What's New in Pain Medicine:

Opioids, NSAIDs and Pain Management in 2022

Andrew Friedman MD

ACP WA Annual Meeting

November 3, 2022

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Disclosures

Nothing to disclose

Impact of Chronic Pain

- 50% of Americans experience chronic or recurrent pain
- 62% of These Would Rate Pain Moderate or Severe
- Causes more disability than heart disease or cancer
- >$200 Billion/year in US in health care and disability

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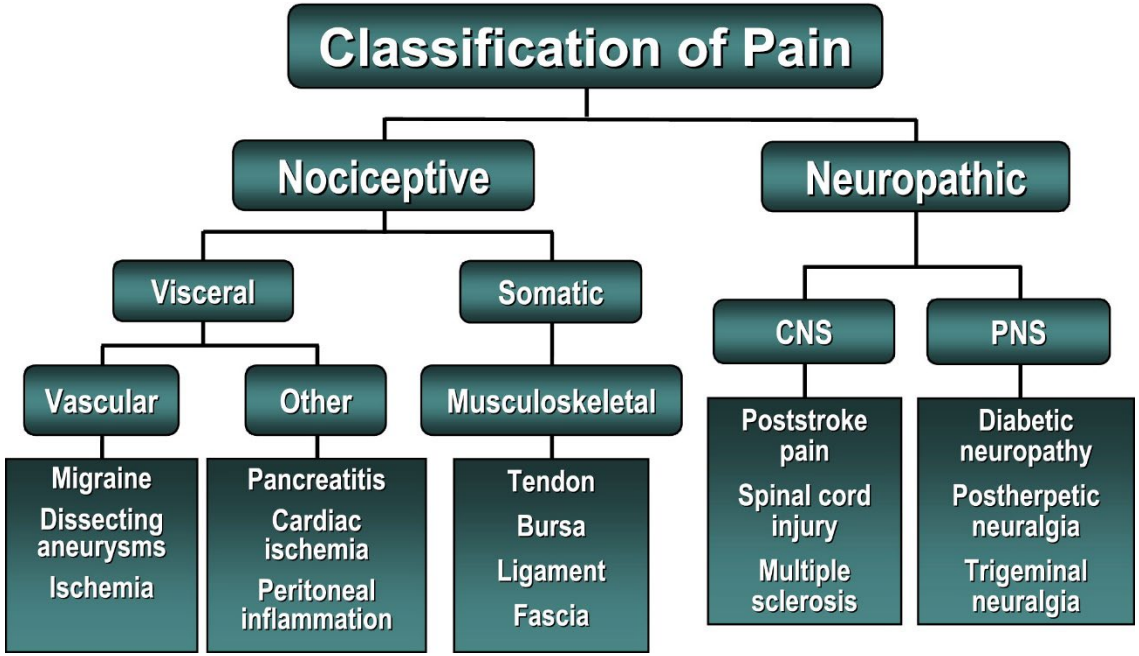
Categories of Pain



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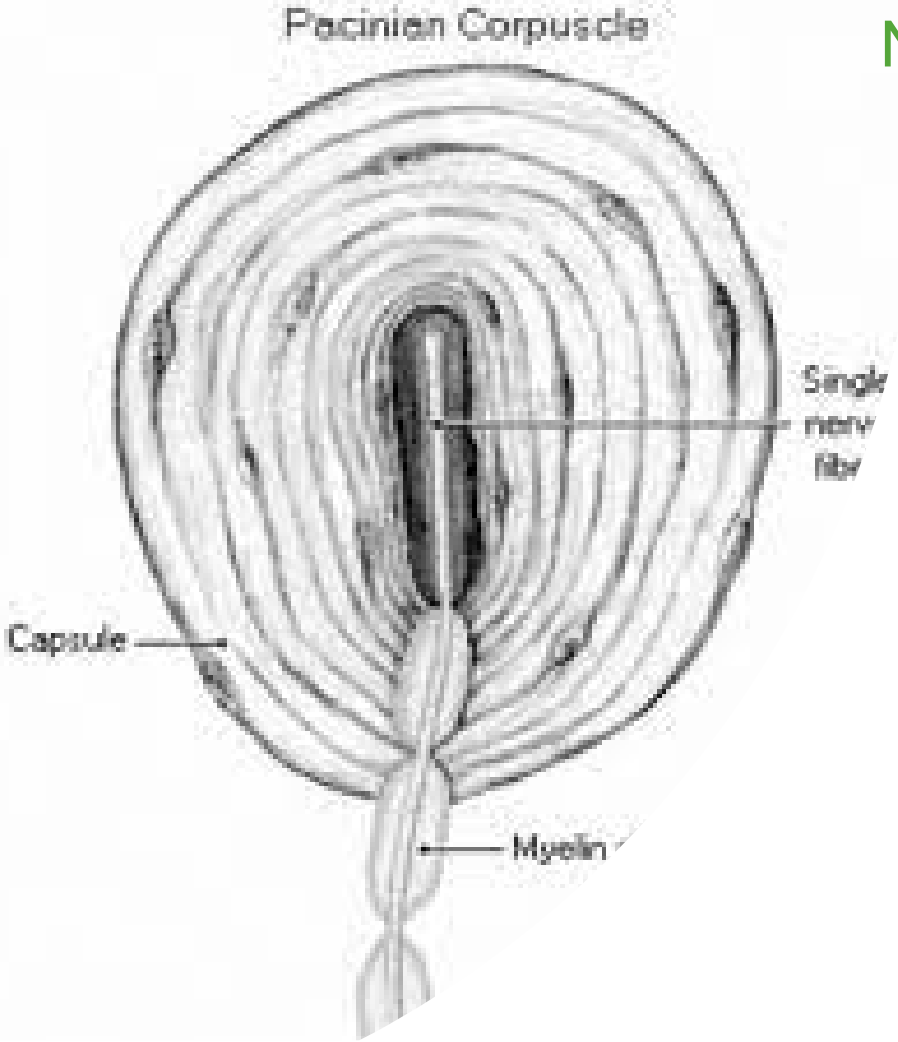
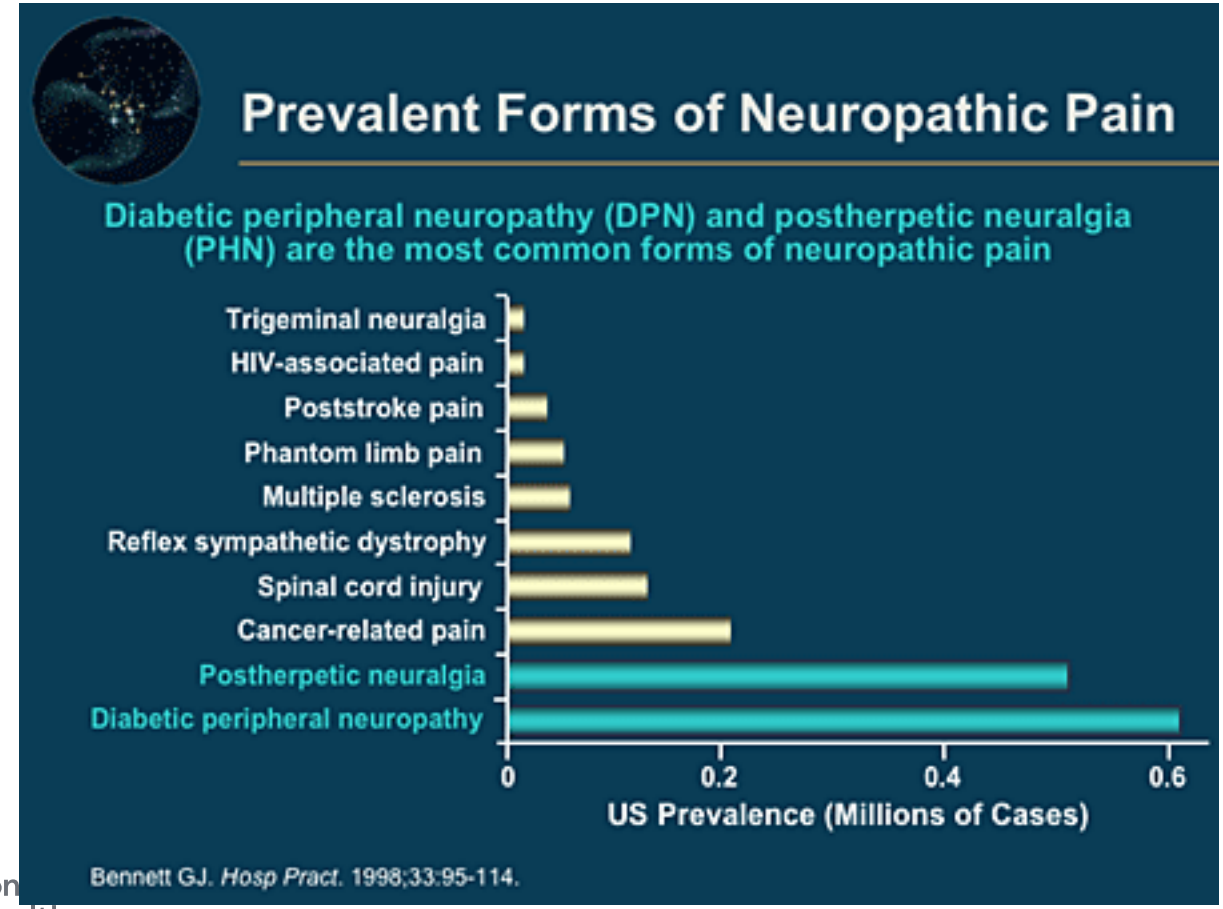
Nociceptive Pain





