((بنام مالک هستی))

دومین رویداد آموزشی سازمان نظام پزشکی کشور

همایش تازه های تشخیص و درمان بیماری های شایع

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مرکز همایشهای بین المللی رازی

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Brief Overview

Pain Definition

"An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage"

(International Association for the Study of Pain, 2014)

(1) Pain Classification

- Acute pain lasts for days to a month after a physiologic insult or injury
- Subacute pain lasts from one to three months after an injury
- Chronic pain is pain that persists longer than three months

(2) Pain Classification

- Acute Pain
  - Less than three months duration
- Chronic Pain
  - More than three months duration
- Acute-on-Chronic Pain
  - Acute pain flare superimposed on underlying chronic pain

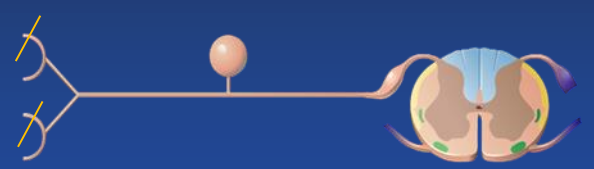
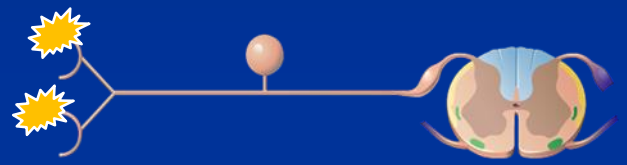
(3) Pain Classification: Physiology

- Nociceptive Pain
  - Normal response to tissue injury

- Inflammatory Pain
  - Activation and sensitization of nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation

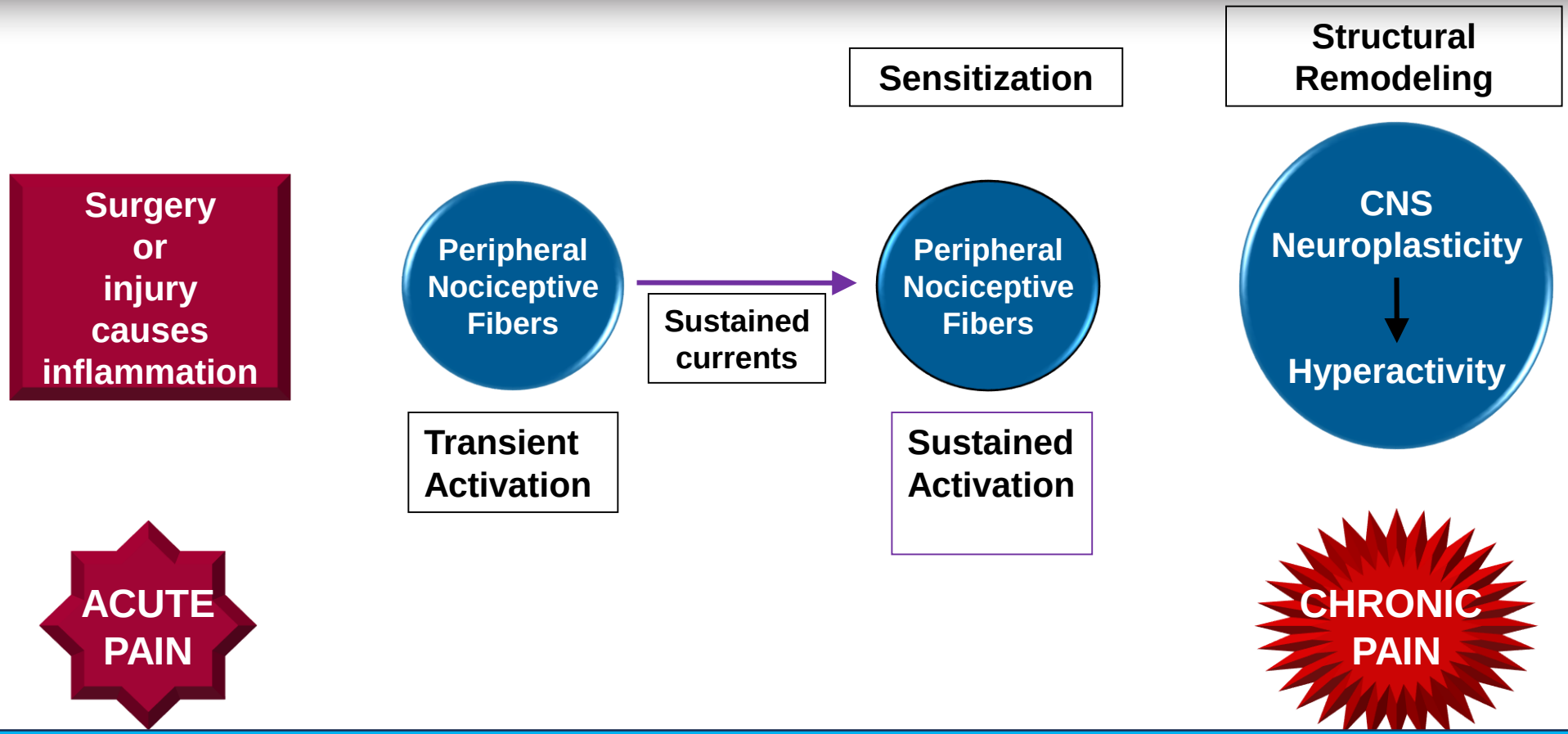
- Neuropathic Pain
  - A primary lesion or disease in the somatosensory nervous system

