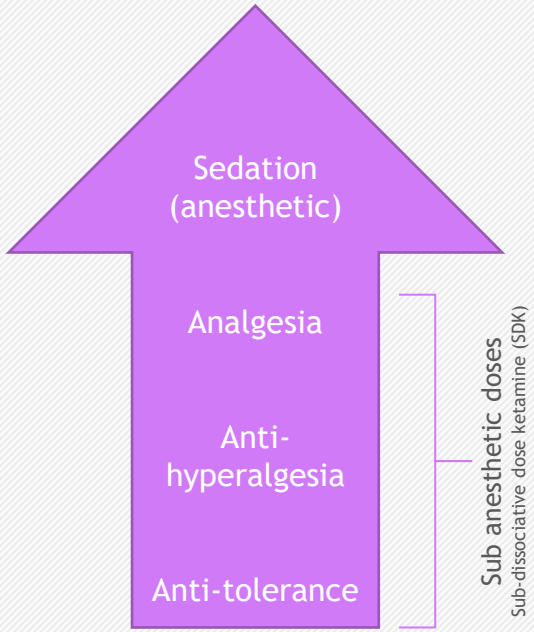
Ketamine



- Reduces nociceptive, inflammatory pain transmission and neuropathic pain
  - Weak evidence, not recommended for immediate relief of: Migraine, PHN, fibromyalgia, cancer pain (Exception: is using opioids), ischemic pain, low back pain
- NMDA receptor antagonist
- Single agent or in combination with opioids. Attractive adjunct therapy:
  - Good for opiate tolerance and central sensitization (hyperalgesia and allodynia)
  - Produces about a 40% opioid sparing effect
  - May alleviate adverse effects associated with opioid treatment (at sub-anesthetic doses)
- Routes of administration
  - IV
  - Subcutaneous, IM (painful)
  - Not FDA approved: Intranasal, oral, topically, rectal
  - Epidural and spinal routes of administration of ketamine are generally not recommended due to unclear toxicity issues
- Doses vary upon the route of administration

Post-herpetic neuralgia (PHN)

Dose-Dependent activity



Optimizing the Treatment of Acute Pain in the Emergency Department. Ann Emerg Med. 2017;70:446.
Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43:521-546.
Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):456-466.
Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8:283-90.
Jouquelet-Lacoste, La Colla L, Schilling D et al. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Pain Med. 2015; 16:383-403.
Vadivelu N, Schermer E, Kodumudi V, et al. Role of ketamine for analgesia in adults and children. J Anaesthesiol Clin Pharmacol. 2016;32:298-306.

Ketamine

Acute pain		Chronic pain	
Indications (examples)	Dose IV	Indications	Dose
-Acute pain in opioid tolerant and pts with central sensitization -After painful surgery or trauma -Chronic sickle cell pain -Exacerbation of chronic painful conditions -Patients with sleep apnea to limit opioids	- Common bolus dose: · 0.3 – 0.35 mg/kg (IVPB over 10 to 15 min or IV push over 5 minutes) · ICU*:0.5 mg/kg IV push x 1 - Usually Infusion dose (may be included or not): · 0.1–0.2 mg/kg/h or less · Up to 1 mg/kg/h · ICU*: 0.06-0.2 mg/kg/h	Spinal cord injury Weak evidence (short term improvement) (chronic neuropathic pain)	Bolus dose: up to 0.35 mg/kg Infusion dose: 0.5 – 2 mg/kg/h, may use up to 7 mg/kg/h in refractory cases for 7 consecutive days
		CRPS (improvement up to 12 weeks!!!!) (chronic neuropathic pain)	22 mg/h for 4 days *or* 0.35 mg/kg per hour over 4 hours daily for 10 days
	Nasal 0.5 – 1 mg/kg, May repeat in 10-15 minutes with 0.25-0.5 mg/kg if necessary	Follow up treatment (after IV) Weak evidence (Example, post-surgery, chronic neuropathic pain)	Oral: 150 mg/day or IV infusion: 0.5 mg/kg every 6h + dextromethorphan 0.5-1 mg/kg PO every 8h
		Breakthrough pain in pts taking opioids ATC + IR Moderate evidence	Intranasal 1-5 sprays of ketamine 10 mg every 6 hours PRN or 0.2-.04 mg/kg every 6 hours PRN or single dose 25 mg every 6 hours PRN

- Long-term effectiveness of ketamine to treat chronic pain remains controversial, as studies often demonstrate contradicting results.