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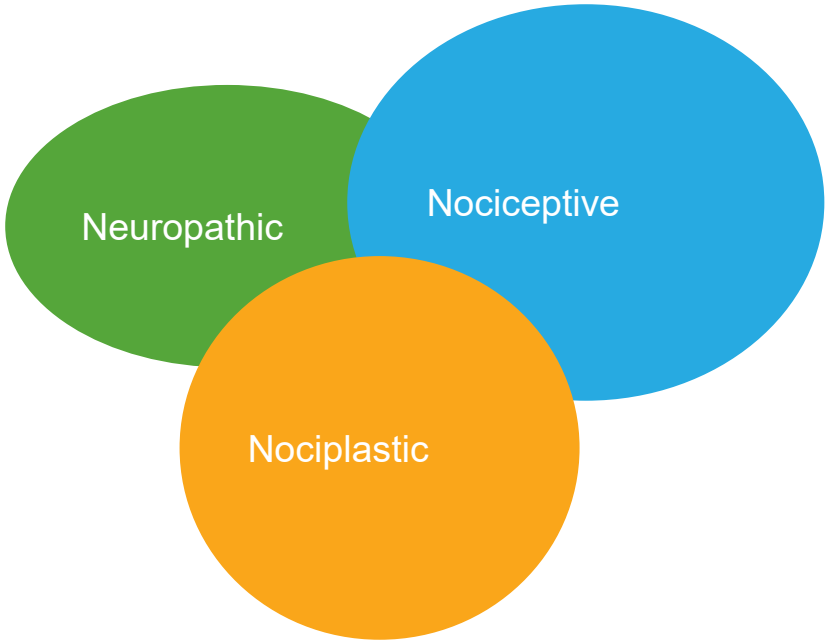
Three Types of Pain



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Pain related to damage of somatic or visceral tissue as a result of trauma or inflammation

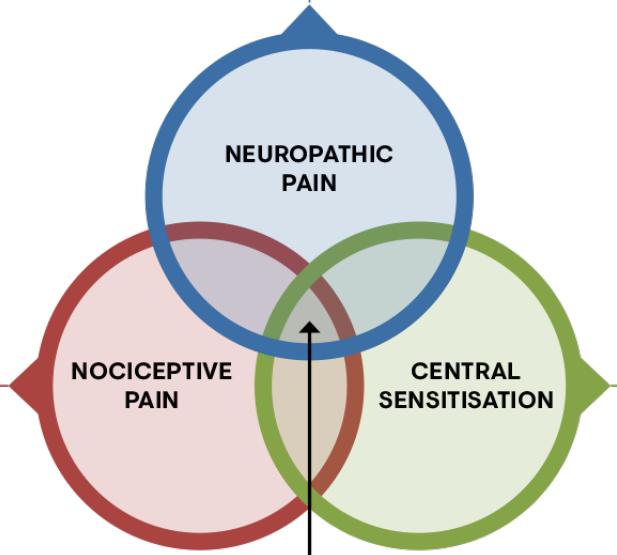
Pain related to damage of peripheral or central nerves

Pain without identifiable nerve or tissue damage thought to result from persistent neuronal dysregulation

NOCICEPTIVE PAIN

NEUROPATHIC PAIN

CENTRAL SENSITISATION



PREDOMINANTLY NEUROPATHIC

- PHN
- pDPN
- Lumbar or cervical radioculopathy
- Stenosis
- Tumour-related neuropathy
- Chemotherapy-induced neuropathy
- Small fibre neuropathy
- Persistent postoperative pain
- Multiple sclerosis pain
- Post-stroke pain
- Pain associated with spin cord injury

PREDOMINANTLY NOCICEPTIVE

- Osteoarthritis
- Rheumatoid arthritis
- Tendonitis, bursitis
- Ankylosing spondylitis
- Gout
- Neck and back pain with structural pathology
- Tumour-related nociceptive pain
- Sickle cell disease
- Inflammatory bowel disease