Pain Types

Type			Examples
Nociceptive	Noxious Peripheral Stimuli		Strains and sprains Bone fractures Postoperative
Inflammatory	Inflammation		Osteoarthritis Rheumatoid arthritis Tendonitis
Neuropathic	Multiple Mechanisms	Peripheral Nerve Damage 	Diabetic peripheral neuropathy Post-herpetic neuralgia HIV-related polyneuropathy
Noninflammatory/ Nonneuropathic	Abnormal Central Processing	No Known Tissue or Nerve Damage 	Fibromyalgia Irritable bowel syndrome

Patients may experience multiple pain states simultaneously

Long-Term Consequences of Acute Pain:



Reasons for pain management

- Avoiding progression to chronic pain
- It is a critical aspect of healthcare
- Alleviating discomfort
- Improving the quality of life
- Decreasing cost
- ….

How to manage?

“ International journal of general medicine Jul 2023 ”

- Various databases, including PubMed, Scopus, and Google Scholar, relevant articles published between 2000 and 2023

- The selected studies encompassed original research, review articles, therapeutic guidelines and randomized controlled trials(RCT).

Results:

I. To optimize pain management outcomes:

1. **Importance of assessing pain intensity**
2. **Determining the underlying etiology**
   - Nociception
   - Inflammation
   - Neuropathy
3. **Utilizing evidence-based guidelines**

Results:

II. A **multimodal** approach combining **various analgesics**

- Pharmacologic Treatments
  - Essential component of strategies to achieve

Enhanced pain relief
&
Minimized adverse effects

    - Non opioid analgesics
    - Opioid analgesics
    - Adjuvant analgesics
    - Corticosteroids
    - …
- Nonpharmacologic treatment
    - …

Pharmacologic Treatments:

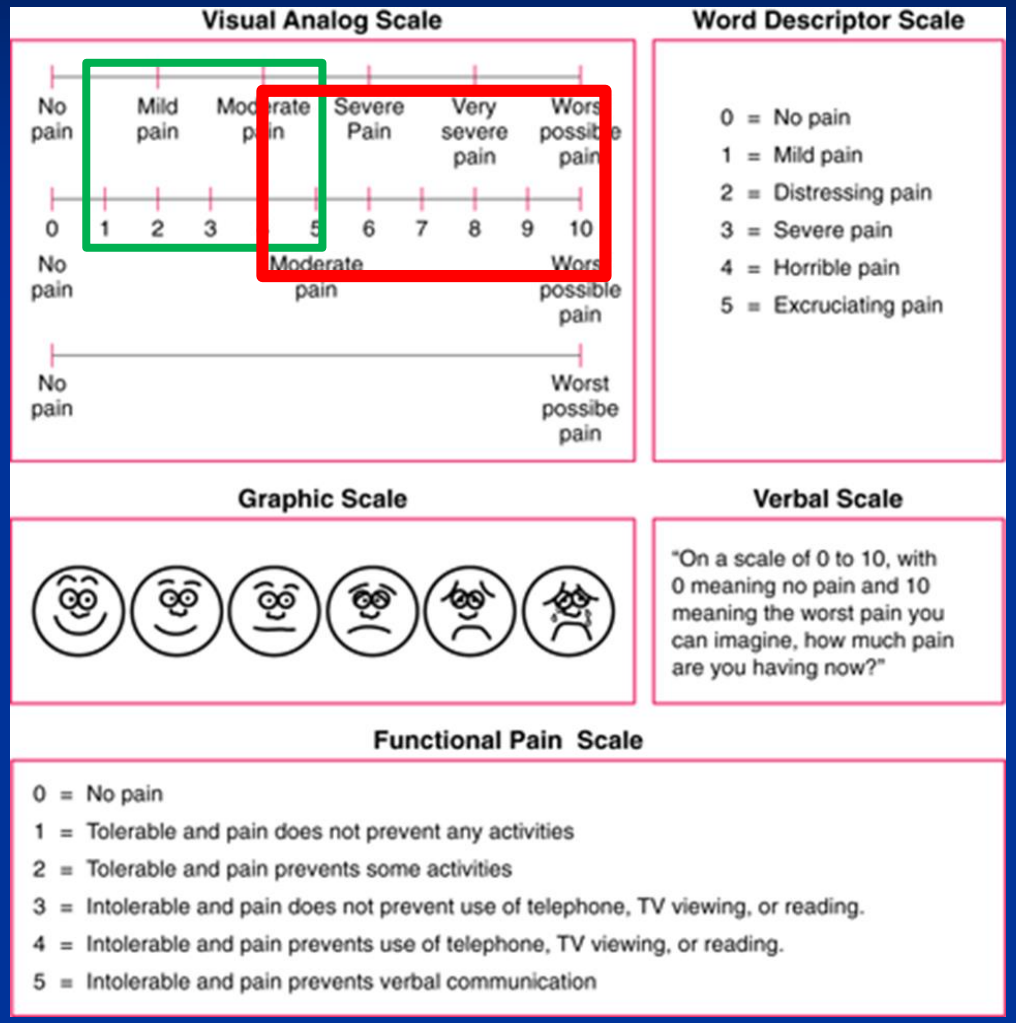
- To treat, you have to know the mechanisms of pain
  - Generation
  - Modulation

  - Nociception
  - Inflammation
  - Neuropathy

It is time to choose the best **medication** & **dosage** regimen:

- Patient-specific factors
  - **The patient's pain type (Nociception , Inflammation , Neuropathy)**
  - **The patient's pain severity**
  - **Underlying medical conditions**
    - Liver or kidney disease
    - Cardiovascular disorders
    - Gastrointestinal issues
    - Age-related physiological changes
    - The patient's medication profile

The patient's pain severity

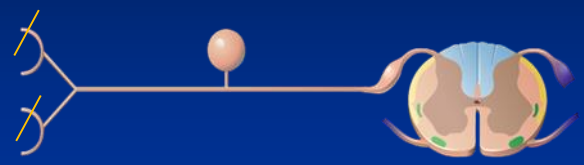


- Mild to moderate pain
  =>Non-opioid analgesics

- Moderate to severe pain
  => Opioid analgesics
  (potent pain relievers)

Pharmacologic therapy for nociceptive pain

- (NSAIDs) – mainstay



- Oral NSAIDs - first-line medications

- Topical NSAIDs - localized arthritis

*Superficially located joints (hand and wrist, foot and ankle, or knee)(focal myofascial pain) with the potential to achieve therapeutic synovial tissue drug levels with lower systemic drug levels compared with oral therapy.

- If NSAIDs are ineffective:

=> Consider : Nociplastic pain, Central sensitization or Neuropathic pain, or a Combination

=> Alternative:opioids, acetaminophen, antidepressant or antiseizure

=> * Opioids: - only when the benefits outweigh the potential risks

- when other therapies have failed

=>lowest effective dose and shortest duration, and combined with other nonopioid

=> * Acetaminophen :

=> concerns for hepatotoxicity when used at a higher than recommended dose.