*Devlin JW, et al. Executive Summary: Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-e873
Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43:521-546.
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Ketamine

- Adverse effects
  - Low doses of ketamine **DID NOT** cause typical responses of increased heart rate and high blood pressure
  - Frequent ketamine can cause short memory impairment
  - Has the potential to cause addiction (C-III)
- t½: ~ 45 min (Short)

- Relative Contraindications:
  - Severe cardiovascular disease or poorly controlled hypertension
  - Elevated intracranial pressure
  - Elevated intraocular pressure
  - Severe hepatic dysfunction (e.g. cirrhosis)
  - Psychosis
  - Pregnancy
- Should be supervised by experienced MD, examples:
  - pain relief specialist
  - palliative medicine specialist
  - anesthesiologist

Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43:521-546.
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A 55 y/o male with hx of hypertension, presented to ER with 10/10 pain that was diagnosed as acute renal colic.

Which of the following would be the most appropriate pain management option?

A. Ketamine 50 mg IV push
B. Ketamine 50 mg intranasal
C. Ketorolac 30 mg IV push
D. Morphine 4 mg IV push

Alpha-2 Adrenergic Agents

- Central and peripheral α2 stimulation
- Inadequate analgesic when used alone
- Short term
- **Clonidine** epidural or intrathecal---- combination with opioids
  - Cancer patients with severe intractable pain, unresponsive to opioid analgesics
  - Postoperative
    - Potentiation of opioids and local anesthetic neuraxial and perineural routes
- Adverse effects: Hypotension and bradycardia (monitoring)
- Not associated with respiratory depression, n/v, pruritus

THE pain SOURCE

TOPICAL COMPOUNDED CREAMS FOR PAIN

Compounding

Drug and Dose Range	Proposed Mechanism of Action	Uses*
NMDA-Ca Channel Blocker		
Ketamine 5-10%	Blocks peripheral NMDA receptors to prevent pain transmission from periphery to the brain. This ultimately "turns off" the positive feedback pain loop involved in chronic pain. -**Ketamine**: highest affinity for NMDA receptor; also blocks peripheral 5-HT (serotonin) and opioid receptors and edema response to inflammation.	•Neuropathic Pain Standard •Chronic Pain - all types •Diabetic Peripheral Neuropathy •Allodynia and Hyperalgesia •Complex Regional Pain Syndrome •Post-op Neuropathic Pain •Lumbar Radiculopathy •Post-herpetic Neuralgia
Sodium and Glutamate Blockers		
Lidocaine 1-10%	Blocks Na channel in hyperexcited neurons to decrease synaptic efficiency of both NMDA and AMPA (glutamate) receptors in periphery. Especially useful in diminishing pain transmission in damaged neurons -**Gabapentin**: may also block glutamate at NMDA receptor	•Neuropathic and Inflammatory Pain
Gabapentin 5-10%		•Neuropathic Pain Standard
Tricyclic Antidepressants		
Amitriptyline 2-10%	NE and 5-HT reuptake blocker; binds opioid receptors; blocks histamine, peripheral alpha-adrenergic and muscarinic receptors; blocks NMDA receptors and Na channels; interacts with adenosine -**Amitriptyline**: has more potent local anesthetic effects than bupivacaine -**Imipramine** and **desipramine** more selective for NE - potential advantage -**Cyclobenzaprine**: structure similar to amitriptyline	•Neuropathic Pain •Diabetic Neuropathy •Post Herpetic Neuralgia •Chronic Inflammatory Pain •Fibromyalgia •Idiopathic Neuropathy •TMJ Pain
Imipramine 2-10%		
Cyclobenzaprine 2%		•Same as above •Muscle Relaxant
GABA-B Agonist		
Baclofen 2%	Activates the GABA-B receptor which produces a neuron inhibitory effect	•Muscle Relaxant •Fibromyalgia Standard •TMJ Pain

Drug and Dose Range	Proposed Mechanism of Action	Uses*
Alpha-2 Agonist		
Clonidine 0.2%	Blocks NE release to prevent activation of peripheral adrenergic receptors (offers pain relief without loss of sensation seen with anesthetics)	•Neuropathic Pain Standard •Sympathetically Maintained •CRPS/Trigeminal Neuralgia •Phantom Limb Pain
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)		
Ketoprofen 10%	Decreases pain receptor sensitivity by blocking production of prostaglandin 2	•Musculoskeletal Pain •Joint Pain •Osteoarthritis •Rheumatoid Arthritis •Soft Tissue Injury •Fibromyalgia •Post-Herpetic Neuralgia •Complex Regional Pain Syndrome •Foot Pain •Sports Injury •Tennis Elbow
Diclofenac 2-10%		
Ketorolac 0.5%		•Same as above •Particularly used for Acute Pain
Calcium Channel Blocker		
Nifedipine 2-16%	Increase blood flow to affected area	•Diabetic Neuropathy •Increase Circulation
Verapamil 6%		•Fibrosis/Scarring