PREDOMINANTLY CENTRAL SENSITISATION

- Fibromyalgia
- Irritable bowel syndrome
- Tension-type headaches
- Interstitial cystisis/pelvic pain syndrome
- Tempo-manibular joint disorder
- Chronic fatigue syndrome
- Restless leg syndrome
- Neck and back pain without structural pathology

Mixed pain conditions with multiple pain pathophysiologies such as chronic low back pain

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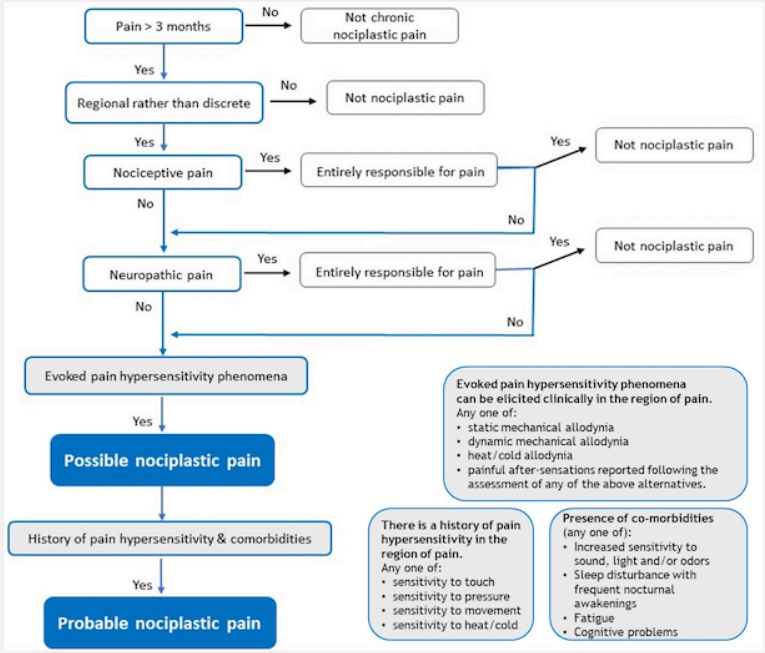
Nociplastic pain affecting the musculoskeletal system:

CLINICAL CRITERIA & grading system developed by the IASP's presidential terminology task force



Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, Mico JA, Rice AS, Sterling M. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*. 2021. doi: 10.1097/j.pain.0000000000002324 Chronic nociplastic pain affecting the musculoskeletal syste... : PAIN (lww.com)

PAIN IN MOTION PAIN IASP

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Common Pain Conditions

Nociceptive Pain

Fracture, Arthritis

Neuropathic Pain

Central—MS, SCI, Post-stroke

Peripheral—PPN, Zoster, TGN

Nociplastic Pain

Fibromyalgia

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Osteoarthritis

Acetaminophen?

NSAIDS

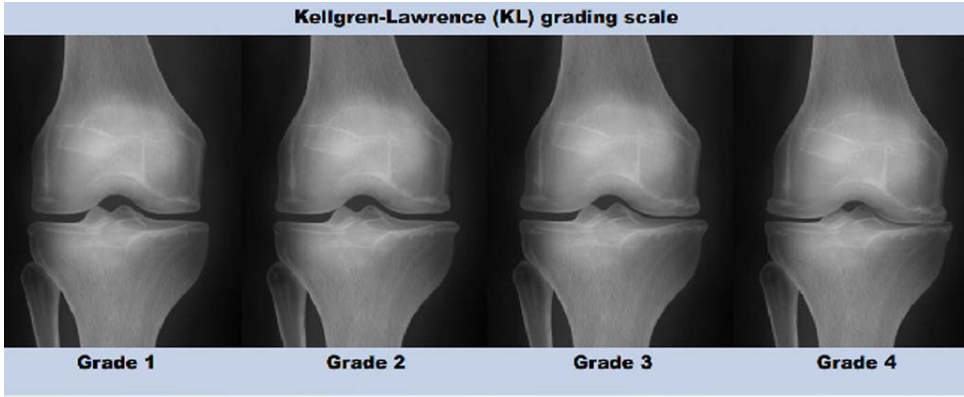
--Pain relief equivalent to exercise

--Topical NSAIDs if oligoarticular

--Oral NSAIDs

Duloxetine

Intraarticular therapies



CLASSIFICATION	Normal	Doubtful	Mild	Moderate	Severe
DESCRIPTION	No features of OA	Minute osteophyte: doubtful significance	Definite osteophyte: normal joint space	Moderate joint space reduction	Joint space greatly reduced: subchondral sclerosis