=> not considered as first line

Pharmacologic therapy for Neuropathic pain, or Nociplastic or Centralized pain

- The choice should be individualized based on:
  - Pain condition (if known)
  - Patient-specific characteristics
  - Co-occurring conditions
  - Medication side effect profile
  - Cost
  - Patient values and preferences
  - Patient's age

Pharmacologic therapy for Neuropathic pain, or Nociplastic or Centralized pain

1. Initial treatment involves

(First line) :

- **TCAs** (nortriptylin)

or

- **SNRIs** (duloxetine)

or

- **Antiseizure medications** (gabapentin / pregabalin)

- In practice, comorbidities and concurrent medications often favor one drug class or another
  - Start with an antidepressant if the patient is depressed or anxious

  or
  - A gabapentinoid when antidepressant drug-interactions or side-effects are problematic

- Appropriate use of first-line medications for neuropathic pain may lead to

>only *partial reduction* in pain or

>*dose-limiting side effects*,

=> thus combination therapy with two agents from different classes is common.

- A 2012 systematic review for neuropathic pain found efficacy of combination therapy.
- Several subsequent trials point to advantages.
  - The data are not robust enough to suggest specific combinations

Pharmacologic therapy for Neuropathic pain, or Nociplastic or Centralized pain

2. Adjunctive topical therapy

- If pain is localized:
  - Topical lidocaine
  - Capsaicin patch
  - ...
- If pain has inflammatory component:
  - NSAIDs
  - Corticosteroid
  - …

Pharmacologic therapy for Neuropathic pain, or Nociplastic or Centralized pain

3. Opioids:

- Opioids should be considered a second- or third-line option

- **Those with high severity intractable pain**
- **Episodic exacerbations of severe pain**
- **Neuropathic cancer pain**

- The efficacy of opioids for neuropathic pain is uncertain.

- In a 2013 review of 31 randomized trials of opioids for neuropathic pain, among patients treated for several days to 12 weeks, compared with patients who received placebo, risk of bias in the included studies was high.

1. NSAIDs

- The most commonly used
- Inhibiting prostaglandins production
- Anti Inflammation
- Classified into two categories:
  1. Selective (COX-2) Celecoxib
  2. Non-selective(COX-1 and COX-2)Aspirin, Ibuprofen, Naproxen
- Additional effects : antipyretic, antiplatelet
- Adverse Effects (NSAIDs)
  - Can cause gastrointestinal (GI) adverse effects,
    - Dyspepsia, Nausea, Vomiting, and Peptic ulcer disease.
  - Can also cause renal adverse effects,
    - Acute kidney injury and chronic kidney disease.
    - Use with caution in patients with renal impairment, heart failure, or a history of GI bleeding.

2. Acetaminophen

- Often used as an alternative to NSAIDs
- Commonly for mild to moderate pain
- Inhibiting the production of PGs in CNS
- Not effective in inflammation
- Low risk of adverse effects
- Acetaminophen is generally well-tolerated, but it can cause hepatotoxicity in overdose.
- The combination of acetaminophen with an NSAID is commonly used for acute pain.

3. Topical agents

- Newer class of non-opioid analgesics
- Applied directly to the skin
- They work by blocking pain signals at the site of application.
- Examples : capsaicin cream, diclofenac gel
- Can cause local adverse effects,
  - Skin irritation, itching, and burning.
- Can cause systemic adverse effects if absorbed through the skin,
  - GI upset, headache, dizziness

4. Opioid Analgesics

- The most potent drugs in pain management
- Can effectively reduce the perception of pain (moderate to severe pain).
- Pharmacological effects :
  - analgesia, sedation, respiratory depression, and euphoria
- Adverse effect : respiratory depression, gastrointestinal adverse effects, hormonal changes(↓testosterone, ↑prolactin), tolerance, dependence, and addiction when used long-term, urinary(retention).
- Careful monitoring is essential to ensure safe and effective pain management.
- Examples : morphine, oxycodone, hydrocodone, fentanyl, and codeine.
- Available by prescription only
- High risk of addiction and dependence
- Limitation : adverse effects in some patients
- The most common adverse effects are related to the central nervous system
  - sedation, dizziness, confusion, addiction
- Respiratory depression can be life-threatening and requires close monitoring
- Sudden cessation => withdrawal symptoms.