* The conditions listed in the "uses" column are NOT FDA-approved, but rather clinical observations

http://thepainsource.com/topical-compounding-creams-used-in-pain-management/

Other Considerations

- For musculoskeletal pain
  - Muscle relaxants (short term)
    - Cyclobenzaprine
      - Fibromyalgia
      - May be short term during pregnancy
    - Others: Carisoprodol, chlorzoxazone, Methocarbamol, orphenadrine
  - Mostly use for spasticity:
    - Baclofen oral
    - Tizanidine, dantrolene
    - Benzodiazepines
    - Baclofen intrathecal

- For bone pain
  - Corticosteroids
  - NSAID's
  - Bisphosphonates (cancer)

- Brain/Spinal Cord inflammation:
  - Corticosteroids

- Corticosteroids
  - Pregnancy: ↓ doses, only when is required (example: arthritis)

A 46 y/o woman has left **breast cancer with metastases to the bone**. She is presenting:

- **Nociceptive pain**:
  - Chest pain: Sharp
  - **Bone metastasis**: aching

- **Neuropathic pain**: Shooting pain down her arm

https://blog.virginiamason.org

1. In addition to morphine she is taking, which co-analgesics would you consider to add?

2. Which factors should you consider with these co-analgesics?

RR is a woman in the 3rd trimester of pregnancy with Hx of vulvodynia and chronic pelvic pain. Her medications are:

- Ibuprofen PRN
- Gabapentin daily
- Duloxetine daily
- Topical lidocaine (vagina) PRN

Which of the following statements is TRUE?

A. Gabapentin should be changed to pregabalin

B. Ibuprofen should be continued.

C. Topical lidocaine should be discontinued due to the risk of systemic absorption.

D. Duloxetine should be continued due to the increased risk of depression.

Question 8

Which medications for chronic pain are compatible with breastfeeding?

Select all that apply.

A. Duloxetine

B. Ibuprofen

C. Topical Lidocaine

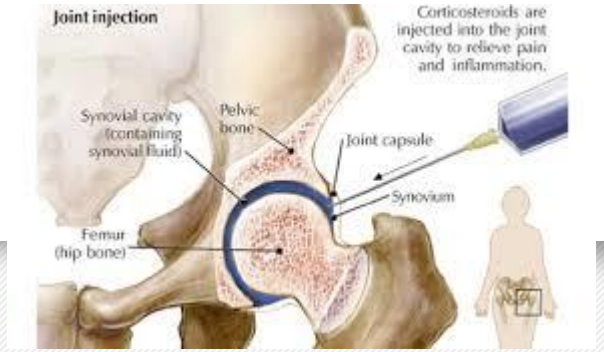
D. Gabapentin

Other treatments

Thermal applications

- Cold (vasoconstricts): Provides immediate pain
  - inflammation...usually first 48 hours
- Hot (vasodilates): Promote tissue healing
  - Chronic aches
  - Peripheral neuropathy

Other treatments



Intraarticular injections

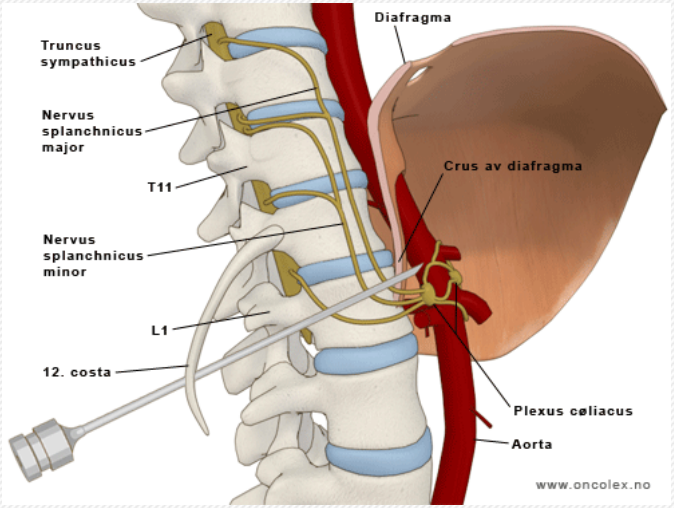
(corticosteroid, hyaluronic acid, platelet rich plasma)

https://www.youtube.com/watch?v=S22xxbS2yuc

Trigger point injections Myofascial pain

(anesthesics/botulinum toxin)