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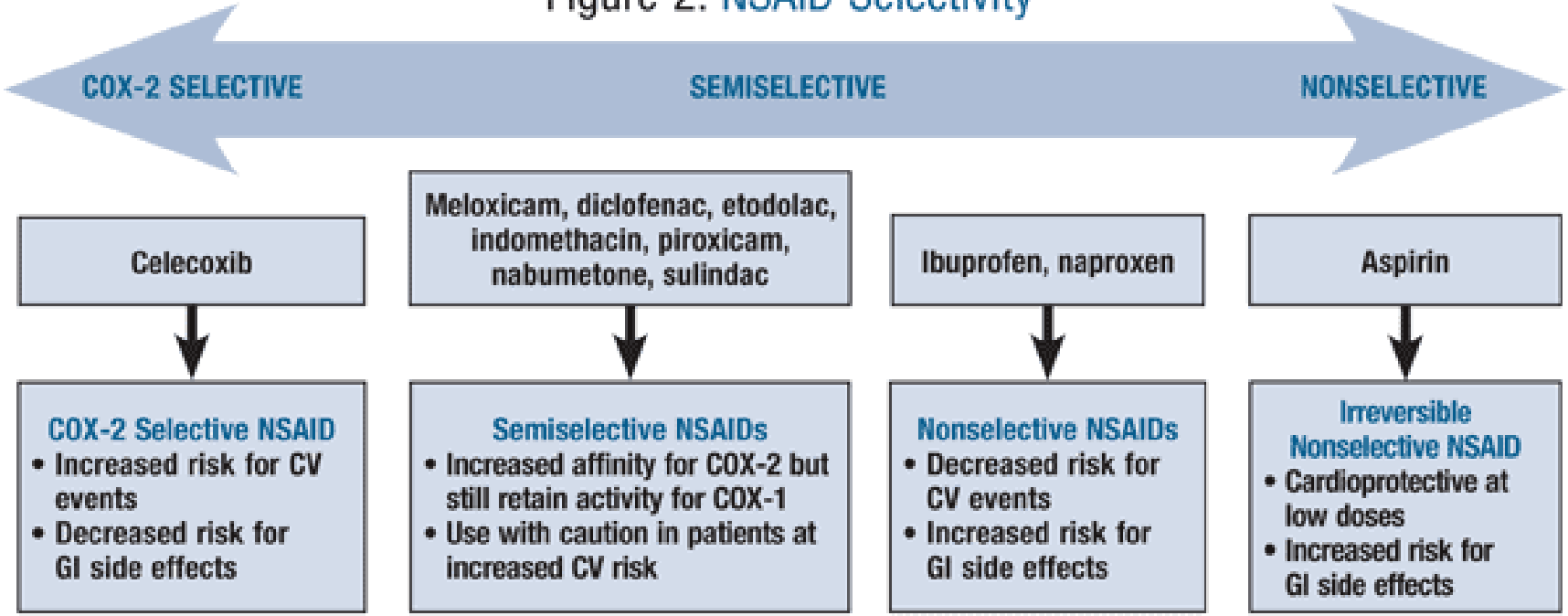
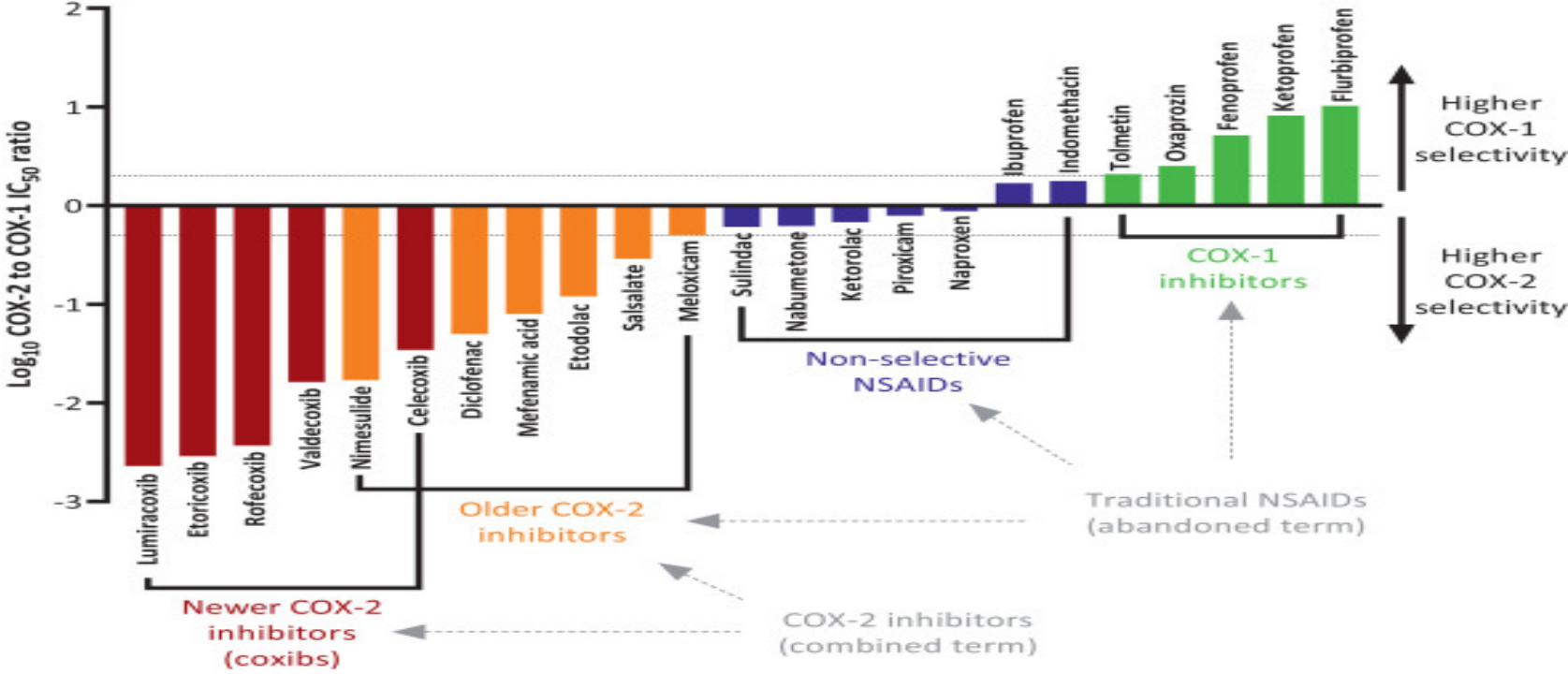
NSAIDs

NSAIDS (non-steroidal anti-inflammatories)

Mechanism of action	Inhibiting cyclooxygenase (COX) enzymes 1&2 to reduce pain and inflammation by reducing prostaglandin, prostacyclin, and thromboxane production at inflammatory sites. COX 1: maintaining GI mucosa, kidney function, platelet aggregation COX 2: expressed during inflammatory response
Dosage forms	PO, topical (diclofenac), IM (ketorolac)
Metabolism	Primarily hepatic metabolism via oxidation
Adverse Effects	Common: nausea, upset stomach, diarrhea, dizziness, edema, heartburn, increased bleeding/bruising risk, elevated blood pressure Serious: GI ulcer and perforation, kidney damage, increased risk of CV disease
Considerations	-ACUTE use Caution patient on concomitant blood thinner/anticoagulants -Taking with food or with PPI to reduce GI intolerances (or misoprostol) -Increasing data with elevated liver enzymes -Higher doses cause more adverse effects and won't work better due to their "ceiling effect."[17]

Figure 2. NSAID Selectivity





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Cardiac and cerebrovascular risks of NSAIDs

Medication	Disease State Risk			
	Heart Failure	Heart Attack / CAD	Blood Pressure	Stroke
Ibuprofen	↑	↑ 1200mg+	↑	↑
Naproxen	↑	Lowest risk	↑	↑↑
Diclofenac	↑	↑↑ 100mg+	↑	↑
Indomethacin	↑↑	↑↑	↑↑	*Not Available*
Meloxicam	↑	↑	↑	↑
Celecoxib	↑	↑↑ 200mg+	↑	↑

NSAIDS (non-steroidal anti-inflammatories)

Ibuprofen	for 200 mg tablets, 1 to 2 tablets every 4 to 6 hours while symptoms persist. The daily limit for ibuprofen is 1200 mg.	Higher doses, higher cardiac adverse risk (lower dose, low risk)
Naproxen	for 220 mg tablets, 1 to 2 tablets every 8 to 12 hours. The daily limit for naproxen sodium is 660 mg.	Moderate GI risk
Diclofenac	PO: 100-150mg in 2-4 divided doses (DR); once daily dosing for (ER); 150mg max dose Topical (gel ex): starting 2g up to 4 times daily	Topical is also available as lotion solution, patch, and rectal suppository
Meloxicam	7.5-15mg once daily	Once daily dosing, longest acting NSAID -no good evidence that IV meloxicam is safer than other injectable NSAIDs
Celecoxib	Starting 100mg twice daily or 200mg once daily, maximum daily dose is 400mg/day	GI risk lowest at low doses Lower bleeding event risk