5. Corticosteroids

- Potent anti-inflammatory + analgesic effects,
- Useful in various types of pain.(RA,OA, acute & chronic pain)

- They reduce the production of pain-inducing substances and inflammatory mediators, such as prostaglandins, leukotrienes, and cytokines.
- Corticosteroids, also have immunosuppressive effects, which can be beneficial in autoimmune diseases, such as rheumatoid arthritis.

- Adverse effects : weight gain, fluid retention, hypertension, mood changes, and GI disturbances(ulcers and bleeding).
- Long-term use can also lead to osteoporosis, muscle weakness, and increased risk of infections.

Adjuvant Analgesics

- Adjuvant analgesics are used in combination with other drugs to enhance their analgesic effects or to manage specific types of pain.

- Examples :

TCAs, SNRIs, Gabapentioids, Benzodiazepins, Topical agents,…

TCAs

- Nortriptyline, amitriptyline, …
- Noticeable analgesic effects may require 2-4 weeks.
- Tapering and discontinuing can be challenging.
- TCAs in general, and most notably nortriptyline, demonstrate the fewest of these discontinuation withdrawal events

- Old age : Starting doses of tricyclics should be reduced by one-half for older patients, who should be watched carefully for untoward effects .
- Side effects : dose related

- Anticholinergic effects do not appear to contribute to analgesia, are common and may lead to dose limitation and discontinuation.
- Among the TCAs, amitriptyline is the most sedating and most potent anticholinergic effects.
- Anticholinergic adverse effects can be reduced by starting with low doses administered at bedtime and with slow titration to higher dose.

SNRI

- Venlafaxine and Duloxetine for treatment of peripheral neuropathic pain.
- Duloxetine and Milnacipran for treatment of fibromyalgia.
- Milnacipran, a more potent inhibitor of norepinephrine reuptake than the other SNRIs, was also modestly effective for pain relief.
- For both duloxetine and milnacipran, standard doses => efficacious as high doses,

- Duloxetine has the largest evidence base to support analgesic efficacy,
- FDA approved for the treatment of painful diabetic neuropathy, fibromyalgia, chronic low back pain, and osteoarthritis.
- The most common side effects :nausea, dry mouth, insomnia, drowsiness, constipation, fatigue, and dizziness
- Side effects are reduced by administering duloxetine30 mg orally once daily for one week before increasing to the usual dose of 60 mg once daily.
- Duloxetine should be avoided in patients with hepatic or severe renal insufficiency.
- Gradual tapering is recommended to avoid withdrawal symptoms.

Antiseizures

- 3 antiseizure (gabapentin, pregabalin, and carbamazepine)- FDA approved for the neuropathic pain.

- Gabapentin has primarily been studied and found effective for postherpetic neuralgia and painful diabetic neuropathy.
- Gabapentin should be initiated at a low dose with gradual increases until pain relief or dose-limiting adverse effects are achieved. (Adjustment for renal impairment is required)

- Pregabalin is the only FDA approved medication for spinal cord injury neuropathic pain.
- The recommended starting dose is 150 mg, divided into two or three doses daily, and increased to a total daily dose of 300 mg based upon tolerability and effect. Further titration (to 600 mg daily) after 2-4 weeks.
- Pregabalin may provide analgesia more quickly than gabapentin,
- Adverse effects – Gabapentin and pregabalin can produce dose-dependent dizziness and sedation that can be reduced by starting with lower doses and titrating slowly.

- Carbamazepine is a first-line therapy for trigeminal neuralgia, and is best studied for this indication.
- Oxcarbazepine is an alternative for patients who do not respond to or tolerate carbamazepine.

Adjuvants we do not recommend

- Muscle relaxants
- Avoid ongoing use of muscle relaxants (methocarbamol) for chronic pain.

- Muscle relaxants have anticholinergic properties, and may also cause CNS depression.

- When true muscular spasticity is present, anti-spasticity drugs, such as baclofen or tizanidine, may alleviate the pain from persistent tonic muscular contractions.