https://www.youtube.com/watch?v=QY9ePL690Dk



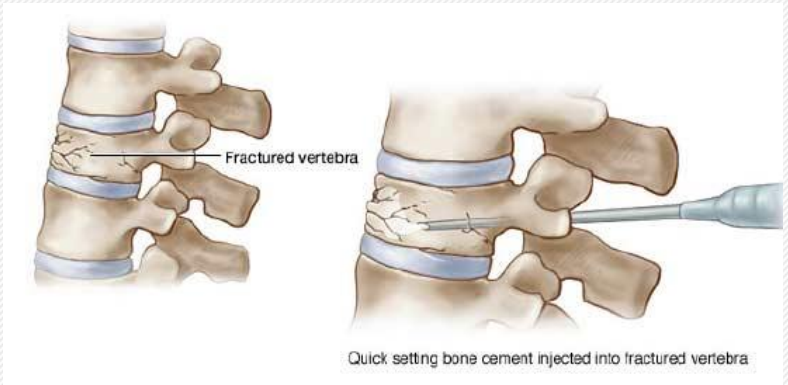
Neurolysis

e.g. chronic neuralgic pain secondary to pancreatic cancer
Relief: 2-3 months

https://www.advancedsportsandspine.com/pain-management/neurolysis-procedure/

Sympathetic nerves block

(e.g. alternative for CRPS)
Relief: weeks- months
Complex regional pain syndrome (CRPS)
https://www.ypo.education/orthopaedics/spine/sympathetic-nerve-block-t27/video/



Cementoplasty

Osteoporosis fractures, bone metastasis fractures

Other treatments

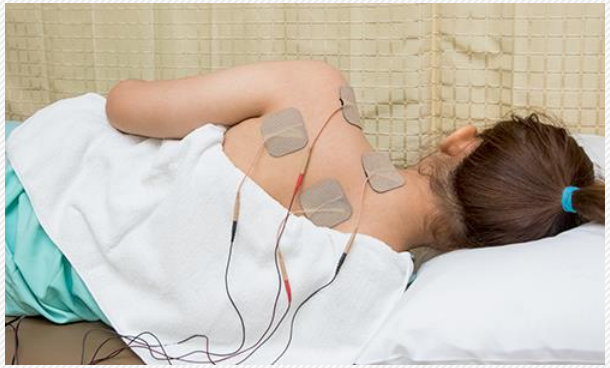
Therapeutic ultrasound

muscles, tendons, joints, and ligaments

https://www.youtube.com/watch?v=0l71b4ZwxK0

Laser therapy

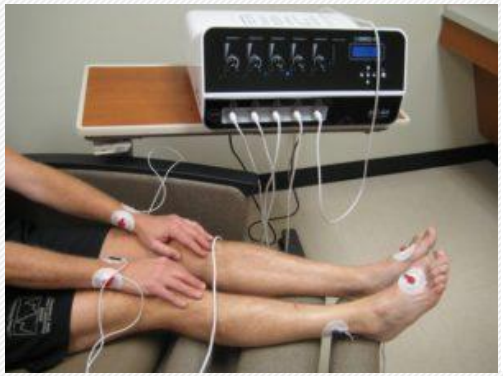
https://www.youtube.com/watch?v=WEHwfKakr7Q



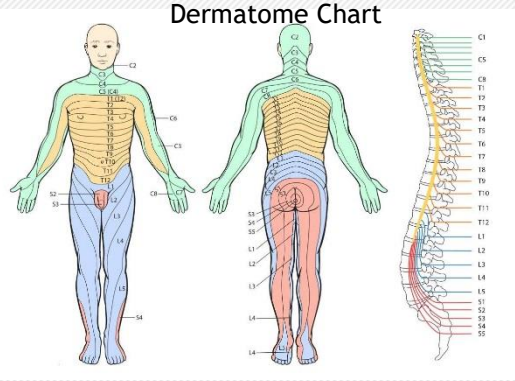
Transcutaneous electrical nerve stimulation (TENS) therapy

Current: Intermittent
Application: Skin, over painful area
Relief: As long as unit is on

https://www.youtube.com/watch?v=KKVbdDssV5s



Dermatome Chart



Scrambler therapy

Current: Intermittent
Application: Skin, over dermatome distribution, by a clinician
Relief: Beyond application time

https://www.ktbs.com/rick-rowe-s-arklatex-made-scrambler-therapy/video_6002b86c-b635-5a03-936d-7fcd0e346aec.html

Spinal cord stimulators

Current: Continuous, +/- paresthesia
Application: Minimally invasive procedure

https://www.youtube.com/watch?v=wzpk0U4KPn4

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