Medications: Acute Low Back Pain

NSAIDs
Skeletal Muscle Relaxants
Opioids

All had small effects on pain e.g VAS change of 2 points. SMR and Opioids were associated with significant sedation

Systemic steroids were not associated with benefit for back or radicular pain

--*Chou etc. al ACP guideline Annals of IM 2017*

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RESEARCH ARTICLE | PAIN

Acute inflammatory response via neutrophil activation protects against the development of chronic pain

MARC PARISIEN, LUCAS V. LIMA, CONCETTA DAGOSTINO, NEHME EL-HACHEM, GILLIAN L. DRURY, AUDREY V. GRANT, JONATHAN HUISING, VIVEK VERMA, CAROLINA B. MELOTO, [...] LUDA DIATCHENKO +11 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE • 11 May 2022 • Vol 14,Issue 644 • DOI: 10.1126/scitranslmed.abj9954

73,695 GET ACCESS

Beneficial inflammation

Chronic pain can develop from an acute pain state. The mechanisms mediating the transition from acute to chronic pain remain to be elucidated. Here, Parisien *et al.* focused on the immune system using samples from patients and animal models.

CURRENT ISSUE

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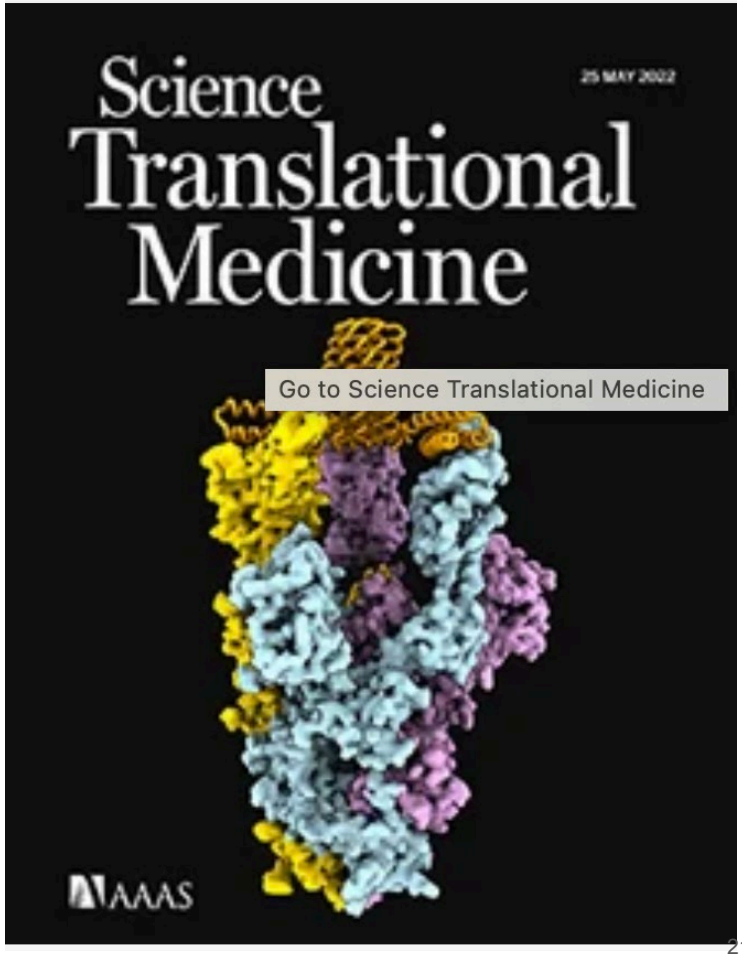
Findings:

1. Normal healing characterized by intense, short-lived inflammation
2. Neutrophil activation-dependent gene products upregulated after pain resolution
3. Patients progressing to chronic pain lacked this upregulation
4. Rodent models demonstrated prolonged pain after NSAIDs or steroids which resolved with infusion of neutrophils
5. Clinical trials showed NSAID use conferred increased risk of chronic pain



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Chronic LBP

Nonsteroidal anti-inflammatory drugs, opioids, and topiramate (Topamax) are more effective than placebo in the short-term treatment of nonspecific chronic low back pain.	**A**	12, 13, 15, 16
Acetaminophen, antidepressants (except duloxetine [Cymbalta]), lidocaine patches, and transcutaneous electrical nerve stimulation are not consistently more effective than placebo in the treatment of chronic low back pain.	**B**	12, 18, 20, 22, 33