Benzodiazepines

- Avoid the use of benzodiazepines in patients with chronic pain, including those with anxiety or post-traumatic stress disorder.
- Benzodiazepines are not first-line anxiolytics or sleep aids and there is no evidence of analgesic efficacy for chronic pain.
- Disadvantages :abuse and addiction, respiratory depression
- In a study of 1220 patients with non-cancer pain on long-term opioids, concurrent benzodiazepine use was associated with greater pain severity, prescription of higher doses of opioids, substance use, and greater co-occurring mental health problems .

Cannabis and cannabinoids

- The use for chronic pain is controversial, and is complicated.
- Systematic reviews and meta-analyses of trials have reported mixed results on efficacy for chronic pain.

- A 2017 report from the National Academies of Sciences, Engineering and Medicine found evidence of significant reduction in chronic pain with the use of cannabis or cannabinoids.

- A 2022 Agency for Health Research and Quality systematic review of various THC-CBD doses and concentrations of synthetic and plant-extracted cannabis products found small, short-term improvements in neuropathic chronic pain and function.
- Conclusions from this review are limited by nonstandardized characterization of various cannabis products, and lack of adequate studies on specific preparations and patient populations.

Botulinum toxin

- Limited literature suggests that
  - Subcutaneous injection of botulinum toxin type A (BTX-A)
  - May reduce opioid requirement for analgesia in patients with severe post herpetic neuralgia .

Tramadol & Tapentadol

- Tramadol may be used as second-line agent for patients with fibromyalgia who have not responded to initial therapy with other agents.
- Efficacy of tramadol for other types of chronic pain, including neuropathic pain, is unclear .
- Combination of tramadol with other serotonin reuptake inhibitors can increase the risk for serotonin syndrome/serotonin toxicity and seizures.

- Tapentadol is also a mixed mechanism opioid with stronger affinity for the mu opioid receptor than tramadol (though weaker than pure mu agonists) and noradrenergic reuptake inhibition.
- It is the only opioid with a specific FDA indication for neuropathic pain (ER form for painful diabetic neuropathy).
- Tapentadol may be associated with fewer GI side effects than potent opioids at similarly effective doses, the authors reserve it for third-line use.
- Like tramadol, combination of tapentadol with other serotonin reuptake inhibitors can increase the risk for serotonin syndrome/serotonin toxicity and seizures may be increased.

Buprenorphine

- Some safety advantages when prescribed for chronic pain, since it
  - produces less physical dependence and
  - less opioid-induced hyperalgesia than other opioids
  - produces less respiratory depression than other opioids
- Similar safety concerns as other opioids.
- Significant respiratory depression can occur if buprenorphine is used along with other benzodiazepines, alcohol, or other respiratory depressants.
- It is an abusable drug.

- For chronic pain indications,
  - available as a transdermal patch or a buccal film;
  - available in the United States in low-moderate dosage formulations, lower than the doses typically used for opioid use disorder OUD.

INFUSION THERAPIES(Ketamine)

- It has long been used in hospital and emergency settings to provide analgesia in acute pain situations (burns, fractures and other trauma, postoperative pain)

- In recent years it has been increasingly used as an intravenous infusion for complex regional pain syndrome (CRPS), neuropathic pain, and other intractable chronic pain states.
- There are several reports of hepatobiliary dysfunction after recurrent ketamine administration.
- In 2020 this prompted an FDA label change (updated in 2021) for ketamine, recommending that liver function tests should be checked before starting therapy, and periodically for those receiving recurrent therapy

Lidocaine infusion

- Used for multimodal analgesia for
  - perioperative pain
  - chronic neuropathic pain.
- In outpatient settings doses of 3 to 5 mg/kg administered over 30 to 60 minutes can relieve neuropathic pain short term, with sustained analgesia in some patients.

- A positive response to IV lidocaine is sometimes viewed as an indication to proceed with
  - other local anesthetics (typically mexiletine) or
  - other sodium channel blocking agents, administered orally.

