What’s New in Pain Medicine:

Opioids, NSAIDs and Pain Management in 2022

Andrew Friedman MD
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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
Categories of Pain
Classification of Pain

Nociceptive

Visceral

Vascular
- Migraine
- Dissecting aneurysms
- Ischemia

Other
- Pancreatitis
- Cardiac ischemia
- Peritoneal inflammation

Musculoskeletal
- Tendon
- Bursa
- Ligament
- Fascia

Neuropathic

CNS
- Poststroke pain
- Spinal cord injury
- Multiple sclerosis

PNS
- Diabetic neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
Nociceptive Pain
Prevalent Forms of Neuropathic Pain

Diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are the most common forms of neuropathic pain.

- Trigeminal neuralgia
- HIV-associated pain
- Poststroke pain
- Phantom limb pain
- Multiple sclerosis
- Reflex sympathetic dystrophy
- Spinal cord injury
- Cancer-related pain
- Postherpetic neuralgia
- Diabetic peripheral neuropathy

US Prevalence (Millions of Cases)

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 NOCICEPTIVE**
- Osteoarthritis
- Rheumatoid arthritis
- Tendonitis, bursitis
- Ankylosing spondylitis
- Gout

**Mixed pain conditions with multiple pain pathophysologies such as chronic low back pain**

**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 spinal cord injury

**PREDOMINANTLY CENTRAL SENSITISATION**
- Fibromyalgia
- Irritable bowel syndrome
- Tension-type headaches
- Interstitial cystitis/pelvic pain syndrome
- Temporomandibular joint disorder
- Chronic fatigue syndrome
- Restless leg syndrome
- Neck and back pain without structural pathology
Nocicplastic pain affecting the musculoskeletal system: CLINICAL CRITERIA & grading system developed by the IASP’s presidential terminology task force

1. Pain > 3 months
   - Yes, Not chronic nocicplastic pain
   - No, Regional rather than discrete

2. Regional rather than discrete
   - Yes, Not nocicplastic pain
   - No, Nociceptive pain

3. Nociceptive pain
   - Yes, Entirely responsible for pain
   - No, Neuropathic pain

4. Neuropathic pain
   - Yes, Entirely responsible for pain
   - No, Evoked pain hypersensitivity phenomena

5. Evoked pain hypersensitivity phenomena
   - Yes, Possible nocicplastic pain
   - No, History of pain hypersensitivity & comorbidities

6. History of pain hypersensitivity & comorbidities
   - Yes, Probable nocicplastic pain
   - No, Presence of co-morbidities

    Presence of co-morbidities (any one of):
    - Increased sensitivity to sound, light, and/or odors
    - Sleep disturbance with frequent nocturnal awakenings
    - Fatigue
    - Cognitive problems

Common Pain Conditions

Nociceptive Pain
Fracture, Arthritis

Neuropathic Pain
Central—MS, SCI, Post-stroke
Peripheral—PPN, Zoster, TGN

Nociplastic Pain
Fibromyalgia
Osteoarthritis

Acetaminophen?
NSAIDS
  --Pain relief equivalent to exercise
  --Topical NSAIDs if oligoarticular
  --Oral NSAIDs
Duloxetine
Intraarticular therapies

![Keilgren-Lawrence (KL) grading scale](image)

- **Normal**: No features of OA
- **Doubtful**: Minute osteophyte; doubtful significance
- **Mild**: Definite osteophyte; normal joint space
- **Moderate**: Moderate joint space reduction
- **Severe**: Joint space greatly reduced; subchondral sclerosis
NSAIDs
# NSAIDS (non-steroidal anti-inflammatory drugs)

## 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.”

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14
Figure 2. NSAID Selectivity

**COX-2 SELECTIVE**

- Celecoxib
  - COX-2 Selective NSAID
  - Increased risk for CV events
  - Decreased risk for GI side effects