Will et. Al, American Family Physician Oct 2018

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SNRIs

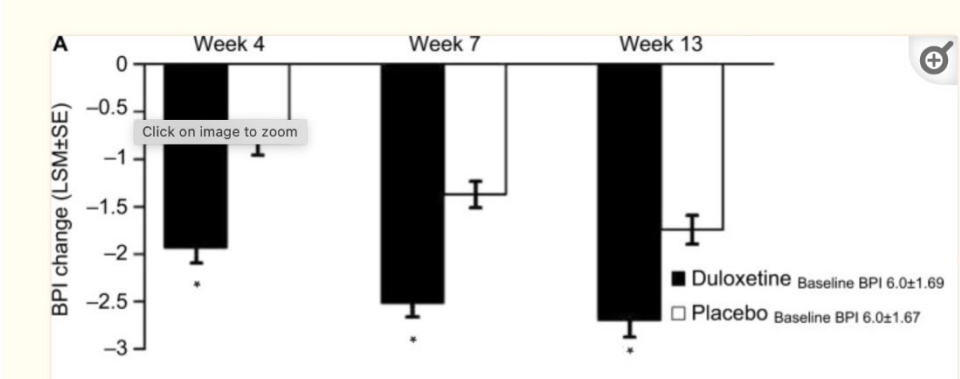
Duloxetine

Venlafaxine

Desvenlafaxine

Milnacipran

Levomilnacipran



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Opioids 2022

--Evolution of opioid drugs of abuse

-- New AHRQ evidence summary and CDC guideline

--Bree Guideline: opioids in older adults

--Buprenorphine for pain

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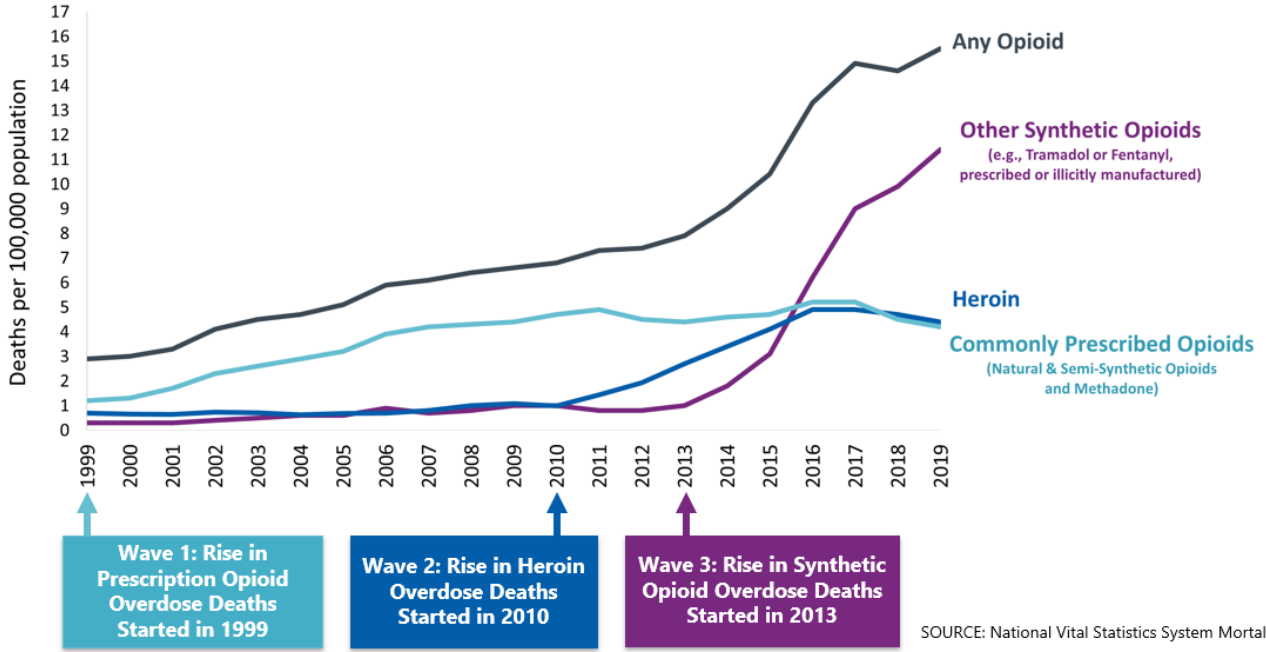
Three Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

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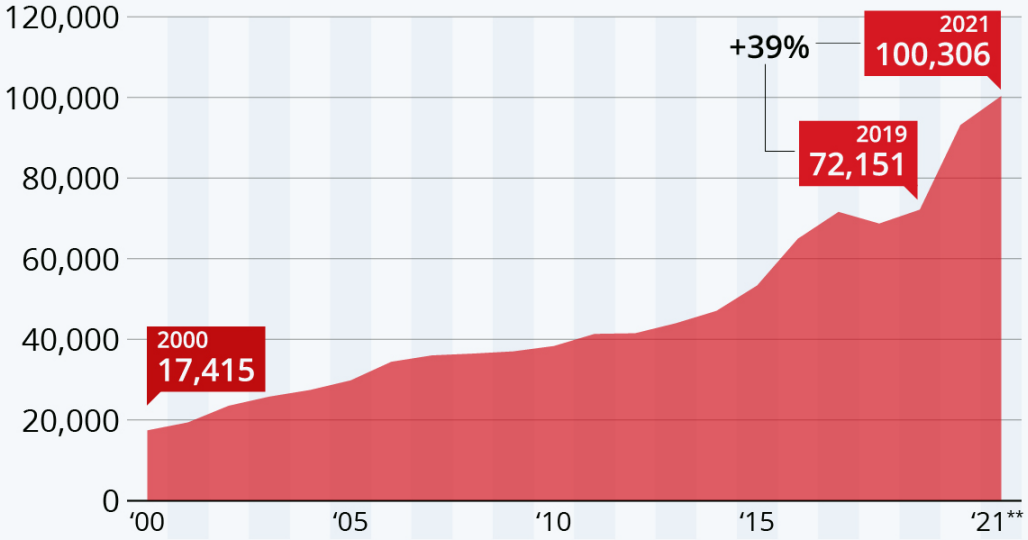
U.S. Drug Overdose Deaths Spike Amid the Pandemic

Number of drug overdose deaths in the United States*



* Estimates for 2020 and 2021 are based on provisional data.
** 2021 estimate refers to 12-month period ending April 2021
Source: Centers for Disease Control and Prevention

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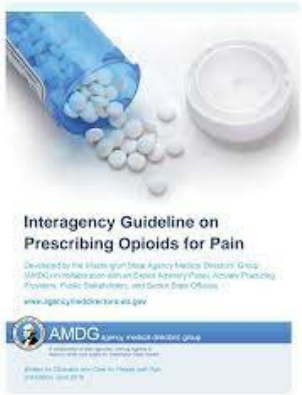
statista

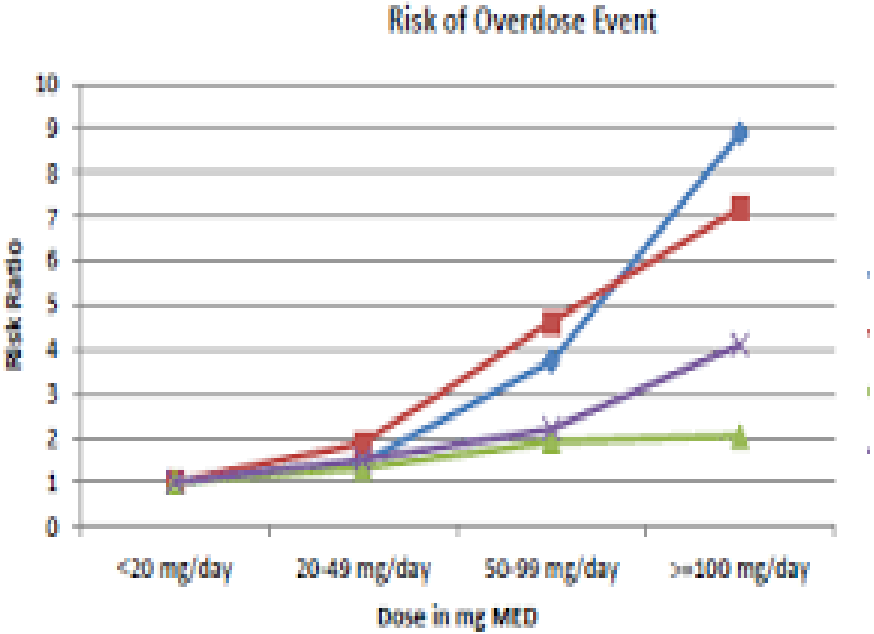
AHRQ Opioids for Chronic Pain

February 10, 2022

Key Messages

- Opioids are associated with small improvements versus placebo in pain and function, and increased risk of harms at short-term (1 to <6 months) followup; evidence on long-term effectiveness is very limited, and there is evidence of increased risk of serious harms that appear to be dose dependent.
- At short-term followup, evidence showed no differences between opioids versus nonopioid medications in improvement in pain, function, mental health status, sleep, or depression.
- Evidence on the effectiveness and harms of alternative opioid dosing strategies and the effects of risk mitigation strategies is lacking, although provision of naloxone to patients might reduce the likelihood of opioid-related emergency department visits, a taper support intervention might improve functional outcomes compared to no taper support, and co-prescription of benzodiazepines and gabapentinoids might increase risk of overdose.
- No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse.