- Lidocaine infusion should be reserved for patients who have not responded to other treatments.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol): Usual oral dosing for adults with pain or inflammation and selected characteristics

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Nonselective NSAIDs*			
Acetic acids			
Diclofenac[¶]	50 mg every 8 to 12 hours	150 mg For rheumatoid arthritis, labeling in United States permits up to 200 mg Approved maximum in Canada is 100 mg	•Dosing for free-acid preparation differs from doses listed here for sodium or potassium salts; refer to Lexicomp drug monograph
Etodolac	200 to 400 mg every 6 to 8 hours	1000 mg	•Relative COX-2 selectivity and minimal effect on platelet function at lower total daily dose of 600 to 800 mg
Indomethacin	25 to 50 mg every 8 to 12 hours	150 mg For rheumatologic conditions, labeling in United States permits up to 200 mg	•Used for treatment of acute gout and certain types of headache •Potent inhibitory effects on renal prostaglandin synthesis •More frequently associated with CNS side effects (eg, headache, altered mental status) compared with other NSAIDs
Sulindac	150 to 200 mg every 12 hours	400 mg	•Rarely used •More frequently associated with hepatic inflammation than other NSAIDs •Metabolites implicated in the formation of renal calculi

Fenamates			
Meclofenamate (meclofenamic acid)	50 mg every 4 to 6 hours or 100 mg 3 times daily up to 6 days for dysmenorrhea	400 mg	•Used for treatment of dysmenorrhea •Relatively higher incidence of GI side effects
Mefenamic acid	250 mg every 6 hours or 500 mg 3 times daily	1000 mg For dysmenorrhea, up to 1500 mg	•Used for treatment of dysmenorrhea; not indicated for treatment of chronic pain or inflammation •Do not exceed 3 days (dysmenorrhea) to 7 days (acute pain) of use •Less potent anti-inflammatory effect

Oxicams			
Meloxicam[Δ]	7.5 to 15 mg once daily (conventional tablet, oral suspension)	15 mg (conventional tablet, oral suspension)	•Long duration of effect; relatively slow onset •Relative COX-2 selectivity and minimal effect on platelet function at lower daily dose of 7.5 mg
	5 to 10 mg once daily (capsule)	10 mg (capsule)	
Piroxicam	10 to 20 mg once daily	20 mg	•Long-acting alternative for treatment of chronic pain and inflammation poorly responsive to other NSAIDs •Prescribing generally limited to specialists with experience in treatment of chronic pain and inflammation

Propionic acids			
Fenoprofen	200 mg every 4 to 6 hours or 400 to 600 mg every 6 to 8 hours	3200 mg	•More frequently associated with acute interstitial nephritis and nephrotic syndrome[1]
Flurbiprofen	50 mg every 6 hours or 100 mg every 8 to 12 hours	300 mg	
Ibuprofen[Δ]	400 mg every 4 to 6 hours or 600 to 800 mg every 6 to 8 hours	3200 mg (acute), 2400 mg (chronic)	•Shorter-acting alternative to naproxen; useful in patients without cardiovascular risks
Ketoprofen	50 mg every 6 hours or 75 mg every 8 hours	300 mg	
	Base: 250 to 500 mg every 12 hours or 250 mg every 6 to 8 hours	Base: 1250 mg (acute); 1000 mg (chronic); may increase to 1500 mg during a disease flare	•Often preferred by UpToDate for treatment of acute or chronic pain and inflammation in patients without relevant comorbidities or risks •Higher dose (eg, 500 mg base twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs;[2] refer to UpToDate topic review of cardiovascular effects of nonselective NSAIDs •Naproxen sodium has a faster onset than naproxen base
Naproxen	Naproxen sodium: 275 to 550 mg every 12 hours or 275 mg every 6 to 8 hours	Naproxen sodium: 1375 mg (acute); 1100 mg (chronic); may increase to 1650 mg during a disease flare	
Oxaprozin	1200 mg once daily	1200 mg or 1800 mg depending on body weight (refer to Lexicomp drug monograph)	•Prolonged half-life (41 to 55 hours); requires several days of treatment to reach full effect