**SEMISELECTIVE**

- Meloxicam, diclofenac, etodolac, indomethacin, piroxicam, nabumetone, sulindac
  - Semiselective NSAIDs
  - Increased affinity for COX-2 but still retain activity for COX-1
  - Use with caution in patients at increased CV risk

**NONSELECTIVE**

- Ibuprofen, naproxen
  - Nonselective NSAIDs
  - Decreased risk for CV events
  - Increased risk for GI side effects

- Aspirin
  - Irreversible Nonselective NSAID
  - Cardioprotective at low doses
  - Increased risk for GI side effects
# Cardiac and cerebrovascular risks of NSAIDs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Disease State Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart Failure</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>↑</td>
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<tr>
<td>Naproxen</td>
<td>↑</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>↑</td>
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<tr>
<td>Indomethacin</td>
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</tr>
<tr>
<td>Meloxicam</td>
<td>↑</td>
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<tr>
<td>Celecoxib</td>
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</table>
## NSAIDS (non-steroidal anti-inflammatories)

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Dosage/Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>for 200 mg tablets, 1 to 2 tablets every 4 to 6 hours while symptoms persist. The daily limit for ibuprofen is 1200 mg.</td>
<td>Higher doses, higher cardiac adverse risk (lower dose, low risk)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>for 220 mg tablets, 1 to 2 tablets every 8 to 12 hours. The daily limit for naproxen sodium is 660 mg.</td>
<td>Moderate GI risk</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>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</td>
<td>Topical is also available as lotion solution, patch, and rectal suppository</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5-15mg once daily</td>
<td>Once daily dosing, longest acting NSAID -no good evidence that IV meloxicam is safer than other injectable NSAIDs</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Starting 100mg twice daily or 200mg once daily, maximum daily dose is 400mg/day</td>
<td>GI risk lowest at low doses Lower bleeding event risk</td>
</tr>
</tbody>
</table>
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
Acute inflammatory response via neutrophil activation protects against the development of chronic pain

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.
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
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.

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.

Will et. Al, American Family Physician Oct 2018
SNRIs

Duloxetine
Venlafaxine
Desvenlafaxine
Milnacipran
Levomilnacipran
Opioids 2022

--Evolution of opioid drugs of abuse

-- New AHRQ evidence summary and CDC guideline

--Bree Guideline: opioids in older adults

--Buprenorphine for pain
Three Waves of the Rise in Opioid Overdose Deaths

- **Any Opioid**
- **Other Synthetic Opioids** (e.g., Tramadol or Fentanyl, prescribed or illicitly manufactured)
- **Heroin**
- **Commonly Prescribed Opioids** (Natural & Semi-Synthetic Opioids and Methadone)

**Wave 1:** Rise in Prescription Opioid Overdose Deaths Started in 1999

**Wave 2:** Rise in Heroin Overdose Deaths Started in 2010

**Wave 3:** Rise in Synthetic Opioid Overdose Deaths Started in 2013

U.S. Drug Overdose Deaths Spike Amid the Pandemic

Number of drug overdose deaths in the United States*

- **2000**: 17,415
- **2019**: 72,151
- **2021**: 100,306

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

Alicia Agno1, MD, MPH; Minh Nguyen1, MD; 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 records from 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 with increased risks of overdose-withdrawal and mental health crisis that persisted up to 2 years after taper initiation.
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
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
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
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 *
Buprenorphine still blocks opioids as it dissipates.

Imperfect Fit – Limited Euphoric Opioid Effect

Perfect Fit - Maximum Opioid Effect

No Withdrawal Pain

Euphoric Opioid Effect

Buprenorphine still blocks opioids as it dissipates.
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

<table>
<thead>
<tr>
<th>Opiate</th>
<th>Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>41.58</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>25.87</td>
</tr>
<tr>
<td>Methadone</td>
<td>3.378</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.346</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.365</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.215</td>
</tr>
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Receptor Occupancy

Patients on High Dose Opioids


**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

Outcome: Those that continued Suboxone for >60 days experienced 2.3 point reduction in pain score
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
Thank you.