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JAMA | Original Investigation

Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids

Alicia Agnoli, MD, MPH, MHS; Guibo Xing, PhD; Daniel J. Tancredi, PhD; Elizabeth Magnan, MD, PhD; Anthony Jerant, MD; Joshua J. Fenton, MD, MPH

IMPORTANCE Opioid-related mortality and national prescribing guidelines have led to tapering of doses among patients prescribed long-term opioid therapy for chronic pain. There is limited information about risks related to tapering, including overdose and mental health crisis.

OBJECTIVE To assess whether there are associations between opioid dose tapering and rates of overdose and mental health crisis among patients prescribed stable, long-term, higher-dose opioids.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using deidentified medical

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Supplemental content
CME Quiz at jamacmelookup.com

Original Investigation | Pharmacy and Clinical Pharmacology

June 13, 2022

Long-term Risk of Overdose or Mental Health Crisis After Opioid Dose Tapering

Joshua J. Fenton, MD, MPH[1,2]; Elizabeth Magnan, MD, PhD[1,2]; Iraklis Erik Tseregounis, PhD[2,3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(6):e2216726. doi:10.1001/jamanetworkopen.2022.16726

Key Points

Question Is opioid dose tapering associated with reduced longer-term risks of overdose, withdrawal, or mental health crisis in patients prescribed long-term opioids?

Findings In this cohort study of 19 377 patients, in a posttaper period (beginning at least 12 months and extending up to 24 months after taper initiation) vs the pretaper period, the adjusted incidence rate ratios were 1.57 for overdose-withdrawal and 1.52 for a mental health crisis. Both were significant.

Meaning These findings suggest that opioid dose tapering was associated increased risks of overdose-withdrawal and mental health crisis that persisted up to 2 years after taper initiation.

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2022 Guideline

--Addresses concerns arising from 2015 Guideline

- --overly broad application
- --interpretation of dose concerns
- --prescriber fears of COT
- --patient abandonment

12 recommendations

--initial use of non-opioids

--establish goals for pain and function

--use short-acting opioids initially

--prescribe short-durations for acute pain

--use the lowest effective dose

-- consider naloxone for MME>50 or Co-Rx

--Identify and treat OUD

--Reevaluate frequently

1-4 weeks for acute pain

q 3 months or more for chronic

Three “pathways”

1. Maintain and monitor
2. Taper
   Recommends HHS 2019 guidance
3. Medications for OUD

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Bree Guideline: Opioid Prescribing in Older adults

Released August 2022

--Prescription overdose deaths in adults >age 65 have increased

--AHRQ reported highest rates of hospitalization in WA, OR

--Older adults are at risk for opioid-related adverse effects

- Changing pharmacodynamics and kinetics
- Increasingly complex medication interactions
- Increased medical co-morbidities
- Cognitive concerns
- Social isolation

Focus Areas

1. Acute prescribing
2. Intermittent opioid prescribing
3. Co-prescribing with CNS active agents
4. Non-opioid pharmacologic management
5. Non-pharmacologic approaches to pain
6. Tapering or de-prescribing

Pearls

1. Start acute opioids at 25-50% of usual dose
2. Avoid complex regimens with other CNS active drugs including gabapentinoids
3. Use caution with morphine due to variable renal function/active metabolites
4. Look for opportunities to deprescribe CNS active agents
5. Encourage participation in Medicare's Medication therapy management program

Other recommendations

1. Refer to Beers Criteria
2. Avoid TCAs
3. Use extra caution with NSAIDS
4. Avoid combination of opioids and gabapentinoids
5. Utilize exercise, Tai Chi or other interventions that may improve both pain and balance
6. Considerations for older patients intolerant of an opioid taper

Buprenorphine

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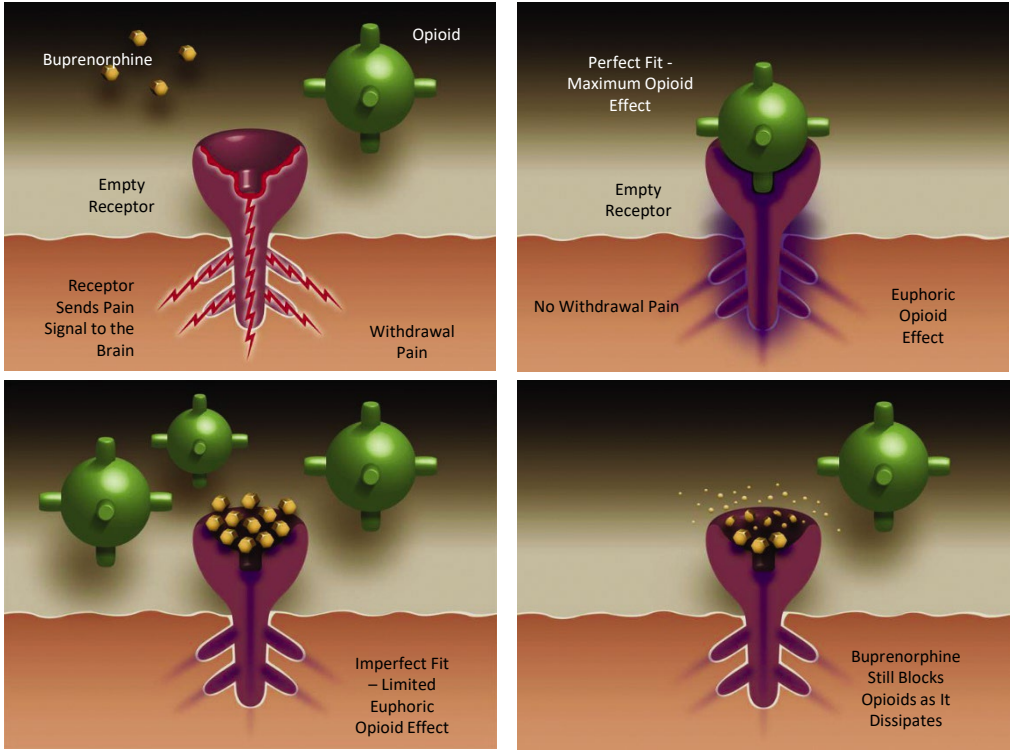
Buprenorphine