Salicylate (acetylated)			
Aspirin	325 to 1000 mg every 4 to 6 hours	4000 mg	•Not commonly used for chronic pain and inflammation •High daily doses have been used as anti-inflammatory therapy; such use is limited by toxicity •Irreversibly inhibits platelet function •Refer to appropriate UpToDate clinical topics and Lexicomp drug monograph for other uses
Salicylates (nonacetylated)			
Diflunisal	500 mg every 8 to 12 hours	1500 mg	•No significant effect on platelet function at usual doses •Relatively lower GI bleeding risk than other nonselective NSAIDs at usual doses •May be tolerated at lower daily doses by adults with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis); refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Magnesium salicylate	1160 mg every 6 hours	4640 mg	
Salsalate	1000 mg every 8 to 12 hours or 1500 mg every 12 hours	3000 mg	

COX-2 selective NSAIDs			
Celecoxib	200 mg daily or 100 mg every 12 hours	400 mg	•Less risk of GI toxicity relative to nonselective NSAIDs; benefit negated by low-dose aspirin, which may require concurrent gastroprotection •No effect on platelet function •Cardiovascular and kidney risks are dose-related and may be similar to nonselective NSAIDs •May be tolerated by patients with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis) who cannot take other NSAIDs; refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Etoricoxib (not available in the United States)	30 to 60 mg once daily	60 mg (chronic pain and inflammation) 120 mg (acute pain for up to 8 days)	•May be associated with more frequent and severe dose-related cardiovascular effects (eg, hypertension) •Other risks and benefits similar to celecoxib
Non-NSAID analgesic			
Acetaminophen (paracetamol)[Δ]	325 to 650 mg every 4 to 6 hours or 1000 mg every 6 hours up to 3 times daily	3000 mg 4000 mg in selected medically supervised patients Avoid or use a lower total daily dose (maximum 2000 mg) in older adults, patients at increased risk for hepatotoxicity (eg, regular alcohol use, malnourished), or patients with organ dysfunction	•Effective for noninflammatory pain; may decrease opioid requirements •Doses ≤2000 mg per day do not appear to increase risk of serious GI complications[3] •Does not alter platelet function •Can cause hepatotoxicity in chronic or acute overdose •To avoid overdose, warn patients about acetaminophen content in combination prescription (eg, oxycodone-acetaminophen) and nonprescription (OTC) preparations

Recommended drug classes for treatment of neuropathic pain

Drug	Effective dose	Comments
First-line therapy		
Antiseizure medications		•Can cause dizziness and sedation; minimize with slow titration •Use lower doses for older patients •Avoid concomitant use with opioids; can cause respiratory depression
Gabapentin	•IR: 300 to 1200 mg orally three times daily •ER: 600 to 1800 mg orally twice daily	•Initiate treatment at a low dose (typically 300 mg orally at night), increasing gradually until pain relief or limiting side effects occur
Pregabalin	•150 to 300 mg orally twice daily	•Initiate treatment at low dose (typically 150 mg orally at night)

Antidepressants		
Serotonin-noradrenaline reuptake inhibitors		
Duloxetine	•IR: 60 to 120 mg orally once daily	
Venlafaxine	•ER:75 to 225 mg orally once daily	
Tricyclic antidepressants (TCAs)		•Initiate treatment at low dose, increase slowly at weekly intervals •May take 6 to 8 weeks, including 2 weeks at highest tolerated dose, for adequate trial
Nortriptyline	•25 to 75 mg orally once daily	•Preferred among TCAs due to less sedation and fewer anticholinergic effects
Amitriptyline	•25 to 125 mg orally once daily	•Most sedating TCA

Second-line therapy		
Capsaicin 8% patch	•1 to 4 patches to painful area for 30 to 60 minutes every three months	•For peripheral pain •Long term safety not established
Lidocaine patch	•1 to 3 patches to painful area for ≤12 hours in a 24 hour period, patch-free period of ≥12 hours	•For peripheral pain
Tramadol	•IR: 100 to 200 mg orally three times daily •ER: 100 to 200 mg orally twice daily	
Third-line therapy		
Botulinum toxin A	•50 to 200 units subcutaneously to painful area every 3 months	Specialist use, for peripheral pain
		Not routinely used for chronic pain
Strong opioids	•Individual titration	•Use only at lowest effective dose, after risk assessment, and with ongoing assessment of risks and benefits Use in combination with nonpharmacologic and nonopioid pharmacologic therapy

Thank you for your time