- Partial mu agonist
- Very high binding affinity for mu receptor—difficult to reverse with naloxone. Full agonist at the delta opioid receptor (possible AD effects)
- May precipitate withdrawal effects
- Buprenorphine/naloxone primary form of drug used in management of OUD
- New x waiver not required for tx of up to 30 patients *



Courtesy of NAABT, Inc. (naabt.org)

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Pharmacodynamics of BUP

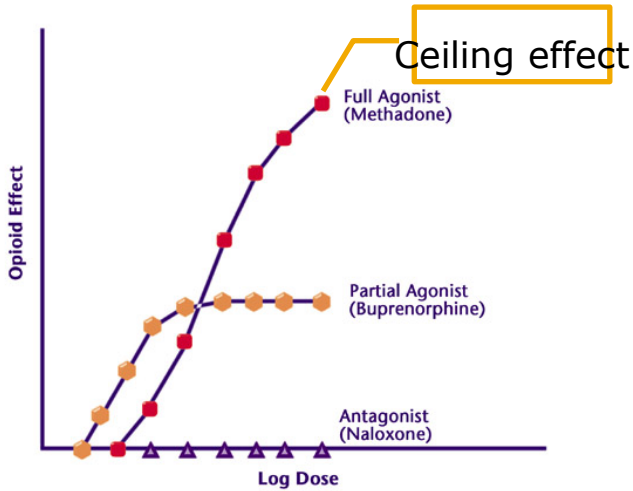
BUP = partial mu-opioid agonist, delta- and kappa-opioid antagonist

Activates mu-receptor and opioid receptor-like 1 (ORL1)

Analgesic duration 6-8hr

Blocks full agonist

Opiate	Ki (nM)
Hydrocodone	41.58
Oxycodone	25.87
Methadone	3.378
Fentanyl	1.346
Hydromorphone	0.365
Buprenorphine	0.215



The National Alliance of Advocates for Buprenorphine Treatment. Thorough technical explanation of buprenorphine. Volpe DA et al. *Regul Toxicol Pharmacol*. 2011;59(3):385-390.

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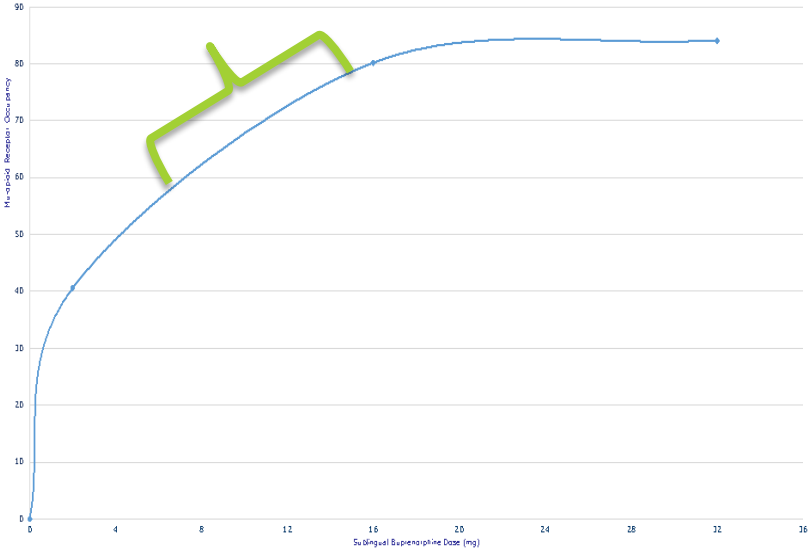
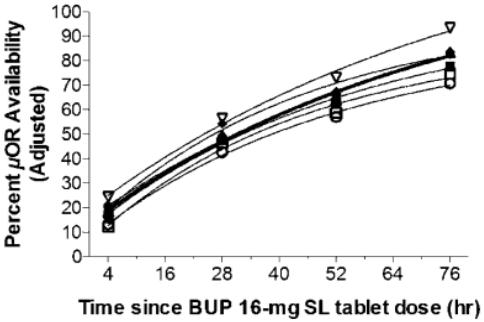
Receptor Occupancy





Greenwald MK et al. *Biol Psychiatry*. 2007;61:101–110.
Greenwald MK et al. *Neuropsychopharmacology*. 2003;28:2000–2009.

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Patients on High Dose Opioids

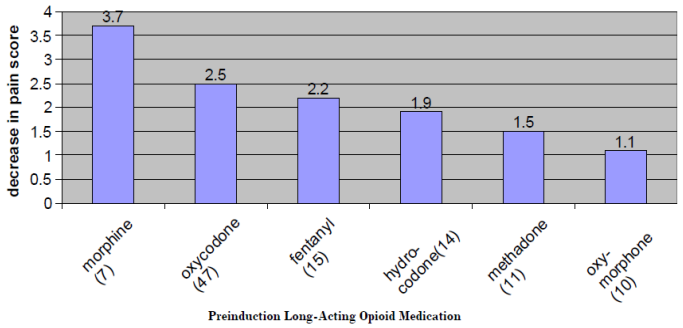
Daitch J et al. *Pain Physician*. 2012;15:ES59-ES66.

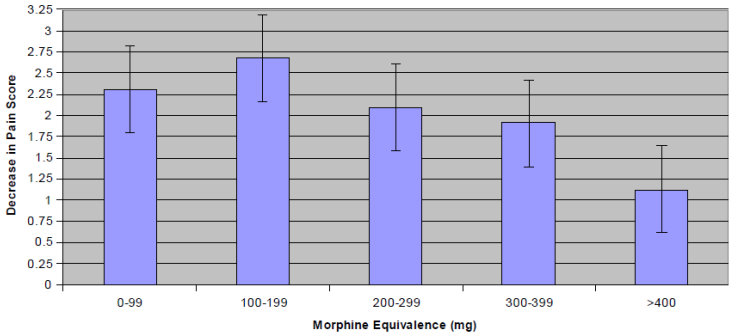
Patients: 104 patients from chronic pain clinic on full opioid agonists – high dose or ineffective use

- Pre-induction MED: 180mg (range 10-840)
- 45% converted from oxycodone, 14% from fentanyl, 13% from hydrocodone, 11% from methadone, 7% from morphine

Intervention: Suboxone starting 24hr after last dose of full agonist

- Starting dose: 8mg, may repeat 8mg 1hr later if pain or withdrawal symptoms





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Summary of Current Recommendations:

1

Prevent transition from acute to chronic opioid therapy

2

Reduce harms by careful management of COT

- --reduce polypharmacy
- --consider gradual dose reduction
- --Do not abandon patients on COT
- --special consideration in older adults

3

Recognize and treat opioid use disorder

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Thank you.

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